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### 44.1 Inflammation

Inflammation is defined as the normal response of living tissue to injury or infection. It is important to emphasize two components of this definition. First, that inflammation is a normal response and, as such, is expected to occur when tissue is damaged. Infact, if injured tissue does not exhibit signs of inflammation this would be considered abnormal and wounds and infections would never heal without inflammation. Secondly, inflammation occurs in living tissue, hence there is need for an adequate blood supply to the tissues in order to exhibit an inflammatory response. The inflammatory response may be triggered by mechanical injury, chemical toxins, and invasion by microorganisms, and hypersensitivity reactions. Three major events occur during the inflammatory response: the blood supply to the affected area is increased substantially, capillary permeability is increased, and leucocytes migrate from the capillary vessels into the surrounding interstitial spaces to the site of inflammation or injury. The inflammatory response represents a complex biological and biochemical process involving cells of the immune system and a plethora of biological mediators. Cell-to-cell communication molecules such as cytokines play an extremely important role in mediating the process of inflammation. Inflammation and platelet activation are critical phenomena in the setting of acute coronary syndromes. An extensive exposition of this complex phenomenon is beyond the scope of this article (Rankin 2004).

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation

and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. However, chronic inflammation can also lead to a host of diseases, such as hay fever, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). It is for that reason that inflammation is normally closely regulated by the body. Acute and chronic inflammation differ in matter of causative agent, major cells involved, primary mediators, onset, duration and final outcomes. Generally speaking, acute inflammation is mediated by granulocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes.

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### 44.2 Cell Adhesion Molecules

Cell adhesion molecules are glycoproteins expressed on the cell surface and play an important role in inflammatory as well as neoplastic diseases. There are four main groups: the integrin family, the immunoglobulin superfamily, selectins, and cadherins. The integrin family has eight subfamilies, designated as  $\beta 1$  through  $\beta 8$ . The immunoglobulin superfamily includes leukocyte function antigen-2 (LFA-2 or CD2), leukocyte function antigen-3 (LFA-3 or CD58), intercellular adhesion molecules (ICAMs), vascular adhesion molecule-1 (VCAM-1), platelet-endothelial cell adhesion molecule-1 (PE-CAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). The selectin family includes L-selectin (CD62L), P-selectin (CD62P), and E-selectin (CD62E). Cadherins are major cell-cell adhesion molecules and include epithelial (E), placental (P), and neural (N) subclasses. The binding sites (ligands/receptors) are different for each of these cell adhesion molecules (e.g., ICAM binds to CD11/CD18; VCAM-1 binds to VLA-4). The specific cell adhesion molecules and their ligands that may be involved in pathologic conditions and potential therapeutic strategies by modulating the expression of these molecules have been discussed (Elangbam et al. 1997). Most adhesion molecules

play fairly broad roles in the generation of immune responses. The three selectins act in concert with other cell adhesion molecules e.g., intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and leukocyte integrins to effect adhesive interactions of leukocytes, platelets, and endothelial cells. The structure and functions of selectins, which belong to C-type lectins family, have been reviewed in Chaps. 26, 27, and 28.

#### 44.2.1 Selectins

The selectin family of lectins consists of three closely related cell-surface molecules with differential expression by leukocytes (L-selectin), platelets (P-selectin), and vascular endothelium (E- and P-selectin). Structural identity of a selectins resides in its unique domain composition (Chap. 26). E-, P-, and L-selectin are >60 % identical in their NH<sub>2</sub> terminus of 120 amino acids, which represent the lectin domain (Chaps. 26, 27, and 28). The ligands (counter structures) of selectins are sialylated and fucosylated carbohydrate molecules which, in most cases, decorate mucin-like glycoprotein membrane receptors. Their common structure consists of an N-terminal Ca<sup>2+</sup>-dependent lectin-type domain, an epidermal growth factor (EGF)-like domain, multiple short consensus repeat (SCR) domains similar to those found in complement regulatory proteins, a transmembrane region, and a short cytoplasmic C-terminal domain. Together this arrangement results in an elongated structure which projects from the cell surface, ideal for initiating interactions with circulating leucocytes. The lectin domain forms the main ligand binding site, interacting with a carbohydrate determinant typified by fucosylated, sialylated, and usually sulphated glycans such as sialyl Lewis X (s-Le<sup>X</sup>). The EGF domain may also play a role in ligand recognition. The short consensus repeat (SCR) domains (two for L-selectin, six for E-selectin, and nine for P-selectin) probably act as spacer elements, ensuring optimum positioning of the lectin and EGF domains for ligand interaction. The EGF repeats have comparable sequence similarity. Each complement regulatory-like module is 60 amino acids in length and contains six cysteinyl residues capable of disulfide bond formation. This feature distinguishes the selectin modules from those found in complement binding proteins, such as complement receptors 1 and 2, which contain four cysteines (Chap. 26).

The selectins cell-surface receptors play a key role in the initial adhesive interaction between leukocytes and endothelial cells at sites of inflammation. Selectins (P, E and L) and their ligands (mainly P-selectin ligand) are involved in the rolling and tethering of leukocytes on the vascular wall. Activation of endothelial cells (EC) with different stimuli induces the expression of E- and P-selectins, and other

adhesion molecules (ICAM-1, VCAM-1), involved in their interaction with circulating cells. Lymphocytes home to peripheral lymph nodes (PLNs) via high endothelial venules (HEVs) in the subcortex and incrementally larger collecting venules in the medulla. HEVs express ligands for L-selectin, which mediates lymphocyte rolling (Horstman et al. 2004). For structure and functions of selectins, the readers are advised to consult Chaps 26–28. In this chapter we will emphasize mainly on the role of selectins in inflammatory disorders including cancer.

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#### 44.3 Atherothrombosis

Atherothrombosis, defined as atherosclerotic plaque disruption with superimposed thrombosis, is the leading cause of mortality in the Western world. Atherosclerosis is a diffuse process that starts early in childhood and progresses asymptotically through adult life. Later in life, it is clinically manifested as coronary artery disease (CAD), stroke, transient ischaemic attack (TIA), and peripheral arterial disease. From the clinical point of view, we should envision this disease as a single pathologic entity that affects different vascular territories. A suggestive analogy is that TIA and intermittent claudication are the unstable angina of the brain and lower limbs, respectively; and stroke and gangrene are the myocardial infarction. Circulating platelets display reversible interactions with atherosclerotic lesions. Atherosclerotic arterial disease is associated with an increased share of platelets unable to express P-selectin and an increased fraction of platelets that microaggregate in citrate anticoagulant. These platelet alterations are not completely explained by either focal arterial injury or abnormal rheology associated with arterial stenosis but appear to be an effect of the atherosclerotic process (McBane et al. 2004). The pathogenesis of arterial thrombotic disease involves multiple genetic and environmental factors related to atherosclerosis and thrombosis.

##### 44.3.1 Venous Thrombosis

Venous Thrombosis is a world wide health problem in the general population. Injury to the endothelium leads to dysfunction. The causes of injury include lipids, immune complexes, microorganisms, smoking, hypertension, aging, diabetes mellitus and trauma. The selectins are thought to be largely responsible for the initial attachment and rolling of leukocytes on stimulated vascular endothelium. Platelet activation is an important process in the pathogenesis of atherothrombosis. Platelet adhesion, activation, and aggregation at the sites of vascular endothelial disruption caused by atherosclerosis are key events in arterial thrombus formation. Platelet tethering and adhesion to the arterial wall,

particularly under high shear forces, are achieved through multiple high-affinity interactions between platelet membrane receptors (integrins) and ligands within the exposed subendothelium, most notably collagen and von Willebrand factor (vWF). Platelet adhesion to collagen occurs both indirectly, via binding of the platelet glycoprotein (GP) Ib-V-IX receptor to circulating vWF, which binds to exposed collagen, and directly, via interaction with platelet receptors GP VI and GP Ia/IIb. Platelet activation, initiated by exposed collagen and locally generated soluble platelet agonists (primarily thrombin, ADP, and thromboxane A<sub>2</sub>), provides the stimulus for the release of platelet-derived growth factors, adhesion molecules and coagulation factors, activation of adjacent platelets, and conformational changes in the platelet  $\alpha$ (IIb) $\beta$ 3 integrin (GP IIb/IIIa receptor). Platelet aggregation, mediated primarily by interaction between the activated platelet GP IIb/IIIa receptor and its ligands, fibrinogen and vWF, results in the formation of a platelet-rich thrombus (Steinhuibl and Moliterno 2005).

#### 44.3.2 Arterial Thrombosis

P-selectin expression in platelets is elevated in disorders associated with arterial thrombosis such as coronary artery disease, acute myocardial infarction, stroke, and peripheral artery disease. During thrombosis, P-selectin is expressed on the surface of activated endothelial cells and platelets. P-selectin mediates rolling of platelets and leukocytes on activated endothelial cells as well as interactions of platelets with leukocytes. Platelet P-selectin interacts with PSGL-1 on leukocytes to form platelet-leukocyte aggregates. Furthermore, this interaction of P-selectin with PSGL-1 induces the upregulation of tissue factor, several cytokines in leukocytes and the production of procoagulant microparticles, thereby contributing to a prothrombotic state. P-selectin is also involved in platelet-platelet interactions, i. e. platelet aggregation which is a major factor in arterial thrombosis. P-selectin interacts with platelet sulfatides, thereby stabilizing initial platelet aggregates formed by GPIIb/IIIa-fibrinogen bridges. Inhibition of the P-selectin-sulfatide interaction leads to a reversal of platelet aggregation. Thus, P-selectin plays a significant role in platelet aggregation and platelet-leukocyte interactions, both important mechanisms in the development of arterial thrombosis. Following activation, P-selectin is rapidly translocated to the cell surface (Merten and Thiagarajan 2004; Wang et al. 2005).

#### 44.3.3 Thrombogenesis in Atrial Fibrillation

Platelet activation occurs in peripheral blood of patients with rheumatic mitral stenosis (MS). The plasma levels of soluble

P-selectin are elevated in permanent atrial fibrillation (AF) patients; the plasma levels of soluble P-selectin in the left atrium do not significantly differ from those in the right atrium, femoral vein, or femoral artery. The venous plasma levels of sP-selectin in patients with moderate-to-severe MS are significantly higher than those in healthy volunteers or patients with lone AF. In addition, in patients with MS, there was no difference in the plasma levels of sP-selectin between the left and right atrial blood and between peripheral and atrial blood. Moreover, there was no change in sP-selectin levels as a result of percutaneous transluminal mitral valvuloplasty (PTMV) (Chen et al. 2004). Lip et al. (2005) studied the relations of plasma vWf (an index of endothelial damage and dysfunction) and sP-selectin levels in relation to the presence and onset of clinical congestive heart failure (CHF) and degree of left ventricular dysfunction in patients taking part in SPAF (stroke prevention in AF). While plasma vWf was higher among patients with AF and CHF, plasma P-selectin concentrations were not affected by presence, onset, or severity of heart failure.

#### 44.3.4 Atherosclerosis

Atherosclerosis is a complex chronic inflammatory disease of the arterial wall. Though the inflammatory nature of atherosclerosis has been established, the initial events that trigger this response in the arterial intima remain obscure. Studies reveal a significant rate of genomic alterations in human atheromas. The accumulation of genomic rearrangements in vascular endothelium and smooth muscle cells are important for disease development. It is well accepted that the induction of EC adhesion molecules is a critical component in acute inflammatory responses as well as allogeneic interactions in vascularized allografts and, possibly, atherogenesis. Inflammation and genetics are both prominent mechanisms in the pathogenesis of atherosclerosis and arterial thrombosis. Accordingly, population studies have explored the association of ischaemic heart disease with gene polymorphisms of the inflammatory molecules: tumor necrosis factors (TNF)  $\alpha$  and  $\beta$ , transforming growth factors (TGF)  $\beta$ 1 and 2, P and E selectins, and platelet endothelial cell adhesion molecule (PECAM) 1. The partly conflicting data provide some evidence that alterations in the genetics of the inflammatory system may modify the risk of ischaemic heart disease.

##### 44.3.4.1 Formation of Reactive Oxygen Species (ROS) as an Initial Event

In recent years, reactive oxygen species (ROS) are considered as initial event in causing atherosclerosis. ROS are a family of molecules including molecular oxygen and its derivatives produced in all aerobic cells. Excessive

production of ROS, outstripping endogenous antioxidant defense mechanisms, has been implicated in processes in which they oxidize biological macromolecules, such as DNA, protein, carbohydrates, and lipids. Many ROS possess unpaired electrons and thus are free radicals. These include molecules such as superoxide anion ( $O_2^-$ ), hydroxyl radical ( $HO^\bullet$ ), nitric oxide ( $NO^\bullet$ ), and lipid radicals. Other reactive oxygen species, such as hydrogen peroxide ( $H_2O_2$ ), peroxyxynitrite ( $ONOO^-$ ), and hypochlorous acid ( $HOCl$ ), are not free radicals per se but have oxidizing effects that contribute to oxidant stress. The cellular production of one ROS may lead to the production of several others via radical chain reactions. For example, reactions between radicals and polyunsaturated fatty acids within cell membrane may result in a fatty acid peroxy radical ( $R-COO^\bullet$ ) that can attack adjacent fatty acid side chains and initiate production of other lipid radicals. Lipid radicals produced in this chain reaction accumulate in the cell membrane and may have a myriad of effects on cellular function, including leakage of the plasmolemma and dysfunction of membrane-bound receptors. Of note, end products of lipid peroxidation, including unsaturated aldehydes and other metabolites, have cytotoxic and mutagenic properties. A decline in NO bioavailability may be caused by decreased expression of the endothelial cell NO synthase (eNOS), a lack of substrate or cofactors for eNOS (Fig. 44.1 and 44.2).

In mammalian cells, potential enzymatic sources of ROS include the mitochondrial respiration, arachidonic acid pathway enzymes lipoxygenase and cyclooxygenase, cytochrome p450s, xanthine oxidase, NADH/NADPH oxidases, NO synthase, peroxidases, and other hemoproteins. Although many of these sources could potentially produce ROS that inactivate  $NO^\bullet$ , 3 sources have been studied extensively in cardiovascular system. These include xanthine oxidase, NADH/NADPH oxidase, and NO synthase (Cai and Harrison 2000; Hamilton et al. 2004; Vijya Lakshmi et al. 2009).

#### 44.3.4.2 CAMs as Predicators of Atherosclerosis

During initial step in atherosclerosis, there is rapid targeting of monocytes to the sites of inflammation and endothelial injury; the adhesion of leukocytes to activated endothelial cells is mediated by ICAM-1. The induction of EC adhesion molecules is a critical component in acute inflammatory responses as well as allogeneic interactions in vascularized allografts and, possibly, atherogenesis. The "inflammatory triad" of IL-1, TNF, and LPS are potent stimulators of the EC activation and adhesion molecules E-selectin or ELAM-1 (or also known as CD62E), ICAM-1 and VCAM-1. PECAM-1 plays also a key role in the transendothelial migration of circulating leukocytes (diapedesis) during vascular inflammation. ICAM-1 and VCAM-1 are

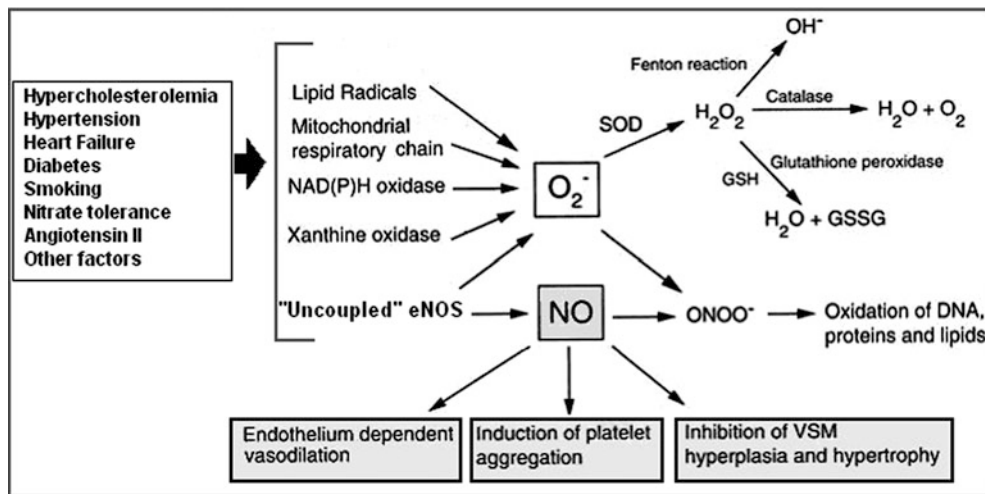
inflammatory predicators of adverse prognosis in patients with acute coronary syndromes (ACS) (Postadzhiyan et al. 2008) (Fig. 44.2).

Levels of P-selectin are increased in the blood of patients with familial hypercholesterolemia (FH) in spite of long-term intensive extracorporeal LDL-elimination, documenting the activity of atherosclerosis. Low levels of P-selectin and MCP-1 after hypolipemic procedure can be used as a marker showing the effectivity of the extracorporeal LDL-cholesterol elimination (Blaha et al. 2004). In an extended study, the levels of expression of tissue factor, ICAM-1, P- and E-selectin, and PAI-1 were found low, whereas those of endothelial protein C receptor and VCAM-1 were high (Merlini et al. 2004).

#### 44.3.4.3 Gene Polymorphisms in E-Selectin

Polymorphisms in the E-selectin gene are associated with accelerated atherosclerosis in young (age <40 years) patients, further suggesting a role of inflammation in atherosclerosis. A further change in endothelial physiology is an increase in the surface expression of E-selectin, which regulate adhesive interactions between certain blood cells and endothelium. Intravascular fibrinolysis induced by tissue-type plasminogen activator or urokinase may contribute to the initiation of atherosclerosis by inducing P-selectin and platelet activating factor as well as to plaque rupture, either directly or indirectly, by activating metalloproteinases. As E-selectin is only expressed on activated endothelium, it provides an opportunity to study pathophysiological aspects of this cell in cardiovascular and other disease. However, sE-selectin can be found in the plasma, which has potential role in the pathogenesis of cardiovascular disease as raised levels have been found in hypertension, diabetes and hyperlipidemia, although its association in established atherosclerosis disease and its value as a prognostic factor is more controversial (Holvoet and Collen 1997).

Polymorphisms for three genes, P-selectin, L-selectin, and E-selectin (genes *P-sel*, *L-sel*, and *E-sel*, respectively) showed that the selectin cluster is linked to markers at chromosome 1q23 (Vora et al. 1994). Significant genomic alterations were found on 1q22-q25 in *Sel-L* gene. The message indicated somatic DNA rearrangements, on loci associated to leukocyte adhesion, vascular smooth muscle cells growth, differentiation and migration, to atherosclerosis development as an inflammatory condition (Arvanitis et al. 2005). Wenzel et al. (1999) and Yoshida et al. (2003) described an adenine to cytosine (A/C) substitution for cDNA position 561 resulting in an amino acid exchange from serine to arginine at position 128 (S/R or Ser<sup>128</sup>Arg) was detected in the epidermal growth factor (EGF) domain. A higher mutation frequency was observed in patients aged 50 years or less with proven severe atherosclerosis as well as in patients aged 40 years or less. If Ser<sup>128</sup>Arg substitution



**Fig. 44.1** Mechanisms for oxidant stress-induced endothelial dysfunction in cardiovascular diseases (Hamilton et al. 2004). Excessive production of ROS has been implicated in processes in which they oxidize biological macromolecules, such as DNA, protein, carbohydrates, and lipids. Many ROS possess unpaired electrons and thus are free radicals. These include molecules such as superoxide anion ( $O_2^-$ ), hydroxyl radical ( $OH^\bullet$ ), nitric oxide ( $NO^\bullet$ ), and lipid radicals. The cellular production of one ROS may lead to the production of several others via radical chain reactions. A decline in NO

bioavailability may be caused by decreased expression of the endothelial cell NO synthase (eNOS), a lack of substrate or cofactors required for eNOS action. Low-density lipoprotein (LDL) is oxidized to oxidized form of LDL (ox-LDL) and initiates the atherosclerotic process in the vessel wall (see Fig. 44.2). Abbreviations:  $O_2^-$ , superoxide; NO, nitric oxide;  $ONOO^-$ , peroxynitrite;  $H_2O_2$ , hydrogen peroxide;  $OH^\bullet$ , hydroxyl radical; SOD, superoxide dismutase; GSH, reduced glutathione; GSSG, oxidised glutathione; VSM, vascular smooth muscle

had an effect on the adhesion of blood cells to the endothelium, the polymorphism could be of interest with respect to association studies in a number of pathological conditions, such as cardiovascular diseases. The Ser<sup>128</sup>Arg polymorphism is associated with a higher risk for early severe atherosclerosis. Yoshida et al. (2003) suggested that the E-selectin Ser<sup>128</sup>Arg polymorphism could functionally alter leukocyte-endothelial interactions as well as biochemical and biological consequences, which may account for the pathogenesis of myocardial infarction (Li et al. 2005).

#### Leu<sup>554</sup>Phe E-selectin mutations in Hypertension and CAD

Wenzel et al. (1996, 1999) detected 17 mutations, five of which resulted in an amino acid substitution. In E-selectin, exchange at Ser<sup>128</sup>Arg in EGF domain and Leu<sup>554</sup>Phe in membrane domain, and a DNA mutation from guanine to thymine (position 98) presented different allele frequencies in young patients with severe atherosclerosis, compared with an unselected population. The bi-allelic A/C polymorphism in the E-selectin gene may be implicated in the clinical expression of erythema nodosum (EN) secondary to sarcoidosis (Amoli et al. 2004). However, the E-selectin polymorphism may be associated with severity of atherosclerotic disease, but it is unknown if it is actually a risk factor for atherosclerosis (Ghilardi et al. 2004). A strong relationship

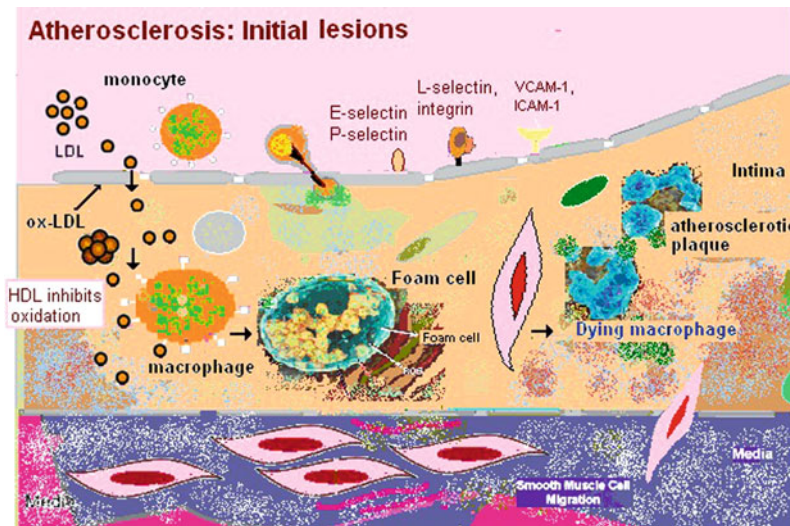
was confirmed between 561A > C and 98G > T polymorphisms of E-selectin gene and susceptibility to CAD by Zak et al. (2008). A body mass index (BMI)-specific effect of Leu<sup>554</sup>Phe polymorphism of E-selectin gene on blood pressure has been reported by Marteau et al. (2004) who strengthened the view that E-selectin is implicated in hypertension (Marteau et al. 2004). Serum levels of E- and P-selectin in patients with essential hypertension (EH) are significantly higher than in controls, where as differences in serum levels of soluble L-selectin, VCAM-1, or ICAM-1 between the patients with EH and the controls were not different (Sanada et al. 2005).

#### 44.3.4.4 Genomic Arrangement of P-Selectin Gene

##### P-Selectin Thr<sup>715</sup>Pro (A/C) Polymorphism

Genetic analyses of P-selectin in the progression of atherosclerosis have provided conflicting results regarding the role of variation within the P-selectin gene and risk for heart disease. Miller et al. (2004b) suggested that the Thr<sup>715</sup>Pro C allele was rare in blacks (0.8 %) and intermediate in South Asians (3.0 %) compared to whites (11.2 %). sP-selectin levels were significantly lower in the individuals with the AC or CC compared to the AA genotype in both whites and South Asians. Thus, in whites and South Asians the C allele of the Thr<sup>715</sup>Pro P-selectin polymorphism is associated with





**Fig. 44.2** Oxidation of LDL initiates the atherosclerotic process in the vessel wall by acting as a potent stimulus for the induction of inflammatory gene products in vascular endothelial cells. By activating the NF- $\kappa$ B transcription factor, oxidized LDL (ox-LDL) stimulates increased expression of cellular adhesion molecules. There are several different types of adhesion molecules with specific functions in the endothelial leukocyte interaction: The selectins tether and trap monocytes and other leukocytes. Importantly, VCAMs and ICAMs mediate firm attachment of these leukocytes to the endothelial layer.

Ox-LDL also augments expression of monocyte chemoattractant protein 1 (MCP-1) and macrophage colony stimulating factor (M-CSF). MCP-1 mediates the attraction of monocytes and leukocytes and their diapedesis through the endothelium into the intima. M-CSF plays an important role in the transformation of monocytes to macrophage foam cells. Macrophages express scavenger receptors, which internalize oxLDL in their transformation into foam cells. Migration of smooth muscle cells (SMCs) from the intima into the media is another early event initiating a sequence that leads to formation of a fibrous atheroma

lower sP-selectin levels (Miller et al. 2004b). The P-selectin Thr<sup>715</sup>Pro polymorphism is not associated with incident CHD or ischemic stroke in either whites or African-Americans (Volcik et al. 2006).

Leu<sup>125</sup>Val polymorphism of PECAM-1 gene and elevated soluble PECAM-1 were related to severe coronary artery stenosis in CAD patients.

#### 44.3.4.5 Predictive Value of sE-Selectin in CAD

In CAD, inflammatory biomarkers have been extensively investigated; more evidence exists for C-reactive protein (CRP; Chap. 8). Fatty acid (FA) composition in serum has been associated with CRP and E-selectin but not with other inflammatory markers (Pettersson et al. 2009). Studies suggest that, besides CRP, other inflammatory biomarkers such as cytokines, s-CD40 ligand, serum amyloid A (SAA), selectins (E-selectin, P-selectin), ICAM-1, VCAM-1, and several others may have a potential role for the prediction of risk for developing CAD and may correlate with severity of CAD (Eikemo et al. 2004; Fang et al. 2004; Potapov et al. 2005; Zakynthinos and Pappa 2009). The combination of natriuretic peptide (BNP) and E-selectin offers increased predictive value. Plasma levels of adhesive molecules are correlated in patients with stable IHD. Cigarette smoke condensate (CSC)-induced surface expression of ICAM-1, E-selectin, and VCAM-1 in HUVEC. Fang et al. (2005) reported a significant decrease in C allele frequency of PECAM-1 gene and showed that

#### 44.3.5 Myocardial Infarction

##### sP-Selectin is Associated with Myocardial Damage:

Platelets are known to be activated during myocardial infarction (MI). Though, the levels of sP-selectin, sE-selectin and sPECAM-1 did not differ significantly in the pathogenesis of atherosclerosis, sP-selectin was substantially increased in patients with acute myocardial infarction (AMI). Yip et al. (2006) tested the hypothesis that platelet activity shown by CD62P is enhanced and predictive of both the extent of myocardial damage and 30-day clinical outcome in patients with ST-se AMI undergoing primary coronary stenting. Xu et al. (2006) suggested that activated-platelets play an important role in the process of myocardial ischemia-reperfusion injury, and platelet-derived P-selectin is a critical mediator. P-selectin expression, along with CD40 ligand and tissue factor is significantly increased in infarcted rabbits with respect to controls. Clopidogrel administration reduced P-selectin expression and CD40 ligand (Molero et al. 2005).

**Hyperhomocysteinemia and Selectins in MI:** Hyperhomocysteinemia is regarded as an independent risk factor for vascular diseases, and homocysteine is supposed to contribute to oxidative stress and endothelial damage. Hyperhomocysteinemia is significantly associated with MI in comparison with controls with an odd ratio of 6.26 (Khare et al. 2005). Folic acid corrected and reduced hyperhomocysteinemia in a large majority of the cases. Although the levels of sP-selectin, sE-selectin and sPECAM-1 decrease after folic acid therapy, it was only sE-selectin which was significantly reduced. Apart from their lipid-lowering capacity, statins also exert anti-inflammatory and antioxidant effects.

**DNA Polymorphism in MI:** Some polymorphisms may increase the risk of MI within specific ethnic groups or in certain populations. P-selectin expression is increased in atherosclerotic plaques, and high plasma levels of this molecule have been observed in patients with unstable angina. DNA polymorphisms in P-selectin gene may be a possible candidate for MI. The P-selectin gene is situated on chromosome 1q21-q24, spans >50 kb and contains 17 exons. Four polymorphisms (Ser<sup>290</sup>Asn, Asn<sup>562</sup>Asp, Leu<sup>599</sup>Val and Thr<sup>715</sup>Pro) predicted a change in the amino acid sequence of P-selectin. In patients with MI from four regions of France and Northern Ireland (the ECTIM study) the P-selectin polymorphisms provided a heterozygosity of 91 %. The polymorphisms were tightly associated with one another and displayed patterns of linkage disequilibrium suggesting the existence of highly conserved ancestral haplotypes. Study illustrates the complexity of the relationship between gene variability and disease and the necessity to explore in detail the polymorphisms of candidate genes (Herrmann et al. 1998; Tregouet et al. 2002).

The E-selectin gene Arg128, 98 T, and Phe554 alleles and PECAM1 Leu1<sup>25</sup>Val and Ser<sup>563</sup>Asn polymorphisms may increase the risk of atherosclerosis, but not necessarily the risk of MI. This association seems to be more pronounced in younger patients and may be especially important in patients with a low risk for developing atherosclerosis. Reports indicated that screening for CD14-260 C/T genotypes is unlikely to be a useful tool for risk assessment and it remains unclear whether CD14 polymorphisms significantly increase the risk of MI. The A<sup>252</sup>G polymorphism of lymphotoxin- $\alpha$  (LTA) gene, a member of the TNF family, is strongly related with the onset of AMI (Auer et al. 2003). Quantitative real-time RT-PCR confirmed that LTA increased the expressions of E-Selectin and VCAM1 both in HUVEC and HCAEC, suggesting the roles of LTA in the development of atherosclerosis. Aminian et al. (2007) determined the possible role of Gly<sup>241</sup>Arg and Lys<sup>469</sup>Glu polymorphisms in development of CAD and acute or chronic MI. Although the

frequency of Gly-Arg and Arg-Arg genotypes were higher in the control group compared to the CHD patients, no strong correlation was found between Gly<sup>241</sup>Arg and Lys<sup>469</sup>Glu polymorphisms and occurrence of CHD and MI in population from Iran.

#### 44.3.6 Atherosclerotic Ischemic Stroke

In ischemic event in patients with atherosclerotic ischemic stroke, though the platelet aggregability was decreased after day 3 compared to that at day 1 of stroke onset, platelet CD63 and P-selectin/CD62P expression remained high even 90 days after the events. This suggested that platelet hyperactivation in atherosclerotic ischemic stroke might be sustained for a considerable period (Cha et al. 2004; Nadar et al. 2004b; Yip et al. 2006). Blood levels of ICAM-1 and CD62P expression in different typing of patients with ischemic stroke are different. Evidences suggest that MPS (Meridian-phlegm stagnancy) group of patients is the key pathogenic factor of ischemic stroke.

Mucosal tolerance to E-selectin after booster tolerization can relieve cerebral ischemia-reperfusion injury and induce ischemia tolerance in rats. The mechanisms may involve decreased frequencies of CD8<sup>+</sup> T cells, heightened mRNA expression of IL-10 and lowered mRNA expression of E-selectin in the ischemic hemisphere (Yun et al. 2008). Selakovic et al. (2009) defined changes of soluble CAMS in cerebrospinal fluid and plasma in the patients with the acute brain infarction, in which significant increase in the level of soluble adhesion molecules occurs within the first seven days. Studies show that hypoxia/reoxygenation stimulates ICAM-1 and apoptosis (Antonova et al. 2009).

Cerebral arteriovenous malformations (AVMs) showed significant upregulation of E-selectin, VCAM-1 and ICAM-1 (Storer et al. 2008; Chan and Sukhatme 2008; Tuttolomondo et al. 2009). Li et al. (2008) showed that ICAM-1 Lys<sup>469</sup>Glu polymorphism was involved in the causation of ischemic stroke, especially in female but not in male (Rodrigues et al. 2008). Two allelic variants were related to ischemic stroke. Multivariable regression analysis after adjustment for vascular risk factors demonstrated that alleles Arg of Ser<sup>128</sup>Arg and Phe of Leu<sup>554</sup>Phe polymorphisms are independent risk factors for ischemic stroke. The combination of two minor alleles of E-selectin genes appeared to be the strongest susceptibility factor for ischemic stroke (Haidari et al. 2009). Sarecka-Hujar et al. (2010) could not confirm the relationship between the 98 G > T polymorphism of the E-selectin gene and childhood ischemic stroke. The G allele of the E-selectin 98 G > T polymorphism was more frequently transmitted to the children after stroke compared to the T allele. There is a need for further studies in these areas.

### 44.3.7 Hypertension

The association between blood pressure and different adhesion molecules appeared to be present in women younger than 50 years, who were likely to be pre-menopausal (Miller et al. 2004a). Serum levels of E- and P-selectin in patients with essential hypertension (EH) are significantly higher than in the controls (Sanada et al. 2005). After adjustment for age, only sE-selectin concentrations were significantly associated with blood pressure. Higher levels of plasma sP-selectin were confirmed in hypertensive patients alone with VEGF (Nadar et al. 2004a). It is stated that decrease in blood pressure may reduce the rate of progression of atherosclerosis by affecting the expression of E- and P-selectin in the endothelium, the platelets, or both.

### 44.3.8 Reperfusion Injury

In vitro studies indicate that complement activation regulates the expression of P-selectin on endothelial cells. This suggests that in disorders such as ischemia/reperfusion injury, in which both complement and P-selectin have been shown to play a role, complement activation is a primary event and the effects of P-selectin are secondary. In mouse kidney model of I/R injury, results indicated that complement and P-selectin-mediated pathways of renal reperfusion injury are mutually independent (Farrar et al. 2004). Induction of circulating polymorphonuclear neutrophils (PMNs) might contribute to the superior outcome following stenting and early intervention compared to conventional balloon angioplasty (PTCA). A substantial increase in sE-selectin levels early after PTCA and stent implantation may predict development of restenosis (Heider et al. 2006; Kilickap et al. 2004). After reperfusion of myocardial vessels, P-selectin expressed on majority of vessels (77 %) though the expression decreased during subsequent remaining duration of reperfusion (Chukwuemeka et al. 2005). In rats, the mRNA expression for several genes was associated with inflammation after transient middle cerebral artery occlusion (MCAO). Gene expression increased in the injured hemisphere for IL-1 $\beta$ , IL-6 and ICAM-1. TNF- $\alpha$  mRNA was upregulated in the injured versus uninjured hemisphere, while E-selectin mRNA showed a significant increase from 6 to 24 h after MCAO (Berti et al. 2002). Both P-selectin and LFA-1 may be important targets to control pathologic inflammation in I/R-induced tissue injury in the colon (Riaz et al. 2002). The study in intestinal ischemia and reperfusion injury (IR/I) using murine models demonstrated the importance of P-selectin in warm and cold IR/I. The blockade of P-selectin using rPSGL1-Ig or the absence of P-selectin KO mice confers a survival advantage and reduction in tissue injury. The mechanism appears to be

independent of neutrophil infiltration (Carmody et al. 2004). Enterocyte apoptosis is increased following intestinal I/R injury. Hyperoxia following intestinal I/R in rat increased E-selectin expression in the jejunum and ileum and a concomitant increase in neutrophil recruitment in the ileum, accompanied by increased cell apoptosis (Braun et al. 2004; Sukhotnik et al. 2008). Germ cell-specific apoptosis that occurs after I/R of murine testis is dependent on neutrophil recruitment to the testis and is dependent on E-selectin. Blockage of E-selectin may be a strategy to treat post-ischaemic testis (Celebi and Paul 2008).

## 44.4 CAMS in Allergic Inflammation

Allergic inflammation is characterized by recruitment of specific leukocyte subpopulations from blood into tissue and requires a series of cell adhesion-molecule-mediated interactions between postcapillary vascular endothelium and the leukocyte cell surface. Three major groups are involved: selectins, integrins, and the immunoglobulin gene superfamily. P- and E-selectin mediate initial leukocyte adhesion, whereas beta 2-integrin/ICAM-1 and VLA-4/VCAM-1 pathways mediate leukocyte arrest and transendothelial migration. Because VLA-4 expression is restricted to eosinophils and lymphocytes, VCAM-1 has been implicated in selective eosinophil recruitment characterizing allergic inflammation. However, additional factors such as profile of cytokine release are likely to operate since tissue eosinophilia has been observed in the absence of VCAM-1 expression (Smith et al. 1993a).

### 44.4.1 Dermal Disorders

E-selectin is highly expressed on vascular endothelium in atopic dermatitis and psoriasis, and in patients with measles. The cutaneous lymphocyte-associated antigen (CLA), which is expressed on peripheral skin-homing helper memory T cells in healthy persons, is at least partly the sialyl 6-sulfo Le<sup>x</sup> determinant (Ohmori et al. 2006) and a ligand for selectins. The differential polyadenylation of E-selectin transcripts may provide the molecular basis for the observed chronic expression of E-selectin in human dermal disorders. In atopic dermatitis, patients express ICAM-1 and ICAM-3, E-selectin and L-selectin (60 %) in the dermis, without expression of E- and L-selectins in the epidermis. A high expression of adhesion molecules in the skin lesions of atopic dermatitis patients may play an important role in the pathogenesis of atopic dermatitis (Lugovic et al. 2006). The blood markers for atopic dermatitis, including soluble forms of E-selectin, VCAM-1 and ICAM-1 were reduced after treatment with cetiridine (Izu and Tokura 2005). The extracts from dust



mites, *Dermatophagoides farinae*, *D. pteronyssinus* and *Euroglyphus maynei* with and without endotoxin (LPS) stimulated endothelial cells to express ICAM-1, VCAM-1, and E-selectin and to secrete IL-6, IL-8, MCP-1, and GM-CSF. Serum levels of sE-selectin are higher in children with measles than in children with atopic dermatitis, atopic asthma and healthy controls. But it was not correlated with measles. There was no correlation between sE-selectin and TNF- $\alpha$  level (Park et al. 2008). Pollinosis from *Parietaria judaica* is one of the main causes of allergy in the Mediterranean area. The treatment of endothelial cells with pollen extract causes an increase of E-selectin and VCAM-1 protein levels as well as an increase of IL-8 production. The stimulation of cell adhesion molecules was paralleled by an increase of adhesion of polymorphonuclear cells (PMNs) to HMVEC-L monolayer (Taverna et al. 2008).

#### 44.4.2 Rhinitis and Nasal Polyposis

Allergic rhinitis is an inflammatory disease of the nasal mucosa, caused by an IgE-mediated reaction after exposure to the allergen. Persistent inflammation is induced by the presence of an inflammatory cell infiltrate, together with ICAM-1 expression in the epithelial cells of the mucosa exposed to the allergen to which they are sensitized, in the absence of clinical symptoms (Montoro et al. 2007). Nasal polyposis is a chronic non-infectious inflammatory disease of the nasal and paranasal cavity mucosa. Eosinophil migration from blood stream to nasal polyps involves different molecules such as ICAM-1, VCAM-1, and L-, P- and E-selectins. Patients with nasal polyposis exhibit a higher expression of VCAM-1, E-selectin, and L-selectin compared to healthy controls (Corsi et al. 2008). *Staphylococcal enterotoxin A* (SEA) and *staphylococcal enterotoxin B* (SEB) infection increased ICAM-1 expression and cytokine secretion (Wang et al. 2007).

#### 44.4.3 Lung Injury

Excessive leukocyte accumulation is involved in the pathogenesis of the sepsis-induced acute lung injury. Studies suggest that P-selectin has a substantial role in the pathogenesis of the lung injury induced by LPS (Ohnishi et al. 1999). In bleomycin-induced fibrosis in mice, the L-selectin and/or ICAM-1 deficiency inhibited skin and lung fibrosis with decreased Th2 and Th17 cytokines and increased Th1 cytokines. In contrast, P-selectin deficiency, E-selectin deficiency with or without P-selectin blockade, or PSGL-1 deficiency augmented the fibrosis in parallel with increased Th2 and Th17 cytokines and decreased Th1 cytokines. Yoshizaki

et al. (2010) suggest that L-selectin and ICAM-1 regulate Th2 and Th17 cell accumulation in skin and the lung, leading to the development of fibrosis, and that P-selectin, E-selectin, and PSGL-1 regulate Th1 cell infiltration, resulting in the inhibition of fibrosis (Yoshizaki et al. 2010). Adult respiratory distress syndrome (ARDS) appears to develop as the acute lung injury in the course of many severe diseases, as the result of damage of alveolar-capillary barrier. Clinical observations suggest that analysis of E-, P-selectin and ICAM-1 concentrations in the serum of patients with ARDS may be helpful in monitoring the course and treatment of the disease (Skiba-Choińska and Rogowski 1996). In the pathogenesis of paracoccidioidomycosis, Gonzalez et al. (2005) suggest that during early stages, up-regulation of ICAM-1, VCAM-1, CD18 and Mac-1 expression may participate in the inflammatory process.

#### 44.4.4 Bronchial Asthma and Human Rhinovirus

The house dust mite (HDM) is the common indoor allergen associated with bronchial asthma. ICAM-1, VCAM-1, and E-selectin are newly synthesized prior to spontaneous asthma attacks, and their expression may play a key role in eosinophil infiltration into the airway (Ohkawara et al. 1995). Crude extract of *D. farinae* induces ICAM-1 expression in EoL-1 cells through signaling pathways involving both NF- $\kappa$ B and JNK (Kwon et al. 2007). Kirchberger et al. (2006) demonstrated that signaling via ICAM-1 induces adhesiveness of mononuclear phagocytes, which critically involves PECAM-1 and is mediated via LFA-1/ICAM-3. The most common acute infection in humans, Human Rhinovirus (HRV) is a leading cause of exacerbations of asthma and chronic obstruction pulmonary disease. ICAM-1 is a critical target-docking molecule on epithelial cells for 90 % HRV serotypes. ICAM-1 regulates not only viral entry and replication but also signaling pathways that lead to inflammatory mediator production (Lau et al. 2008; Lee et al. 2008). The sICAM-1 but not sE-selectin from patients with asthma is significantly higher than healthy controls. Although serum levels of sICAM-1 are higher in asthmatics, it may be necessary to establish individual baseline values for serial estimation to evaluate their clinical relevance (Bijanazadeh et al. 2009). The serum levels of sICAM-1 were significantly higher in obese nonasthmatic and obese asthmatic children versus control and lean asthmatic children (Huang et al. 2008). P-selectin is an important controller of the inflammation by mediating selective eosinophil cell influx to the lung. It can be used as a sensitive marker in mild asthma (Sjosward et al. 2004).

## 44.5 Autoimmune Diseases

Adhesion molecule expression and interactions are involved in initiation and propagation of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroid disease, multiple sclerosis, systemic sclerosis (SSc) and diabetes mellitus. Increased adhesion molecule expression and avidity changes occurring with cellular activation are the principal methods regulating leukocyte adhesion. Although differences between specific autoimmune diseases exist, key interactions facilitating the development of autoimmune inflammation appear to include L-selectin/P-selectin/E-selectin, LFA-1/ICAM-1, very late antigen-4 (VLA-4)/VCAM-1, and  $\alpha$ 4B7/MadCAM or VCAM-1 adhesion. A vast array of adhesive interactions occurs between immunocompetent cells, endothelium, extracellular matrix, and target tissues during the evolution of an autoimmune disease. Dermatitis herpetiformis (DH) and bullous pemphigoid (BP), the autoimmune diseases, are characterized by destruction of the basement membrane zone (BMZ) and anchoring fibres by autoantibodies and infiltration. Skin biopsies from patients with DH, with BP, and from healthy subjects showed the expression of E and L selectins mainly in the skin leukocytes in all samples where as  $\beta$ 1,  $\beta$ 3 integrins was detected mainly in basal keratinocytes. Integrins and selectins seem to play an important role in the destruction of BMZ in DH and BP (Erkiert-Polguj et al. 2009). P-selectin levels were significantly higher than normal in RA and SSc, but not in SLE. In contrast, mean L-selectin levels were significantly higher than normal in SLE, but not in RA or SSc. Where as soluble IL-2 receptors in patients with active RA, SSc and SLE were almost double the normal level, showing a strong positive correlation only between L-selectin and sIL-2R, and only in patients with SLE. These findings indicated a distinct pattern of immune cell activation in chronic diseases that share an over-activation of T-lymphocytes (Sfikakis and Mavrikakis 1999).

### 44.5.1 Endothelial Dysfunction in Diabetes (Type 1 Diabetes)

Adhesion molecules have been implicated in the development and progression of cardiovascular disease, particularly in people with diabetes. Diabetes mellitus type 1 (Type 1 diabetes or T1DM, also called insulin-dependent diabetes mellitus—IDDM, or, formerly, juvenile diabetes) is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing  $\beta$  cells of the pancreas. The chronic hyperglycemic state in T1DM patients produces an aggression to vascular endothelium leading to a premature

development of atherosclerosis. In both boys and girls, sE-selectin is an early marker of endothelial dysfunction and a probable risk marker of atherosclerosis in children with T1DM (Carrizo et al. 2008). The levels of C-reactive protein, E-selectin, and cytokines in association with severity index were significantly increased in T1DM and type 1 diabetic patients with microvascular complications (T1DM-MV patients) compared with control subjects (Devaraj et al. 2007). Nerve microvasculitis and ischemic injury appear to be the primary and important pathogenic alterations in lumbosacral radiculoplexus neuropathy (LRPN) of patients with diabetes mellitus (DLRPN) and without diabetes mellitus (LRPN). The up-regulation of inflammatory mediators target different cells at different disease stages and that these mediators may be sequentially involved in an immune-mediated inflammatory process that is shared by both DLRPN and LRPN (Kawamura et al. 2008).

Adhesion molecules are upregulated in endothelial cells of the placental bed in pregnancies complicated by T1DM in association with increased adherence of peripheral blood monocytes. The increase in monocyte adhesion to decidual endothelial cells from diabetic pregnancies was associated with increased endothelial cell expression of ICAM-1, but not VCAM-1. ICAM-1 expression in normal decidual endothelial cells was stimulated by pro-atherogenic and pro-inflammatory stimuli (Xie et al. 2008; Telejko et al. 2009).

**Type 2 Diabetes:** In contrast to T1DM, type 2 diabetes mellitus (T2DM) results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency (Formerly referred to as non-insulin-dependent diabetes mellitus, NIDDM for short). Endothelial dysfunction in type 2 diabetic patients is associated with inflammation, increased levels of circulating soluble adhesion molecules (VCAM-1 and E-selectin), and inducing production of ROS, and urinary albumin excretion (Potenza et al. 2009). Diabetic patients have increased susceptibility to infection, which may be related to impaired inflammatory response observed in experimental models of diabetes, and restored by insulin treatment (Riad et al. 2008; West et al. 2008).

**Serum Levels of CAMs in Diabetic Patients:** Abnormal levels some of serum ICAM-1, VCAM-1, E-selectin, P-selectin, L-selectin have been detected in T2DM. High-fat load and glucose alone produce an increase of nitrotyrosine, ICAM-1, VCAM-1, and E-selectin plasma levels in normal and diabetic subjects. A decrease in neutrophil surface CD62L expression and significantly higher concentrations of sICAM-1, sVCAM-1, sE-selectin, vWF, hsCRP, IL-6 and fibrinogen in patients with diabetic microangiopathy in comparison with diabetic group without microangiopathic complications and

healthy controls suggested that: (1) diabetic microangiopathy is accompanied by increase in CD11b expression and decrease in CD62L (L-selectin) expression on peripheral blood neutrophils; (2) neutrophil activation and intensified adhesion; (3) the development of diabetic microangiopathy is accompanied by an increase in soluble adhesion molecules and inflammatory markers concentrations in the blood (Lim et al. 2004; Mastej and Adamiec; 2008). Levels of E-selectin positively correlated with high triglyceride levels in type 2 diabetic subjects with silent ischemia (Adamikova et al. 2008; Okapcova and Gabor 2004; Rubio-Guerra et al. 2008). Though, baseline plasma levels of vascular markers (hsCRP, sICAM-1, sVCAM-1, E-selectin and P-selectin) were significantly elevated, they did not improve after aerobic exercise. The sE-selectin and vWF are elevated in chronic heart failure patients with DM but not in those without DM. High sE-selectin levels may be associated with ischaemic events in patients with DM (Kistorp et al. 2008).

**Diabetic Nephropathy (DN) and Diabetic Heart:** Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) (Malatino et al. 2007). Although the pathogenesis of DN is multifactorial, local inflammatory stress may result from both the metabolic and hemodynamic derangements observed in DN. The current evidence supporting the role of inflammation in the early phases of clinical and experimental DN has been reviewed (Fornoni et al. 2008). Inflammatory markers such as IL-18 and TNF- $\alpha$  are increased in the serum of patients with diabetes and DN. This occurs at an early stage of disease, and correlates with the degree of albuminuria. The pharmacologic interventions for DN by angiotensin converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists may have anti-inflammatory effects, which are independent of their hemodynamic effect.

**Diabetic Retinopathy:** The association between soluble adhesion molecules levels and retinopathy in type 2 diabetic patients has been clarified. sE-selectin levels are elevated in diabetic patients compared to control subjects, with no significant difference in sICAM-1 and sVCAM-1 levels. The progression of retinopathy was not associated with an increase in soluble adhesion molecules. However, Nowak et al. (2008) observed that serum levels of sICAM-1 and sELAM-1 were significantly elevated and the concentration sVCAM-1 was elevated but not significantly in diabetic patients. Increase in sICAM-1 and sVCAM-1 levels, as well as their correlation with high vitreous IL-6 and TNF- $\alpha$  concentrations in patients with diabetic retinopathy seems to confirm the inflammatory-immune nature of this process. Significantly increased TNF- $\alpha$  concentration in the vitreous body was related to the rise of VCAM-1 (Adamiec-Mroczek

and Oficjalska-Mtyńczak 2008; Leal et al. 2008; Khalfaoui et al. 2008). Intravitreal injection of corticosteroid has been used to treat diabetic macular edema.

#### 44.5.2 Rheumatic Diseases

Plasma levels of vWF and sP-selectin (but not sE-selectin) are significantly higher among Rheumatoid disease (RD) patients compared to controls. Levels of vWF progressively rise with increasing cardiovascular risk (Bhatia et al. 2009). Serum levels of ICAM-1, ICAM-3, VCAM-1, L-selectin, and E-selectin have been determined in children with a variety of pediatric rheumatic diseases. A trend toward higher levels of sE-selectin was found in vasculitis vs other diagnoses. The sICAM-1 was higher in patients with active vs inactive disease across all diagnoses. Report suggests that (1) elevated E-selectin levels in vasculitis likely reflect the high degree of endothelial activation and possibly overt vascular damage in those conditions. (2) The correlation of sL-selectin with C4 in SLE may indicate that downregulation of shedding of cell surface L-selectin is involved in continued adherence of leukocytes to endothelium, possibly causing further damage and immune complex deposition in this condition. (3) The trend toward inverse correlation between sE-selectin and vWF:Ag in diabetes mellitus is interesting. (4) Levels of sICAM-1 may be a useful marker of active vs quiescent disease in general in the pediatric rheumatic diseases, although lack of correlation with disease activity indices indicates that it is too insensitive to smaller differences in disease activity to be recommended for routine clinical use (Bloom et al. 2002).

#### 44.5.3 Rheumatoid Arthritis

Considerable evidence indicates that patients with Rheumatoid arthritis (RA) are at greater risk of developing atherosclerosis and cardiovascular disease. Atherosclerotic cardiovascular mortality is increased in RA patients. The markers proposed for assessing RA activity include rheumatoid factor, anti-citrullinated protein/peptide antibodies, IgM anti-IgG advanced glycation end products, markers of bone/cartilage metabolism, mannose-binding lectin, E-selectin, IL-6, and leptin. Various studies have investigated the correlation between some of these markers and other variables that might indicate disease activity, e.g., inflammatory activity tests and disease activity scores. However, there is as yet insufficient evidence that any of these markers, in isolation or in combination, are useful in the assessment of RA activity. Many numerous endothelial cells become positive for E-selectin and E-selectin mRNA in RA synovial membranes

and the E-selectin expression appeared to correlate with inflammatory activity. P-selectin deficiency in mice resulted in accelerated onset of joint inflammation in the murine collagen-immunized arthritis model. Mice deficient either in E-selectin or in E-selectin and P-selectin (E/P-selectin mutant) also exhibit accelerated development of arthritis compared with wild type mice in CIA model. The strong vascular expression of E-selectin indicates an activation of endothelial cells in the recruitment of cells associated with the chronic inflammation of RA (Foster et al. 2009; da Mota et al. 2009). E-Selectin and ICAM-1 are upregulated on the synovial endothelium, while VCAM-1 plays an important role in synovial lining layer cells and within the synovial stroma. The expression of CAMs may be blocked by mAbs and modified by nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs. (Cobankara et al. 2004). Serum soluble adhesion molecules concentrations are down-regulated following anti-TNF- $\alpha$  antibody therapy combined with methotrexate (MTX) (Klimiuk et al. 2004, 2007; Levälampi et al. 2007; Bosello et al. 2008).

In comparison with osteoarthritis (OA), patients with early RA are characterized by high serum concentrations of sICAM-1, sVCAM-1, and sE-selectin (Yildirim et al. 2005), while LDL-cholesterol was decreased in all RA patients (Pemberton et al. 2009). P-selectin deficiency in mice results in accelerated onset of joint inflammation in the murine collagen-immunized arthritis model. Mice deficient either in E-selectin or in E-selectin and P-selectin (E/P-selectin mutant) also exhibit accelerated development of arthritis compared with wild type mice, suggesting that these adhesion molecules perform overlapping functions in regulating joint disease. Ruth et al. (2005) suggested that E-selectin and P-selectin expression can significantly influence cytokine and chemokine production in joint tissue, and that these adhesion molecules play important regulatory roles in the development of RA in E/P-selectin mutant mice (Singh et al. 2008).

In RA patients, P-selectin expression, PMC and sCD40L levels were increased when compared with controls. The increase in markers of active platelets, P-selectin and sCD40L, and platelet-monocyte levels might be associated with the increased cardiovascular mortality in RA. Psoriatic arthritis (PsA) is associated with the development of endothelial dysfunction and increased atherosclerotic complications. Endothelial activation might have a role in the pathogenesis of both psoriasis and PsA. Among parameters of platelet activation, only PMC might play a role in the pathogenesis of PsA (Pamuk et al. 2008, 2009). Though, sE-selectin correlated with severity of joint disease, further follow-up studies should evaluate if sE-selectin is useful as prognosis marker for progression of articular damage (Corona-Sanchez et al. 2009).

#### 44.5.4 Other Autoimmune Disorders

**Systemic Lupus Erythematosus (SLE):** Elevated serum concentrations of ET-1, s-thrombomodulin (TM), and sE-selectin reflect persisting endothelial cell activation in SLE, and point to an important role of ET-1 in the pathogenesis of internal organ involvement (Kuryliszyn-Moskal et al. 2008). The s-E-selectin, TM and s-VCAM-1 are significantly elevated in lupus nephritis (LN) with renal vascular lesions (VLS) than in LN without VLS. A positive correlation was found between TM and serum creatinine in patients with vascular lesions. Therefore, serum TM and s-VCAM-1 can be biomarkers of VLS in LN patients (Yao et al. 2008, Rho et al. 2008).

**Autoimmune Thyroiditis:** Autoimmune thyroiditis is multifactorial in etiology with genetic and environmental factors contributions. Patients with untreated Graves' disease (GD) show high serum level of sE-selectin, which correlated with the activity of the disease. The expression of ICAM-1 and VCAM-1 was increased in EC from patients from Graves' disease (GD) and Hashimoto's thyroiditis (HT). Results suggest that both the LFA-1/ICAM-1, ICAM-3 and VLA-4/VCAM-1 pathways could play a relevant role in autoimmune thyroid disorders (Marazuela et al. 1994). In patients with GD, the 721 G-A polymorphism was associated with an earlier age of GD onset (before age 40) and that the 1405A-G polymorphism could predispose to Graves ophthalmopathy. It was concluded that G241R and K469E amino acid substitutions in the ICAM1 molecule could influence the intensity/duration of the autoimmunity process and the infiltration of orbital tissues (Kretowski et al. 2003). Chen et al. (2008) suggested that common *SELE* variants may be associated with susceptibility to GD in Chinese population, though the limitation of sample size and multiple test problems exists (Chen et al. 2008).

**Sjogren's Syndrome:** CAMs are involved in the lymphoid cell infiltration of the salivary and lacrimal glands in Sjogren's syndrome (SS) patients. Biopsies from SS patients showed a marked expression of VCAM-1 and ICAM-1 in the venules surrounded by infiltrated CD4<sup>+</sup> CD45RO<sup>+</sup> T cells. E-selectin was expressed on vascular endothelium with weak intensity (Saito et al. 1993). Pisella et al. (2000) reported that a significant increase of HLA-DR and ICAM1 expression by epithelial cells was consistently found in patients with keratoconjunctivitis sicca (Sjogren syndrome). These markers were well correlated with each other and correlated inversely with tear break-up time and tear production. Cytokine-mediated up-regulation of VCAM-1 and ICAM-1 that facilitates the recruitment of VLA-4 and LFA-1 expressing T cells might contribute to lymphoid cell infiltration in the salivary and lacrimal glands in SS



## 44.6 CAMs in System Related Disorders

### 44.6.1 Gastric Diseases

CAMs mediate the extravasation of leukocytes and their accumulation in inflamed intestinal mucosa. Eosinophilic inflammation is a common feature of numerous eosinophil-associated gastrointestinal (EGID) diseases. Increased intestinal expression of E-selectin has been associated with multiple organ failure and an adverse outcome. VCAM-1 is not altered in in mucosa of patients with inflammatory bowel disease (IBD) regardless of the activity of the inflammatory process. In contrast, E-selectin was not detected in normal colonic mucosa or in colonic mucosa of patients with IBD. However, high levels of E-selectin were consistently found on endothelial surfaces in association with active inflammation in affected areas of colonic mucosa in patients with either ulcerative colitis or Crohn's colitis. In addition, E-selectin appeared to be present within neutrophils which had migrated into crypt abscesses in affected mucosa. Thus E-selectin may play an important role in facilitating leukocyte migration into sites of active IBD involvement (Koizumi et al. 1992)

ICAM-1 was expressed to a greater degree in ulcerative colitis (UC) specimens. Serum ICAM-1 levels in UC patients showed lower levels than those in the control group and were found to vary according to degree of clinical severity (Ogawa et al. 2008). Characterization of integrin expression on colonic eosinophils revealed that colonic CC chemokine receptor 3<sup>+</sup> eosinophils express ICAM-1 counter-receptor integrins  $\alpha$ L,  $\alpha$ M, and  $\beta$ 2. It appears that  $\beta$ 2-integrin/ICAM-1-dependent pathways are integral to eosinophil recruitment in colon during GI inflammation associated with colonic injury (Forbes et al. 2006).

McCafferty et al. (1999) examined the role of P-selectin in intestinal inflammation in P-selectin deficient mice alone or in combination with either ICAM-1 or E-selectin and suggested that anti-adhesion therapy might play only a limited, beneficial role and often a detrimental role in intestinal inflammation. The sE-selectin levels of Crohn's disease patients with active disease are higher than those with remission of the disease. L-selectin does not change in patients with active disease compared to those with remission. Thus, determination of sE-selectin in children with Crohn's disease is of significance in estimation of inflammation activity (Adamska et al. 2007).

Khazen et al. (2009) investigated mutations in CAM genes in Tunisian patients, implicated in determining susceptibility to ulcerative colitis (UC) and Crohn's disease (CD). A significant increase in allele frequencies of 206 L of L-selectin and the associated genotype F/L was observed in patients with UC and CD compared with controls; the L206 allele and F/L206 genotype frequencies were

significantly increased in UC patients with left-sided type; whereas, the F/L206 genotype was significant in CD patients with ileocolonic location. No significant differences in allele or genotype frequencies were observed for ICAM-1 K469E, E-selectin, and PECAM-1 polymorphisms between UC patients, CD patients, and controls. Khazen et al. (2009) suggest an association of inflammatory bowel disease with allele L206 of L-selectin gene, whereas genotype L/F was associated with a subgroup of UC (left-sided type) and CD patients with more extensive location of disease and stricturing behavior.

However, Vischer et al. (2008) did not reveal any difference in mRNA and protein expression levels for any construct or a major impact of missense variants on ICAM-1 biological function. Pulse-chase experiments showed that two variants, K469E and arg478 to trp (R478W), had a prolonged half-life compared with wildtype ICAM1, whereas two other variants, G241R and pro352 to leu (P352L), had a decreased half-life, implying differences in protein degradation.

**Celiac Disease:** Celiac disease is a chronic intestinal inflammatory disease that develops in genetically susceptible individuals after gluten ingestion. The *ICAM-1* gene, located in the Celiac disease linkage region 19p13, encodes ICAM-1 involved in inflammatory processes. Increased levels of ICAM-1 were observed in intestinal biopsies and in sera of Celiac disease patients. In addition, an association between the ICAM1 polymorphism G241R and Celiac disease patients has been described in a French population. though, in spanish population results discard the importance of ICAM1 G241R in celiac disease (Dema et al. 2008).

**Behçet Syndrome:** Behçet's disease/syndrome (BD/BS) is a multisystemic inflammatory disorder of which oral aphthous ulceration is a major feature. CD3 and  $\gamma\delta$  T-cell expression and other adhesion molecules including VCAM-1 and ICAM-1 were upregulated, whereas CD40 showed little change in BD. The changes in cell-cell and cell-extracellular matrix interactions may affect cell homeostasis and participate in the formation of oral ulcers in BD (Kose et al. 2008). However, Demirkesen et al. (2008) found no significant differences between the BS and control groups in regard to E-selectin, P-selectin, VCAM-1, PNCAM-1 except for ICAM-1.

**Systemic Sclerosis or Systemic Scleroderma:** Systemic sclerosis or systemic scleroderma is a systemic autoimmune disease or systemic connective tissue disease that is a subtype of scleroderma. Severe fibrosis and increased expression of profibrotic cytokines are important hallmarks in the gastric wall of patients with systemic sclerosis (SSc; scleroderma). The CD4<sup>+</sup>/CD8<sup>+</sup> T cell ratio is significantly increased in SSc specimens. T cells strongly express the activation markers

VLA-4, LFA-1, and ICAM-1. Endothelial cells showed corresponding surface activation with strong expression of VCAM-1 and ICAM-1. These results provide the evidence that endothelial/lymphocyte activation leading to prominent CD4<sup>+</sup> T cell infiltration may play a key pathogenetic role within the gastric wall of patients with SSc (Manetti et al. 2008). In patients with SSc with and without pulmonary arterial hypertension (PAH), serum sICAM-1, sVCAM-1, sP-selectin and sPECAM-1 levels were higher than in healthy donors (HD) at baseline and fell to normal values after 12 months of bosentan therapy. Endothelial activation occurs in SSc, and that changes in the T cell/endothelium interplay take place in SSc-associated PAH. Bosentan seems to be able to hamper these changes and restore T cell functions in these patients (Iannone et al. 2008).

#### 44.6.2 Liver Diseases

Soluble adhesion molecules play a significant role in hepatitis. Biliary atresia (BA) is a congenital or acquired liver disease and one of the principle forms of chronic rejection of a transplanted liver allograft. In the congenital form, the common bile duct between the liver and the small intestine is blocked or absent. The acquired type most often occurs in the setting of autoimmune disease, and is one of the principle forms of chronic rejection of a transplanted liver allograft. The serum sE-selectin of BA patients was higher than that of controls. Subgroup analysis showed that there was an increase in sE-selectin levels of BA patients with jaundice compared to those without jaundice. Also, sE-selectin was positively correlated with serum alanine transferase (ALT), a marker for liver injury, but not with serum gamma glutamyl transpeptidase (GGT) (Vejchapipat et al. 2008).

Cholangitis without a modifier—from Greek *chol-*, bile + *ang-*, vessel + *itis-*, inflammation) is an infection of the bile duct (cholangitis). In secondary cholangitis, ICAM-1 expression is increased along with de novo VCAM-1 and E-selectin appearance on the endothelium of microvessels in chronic exacerbated cholangitis (Gulubova et al. 2008).

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver marked by the slow progressive destruction of the small bile ducts (bile canaliculi) within the liver. Patients with PBC, primary sclerosing cholangitis and chronic active hepatitis (autoimmune) show significant increase in sICAM-1 compared with normal healthy subjects. Significant elevation in sICAM-1 is also detected in patients with inactive alcoholic cirrhosis, suggesting that impaired liver may, in part, account for the increased serum level in patients with autoimmune liver disease. In contrast, sE-selectin did not differ significantly from healthy controls. Although, peripheral blood mononuclear cells (PBMC) may be a source of sICAM-1, Thomson et al. (1994) suggested that PBMC may

not be a significant source of sICAM-1 in this disease. The differential expression of CAMs in the liver is consistent with the suggestion of selectins involvement in neutrophil rolling in the vasculature and ICAM-1 in transendothelial migration and adherence to parenchymal cells (Essani et al. 1995).

Wu et al. (2009) investigated the relationships between the polymorphisms of E-selectin gene and plasma sE-selectin levels in relation to disease progression in a hepatitis B virus (HBV)-infected Chinese Han population. The frequency of C allele (AC or CC) of the A<sup>561</sup>C polymorphism was significantly increased in patients with liver cirrhosis (LC) compared to normal population. There was no difference in allele distribution of the G<sup>98</sup>T polymorphism. The A<sup>561</sup>C polymorphism of E-selectin gene may be associated with disease progression in patients with chronic HBV infection and control the expression of plasma soluble levels, while the G<sup>98</sup>T polymorphism may be related to fibrotic severity in Chinese population (Wu et al. 2009).

Mice with targeted deletion of the P-selectin gene developed unpolarized type 1/type 2 cytokine responses and severely aggravated liver pathology following infection pathogen *Schistosoma mansoni*. Liver fibrosis increased 6 fold, despite simultaneous induction of IFN- $\gamma$  and increase in inflammation in absence of P-selectin. This suggested a critical role of P-selectin in the progression of chronic liver disease caused by schistosome parasites (Wynn et al. 2004).

#### 44.6.3 Neuro/Muscular Disorders

Axonal degeneration was confirmed as the major pathological feature of critical illness polyneuropathy (CIP). Expression of E-selectin was significantly increased in endothelium of epineurial and endoneurial vessels, suggesting endothelial cell activation (Fenzi et al. 2003). Increasing evidence indicates that inflammatory responses are implicated in the pathogenesis of cerebral vasospasm after aneurismal subarachnoid hemorrhage (SAH). Murine SAH model provided the evidence of effective prevention of SAH-induced vasospasm by a mAb implied the possible role of E selectin in the pathogenesis of vasospasm after SAH (Lin et al. 2005).

Neuroinflammation is present in the substantia nigra (SN) of patients of Parkinson disease (PD). A large number of ICAM-1-positive reactive astrocytes have been observed in the SN of patients with neuropathologically confirmed PD, including three of familial origin. The ICAM-1-positive reactive astrocytes were mainly concentrated around residual neurons in areas of heavy neuronal loss and extracellular melanin accumulation (Miklossy et al. 2006). The sVCAM-1 plasma levels were higher in late onset Alzheimer's disease (LOAD) and vascular dementia (VD) compared with controls. Among patients (LOAD, VD, and not-dementia

(CDND), sE-selectin levels were higher in individuals with most severe cerebrovascular disease on CT scan. Increased sVCAM-1 plasma levels in LOAD and VD suggest the existence of endothelial dysfunction in both types of dementia. Results support the possible role of E-selectin in the pathogenesis of cerebrovascular disease (Zuliani et al. 2008).

#### 44.6.4 Acute Pancreatitis

Upregulation of ICAM-1, LFA-1, Mac-1 and subsequent leukocyte infiltration appears to be significant events of pancreatic and pulmonary injuries in Acute pancreatitis (AP) (Sun et al. 2006). Proinflammatory cytokines and oxidative stress seem to be involved in the development of local and particularly systemic complications in AP patients. Acute pancreatitis patients show VCAM-1 and P-selectin concentrations significantly lower and L-selectin concentrations significantly higher than the healthy subjects. Only E-selectin was significantly higher in severe than in mild disease (Pezzilli et al. 2008). Kleinhans et al. (2009) showed that the endothelial cell expression of PECAM-1, VCAM, E-selectin, and P-selectin was upregulated in severe porcine pancreatitis. In acute pancreatitis, plasma levels of sE-selectin and soluble thrombomodulin (sTM) serve as endothelial markers; the former is an endothelial activation marker, while the latter is an endothelial injury marker (Chooklin 2009; Ida et al. 2009).

#### 44.6.5 Renal Failure

In patients affected by microscopic polyangiitis (MPA) and associated with myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibodies (ANCA), higher sICAM-1 and sE-selectin levels during active phase and their slower decline during the treatment period, could be a prognostic risk factor for chronic renal failure development (Di Lorenzo et al. 2004; Musial et al. 2005). An increased level of sE-selectin in patients susceptible to restenosis supports a role for white blood cell/endothelial interaction in restenosis after angioplasty (Sainani and Maru 2005). The impairment of vascular endothelial function was obvious in uremic patients with maintaining hemodialysis (MHD). The changes of ICAM-1 and E-selectin could be accepted as biochemical criteria of vascular endothelial injury (Li et al. 2005). Diuresis, serum creatinine, urea, and enzyme elimination are pathological among patients with acute renal failure (ARF). Higher elimination rates of sICAM-1 and higher values of sE-selectin compared to patients without ARF indicated additional parameters for early signs of kidney damage (Dehne et al. 2008). Both circulating and urinary TNF- $\alpha$  levels are increased in inflammatory chronic renal diseases. TNF- $\alpha$

appeared to play a crucial role in the immunopathogenesis of nephritis by the induction of chemokine, ICAM-1 and VCAM-1 expression via the activation of the intracellular MAPK signaling pathway, which may contribute to macrophage and lymphocyte infiltration (Ho et al. 2008; Li et al. 2008).

**SNPs in Selectin genes and IgA Nephropathy:** Although intensive efforts have been made to elucidate the genetic basis of Ig A nephropathy (IgAN), genetic factors associated with the pathogenesis of this disease are not well understood. A case-control study, based on linkage disequilibrium among SNPs in selectin gene cluster on chromosome 1q24-25 revealed two SNPs in the E-selectin gene (*SELE8* and *SELE13*) and six SNPs in the L-selectin gene (*SELL1*, *SELL4*, *SELL5*, *SELL6*, *SELL10*, and *SELL11*), that were significantly associated with IgAN in Japanese patients. *SELE8* and *SELL10* caused amino acid substitutions from His to Tyr and from Pro to Ser for His-to-Tyr substitutions; and *SELL1* could affect promoter activity of the L-selectin gene. The TGT haplotype at these three loci was associated significantly with IgAN. These SNPs in selectin genes may be useful for screening populations susceptible to the IgAN phenotype. (Takei et al. 2002)

**Transplant Rejection:** Soluble adhesion molecules are not valuable markers for stable kidney graft (STx) rejection reaction. However, patients with chronic renal failure showed increased levels of adhesion molecules, which could reflect an impaired elimination (Alcalde et al. 1995). The expression levels of ICAM-1 and VCAM-1 show positive correlation with the severity of graft rejection and can provide evidence for early diagnosis and prevention of CR. Chronic allograft failure (CAF) is the major cause for late graft loss in renal transplantation. ICAM-1 polymorphisms may represent a predetermined genetic risk factor for CAF. This was substantiated by the polymorphism in exon 4 at the Mac-1 binding site and in exon 6 at fifth Ig-like domain (McLaren et al. 1999). Khazen et al. (2007) found no evidence for an association of any polymorphism with acute rejection in E- and L-selectin. During kidney reperfusion, E-selectin, ICAM-1, and VCAM-1 concentrations correlated positively with hypoxanthine concentrations during reperfusion, whereas concentrations of ICAM-1 correlated negatively with xanthine concentrations, indicating metabolic changes in renal tissue (Domanski et al. 2009).

#### 44.6.6 Other Inflammatory Disorders

Serum CAM levels have been analyzed in many organ diseases, including diseases of nervous system, endocrine disorders and others. Immune dysfunction has been

proposed as a mechanism for pathophysiology of autistic-spectrum disorders. Levels of sP-selectin and sL-selectin were significantly lower in patients than in controls. Furthermore, sP-selectin levels were negatively correlated with impaired social development during early childhood (Iwata et al. 2008). In multiple sclerosis and in its animal model experimental autoimmune encephalomyelitis (EAE), inflammatory cells migrate across the endothelial blood–brain barrier (BBB) and gain access to the CNS. The role of E- and P-selectin in this process has been controversial. Döring et al. (2007) suggest that absence of E- and P-selectin did neither influence the activation of myelin-specific T cells nor the composition of the cellular infiltrates in the CNS during EAE. Thus, E- and P-selectin are not required for leukocyte recruitment across BBB and the development of EAE in C57BL/6 and in SJL mice (Döring et al. 2007). No significant differences in allelic or genotypic frequency in all the SNPs (rs6133, rs4987310 and rs5368 substitutions) tested were found in the Italian population (Fenoglio et al. 2009).

The pathophysiology of cluster headache (CH) is supposed to involve the lower posterior part of the hypothalamus, the trigeminal nerve, autonomic nerves and vessels in the orbital/retro-orbital region. Remahl et al. (2008) compared serum levels of sICAM-1, sVCAM-1 and sE-selectin in patients with episodic CH and in patients with biopsy-positive giant cell arteritis (GCA), a vasculitic disorder of large and medium-sized arteries. Within the CH group, sICAM-1, sVCAM-1 and sE-selectin showed an increasing trend in remission compared with active cluster headache period, but sE-selectin only was significant. Remahl et al. (2008) suggest that cluster headache is not a vasculitic disorder of medium-sized arteries, but CH patients may have an immune response that reacts differently from that of healthy volunteers.

Adhesion molecules have a role in many vasculitic disorders. Compared to controls, Takayasu's arteritis (TA) patients had elevated levels of sE-selectin, sVCAM-1, and sICAM-1. Compared to controls, patients with inactive TA also had elevated levels of sE-selectin, sVCAM-1, and sICAM-1. There was no difference between active TA and controls. The sE-selectin had a trend towards increased levels in inactive versus active TA, but there was no difference in sVCAM-1 and sICAM-1 levels between the groups. Patients with inactive TA had elevated levels of sE-selectin, sVCAM-1, and sICAM-1 that might indicate persistent vasculopathy in clinically inactive disease (Tripathy et al. 2008).

#### 44.6.7 Inflammation in Hereditary Diseases

Serum levels of sVCAM-1, sICAM-1, sTM, P-selectin, E-selectin and CRP levels as inflammation markers are increased in patients of  $\beta$ -thalassemia intermedia and not influenced by treatment (Kanavaki et al. 2009). Pseudoxanthoma elasticum (PXE) is a hereditary disorder predominantly affecting the skin, retina and vascular system. P-selectin concentrations were increased in male and female PXE patients and levels correlated with the ABCC6 gene status of the patients. Patients harboring two mutant ABCC6 alleles had 1.5-fold increased P-selectin concentrations in comparison to patients with at least one wild-type allele. E- and L-selectin levels were within normal range and the allelic frequencies did not differ between from controls. Elevated P-selectin levels in PXE patients are potentially due to oxidative stress and elevated protease activity in PXE (Götting et al. 2008).

Fabry disease, an X-linked systemic vasculopathy, is caused by a deficiency of  $\alpha$ -galactosidase A resulting in globotriaosylceramide (Gb<sub>3</sub>) storage in cells. Accumulation of Gb<sub>3</sub> in the vascular endothelium of Fabry disease is associated with increased production of reactive oxygen species (ROS) and increased expression of CAMs. Increased Gb<sub>3</sub> induces expression of ICAM-1, VCAM-1, and E-selectin. Reduction of endogenous Gb<sub>3</sub> by treatment of the cells with an inhibitor of glycosphingolipid synthase or  $\alpha$ -galactosidase A led to decreased expression of adhesion molecules. This study indicates that excess intracellular Gb<sub>3</sub> induces oxidative stress and up-regulates the expression of CAMs in vascular endothelial cells (Shen et al. 2008).

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#### 44.7 Role of CAMs in Cancer

Recent reports have expanded the concept that inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation and inflammation. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. In addition, tumor cells have co-opted some of the signaling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis. These insights are fostering new anti-inflammatory therapeutic approaches to cancer development



### 44.7.1 Selectin Ligands in Cancer cells

#### Sialosyl Lewis<sup>a</sup> in Adhesion of Colon and other Cancers:

The complexity of the tumor microenvironment has been revealed in the past decade. The CAMs in the process of inflammation are responsible for recruiting leukocytes onto the vascular endothelium before extravasation to the injured tissues. Some circulating cancer cells have been shown to extravasate to a secondary site using a process similar to inflammatory cells. The most studied ligands for CAMs expressed on cancer cells, s-Lewis<sup>a</sup> and s-Lewis<sup>x</sup> antigens, are shown to be involved in adhesion to endothelial cells by binding to E-selectin. This process, shared by inflammatory cells and cancer cells, may partially explain the link between inflammation and tumorigenesis. The adhesion of colon cancer cells to E-selectin can be directly affected by changes in the expression level of sialosyl Le<sup>a</sup> antigen. The specific lack of expression of sialosyl Le<sup>a</sup> carbohydrate structure on the surface of colon cancer cells completely abolished their adhesion to E-selectin. It is proposed that glycoproteins as well as gangliosides carrying sialosyl Le<sup>a</sup> structures, when properly exposed and present in high density on surface of cancer cells, can effectively support the adhesion of cancer cells to E-selectin (Klopocki et al. 1998; Kobayashi et al. 2007). In addition to endogenous ligands for L-, P-, and E-selectins (Chap. 26, 27, and 28), several proteins are found in cancer cell lines or solid tumors that act as ligands for E, L, and P selectins. Selectin ligands present in cancers are:

(1) Glycodelin A (GdA) is primarily produced in endometrial and decidual tissue and secreted to amniotic fluid. GdA is expressed in ovarian cancer where it can act as an inhibitor of lymphocyte activation and/or adhesion (Jeschke et al. 2009); (2) The cysteine-rich fibroblast growth factor receptor (FGF-R) represents the main E-selectin ligand (ESL-1) on granulocytes. Hepatic stellate cells (HSC) are pericytes of liver sinusoidal endothelial cells, which are involved in the repair of liver tissue injury and angiogenesis of liver metastases. HSC express FGF-R together with FucT7 and exhibit a functional E-selectin binding activity on their cell surface (Antoine et al. 2009). (3) Although B-cell precursor acute lymphoblastic leukemia (BCP-ALL) cell lines do not express the ligand PSGL-1, a major proportion of carbohydrate selectin ligand was carried by another sialomucin, CD43, in NALL-1 cells. CD43 plays an important role in extravascular infiltration of NALL-1 cells and the degree of tissue engraftment of BCP-ALL cells may be controlled by manipulating CD43 expression (Nonomura et al. 2008). (4) Thomas et al. (2009a) identified podocalyxin-like protein (PCLP) as an alternative selectin ligand. PCLP on LS174T colon carcinoma cells possesses E-/L-, but not P-, selectin binding activity. PCLP functions as an alternative acceptor for selectin-binding glycans. The

finding that PCLP is an E-/L-selectin ligand on carcinoma cells offers a unifying perspective on the apparent enhanced metastatic potential associated with tumor cell PCLP overexpression and the role of selectins in metastasis (Thomas et al. 2009b). (5) E-selectin has been shown to play a pivotal role in mediating cell-cell interactions between breast cancer cells and endothelial monolayers during tumor cell metastasis. The counterreceptor for E-selectin was found as CD44v4. However, CD44 variant (CD44v) isoforms was functional P-, but not E-/L- selectin ligands on colon carcinoma cells. Furthermore, a ~180-kDa sialofucosylated glycoprotein(s) mediated selectin binding in CD44-knockdown cells. This glycoprotein was identified as carcinoembryonic antigen (CEA). CEA serves as an auxiliary L-selectin ligand, which stabilizes L-selectin-dependent cell rolling against fluid shear (Thomas et al. 2009b). Zen et al. (2008) identified a ~170 kDa human CD44 variant 4 (CD44v4) as E-selectin ligand, which has a high affinity for E-selectin via sLe<sup>x</sup> moieties.

### 44.7.2 E-Selectin-Induced Angiogenesis

Angiogenesis plays an important role in a variety of pathophysiological processes, including tumor growth and rheumatoid arthritis. Studies on capillary morphogenesis and angiogenesis in vitro have suggested a role for E-selectin in the process of differentiation into tube-like structures. Soluble E-selectin is a potent mediator of human dermal microvascular endothelial cell (HMVEC) chemotaxis, which is predominantly mediated through the Src and the phosphatidylinositol 3-kinase (PI3K) pathways (Kumar et al. 2003). Gastrin-17 (G17) has marked proangiogenic effects in vivo on experimental gliomas and in vitro on HUVECs and transiently decreased the expression of E-selectin, but not P-selectin, whereas IL-8 increased the expression of E-selectin. Specific antisense oligonucleotides against E- and P-selectin decreased HUVEC tubulogenesis processes in vitro. This showed that gastrin has marked proangiogenic effects in vivo on experimental gliomas and in vitro on HUVECs. This effect depends in part on the level of E-selectin activation, but not on IL-8 expression/release by HUVECs (Lefranc et al. 2004).

### 44.7.3 E-Selectin in Cancer Cells

Adhesion molecules are thought to have a role in the host defense against carcinogenesis. Significantly increased P-selectin, s-VCAM-I and s-ICAM-I levels were observed in patients with bladder cancer, and s-VCAM-I levels correlated with tumor stage (Coskun et al. 2006). Selectins mediate attachment of leukocytes to activated endothelium

as well as the adhesion reaction of tumor cells during malignancy (Borsig 2007). In a breast tumor xenograft model, the effect of combined TNF- $\alpha$  and IFN- $\gamma$  therapy involved the selective destruction of the tumor vasculature and death of tumor cells. Concomitant with these changes RT-PCR analysis revealed the increase of stromal mRNA levels for a series of stromal cytokines, cytokine receptors including TNF- $\alpha$ , sICAM-1, VCAM-1, P-selectin, which could be implicated in the observed events (de Kossodo et al. 1995).

**Squamous Cell Carcinomas:** In order to evaluate the risk of postoperative haematogenic recurrence of esophageal squamous cell carcinoma (SCC) patients, Shimada et al. (2003) examined the preoperative serum levels of sE-selectin and pathological status of the patients. The patients with a high serum soluble E-selectin concomitant with expression of s-Lewis antigens had a significant risk of postoperative haematogenic recurrence. SCCs of sun-induced skin cancers are particularly numerous in patients on T cell immunosuppression. Blood vessels in SCCs did not express E-selectin, and tumors contained few cutaneous lymphocyte antigen (CLA<sup>+</sup>) T cells, the cell type thought to provide cutaneous immunosurveillance. Clark et al. (2008) found that SCCs evade the immune response at least in part by down-regulating E-selectin and recruiting T<sub>reg</sub> cells.

**Cutaneous T-Cell Lymphoma (CTCL):** The CTCL is characterized by accumulation of malignant CD4<sup>+</sup> T cells in the skin. In malignant T cells from Sezary syndrome (SS), a leukemic variant of CTCL, in dermal microvessels in mouse skin, Hoeller et al. (2009) found that SS cells rolled along dermal venules in a P-selectin- and E-selectin-dependent manner at ratios similar to CD4<sup>+</sup> memory T cells from normal donors. Chemokine CCL17/TARC was sufficient to induce the arrest of SS cells in the microvasculature. Together, experiments suggested molecular adhesion cascade operant in SS cell homing to the skin in vivo. Patients with CTCL showed increased levels of sICAM-1 and sICAM-3 when compared with healthy individuals and patients with inflammatory dermatosis. The sE-selectin and sVCAM-1 levels were not affected (López-Lerma and Estrach 2009).

**Hodgkin's Disease:** Increased sICAM-1 and sE-selectin have been observed in Hodgkin's Disease/lymphoma (HD/HL) patients at diagnosis and sVCAM-1 at diagnosis correlated with both sICAM-1 and sE-selectin levels. Chemotherapy resulted in a significant decrease of sICAM-1 and sE-selectin (Syrigos et al. 2004). Serum sICAM-1 level increases at advanced stages of untreated multiple myeloma (MM) patients, but did not differ significantly from controls.

A positive correlation of IL-6 appeared with sICAM-1 and sE-selectin (Uchihara et al. 2006). Epstein-Barr virus (EBV)-positive NK/T cells showed affinity to vascular components. EBV-positive NK lymphoma cells express ICAM-1 and VCAM-1 at much higher levels than those in EBV-negative T cell lines. Furthermore, NK lymphoma cell lines exhibited increased adhesion to cultured endothelial cells stimulated with TNF- $\alpha$  or IL-1 $\beta$ . The up-regulated expression of VCAM-1 on cytokine-stimulated endothelial cells can be important to initiate the vascular lesions (Kanno et al. 2008).

**Non-small Cell Lung Cancer:** Serum levels of ICAM-1 increased in advanced stage non-small cell lung cancer (NSCLC) patients, whereas sE-selectin levels were not significantly different from healthy controls. Reports suggest that higher serum ICAM-1 can be useful for diagnosis while E-selectin levels have prognostic significance and could be a potential prognostic factor in NSCLC patients (Dowlati et al. 2008; Guney et al. 2008). The Cyfra 21-1 and sE-selectin showed good performance in detecting lung cancer from normal groups. However, Cyfra 21-1 was superior to sE-selectin in discriminating lung cancer from benign lung diseases (Swellam et al. 2008).

#### 44.7.3.1 Thyroid Cancer

Maspin, a serine protease inhibitor belonging to serpin family, is known as a tumor-suppressor protein and also exhibits an inhibitor effect on angiogenesis. Positive correlations were found for maspin positivity and lymph node metastases; E-selectin positivity and lymph node metastases, and P-selectin positivity and lymph node metastases and lymphovascular invasion. Correlations do exist between maspin, E- and P-selectin expressions with each other and with tumor stage. Inactive cytoplasmic maspin cannot act as a tumor suppressor. Expression of E- and P-selectins in tumor cells facilitates the occurrence of metastases, lymphovascular invasion, and perithyroidal soft tissue invasion. Further studies are needed to reveal detailed interactions between maspin, E-selectin, and P-selectin expression (Bal et al. 2008).

**Primary Hyperparathyroidism:** Patients with primary hyperparathyroidism (PHPT) have impaired vasodilation. Based on small number of patients, a study suggested that classic cardiovascular risk factors seem to be the main determinants for the high plasma levels of sE-selectin and vWF in PHPT. Together with unaltered thrombomodulin and sE-selectin levels, the vWF decrease in plasma after parathyroidectomy reflects a specific mechanism of its endothelial calcium- and/or PTH-stimulated secretion in some PHPT patients without risk factors (Fallo et al. 2006).

**Colorectal Cancer:** Plasma level of sP-selectin, sE-selectin and ICAM-1 were significantly higher in colorectal cancer (CRC) patients. The highest levels of sE-selectin and ICAM-1 were observed in patients with liver metastasis. There was no correlation between sP-selectin and sE-selectin, but a significant correlation was seen between sE-selectin and ICAM-1 in all patients. Plasma concentration of E-selectin and ICAM-1 may indicate tumor progression and liver metastasis (Dymicka-Piekarska and Kemono 2009; Sato et al. 2010).

The interaction between rE-selectin and CRC cells alters the gene expression profile of cancer cells. A DNA microarray analysis indicated that E-selectin-mediated alterations were significantly more pronounced in metastatic CRC variants SW620 and KM12SM than in the corresponding non-metastatic local SW480 and KM12C variants. The number of genes altered by E-selectin in metastatic variants was 10-fold higher than the number of genes altered in the corresponding local variants. Analysis indicated that E-selectin down regulated (at least by 1.6-folds) the expression of seven genes in a similar fashion, in both metastatic cells. Confocal microscopy indicated that E-selectin down-regulated the cellular expression of HMGB1 protein and enhanced the release of HMGB1 into the culture medium. The released HMGB1 in turn, activated endothelial cells to express E-selectin (Aychek et al. 2008).

The entrapment of malignant cells within the hepatic sinusoids and their interactions with resident non-parenchymal cells are considered very important for the whole metastatic sequence. In the sinusoids, cell connection and signaling is mediated by multiple cell adhesion molecules, such as the selectins. The three members of the selectin family, E-, P- and L-selectin, in conjunction with sialylated Lewis ligands and CD44 variants, regulate colorectal cell communication and adhesion with platelets, leucocytes, sinusoidal endothelial cells and stellate cells. Therefore, trials have already commenced aiming to exploit selectins and their ligands in the treatment of benign and malignant diseases. Multiple pharmacological agents have been developed that are being tested for potential therapeutic applications (Schnaar et al. 2008; Paschos et al. 2010; Zigler et al. 2010).

#### 44.7.4 Metastatic Spreading

The degree of selectin ligand expression by cancer cells is well correlated with metastasis and poor prognosis for cancer patients. Initial adhesion events of cancer cells facilitated by selectins result in activation of integrins, release of chemokines and are possibly associated with the formation of permissive metastatic microenvironment. While E-selectin is one of the initiating adhesion events during

metastasis, it is becoming apparent that P-selectin and L-selectin-mediated interactions significantly contribute to this process as well (Gout et al. 2008; Läubli and Borsig 2010).

#### **E-Selectin in Progression of Metastasis of Breast Cancer:**

Extravasation of cancer cells is a pivotal step in the formation of hematogenous metastasis. Extravasation is initiated by the loose adhesion of cancer cells to endothelial cells via an interaction between endothelial selectins and selectin ligands expressed by the tumor cells. Metastatic spreading is a dreadful complication of neoplastic diseases that is responsible for most deaths due to cancer. It consists in the formation of secondary neoplasms from cancer cells that have detached from the primary site. Leukocytes and tumor cells use E-selectin binding ligands to attach to activated endothelial cells expressing E-selectin during inflammation or metastasis. The formation of these secondary sites is not random and several clinical observations indicate that the metastatic colonization exhibits organ selectivity. This organ tropism relies mostly on the complementary adhesive interactions between cancer cells and their microenvironment. E-selectin and sLewis antigens might play important role in breast tumor, lymph node and liver metastasis. High levels of sE-selectin have been reported in melanoma and some epithelial tumors, especially in colorectal carcinoma. But sE-selectin may not be used as a predictive marker of metastasis in colorectal carcinoma, though high levels of sE-selectin may support diagnosis of liver metastasis (Uner et al. 2004; Eichbaum et al. 2004). It appeared that serum levels of sE-selectin are associated with the clinical course of liver metastases from breast cancer. Eichbaum et al. (2004) observed a possible trend for certain unfavorable prognostic parameters (e.g., young women, low-graded tumors, human epidermal growth factor receptor 2 over-expression) that could be related to higher serum levels of sE-selectin.

**Role of E-Selectin in Diapedesis of Cancer Cells:** Diapedesis is a vital part of tumor metastasis, whereby tumor cells attach to and cross the endothelium to enter the circulation. E-selectin was found to regulate initial attachment and rolling of colon cancer cells and also the subsequent diapedesis through the endothelium. Evidence indicates that E-selectin-dependent paracellular extravasation is independent of ICAM and VCAM and that it requires the activation of extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase downstream of E-selectin. Studies establish the role of E-selectin in diapedesis of circulating cancer cells (Tremblay et al. 2008; Woodward 2008).

Polymorphisms within E-selectin gene, especially the S<sup>128</sup>R polymorphism, may increase the risk of metastases by facilitating adhesion of tumor cells to endothelium. Blood DNA from patients treated for stage II or III colorectal

cancer (CRC) and from healthy controls was assessed for three polymorphisms within E-selectin gene (S<sup>128</sup>R, G<sup>98</sup>T and L<sup>554</sup>F) and one within the P-selectin gene (V<sup>640</sup>L). The S<sup>128</sup>R polymorphism was detected in 22.3 % patients and was correlated with G<sup>98</sup>T polymorphism. In multivariate analysis, the S<sup>128</sup>R polymorphism was associated with shorter event-free survival (EFS) and overall survival (OS) in whole population, in patients with stage II CRC, and in patients with stage III CRC. L<sup>554</sup>F and V<sup>640</sup>L polymorphisms had no prognostic value. The S<sup>128</sup>R polymorphism is a constitutional factor associated with a higher risk of relapse and death in patients treated for CRC and its detection may permit better selection of patients suitable for adjuvant therapy, especially among those with stage II disease (Hebbar et al. 2009).

**P-selectin Deficiency Attenuates Tumor Growth and Metastasis:** Metastasis is thought to involve the formation of tumor-platelet-leukocyte emboli and their interactions with the endothelium of distant organs. A link between these observations shows that P-selectin, which normally binds leukocyte ligands, can promote tumor growth and facilitate the metastatic seeding of a mucin-producing carcinoma. P-selectin-deficient (P-sele<sup>-/-</sup>) mice showed three potential pathophysiological mechanisms: (1) intravenously injected tumor cells home to the lungs of P-sele<sup>-/-</sup> mice at a lower rate; (2) P-sele<sup>-/-</sup> mouse platelets fail to adhere to tumor cell-surface mucins; and (3) tumor cells lodged in lung vasculature after intravenous injection often are decorated with platelet clumps, and these are markedly diminished in P-selectin<sup>-/-</sup> animals (Kim et al. 1998). However, the surgical procedure did not totally eliminate the factors responsible for platelet activation and did not normalize platelet activation (Dymicka-Piekarska et al. 2005; Hanley et al. 2006).

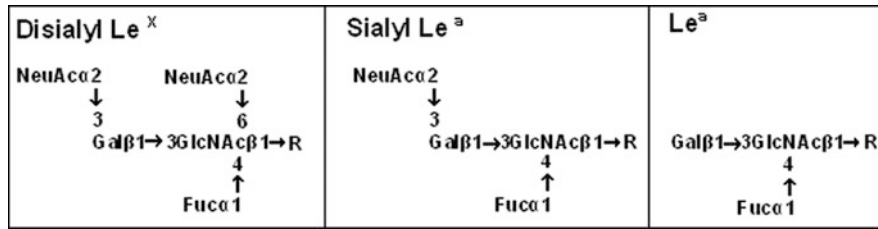
**Role of Sialyl-Lewis Antigens:** During inflammation, E- and P-selectins appear on activated endothelial cells to interact with leukocytes through sialyl-Lewis X (sLe<sup>x</sup>) and sialyl-Lewis A (sLe<sup>a</sup>). These selectins can also interact with tumor cells in a sialyl-Lewis-dependent manner and hence, they are thought to play a key role in metastasis. Diverting the biosynthesis of sialyl-Lewis antigens toward nonadhesive structures is an attractive gene therapy for preventing the hematogenous metastatic spread of cancers. The transduced  $\alpha$ 1,2-fucosyltransferase-1 (FUT1) efficiently fucosylated the P-selectin ligand PSGL-1 without altering P-selectin binding (Mathieu et al. 2004).

The metastasis of cancer cells and leukocyte extravasation into inflamed tissues share common features. Carbohydrate antigen sLe<sup>a</sup> (CA19-9) is the most frequently applied serum tumor marker for diagnosis of cancers in the digestive

organs. The normal counterpart of the determinant, namely disialyl-Le<sup>a</sup> is predominantly expressed in non-malignant epithelial cells of the digestive organs. The disialyl-Le<sup>a</sup> determinant carries one extra sialic residue attached through a 2 → 6 linkage to GlcNAc moiety compared to cancer-associated sLe<sup>a</sup>, which carries only one 2 → 3 linked sialic acid residue (monosialyl Lewis A) (Fig. 44.3). Disialyl-Le<sup>a</sup> in normal epithelial cells serves as a ligand for immunosuppressive receptors such as sialic acid binding Ig-like lectins (siglec-7 and -9) expressed on resident monocytes/macrophages and maintains immunological homeostasis of mucosal membranes in digestive organs. Epigenetic silencing of a gene for a 2 → 6 sialyl-transferase in the early stages of carcinogenesis results in impairment of 2 → 6 sialylation, leading to incomplete synthesis and accumulation of sLe<sup>a</sup>, which lacks the 2 → 6 linked sialic acid residue, in cancer cells. Simultaneous determination of serum levels of sLe<sup>a</sup> and disialyl-Le<sup>a</sup>, and calculation of the sLe<sup>a</sup>/disialyl-Le<sup>a</sup> ratio provides information useful for excluding a false-positive serum diagnosis. During cancer progression in locally advanced cancers, tumor hypoxia induces transcription of several glyco genes involved in sLe<sup>a</sup> synthesis. Expression of the determinant, consequently, is further accelerated in more malignant hypoxia-resistant cancer cell clones, which become predominant clones in advanced stage cancers and frequently develop hematogenous metastasis. sLe<sup>a</sup>, as well as its positional isomer sLe<sup>x</sup>, serves as a ligand for vascular E-selectin and facilitates hematogenous metastasis through mediating adhesion of circulating cancer cells to vascular endothelium. Patients having both strong sLe<sup>a</sup> expression on cancer cells and enhanced E-selectin expression on vascular beds are at a greater risk of developing distant hematogenous metastasis (Kannagi 2007). In a human-mouse model, the selectin ligand s-Le<sup>a</sup> is involved in in vivo extravasation of colorectal carcinoma (CRC) cells. Highly metastatic CRC cells expressing high levels of s-Le<sup>a</sup> extravasate more efficiently than non-metastatic CRC cells expressing low levels of s-Le<sup>a</sup>. Down-regulating the expression of s-Le<sup>a</sup> in CRC cells by genetic manipulations, significantly reduced CRC extravasation. The arrest and adhesion of CRC cells, and possibly of other types of cancer cells as well, to endothelium depend on the expression of the selectin ligand sLe<sup>a</sup> by the tumor cells (Ben-David et al. 2008). 3'-Sulfo-Le<sup>a</sup> is known to be the potent ligand of E-selectin which is important in cell adhesion and migration. The serum 3'-sulfo-Le<sup>a</sup> can provide important information in patients with primary gastric cancer, which might be useful as a predictive marker especially for the detection of tumor metastasis (Zheng et al. 2009).

Specialized carbohydrates modified with sLe<sup>x</sup> antigens on leukocyte membranes are ligands for selectin adhesion molecules on activated vascular endothelial cells at





**Fig. 44.3** Structures of three carbohydrate determinants, disialyl Lewis x (Le<sup>x</sup>), sialyl Lewis a and Lewis a (Le<sup>a</sup>). In panel, note that the only difference between the three determinants is the linkage of sialic

acid residues. The  $\alpha(2 \rightarrow 6)$  sialic acid residue in disialyl Le<sup>a</sup> is synthesized by a sialyltransferase ST6GalNAcVI, which shows a significant decrease in its mRNA level upon malignant transformation

inflammatory sites. The sLe<sup>x</sup> expression of invasive micropapillary carcinoma was higher than that of invasive ductal carcinoma, which was also associated with lymph node metastasis. E-selectin combined with sLe<sup>x</sup> might play an important role in lymph node metastasis in invasive micropapillary carcinoma. The expression pattern of sLe<sup>x</sup> in invasive micropapillary carcinoma suggested that the reversal of cell polarity of invasive micropapillary carcinoma might be as an important factor for the morphogenesis and possibly the pathogenesis, especially their higher rates of lymph node metastasis (Wei et al. 2010). The activity of core 2  $\beta$ 1,6 N-acetylglucosaminyltransferase (C2GnT1) in leukocytes greatly increases their ability to bind to endothelial selectins. C2GnT1 is essential for the synthesis of core 2-branched O-linked carbohydrates terminated with sLe<sup>x</sup> (C2-O-sLe<sup>x</sup>). E-selectin and its ligand-sLe<sup>x</sup> are closely correlated with the metastasis of hepatocellular carcinoma. C2-O-sLe<sup>x</sup> is a potentially useful early predictor of metastasis (Zhang et al. 2002). The expression profiles of C2-O-sLe<sup>x</sup> in the malignant progression and metastasis of colorectal adenocarcinomas is upregulated in colorectal adenocarcinomas and metastatic liver tumors (St Hill et al. 2009).

#### 44.7.5 Survival Benefits of Heparin

##### Endothelial P-Selectin as a Target of Heparin Action:

Metastasis can be effectively inhibited by the anticoagulant heparin in different tumor models. At the cellular level, many of the antimetastatic effects of heparin in vivo are due to its action on P-selectin-mediated binding. Ludwig et al. (2007) addressed the potential contribution of endothelial P-selectin expression to adhesive events between the microvasculature and melanoma cells in vivo. Heparin not only inhibits P-selectin-mediated melanoma cell rolling but also attenuates melanoma metastasis formation in vivo, supporting the concept that endothelial P-selectin expression may represent an additional target of heparin in

experimental melanoma lung metastasis (Ludwig et al. 2007). The low molecular weight heparin (LMWH) significantly improved colonic inflammation in rats with trinitrobenzene sulphonic acid (TNBS) induced colitis. The effect is possibly related to inhibition of proinflammatory cytokine IL-8, but not involved platelet surface P-selectin expression (Xia et al. 2004). The survival benefits in patients with cancer treated with LMWH may result from a LMWH-mediated effect on the immune system or on the cross-talk between platelets and tumor cells. However, survival observed with LMWH in patients with cancer apparently cannot be explained by a LMWH effect on these circulating markers (Di Nisio et al. 2005). Nonetheless, in vivo anti-metastatic effects of heparins reflect their action on P-selectin-mediated binding. Therefore, these commonly used anticoagulants widely differ in their potential to interfere with P-selectin mediated cell binding. Importantly, the superior inhibitory capacity on P-selectin function of unfractionated heparin and LMWH nadroparin as opposed to LMWH enoxaparin and synthetic heparin pentasaccharide fondaparinux strongly correlated to the inhibitory potency of each in inhibiting experimental lung metastasis in vivo. Hence, P-selectin inhibition constitutes a valuable feature to identify anticoagulants that are suitable for anticancer therapy (Ludwig et al. 2006). Stevenson et al. (2005) studied metastasis inhibition by clinically relevant levels of various heparins and investigated the structural basis for selectin inhibition differences. Five clinically approved heparins were evaluated for inhibition of P-selectin and L-selectin binding to carcinoma cells and showed differing abilities to inhibit selectins, likely explained by size distribution. It should be possible to size fractionate heparins and inhibit selectins at concentrations that do not have a large effect on coagulation. Gao et al. (2005) prepared periodate-oxidized, borohydride-reduced heparin (RO-heparin) and tested its anticoagulant and anti-inflammatory activities. Compared with heparin, RO-heparin had greatly reduced anticoagulant activity. Intravenous administration of this compound led to reduction in the peritoneal infiltration of neutrophils in a

mouse acute inflammation model. *In vitro* studies showed that the effect of RO-heparin on inflammatory responses was mainly due to inhibiting the interaction of P-selectin with its ligands. These results indicate that RO-heparin may be a safer treatment for inflammation than heparin, especially when selectin is targeted.

To clarify the mechanism of heparin antimetastatic activity, several biological effects are being investigated. Cancer progression and metastasis are associated with enhanced expression of heparanase, which is inhibited efficiently by heparin. Heparin is also a potent inhibitor of selectin-mediated interactions. P- and L-selectin were shown to contribute to the early stages of metastasis, which is associated with platelet-tumor cell thrombi formation. Low anticoagulant heparin preparations still inhibited metastasis efficiently indicating that anticoagulation is not a necessary component for heparin attenuation of metastasis. Modified heparins characterized for heparanase inhibitory activity are also potential inhibitors of selectins. Selectin inhibition is a clear component of heparin inhibition of metastasis. The contribution of selectin or heparanase inhibition by heparin can provide evidence about its antimetastatic activity (Borsig 2007). One of the mechanisms by which heparin inhibits metastasis is by blocking the P-selectin-based interaction of platelets with tumor cell. The sulfate groups at C6/N and especially C6, but not C2 and C3, of heparin play a critical role in P-selectin recognition and that 2-O,3-O-desulfated heparin can block P-selectin-mediated A375 human melanoma cell adhesion. Thus chemical modification of heparin, especially 2-O,3-O-desulfation, may result in a therapeutic agent that is anti-metastatic because it blocks unwanted P-selectin-dependent adhesion but that lacks dose-limiting anticoagulant effects (Wei et al. 2005).

**Heparin-Induced Thrombocytopenia:** The pathophysiology of heparin-induced thrombocytopenia (HIT) is a complex process which involves platelets, vascular endothelium, and leukocytes. The activation products from these sites also contribute to the activation of coagulation and to the fibrinolytic deficit. Many of the markers of hemostatic activation processes have been found to be at increased levels during acute phases of the HIT syndromes. Since the pathophysiology of HIT involves the activation of platelets, endothelium, and leukocytes, it is expected that activation products related to these hemostatic systems, including soluble selectins, will also be increased in circulating blood. These alterations may provide an index of the pathophysiological process. Fareed et al. (1999) reviewed on the circulating levels of P-, E-, and L-selectins in HIT patients and their modulation after therapeutic intervention. With the availability of recombinant hirudin, it is now possible to

provide alternate anticoagulants to HIT patients. However, Fareed et al. (1999) suggest that the immunoactivation of platelets and other cells may require additional adjunct therapeutic approaches.

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## 44.8 Adhesion Proteins in Transplantation

Activated protein C (APC) is the major physiological anticoagulant with concomitant anti-inflammatory properties. Turunen et al. (2005) suggest that APC has an anti-inflammatory role in I/R injury in clinical renal transplantation (Turunen et al. 2005). Bimosiamose prolongs survival of kidney allografts. Binding of the P-, L-, and E-selectins to sLe X retards circulating leukocytes, thereby facilitating their attachment to the blood vessels of allografts. Selectin inhibitor bimosiamose (BIMO) inhibits the rejection process of kidney allografts in a rat model in association with reduced intragraft expression of P-selectin glycoprotein ligand-1, CX (3)CL1, CCL19, CCL20, and CCL2. Thus, BIMO blocks allograft rejection by reduction of intragraft expression of cytokines and chemokines (Langer et al. 2004).

Brain death (BD), a significant antigen-independent process, the donor-related injury up-regulates variety of inflammatory mediators in peripheral organs. One of the immediate responses is the expression of selectins by endothelial cells of the transplanted tissues, which in turn trigger a cascade of nonspecific events that may enhance host alloresponses. Using a rat model in which donor BD accentuates subsequent renal allograft injury, Gasser et al. (2005) tested the effects of therapy with rPSGL-Ig alone, or in combination with sirolimus (SRL) and cyclosporin A. It was found that in contrast to the effects of standard doses of SRL or cyclosporine, rPSGL-Ig decreased inflammation in the early posttransplant period such that lower doses of maintenance immunosuppression were sufficient to maintain long-term graft function.

Intestinal transplantation (ITx) is severely limited by ischemia-reperfusion (I/R) injury. T lymphocyte is an important regulatory cell in this inflammatory process (Farmer et al. 2005a). rPSGL-Ig treatment leads to marked improvement in the outcome. The mechanism of action seems to involve the blockade of neutrophil and lymphocyte infiltration that leads to a decreased inflammatory response possibly driven by Th2 cytokines (Farmer et al. 2005b).

It was suggested that liver transplantation and liver resection, together with portal clamping time, might be a potential stimulus for platelet activation. Becker et al. (2004) indicated that neither liver transplantation nor liver resection influences GPIIb/IIIa and P-selectin expression on circulating platelets (Becker et al. 2004).

## 44.9 Inflammation During Infection

### 44.9.1 Microbial Pathogens

Endothelial activation contributes significantly to the systemic inflammatory response to bacteraemia. Release of soluble endothelial markers into the circulation has been demonstrated together with elevated plasma levels of CAMs and has been reported in bacteraemic patients. It has been proposed that the infection of endothelial cells with *Staphylococcus aureus*, *Streptococcus sanguis*, or *Staphylococcus epidermidis* induces surface expression of ICAM-1 and VCAM-1 and monocyte adhesion. In general, leukocyte/endothelial cell interactions such as capture, rolling, and firm adhesion should be viewed as a series of overlapping synergistic interactions among adhesion molecules resulting in an adhesion cascade. These cascades thereby direct leukocyte migration, which is essential for the generation of effective inflammatory responses and the development of rapid immune responses (Golias et al. 2007). *Helicobacter pylori* is a common bacterial pathogen that infects world's population up to 50 %. Carbohydrate components on *H. pylori* (sequences related to Le<sup>x</sup> or Le<sup>a</sup> antigens) are responsible for the persistent inflammation through interactions with leukocyte-endothelial adhesion molecules of the host. *H. pylori* isolates from patients with chronic gastritis, duodenal ulcer and gastric cancer interact with E- and L-selectins (Galustian et al. 2003). Expression of E-selectin was specifically upregulated in *H. pylori*-induced gastritis but not in gastritis induced by acetylsalicylic acid or pouchitis. The upregulated E-selectin expression was localized to the gastric mucosa rather than being a systemic response to the infection (Svensson et al. 2009).

Although mice with mutations in individual selectins showed no spontaneous disease and had a mild or negligible deficiencies of inflammatory responses, Bullard et al. (1996), in contrast, found that mice with null mutations in both endothelial selectins (P and E) develop a phenotype of leukocyte adhesion deficiency characterized by mucocutaneous infections in response to intraperitoneal *S. pneumoniae* peritonitis. These mice provide strong evidence for the functional importance of selectins in vivo (Bullard et al. 1996). Anthrax lethal toxin (LT), a key virulence factor of *Bacillus anthracis*, enhanced VCAM-1 expression on primary human endothelial cells suggesting a causative link between dysregulated adhesion molecule expression and the poor immune response and vasculitis associated with anthrax. Results suggest that LT can differentially modulate NF- $\kappa$ B target genes and highlight the importance of VCAM-1 enhancement (Warfel and D'Agnillo 2008). Vascular endothelium stimulation in vitro that lead to the upregulation of CAMs is known for the pathogenic

spirochaetes, including rLIC10365 of *Leptospira interrogans*. The recombinant proteins of *L. interrogans* in *E. coli* as a host were capable to promote the upregulation of ICAM-1 and E-selectin on monolayers of HUVECS. In addition, pathogenic and non-pathogenic *Leptospira* are both capable to stimulate endothelium E-selectin and ICAM-1, but the pathogenic *L. interrogans* serovar *Copenhageni* strain promoted a higher activation than the non-pathogenic *L. biflexa* serovar *Patoc* (Atzingen et al. 2009; Gómez et al. 2008). *Chlamydia pneumoniae* has been associated with cardiovascular disease and atherosclerosis. To determine the ability of *C. pneumoniae* to elicit inflammation, Högdahl et al. (2008) infected human coronary artery endothelial cells (HCAEC) with *C. pneumoniae*. Secretion of IL-8, MCP-1, and ICAM-1 was significantly increased after *C. pneumoniae* infection of HCAEC in comparison with uninfected controls, where as release of E-selectin or MMP-1 did not change. This suggested that *C. pneumoniae* initiates and propagates vascular inflammation in ways that contribute to coronary artery disease (Högdahl et al. 2008).

**CAMs in Gingival Crevicular Fluid:** The sICAM-1, sVCAM-1, and sE-Selectin are present in gingival crevicular fluid (GCF) and changes in their levels may be a sensitive indicator to differentiate healthy sites from those with periodontitis (Hannigan et al. 2004; Tamai et al. 2007). *Porphyromonas gingivalis* is a Gram-negative bacterium that is an important etiologic agent of human adult periodontitis. *E. coli* LPS and isoforms of *P. gingivalis* LPS were potent in stimulating the expression of inflammatory markers, with *E. coli* LPS being more potent (Liu et al. 2008). DNA samples from blood of periodontitis patients genotyped for E-selectin Ser<sup>128</sup>Arg and L-selectin Phe<sup>206</sup>Leu revealed a significant difference in the Ser<sup>128</sup>Arg polymorphism of E-selectin, but not in L-selectin, between periodontal patients and controls; the 128Arg allele was present more frequently in patients. Houshmand et al. (2009) suggested that Ser<sup>128</sup>Arg polymorphism of E-selectin might contribute to the susceptibility of Iranian individuals to periodontitis.

**CAMs in Subjects with HIV Disease:** Swingler et al. (2003) suggested that while both soluble CD23 and ICAM1 promote resting cell HIV1 infection, productive infection of cycling cells requires soluble ICAM1. Swingler et al. (2003) noted that these results may explain in part the existence of a resting T-cell reservoir infected with HIV-1. Subjects with HIV disease have multiple risk factors for cardiovascular disease, including elevated levels of ICAM-1 and VCAM-1. Many of the variables associated with

ICAM-1 and VCAM-1 levels can be related to their impact on inflammation (Melendez et al. 2008). The LFA-1, ICAM-1, and ICAM-3 are enriched at virological synapse (VS). The cognate adhesion molecule interactions at VS are important for HIV-1 spread between T cells (Jolly et al. 2007).

#### 44.9.2 Yeasts and Fungi

Zuccarello et al. (2002) described a distinct form of familial chronic mucocutaneous candidiasis characterized by early-onset infections by different species of *Candida*, restricted to the nails of the hands and feet and associated with low serum concentration of ICAM-1. Phan and Filler (2009) measured the effects of *C. albicans* on the endothelial cell production of E-selectin and TNF- $\alpha$  in vitro. During invasive pulmonary aspergillosis, *A. fumigatus* hyphae invade the abluminal endothelial cell surface, whereas they invade the luminal endothelial cell surface during haematogenous dissemination. Infection with hyphae stimulates endothelial cells to synthesize E-selectin, VCAM-1, IL-8, and TNF- $\alpha$  in vitro. In neutropenic mice infected with wild-type *A. fumigatus*, increased pulmonary expression of E-selectin and TNF- $\alpha$  occurred only when neutropenia had resolved. In nonneutropenic mice immunosuppressed with corticosteroids, *A. fumigatus* stimulated earlier pulmonary expression of E-selectin and VCAM-1, while expression of ICAM-1 and TNF- $\alpha$  was suppressed. In both mouse models, expression of E-selectin was associated with high pulmonary fungal burden, angiogenesis, and neutrophil adherence to endothelial cells (Chiang et al. 2008; Kawai et al. 2009).

#### 44.9.3 Parasites and Amoeba

##### 44.9.3.1 Falciparum Malaria

Significant differences are observed between falciparum malaria patients and the healthy people in term of levels of both sE-selectin and thrombomodulin (TM). The levels of both sE-selectin and TM correlated positively with temperature, levels of IFN- $\gamma$  and levels of TNF- $\alpha$ ; and negatively with hemoglobin levels. Trends of positive correlations were observed between sP-selectin or vWF and temperature (Matondo et al. 2008). Evidence from autopsy and in vitro binding studies suggests that adhesion of erythrocytes infected with *Plasmodium falciparum* to the human host ICAM-1 receptor is important in the pathogenesis of severe malaria. Fernandez-Reyes et al. (1997) identified a mutation (K29M) in the ICAM1 gene, which they designated 'ICAM1 Kilifi,' that was associated with susceptibility to cerebral malaria with relative risks of 2.23 and 1.39 for homozygotes

and heterozygotes, respectively. The available epidemiological, population genetic and functional evidence link ICAM-1(Kilifi) to severe malaria susceptibility (Fry et al. 2008; Cojean et al. 2008).

Increased serum concentrations of soluble sICAM-1, CD54 and of soluble E-, but not soluble P- and L-selectins were detected in Malagasy patients living in hyperendemic focus of *Schistosoma mansoni*. Serum levels of ICAM-1 were significantly correlated with the disease severity (Esterre et al. 1998). Studies in several models of inflammation have underscored the importance of P- and E-selectins in the migration of T cells to inflamed tissues. CD4<sup>+</sup> T cells recruited to the cutaneous compartment during infection with *Leishmania major* express P- and E-selectin ligands. Results suggest that by blocking P- and E-selectins, the immune pathology associated with cutaneous leishmaniasis might be ameliorated without compromising immunity to infection (Zaph and Scott 2003). Invasive amebiasis offers a new model that poses an inadequate immune response leading to a continuous and prolonged activation of endothelial cells (ECs) by amebas, amebic molecules and cytokines, leading to necrosis. Hyperactivated endothelial cells continuously express ICAM-1 and E-selectin, pro-coagulant molecules (tissue factor, vWF, and the plasminogen activator inhibitor), resulting in ever greater inflammation and thrombosis (Campos-Rodríguez et al. 2009)

##### 44.9.3.2 Sepsis

Sepsis is a multifactorial, and often fatal, disorder typically characterized by widespread inflammation and immune activation with resultant endothelial activation. Though bacterial sepsis is most common, sepsis occurs with fungal, parasitic and mycobacterial organisms. During bacterial sepsis in vivo, in wild-type mice and mice with E-, P-, or E/P-selectin deficiencies, a phenotypic abnormality in E-selectin-deficient mice suggested that E- and P-selectin are important in the host defense against *S. pneumoniae* infection (Munoz et al. 1997). P-selectin is an important mediator of eosinophil recruitment to the cornea from limbal vessels to the corneal stroma, suggesting that P-selectin interactions may be potential targets for immunotherapy in eosinophil-mediated ocular inflammation (Kaifi et al. 2000).

*Staphylococcus aureus* is one of the most significant pathogens in human sepsis and endocarditis. Peptidoglycan induced surface expression of EC inflammation markers ICAM-1 and VCAM-1, which supported the adhesion of monocytes to these ECs (Mattsson et al. 2008). Teoh et al. (2008) assigned adiponectin as a modulator of survival and endothelial inflammation in experimental sepsis and a potential mechanistic link between adiposity and increased sepsis. Newborn infants with clinical diagnosis of sepsis demonstrated significantly higher plasma sE-selectin levels



in infected infants. Infants with gram-negative sepsis had higher sE-selectin levels than did those with gram-positive sepsis. C-reactive protein was the best test for diagnosis of neonatal sepsis (Zaki and el-Sayed 2009).

Hofer et al. (2008) compared two different models of sepsis LPS-induced endotoxemia and cecal ligation perforation (CLP) bacteremia in rats with respect to changes in endothelial expression of CAMS as a marker for capillary breakdown of the blood brain barrier. Increased ICAM-1 expression might be an early factor involved in these pathogenic events. Although the role of PECAM-1 could not be determined, it was possible to show its expression on cerebral endothelium in all groups (Hofer et al. 2008). In mouse models of sepsis, Shapiro et al. (2009) demonstrated increased circulating levels of sE-selectin, sICAM-1, sVCAM-1 and sP-selectin at 24 h, while CLP was associated with increased levels of sE-selectin alone. In real-time PCR, mRNA levels for P-selectin, ICAM-1 and PAI-1 were increased in skin from endotoxemic mice. In CLP, mRNA levels for P-selectin, ICAM-1, E-selectin and PAI-1 were elevated, while VCAM-1 expression was reduced in skin. Most, but not all of these changes correlated with alterations in immunohistochemical staining (Shapiro et al. 2009).

#### 44.10 Action of Drugs and Physical Factors on CAMS

The field of selectin inhibition has matured significantly in recent years in the ability to inhibit selectin/ligand interactions with drug-like molecules and to demonstrate disease modification in human trials. A comprehensive review of new developments in the field of selectin inhibition through discussion of patents/patent applications from 2003 to August 2009 has been reported by Bedard and Kaila (2010)

##### 44.10.1 Inhibitors of Gene Transcription

Treatment of human endothelial cells with cytokines such as IL-1, TNF- $\alpha$  or IFN- $\gamma$  induces the expression of specific leukocyte adhesion molecules on the endothelial cell surface. Interfering with either leukocyte adhesion or upregulation of adhesion protein is an important therapeutic target as evidenced by the potent anti-inflammatory actions of neutralizing antibodies to these ligands in various animal models and in patients. The induction of E-selectin, VCAM-1, and ICAM-1 genes requires the transcription factor NF- $\kappa$ B. Pharmaceutical agents, which prevent the induced expression of one or more of cell adhesion molecules on endothelium, might be expected to provide a novel mechanism to

attenuate the inflammatory responses associated with chronic inflammatory diseases. E-selectin expression is induced on the endothelial cell surface of vessels in response to inflammatory stimuli but is absent in the normal vessels. Thus, E-selectin is an attractive molecular target, and high affinity ligands for E-selectin could be powerful tools for the delivery of therapeutics and/or imaging agents to inflamed vessels. Zimmerman and Blanco (2008) reviewed the structure and regulation of LFA-1 and different classes of inhibitors that interfere LFA-1/ICAM-1 interactions. Alicaforsten (ISIS 2302), an antisense to ICAM-1, designed to inhibit ICAM-1 expression did not reveal significant effect in Crohn's disease. However, topical enemas for ulcerative colitis demonstrated some effect in secondary outcomes, and initial studies in pouchitis are promising (Philpott and Miner 2008). ICAM-1 antibody (UV3) was highly effective at slowing the growth of tumors and/or prolonging survival in SCID mice xenografted with human multiple myeloma, lymphoma, melanoma and other cell lines (Brooks et al. 2008). A structurally diverse collection of small molecule inhibitors has been characterized and developed either to bind the IDAS site of  $\alpha_L$  I-domain or to the MIDAS of the  $\beta_2$  I-like domain.

##### 44.10.2 Anti-NF- $\kappa$ B Reagents

CAMS play important roles in a critical step of tumor metastasis and arrest of tumor cells onto the venous or capillary bed of the target organ. In this process, IL-1 $\beta$  induces nuclear translocation of NF- $\kappa$ B in HUVE cells, followed by induction of cell surface expression of E-selectin, ICAM-1, and VCAM-1, and subsequent adhesion of those cancer cells expressing sialyl Le<sup>X</sup> antigen, which is a ligand to E-selectin. The adhesion of tumor cells to IL-1 $\beta$ -treated HUVE cells can be inhibited by anti-NF- $\kappa$ B reagents such as N-acetyl L-cysteine, aspirin, or pentoxifylline. These observations indicate the involvement of NF- $\kappa$ B in cancer metastasis and the feasibility of using anti-NF- $\kappa$ B reagents in preventing metastasis (Tozawa et al. 1995). Incubation of HUVEC with N,N,N-trimethylsphingosine (TMS) resulted in a dose-dependent inhibition of IL-1 $\beta$ -induced E-selectin expression. Sphingosine or N,N-dimethylsphingosine had no effects on the expression. This inhibitory effect of TMS on IL-1 $\beta$ -dependent endothelial cell activation may partly explain the known anti-inflammatory or anti-metastatic effect of TMS in vivo (Masamune et al. 1995). Cimetidine inhibits the expression of E-selectin on vascular endothelial cells in gastric- and colorectal cancer patients, treated for chemotherapy (Kawase et al. 2005). Since the expression of E-selectin and Mac-1 is regulated either directly or indirectly by NF- $\kappa$ B, studies provide in vivo evidence that

tepoxalin is a potent inhibitor of NF- $\kappa$ B mediated events in animal models and this novel molecular mechanism clearly defines it as a new class of anti-inflammatory compounds. E-selectin transcription requires binding of transcription factors, NF- $\kappa$ B, ATF-2, and HMG-I(Y). HUVE cells treated with TNF- $\alpha$  showed E-selectin surface expression, which peaked at 4 h and then declined. However, ATF-2 binding was unchanged after stimulation with TNF- $\alpha$ . The termination of E-selectin expression is controlled at the level of transcription, with loss of protein-DNA interactions at only one of three NF- $\kappa$ B-binding sites in the E-selectin promoter (Boyle et al. 1999).

E-selectin is synthesized following X-ray exposure to doses as low as 0.5 Gy. X-ray-induced expression of E-selectin and ICAM-1 has been proposed to contribute to radiation injury in normal tissues. E-selectin expression does not require cytokine synthesis, but involves NF- $\kappa$ B activation (Hallahan et al. 1995). NF $\kappa$ B inhibition using NF $\kappa$ B inhibitors abrogates X-ray induced inflammatory mediators (Hallahan et al. 1998). Andrographolide, the principal component of medicinal plant *Andrographis paniculata*, has been shown to inhibit NF- $\kappa$ B activity and may attenuate allergic asthma via inhibition of the NF- $\kappa$ B signaling pathway. Andrographolide attenuated OVA-induced lung tissue eosinophilia and airway mucus production, mRNA expression of E-selectin, and inducible NOS in lung tissues. Findings implicate a potential therapeutic value of andrographolide in the treatment of asthma (Bao et al. 2009; Jiang et al. 2007).

#### **Effects of TGF- $\beta$ and IFN- $\gamma$ on E-Selectin Expression:**

Transforming growth factor (TGF- $\beta$ ) has been shown to decrease the adhesiveness of endothelial cells for neutrophils, lymphocytes, and tumor cells. TGF- $\beta$  inhibits the basal E-selectin expression and TNF-stimulated expression. While TGF- $\beta$  had no effect on the expression of VCAM-1 and ICAM-1, the effect was additive with IL-4 in inhibiting the expression of E-selectin. Thus, perivascular TGF- $\beta$  appears to act as an inhibitor of inflammatory responses involving neutrophils and a subset of lymphocytes (Gamble et al. 1993). IFN- $\gamma$  down-regulates the induction by a viral mimetic, polyinosinic-polycytidylic acid [poly(I:C)], of E-selectin. The inhibitory effect of IFN- $\gamma$  on poly(I:C)-induced E-selectin was specific for dsRNA. Results indicated the role for IFN- $\gamma$  in the regulation of E-selectin gene expression in response to dsRNA by a transcriptional mechanism independent of NF- $\kappa$ B, as well as by a minor decrease in message stability (Faruqi and DiCorleto 1997).

**Retinoic Acid Inhibits the Expression of VCAM-1 but not E-Selectin:** Several genes are regulated by tocopherols which can be categorized, based on their function. Genes that are related to inflammation, cell adhesion and platelet

aggregation include E-selectin, ICAM-1, and others (Azzi et al. 2004). Retinoic acid and synthetic derivatives are known to exert anti-inflammatory effects in cutaneous diseases. Pretreatment with all-trans-retinoic acid (t-RA) specifically prevented TNF $\alpha$ -induced VCAM-1 expression, but not ICAM-1 and E-selectin induction (Gille et al. 1997). The TNF $\alpha$ -mediated activation of the human VCAM-1 promoter was also inhibited after t-RA treatment, while the ICAM-1 promoter activation was unaffected, indicating that the selective inhibition of CAM expression is regulated in part at the level of gene transcription. Furthermore, the transcriptional inhibition by t-RA appears to be mediated by its effects upon the activation of NF- $\kappa$ B-dependent complex formation. The specific inhibition of cytokine-mediated VCAM-1 gene expression in vitro provides a potential basis by which retinoids exert their biological effects at sites of inflammation in vivo (Gille et al. 1997). Radiation-induced expression of E-selectin was also blocked by t-RA, whereas 9-cis retinoic acid was ineffective. Application of statins and t-RA might have clinical impact in protecting against E-selectin-promoted metastasis, which might arise as an unwanted side effect from radiation treatment (Holler et al. 2009; Nubel et al. 2004).

#### **Methylation of E-Selectin Promoter Gene Represses NF- $\kappa$ B Transactivation:**

The E-selectin promoter in cultured endothelial cells is under-methylated in comparison with non-expressing HeLa cells. Thus, methylation is likely to play a role in blocking E-selectin expression in non-endothelial cells (Smith et al. 1993). In intestine, MUC2 is the main mucin carrying s-Le<sup>x</sup>, which interacts with E-selectin. This interaction may contribute to the extravasation of tumor cells and thus to the metastases. In several colorectal carcinoma cell lines the methylation of the 5'-flanking region of MUC2 correlated with the suppression of the MUC2 gene. The increase in MUC2 expression after the inhibition of the methylation with 5-aza-2' deoxycytidine strongly supports the notion that the suppression of MUC2 gene is related to the methylation of the promoter (Riede et al. 1998).

### **44.10.3 Strategies to Combat Atherogenesis and Venous Thrombosis**

The advances in the development of adhesion molecule blocking agents, as well as an insight into the potential of these molecules in cardiovascular therapy have been reviewed from time to time (Lutters et al. 2004). Prophylactic dosing of a recombinant P-selectin ligand decreases venous thrombosis in a dose-dependent fashion in both feline and nonhuman primate animal models. Additionally,

treatment of 2-day iliac thrombi with a recombinant protein, P-selectin inhibitor, significantly improves vein reopening in nonhuman primates (Register 2009). It is interesting to note that P-selectin inhibition decreases thrombosis without adverse anticoagulation. Myers et al. (2005) evaluated an orally bioavailable inhibitor of P-selectin (PSI-697), which decreased thrombosis. Since, P-selectin is expressed on the surface of activated endothelial cells and platelets during thrombosis, targeting the plasminogen activator (PA) to P-selectin would enhance local thrombolysis and reduce bleeding risk. A urokinase (uPA)/anti-P-selectin antibody (HuSZ51) fusion protein is known to increase fibrinolysis in a hamster pulmonary embolism (Dong et al. 2004)

Aspirin reduces risks of myocardial infarction, stroke and cardiovascular death (Serebruany et al. 2004). The impact of cyclooxygenase (COX)-2 antagonist treatment on acute coronary risk is controversial. Prolonged COX-2 inhibition attenuates CRP and IL-6, does not modify P-selectin and MMP-9, and has no deleterious effect on endothelial function in stable patients with a history of recurrent acute coronary events and raised C-reactive protein (CRP) (Bogaty et al. 2004). Statins used in the control of hypercholesterolemia exert a protective effect on the endothelium reflected by a reduced level of circulating adhesion molecules. Statins exert a beneficial effects on endothelial function and atherosclerotic plaque, modulating oxidative stress and inflammation, with subsequent, well documented, primary and secondary prevention of CAD. Following statin treatment, sP-selectin, and ICAM-1 and highly sensitive CRP decreased compared to baseline levels. Other proteins (sVCAM-1, sE-selectin and platelet ECAM-1) did not show significant changes. In contrast to CRP, the reduction of sP-selectin concentrations correlated directly with the lowering of total cholesterol and inversely with the progression of CAD (Marschang et al. 2006)

#### 44.10.4 Anti-inflammatory Drugs

While diclofenac is capable of inhibiting the expression of E-selectin, ICAM-1 and VCAM-1, the SJC13 is selective in inhibiting the expression of E-selectin and VCAM-1, but not ICAM-1 in endothelial cells. Nonsteroidal anti-inflammatory agents, such as sodium salicylate and aspirin, inhibit NF- $\kappa$ B-dependent gene activation. Salicylate blocked the TNF- $\alpha$ -induced increase in mRNA levels of adhesion molecules and gave a dose-dependent inhibition of TNF- $\alpha$ -induced surface expression of VCAM-1 and ICAM-1 with higher doses required to inhibit E-selectin expression. Ibuprofen appeared a potent inhibitor of IL-1 $\alpha$  and TNF- $\alpha$ -induced

surface expression of VCAM-1 and a less potent inhibitor of ICAM-1. Indomethacin, a nonsalicylate cyclooxygenase inhibitor, had no effect on surface expression of adhesion molecules, suggesting that the effects were not due to inhibition of cyclooxygenase (Pierce et al. 1996). Methimazole, used in treating autoimmune diseases, may also diminish pathological inflammation by suppressing E-selectin expression. The phenyl methimazole can also reduce cytokine-induced E-selectin expression and consequent leukocyte adhesion. Compound 10, which dramatically inhibits TNF- $\alpha$ -induced VCAM-1 mRNA and protein expression in human aortic endothelial cells, has a modest inhibitory effect on TNF- $\alpha$  induced E-selectin expression and has no effect on ICAM-1 expression (Dagia et al. 2004).

A thieno(2,3-d)pyrimidine, A-155918 inhibits the TNF $\alpha$ -induced expression of E-selectin, ICAM-1, or VCAM-1 on HEVCs (Stewart et al. 2001). Co-treatment of human endothelial cells with certain hydroxyflavones and flavanols blocks cytokine-induced ICAM-1, VCAM-1, and E-selectin expression on human endothelial cells. One of the potent flavones, apigenin, exhibited a dose- and time-dependent, reversible effect on adhesion protein expression as well as inhibiting adhesion protein upregulation at the transcriptional level (Gerritsen et al. 1996). Enalapril and losartan but not placebo induced a small but stable decrease of cardiovascular ICAM-1 and VCAM-1, while E-selectin and leukocyte expression of ICAM-1 remained unchanged. The lowering of plasma adhesion molecules may indicate an antiatherogenic effect of angiotensin II blockade in hypercholesterolemia (Graninger et al. 2004).

#### Carbohydrates, Synthetic Oligopeptides and Steroids

Targeting interaction of selectins and appropriate carbohydrate ligand is a promising approach to treat chronic inflammation.  $\beta$ -1,3-glucan sulfate (PS3) has inhibitory activity toward L and P-selectins under static conditions (Alban et al. 2009). Access to synthetic carbohydrates is an urgent need for the development of carbohydrate-based drugs, vaccines, adjuvants as well as novel drug delivery systems. Besides traditional synthesis in solution, synthetic carbohydrates have been generated by chemoenzymatic methods as well as automated solid-phase synthesis. Synthetic oligosaccharides have proven to be useful for identifying ligands of carbohydrate-binding proteins such as C-type lectins and siglecs using glycan arrays. Furthermore, glyconanoparticles and glycodendrimers have been used for specific targeting of lectins of the immune system such as selectins, DC-SIGN, and CD22 (Lepeniec et al. 2010).

Compounds that target both heparanase and selectins offer a promising approach for cancer therapy. Borsig et al.

(2011) reported semisynthetic sulfated tri mannose C-C-linked dimers (STMCs) which are endowed with heparanase and selectin inhibitory activity. STMC hexasaccharide is an effective inhibitor of P-selectin *in vivo*. P-selectin-specific STMC attenuated metastasis in animal models, indicating that inhibition of tumor cell interaction with the vascular endothelium is critical for cancer dissemination. The small size, the stability of the C-C bond, and the chemically defined structure of STMCs make them superior to heparin derivatives and signify STMCs as valuable candidates for further evaluation.

Steroids down-regulate the expression of CAMs in endothelial cells stimulated by LPS *in vitro*. Low-dose hydrocortisone is a new treatment of patients with septic shock, a state that is characterized by an endothelial injury. Treatment with glucocorticoids differently affected the pattern of evolution of sCAMs, with sE-selectin being decreased and sICAM-1 being increased. Expression of sP-selectin and sVCAM-1 was not affected (Leone et al. 2004). Methotrexate (MTX) markedly reduces the expression of vascular E-selectin. A positive correlation between disease severity and the frequency of cutaneous lymphocyte-associated antigen (CLA)-positive T cells in the blood of untreated patients with psoriasis has been observed. It is suggested that MTX decreases the expression of CLA and E-selectin and that this may be a major mechanism for the therapeutic effect of MTX on psoriatic skin lesions (Sigmundsdottir et al. 2004).

## References

- Adamiec-Mroczek J, Oficjalska-Młyńczak J (2008) Assessment of selected adhesion molecule and proinflammatory cytokine levels in the vitreous body of patients with type 2 diabetes—role of the inflammatory-immune process in the pathogenesis of proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 246:1665–1670
- Adamikova A, Kojecy V, Rybka J, Svacina S (2008) Levels of adhesion molecules bear a relationship to triglyceride levels in type 2 diabetic subjects with proven silent ischemia. *Int Angiol* 27:307–312
- Adamska I, Czerwionka-Szaflarska M, Kulwas A et al (2007) Value of E-selectin and L-selectin determination in children and youth with inflammatory bowel disease. *Med Wieku Rozwoj* 11:413–418
- Alban S, Ludwig RJ, Bendas G et al (2009) PS3, a semisynthetic  $\beta$ -1,3-glucan sulfate, diminishes contact hypersensitivity responses through inhibition of L- and P-selectin functions. *J Invest Dermatol* 129:1192–1202
- Alcalde G, Merino J, Sanz S et al (1995) Circulating adhesion molecules during kidney allograft rejection. *Transplantation* 59:1695–1699
- Aminian B, Abdi Ardekani AR, Arandi N (2007) ICAM-1 polymorphisms (G241R, K469E), in coronary artery disease and myocardial infarction. *Iran J Immunol* 4:227–235
- Amoli MM, Llorca J, Gomez-Gigirey A et al (2004) E-selectin polymorphism in erythema nodosum secondary to sarcoidosis. *Clin Exp Rheumatol* 22:230–232
- Antoine M, Tag CG, Gressner AM et al (2009) Expression of E-selectin ligand-1 (CFR/ESL-1) on hepatic stellate cells: implications for leukocyte extravasation and liver metastasis. *Oncol Rep* 21:357–362
- Antonova OA, Loktionova SA, Romanov YA et al (2009) Activation and damage of endothelial cells upon hypoxia/reoxygenation. Effect of extracellular pH. *Biochemistry (Mosc)* 74:605–612
- Arvanitis DA, Flouris GA, Spandidos DA (2005) Genomic rearrangements on VCAM1, SELE, APEG1 and AIF1 loci in atherosclerosis. *J Cell Mol Med* 9:153–159
- Atzingen MV, Gómez RM, Schattner M et al (2009) Lp95, a novel leptospiral protein that binds extracellular matrix components and activates E-selectin on endothelial cells. *J Infect* 59:264–276
- Auer J, Weber T, Berent R et al (2003) Genetic polymorphisms in cytokine and adhesion molecule genes in coronary artery disease. *Am J Pharmacogenomics* 3:317–331
- Aycheh T, Miller K, Sagi-Assif O et al (2008) E-selectin regulates gene expression in metastatic colorectal carcinoma cells and enhances HMGB1 release. *Int J Cancer* 123:1741–1750
- Azzi A, Gysin R, Kempna P et al (2004) Regulation of gene expression by  $\alpha$ -tocopherol. *J Biol Chem* 279:585–591
- Bal N, Kocer NE, Ertorer ME et al (2008) E-selectin, and P-selectin expressions in papillary thyroid carcinomas and their correlation with prognostic parameters. *Pathol Res Pract* 204:743–750
- Bao Z, Guan S, Cheng C et al (2009) A novel antiinflammatory role for andrographolide in asthma via inhibition of the nuclear factor- $\kappa$ B pathway. *Am J Respir Crit Care Med* 179:657–665
- Becker T, Juttner B, Elsner HA et al (2004) Platelet P-selectin and GPIIb/IIIa expression after liver transplantation and resection. *Transpl Int* 17:442–448
- Bedard PW, Kaila N (2010) Selectin inhibitors: a patent review. *Expert Opin Ther Pat* 20:781–793
- Ben-David T, Sagi-Assif O, Meshel T et al (2008) The involvement of the sLe<sup>a</sup> selectin ligand in the extravasation of human colorectal carcinoma cells. *Immunol Lett* 116:218–224
- Berti R, Williams AJ, Moffett JR et al (2002) Quantitative real-time RT-PCR analysis of inflammatory gene expression associated with ischemia-reperfusion brain injury. *J Cereb Blood Flow Metab* 22:1068–1079
- Bhatia GS, Sosin MD, Patel JV et al (2009) Plasma indices of endothelial and platelet activation in Rheumatoid Disease: relationship to cardiovascular co-morbidity. *Int J Cardiol* 134:97–103
- Bijanzadeh M, Ramachandra NB, Mahesh PA et al (2009) Soluble intercellular adhesion molecule-1 and E-selectin in patients with asthma exacerbation. *Lung* 187:315–320
- Blaha M, Krejsek J, Blaha V et al (2004) Selectins and monocyte chemotactic peptide as the markers of atherosclerosis activity. *Physiol Res* 53:273–278
- Bloom BJ, Miller LC, Blier PR (2002) Soluble adhesion molecules in pediatric rheumatic diseases. *J Rheumatol* 29:832–836
- Bogaty P, Brophy JM, Noel M et al (2004) Impact of prolonged cyclooxygenase-2 inhibition on inflammatory markers and endothelial function in patients with ischemic heart disease and raised C-reactive protein: a randomized placebo-controlled study. *Circulation* 110:934–939
- Borsig L (2007) Antimetastatic activities of modified heparins: selectin inhibition by heparin attenuates metastasis. *Semin Thromb Hemost* 33:540–546
- Borsig L, Vlodavsky I, Ishai-Michaeli R et al (2011) Sulfated hexasaccharides attenuate metastasis by inhibition of P-selectin and heparanase. *Neoplasia* 13:445–452
- Bosello S, Santoliquido A, Zoli A et al (2008) TNF- $\alpha$  blockade induces a reversible but transient effect on endothelial dysfunction in patients with long-standing severe rheumatoid arthritis. *Clin Rheumatol* 27:833–839
- Boyle EM Jr, Sato TT, Noel RF Jr et al (1999) Transcriptional arrest of the human E-selectin gene. *J Surg Res* 82:194–200



- Braun F, Hosseini M, Wieland E et al (2004) Expression of E-selectin and its transcripts during intestinal ischemia-reperfusion injury in pigs. *Transplant Proc* 36:265–266
- Brooks KJ, Coleman EJ, Vitetta ES (2008) The antitumor activity of an anti-CD54 antibody in SCID mice xenografted with human breast, prostate, non-small cell lung, and pancreatic tumor cell lines. *Int J Cancer* 123:2438–2445
- Bullard DC, Kunkel EJ, Kubo H, Hicks MJ et al (1996) Infectious susceptibility and severe deficiency of leukocyte rolling and recruitment in E-selectin and P-selectin double mutant mice. *J Exp Med* 183:2329–2336
- Cai H, Harrison DG (2000) Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 87:840–844
- Campos-Rodríguez R, Jarillo-Luna RA, Larsen BA et al (2009) Invasive amebiasis: A microcirculatory disorder? *Med Hypotheses* 73:687–697
- Carmody IC, Meng L, Shen XD et al (2004) P-selectin knockout mice have improved outcomes with both warm ischemia and small bowel transplantation. *Transplant Proc* 36:263–264
- Carrizo Tdel R, Prado MM, Velarde MS et al (2008) Soluble E-selectin in children and adolescents with type 1 diabetes. *Medicina (B Aires)* 68:193–197
- Celebi M, Paul AG (2008) Blocking E-selectin inhibits ischaemia-reperfusion-induced neutrophil recruitment to the murine testis. *Andrologia* 40:235–239
- Cha JK, Jo WS, Shin HC et al (2004) Increased platelet CD63 and P-selectin expression persist in atherosclerotic ischemic stroke. *Platelets* 15:3–7
- Chan B, Sukhatme VP (2009) Receptor tyrosine kinase EphA2 mediates thrombin-induced upregulation of ICAM-1 in endothelial cells in vitro. *Thromb Res* 123:745–752
- Chen MC, Chang HW, Juang SS et al (2004) Increased plasma levels of soluble P-selectin in rheumatic mitral stenosis. *Chest* 126:54–58
- Chen H, Cui B, Wang S et al (2008) The common variants of E-selectin gene in Graves' disease. *Genes Immun* 9:182–186
- Chiang LY, Sheppard DC, Gravelat FN et al (2008) *Aspergillus fumigatus* stimulates leukocyte adhesion molecules and cytokine production by endothelial cells in vitro and during invasive pulmonary disease. *Infect Immun* 76:3429–3438
- Chooklin S (2009) Pathogenic aspects of pulmonary complications in acute pancreatitis patients. *Hepatobiliary Pancreat Dis Int* 8:186–192
- Chu JW, Abbasi F, Lamendola C et al (2005) Effect of rosiglitazone treatment on circulating vascular and inflammatory markers in insulin-resistant subjects. *Diab Vasc Dis Res* 2:37–41
- Chukwuemeka AO, Brown KA, Venn GE et al (2005) Changes in P-selectin expression on cardiac microvessels in blood-perfused rat hearts subjected to ischemia-reperfusion. *Ann Thorac Surg* 79:204–211
- Clark RA, Huang SJ, Murphy GF et al (2008) Human squamous cell carcinomas evade the immune response by down-regulation of vascular E-selectin and recruitment of regulatory T cells. *J Exp Med* 205:2221–2234
- Cobankara V, Ozatli D, Kiraz S et al (2004) Successful treatment of rheumatoid arthritis is associated with a reduction in serum sE-selectin and thrombomodulin level. *Clin Rheumatol* 23:430–434
- Cojean S, Jafari-Guemouri S, Le Bras J, Durand R (2008) Cytoadherence characteristics to endothelial receptors ICAM-1 and CD36 of *Plasmodium falciparum* populations from severe and uncomplicated malaria cases. *Parasite* 15:163–169
- Collins RG, Velji R, Guevara NV et al (2000) P-Selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *J Exp Med* 191:189–194
- Corona-Sanchez EG, Gonzalez-Lopez L, Muñoz-Valle JF et al (2009) Circulating E-selectin and tumor necrosis factor-alpha in extraarticular involvement and joint disease activity in rheumatoid arthritis. *Rheumatol Int* 29:281–286
- Corsi MM, Pagani D, Dogliotti G, Perona F, Sambataro G, Pignataro L (2008) Protein biochip array of adhesion molecule expression in peripheral blood of patients with nasal polyposis. *Int J Biol Markers* 23:115–120
- Coskun U, Sancak B, Sen I et al (2006) Serum P-selectin, soluble vascular cell adhesion molecule-I (s-VCAM-I) and soluble intercellular adhesion molecule-I (s-ICAM-I) levels in bladder carcinoma patients with different stages. *Int Immunopharmacol* 6:672–677
- da Mota LM, dos Santos Neto LL, de Carvalho JF (2009) Autoantibodies and other serological markers in rheumatoid arthritis: predictors of disease activity? *Clin Rheumatol* 28:1127–1134
- Dagia NM, Harii N, Meli AE et al (2004) Phenyl methimazole inhibits TNF- $\alpha$ -induced VCAM-1 expression in an IFN regulatory factor-1-dependent manner and reduces monocytic cell adhesion to endothelial cells. *J Immunol* 173:2041–2049
- de Kossodo S, Moore R, Gschmeissner S et al (1995) Changes in endogenous cytokines, adhesion molecules and platelets during cytokine-induced tumor necrosis. *Br J Cancer* 72:1165–1172
- Dehne MG, Sablotzki A, Mühlhling J et al (2008) Evaluation of sE-Selectin and sICAM-1 as parameters for renal function. *Ren Fail* 30:675–684
- Dema B, Martínez A, Polanco I et al (2008) ICAM1 R241 is not associated with celiac disease in the Spanish population. *Hum Immunol* 69:675–678
- Demirkesen C, Tüzüner N, Senocak M et al (2008) Comparative study of adhesion molecule expression in nodular lesions of Behçet syndrome and other forms of panniculitis. *Am J Clin Pathol* 130:28–33
- Devaraj S, Cheung AT, Jialal I et al (2007) Evidence of increased inflammation and microcirculatory abnormalities in patients with type 1 diabetes and their role in microvascular complications. *Diabetes* 56:2790–2796
- Di Lorenzo G, Pacor ML, Mansueto P et al (2004) Circulating levels of soluble adhesion molecules in patients with ANCA-associated vasculitis. *J Nephrol* 17:800–807
- Di Nisio M, Niers TM, Reitsma PH, Buller HR (2005) Plasma cytokine and P-selectin levels in advanced malignancy: prognostic value and impact of low-molecular weight heparin administration. *Cancer* 104:2275–2281
- Domanski L, Pawlik A, Safranow K et al (2009) Circulating adhesion molecules and purine nucleotides during kidney allograft reperfusion. *Transplant Proc* 41:40–43
- Dong N, Da Cunha V, Citkowicz A et al (2004) P-selectin-targeting of the fibrin selective thrombolytic Desmodus rotundus salivary plasminogen activator alpha1. *Thromb Haemost* 92:956–965
- Döring A, Wild M, Vestweber D et al (2007) E- and P-selectin are not required for the development of experimental autoimmune encephalomyelitis in C57BL/6 and SJL mice. *J Immunol* 179:8470–8479
- Dowlati A, Gray R, Sandler AB et al (2008) Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab—an Eastern Cooperative Oncology Group Study. *Clin Cancer Res* 14:1407–1412
- Dymicka-Piekarska V, Kemona H (2009) Does colorectal cancer clinical advancement affect adhesion molecules (sP-selectin, sE-selectin and ICAM-1) concentration? *Thromb Res* 124:80–83
- Dymicka-Piekarska V, Butkiewicz A, Matowicka-Karna J et al (2005) Soluble P-selectin concentration in patients with colorectal cancer. *Neoplasma* 52:297–301
- Eichbaum MH, de Rossi TM, Kaul S, Bastert G (2004) Serum levels of soluble E-selectin are associated with the clinical course of metastatic disease in patients with liver metastases from breast cancer. *Oncol Res* 14:603–610
- Eikemo H, Sellevold OF, Videm V (2004) Markers for endothelial activation during open heart surgery. *Ann Thorac Surg* 77:214–219

- Elangbam CS, Qualls CW Jr, Dahlgren RR (1997) Cell adhesion molecules—update. *Vet Pathol* 34:61–73
- Erkiert-Polguj A, Pawliczak R, Sysa-Jedrzejowska A (2009) Expression of selected adhesion molecules in dermatitis herpetiformis and bullous pemphigoid. *Pol J Pathol* 60:26–34
- Essani NA, McGuire GM, Manning AM, Jaeschke H (1995) Differential induction of mRNA for ICAM-1 and selectins in hepatocytes, Kupffer cells and endothelial cells during endotoxemia. *Biochem Biophys Res Commun* 211:74–82
- Esterre P, Raobelison A, Ramarokoto CE et al (1998) Serum concentrations of sICAM-1, sE-, sP- and sL-selectins in patients with *Schistosoma mansoni* infection and association with disease severity. *Parasite Immunol* 20:369–376
- Fallo F, Cella G, Casonato A et al (2006) Biochemical markers of endothelial activation in primary hyperparathyroidism. *Horm Metab Res* 38:125–129
- Fang L, Wei H, Mak KH et al (2004) Markers of low-grade inflammation and soluble cell adhesion molecules in Chinese patients with coronary artery disease. *Can J Cardiol* 20:1433–1438
- Fang L, Wei H, Chowdhury SH et al (2005) Association of Leu125Val polymorphism of platelet endothelial cell adhesion molecule-1 (PECAM-1) gene & soluble level of PECAM-1 with coronary artery disease in Asian Indians. *Indian J Med Res* 121:92–99
- Fareed J, Walenga JM, Hoppensteadt DA et al (1999) Selectins in the HIT syndrome: pathophysiological role and therapeutic modulation. *Semin Thromb Hemost* 25(Suppl 1):37–42
- Farmer DG, Anselmo D, Da Shen X et al (2005a) Disruption of P-selectin signaling modulates cell trafficking and results in improved outcomes after mouse warm intestinal ischemia and reperfusion injury. *Transplantation* 80:828–835
- Farmer DG, Shen XD, Amersi F et al (2005b) CD62 blockade with P-Selectin glycoprotein ligand-immunoglobulin fusion protein reduces ischemia-reperfusion injury after rat intestinal transplantation. *Transplantation* 79:44–51
- Farrar CA, Wang Y, Sacks SH, Zhou W (2004) Independent pathways of P-selectin and complement-mediated renal ischemia/reperfusion injury. *Am J Pathol* 164:133–141
- Faruqi TR, DiCorleto PE (1997) IFN- $\gamma$  inhibits double-stranded RNA-induced E-selectin expression in human endothelial cells. *J Immunol* 159:3989–3994
- Fenoglio C, Scalabrini D, Piccio L et al (2009) Candidate gene analysis of selectin cluster in patients with multiple sclerosis. *J Neurol* 256:832–833
- Fenzi F, Latronico N, Refatti N, Rizzuto N (2003) Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol (Berl)* 106:75–82
- Fernandez-Reyes D, Craig AG, Kyes SA et al (1997) A high frequency African coding polymorphism in the N-terminal domain of ICAM-1 predisposing to cerebral malaria in Kenya. *Hum Molec Genet* 6:1357–1360
- Forbes E, Hulett M, Ahrens R et al (2006) ICAM-1-dependent pathways regulate colonic eosinophilic inflammation. *J Leukoc Biol* 80:330–341
- Fornoni A, Ijaz A, Tejada T, Lenz O (2008) Role of inflammation in diabetic nephropathy. *Curr Diabetes Rev* 4:10–17
- Foster W, Shantsila E, Carruthers D, Lip GY, Blann AD (2009) Circulating endothelial cells and rheumatoid arthritis: relationship with plasma markers of endothelial damage/dysfunction. *Rheumatology (Oxford)* 48:285–288
- Fry AE, Auburn S, Diakite M et al (2008) Variation in the ICAM1 gene is not associated with severe malaria phenotypes. *Genes Immun* 9:462–469
- Galustian C, Elviss N, Chart H et al (2003) Interactions of the gastrotropic bacterium *Helicobacter pylori* with the leukocyte-endothelium adhesion molecules, the selectins—A preliminary report. *FEMS Immunol Med Microbiol* 36:127–134
- Gamble JR, Khew-Goodall Y, Vadas MA (1993) Transforming growth factor-beta inhibits E-selectin expression on human endothelial cells. *J Immunol* 150:4494–4503
- Gao Y, Li N, Fei R et al (2005) P-Selectin-mediated acute inflammation can be blocked by chemically modified heparin, RO-heparin. *Mol Cells* 19:350–355
- Gasser M, Waaga-Gasser AM, Grimm MW et al (2005) Selectin blockade plus therapy with low-dose sirolimus and cyclosporin A prevent brain death-induced renal allograft dysfunction. *Am J Transplant* 5:662–670
- Gerritsen ME, Shen CP, Atkinson WJ et al (1996) Microvascular endothelial cells from E-selectin-deficient mice form tubes in vitro. *Lab Invest* 75:175–184
- Ghilardi G, Biondi ML, Turri O et al (2004) Ser128Arg gene polymorphism for E-selectin and severity of atherosclerotic arterial disease. *J Cardiovasc Surg (Torino)* 45:143–147
- Gille J, Paxton LL, Lawley TJ et al (1997) Retinoic acid inhibits the regulated expression of vascular cell adhesion molecule-1 by cultured dermal microvascular endothelial cells. *J Clin Invest* 99:492–500
- Golias C, Tsoutsis E, Matziridis A et al (2007) Leukocyte and endothelial cell adhesion molecules in inflammation focusing on inflammatory heart disease. *In Vivo* 21:757–769
- Gómez RM, Vieira ML, Schattner M et al (2008) Putative outer membrane proteins of *Leptospira interrogans* stimulate human umbilical vein endothelial cells (HUVECS) and express during infection. *Microb Pathog* 45:315–322
- Gonzalez A, Lenzi HL, Motta EM et al (2005) Expression of adhesion molecules in lungs of mice infected with *Paracoccidioides brasiliensis* conidia. *Microbes Infect* 7:666–673
- Götting C, Adam A, Szliska C, Kleesiek K (2008) Circulating P-, L- and E-selectins in pseudoxanthoma elasticum patients. *Clin Biochem* 41:368–374
- Gout S, Tremblay PL, Huot J (2008) Selectins and selectin ligands in extravasation of cancer cells and organ selectivity of metastasis. *Clin Exp Metastasis* 25:335–344
- Graninger M, Reiter R, Drucker C et al (2004) Angiotensin receptor blockade decreases markers of vascular inflammation. *J Cardiovasc Pharmacol* 44:335–339
- Gulubova M, Vlaykova T, Manolova I et al (2008) Implication of adhesion molecules in inflammation of the common bile duct in patients with secondary cholangitis due to biliary obstruction. *Hepatogastroenterology* 55:836–841
- Guney N, Soyuncu HO, Derin D et al (2008) Serum levels of intercellular adhesion molecule ICAM-1 and E-selectin in advanced stage non-small cell lung cancer. *Med Oncol* 25:194–200
- Haidari M, Hajilooi M, Rafiei AR et al (2009) E-selectin genetic variation as a susceptibility factor for ischemic stroke. *Cerebrovasc Dis* 28:26–32
- Hallahan D, Clark ET, Kuchibhotla J et al (1995) E-selectin gene induction by ionizing radiation is independent of cytokine induction. *Biochem Biophys Res Commun* 217:784–795
- Hallahan DE, Virudachalam S, Kuchibhotla J (1998) Nuclear factor kappaB dominant negative genetic constructs inhibit X-ray induction of cell adhesion molecules in the vascular endothelium. *Cancer Res* 58:5484–5488
- Hamilton CA, Miller WH, Al-Benna S, Brosnan MJ et al (2004) Strategies to reduce oxidative stress in cardiovascular disease. *Clin Sci* 106:219–234
- Hanley WD, Napier SL, Burdick MM et al (2006) Variant isoforms of CD44 are P- and L-selectin ligands on colon carcinoma cells. *FASEB J* 20:337–339
- Hannigan E, O'Connell DP, Hannigan A, Buckley LA (2004) Soluble cell adhesion molecules in gingival crevicular fluid in periodontal health and disease. *J Periodontol* 75:546–550

- Hebbar M, Adenis A, Révillion F et al (2009) E-selectin gene S128R polymorphism is associated with poor prognosis in patients with stage II or III colorectal cancer. *Eur J Cancer* 45:1871–1876
- Heider P, Wildgruber MG, Weiss W et al (2006) Role of adhesion molecules in the induction of restenosis after angioplasty in the lower limb. *J Vasc Surg* 43:969–977
- Herrmann SM, Ricard S, Nicaud V et al (1998) The P-selectin gene is highly polymorphic: reduced frequency of the Pro715 allele carriers in patients with myocardial infarction. *Hum Mol Genet* 7:1277–1284
- Ho AW, Wong CK, Lam CW (2008) Tumor necrosis factor- $\alpha$  up-regulates the expression of CCL2 and adhesion molecules of human proximal tubular epithelial cells through MAPK signaling pathways. *Immunobiology* 213:533–544
- Hoeller C, Richardson SK, Ng LG et al (2009) In vivo imaging of cutaneous T-cell lymphoma migration to the skin. *Cancer Res* 69:2704–2708
- Hofer S, Bopp C, Hoerner C et al (2008) Injury of the blood brain barrier and up-regulation of ICAM-1 in polymicrobial sepsis. *J Surg Res* 146:276–281
- Högdahl M, Söderlund G, Kihlström E (2008) Expression of chemokines and adhesion molecules in human coronary artery endothelial cells infected with Chlamydia (Chlamydia) pneumoniae. *APMIS* 116:1082–1088
- Holler V, Buard V, Gaugler MH et al (2009) Pravastatin limits radiation-induced vascular dysfunction in the skin. *J Invest Dermatol* 129:1280–1291
- Holvoet P, Collen D (1997) Thrombosis and atherosclerosis. *Curr Opin Lipidol* 8:320–328
- Horstman LL, Jy W, Jimenez JJ, Ahn YS (2004) Endothelial microparticles as markers of endothelial dysfunction. *Front Biosci* 9:1118–1135
- Houshmand B, Rafiei A, Hajilooi M et al (2009) E-selectin and L-selectin polymorphisms in patients with periodontitis. *J Periodontol Res* 44:88–93
- Huang F, del-Río-Navarro BE, Monge JJ et al (2008) Endothelial activation and systemic inflammation in obese asthmatic children. *Allergy Asthma Proc* 29:453–460
- Iannone F, Riccardi MT, Guiducci S et al (2008) Bosentan regulates the expression of adhesion molecules on circulating T cells and serum soluble adhesion molecules in systemic sclerosis-associated pulmonary arterial hypertension. *Ann Rheum Dis* 67:1121–1126
- Ida S, Fujimura Y, Hirota M, Imamura Y et al (2009) Significance of endothelial molecular markers in the evaluation of the severity of acute pancreatitis. *Surg Today* 39:314–319
- Iwata Y, Tsuchiya KJ, Mikawa S et al (2008) Serum levels of P-selectin in men with high-functioning autism. *Br J Psychiatry* 193:338–339
- Izu K, Tokura Y (2005) The various effects of four H1-antagonists on serum substance P levels in patients with atopic dermatitis. *J Dermatol* 32:776–781
- Jeschke U, Mylonas I, Kunert-Keil C et al (2009) Immunohistochemistry, glycosylation and immunosuppression of glycodelin in human ovarian cancer. *Histochem Cell Biol* 131:283–295
- Jiang CG, Li JB, Liu FR et al (2007) Andrographolide inhibits the adhesion of gastric cancer cells to endothelial cells by blocking E-selectin expression. *Anticancer Res* 27:2439–2447
- Jolly C, Mitar I, Sattentau QJ (2007) Adhesion molecule interactions facilitate human immunodeficiency virus type 1-induced virological synapse formation between T cells. *J Virol* 81:13916–13921
- Kaifi JT, Hall LR, Diaz C et al (2000) Impaired eosinophil recruitment to the cornea in P-selectin-deficient mice in *Onchocerca volvulus* keratitis (River blindness). *Invest Ophthalmol Vis Sci* 41:3856–3861
- Kamai Y, Lossinsky AS, Liu H et al (2009) Polarized response of endothelial cells to invasion by *Aspergillus fumigatus*. *Cell Microbiol* 11:170–182
- Kanavaki I, Makrythanasis P, Lazaropoulou C et al (2009) Soluble endothelial adhesion molecules and inflammation markers in patients with  $\beta$ -thalassemia intermedia. *Blood Cells Mol Dis* 43:230–234
- Kannagi R (2007) Carbohydrate antigen sialyl Lewis A—its pathophysiological significance and induction mechanism in cancer progression. *Chang Gung Med J* 30:189–209
- Kanno H, Watabe D, Shimizu N, Sawai T (2008) Adhesion of Epstein-Barr virus-positive natural killer cell lines to cultured endothelial cells stimulated with inflammatory cytokines. *Clin Exp Immunol* 151:519–527
- Kawamura N, Dyck PJ, Schmeichel AM et al (2008) Inflammatory mediators in diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. *Acta Neuropathol* 115:231–239
- Kawase J, Ozawa S, Kobayashi K et al (2009) Increase in E-selectin expression in umbilical vein endothelial cells by anticancer drugs and inhibition by cimetidine. *Oncol Rep* 22(6):1293–1297
- Khalifaoui T, Lizard G, Ouertani-Meddeb A (2008) Adhesion molecules (ICAM-1 and VCAM-1) and diabetic retinopathy in type 2 diabetes. *J Mol Histol* 39:243–249
- Khare A, Shetty S, Ghosh K et al (2005) Evaluation of markers of endothelial damage in cases of young myocardial infarction. *Atherosclerosis* 180:375–380
- Khazen D, Jendoubi-Ayed S, Gorgi Y et al (2007) Adhesion molecule polymorphisms in acute renal allograft rejection. *Transplant Proc* 39:2563–2564
- Khazen D, Jendoubi-Ayed S, Aleya WB et al (2009) Polymorphism in ICAM-1, PECAM-1, E-selectin, and L-selectin genes in Tunisian patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 21:167–175
- Kilickap M, Tutar E, Aydintug O et al (2004) Increase in soluble E-selectin level after PTCA and stent implantation: a potential marker of restenosis. *Int J Cardiol* 93:13–18
- Kim YJ, Borsig L, Varki NM, Varki A (1998) P-selectin deficiency attenuates tumor growth and metastasis. *Proc Natl Acad Sci USA* 95:9325–9330
- Kirchberger S, Vetr H, Majdic O et al (2006) Engagement of ICAM-1 by major group rhinoviruses activates the LFA-1/ICAM-3 cell adhesion pathway in mononuclear phagocytes. *Immunobiology* 211:537–547
- Kistorp C, Chong AY, Gustafsson F et al (2008) Biomarkers of endothelial dysfunction are elevated and related to prognosis in chronic heart failure patients with diabetes but not in those without diabetes. *Eur J Heart Fail* 10:380–387
- Kleinans H, Kaifi JT, Mann O, Reinknecht F et al (2009) The role of vascular adhesion molecules PECAM-1 (CD 31), VCAM-1 (CD 106), E-selectin (CD62E) and P-selectin (CD62P) in severe porcine pancreatitis. *Histol Histopathol* 24:551–557
- Klimiuk PA, Sierakowski S, Domyslawska I et al (2004) Reduction of soluble adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor levels in serum of rheumatoid arthritis patients following multiple intravenous infusions of infliximab. *Arch Immunol Ther Exp (Warsz)* 52:36–42
- Klimiuk PA, Fiedorczyk M, Sierakowski S, Chwiecko J (2007) Soluble cell adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) in patients with early rheumatoid arthritis. *Scand J Rheumatol* 36:345–350
- Klopocki AG, Laskowska A, Antoniewicz-Papis J et al (1998) Role of sialosyl Lewis(a) in adhesion of colon cancer cells—the antisense RNA approach. *Eur J Biochem* 253:309–318
- Kobayashi H, Boelte KC, Lin PC (2007) Endothelial cell adhesion molecules and cancer progression. *Curr Med Chem* 14:377–386

- Koizumi M, King N, Lobb R et al (1992) Expression of vascular adhesion molecules in inflammatory bowel disease. *Gastroenterology* 103:840–847
- Kose O, Stewart J, Waseem A et al (2008) Expression of cytokeratins, adhesion and activation molecules in oral ulcers of Behçet's disease. *Clin Exp Dermatol* 33:62–69
- Kretowski A, Wawrusiewicz N, Mironczuk K et al (2003) Intercellular adhesion molecule 1 gene polymorphisms in Graves' disease. *J Clin Endocr Metab* 88:4945–4949
- Kumar P, Amin MA, Harlow LA et al (2003) Src and phosphatidylinositol 3-kinase mediate soluble E-selectin-induced angiogenesis. *Blood* 101:3960–3968
- Kuryliszyn-Moskal A, Klimiuk PA, Ciolkiewicz M, Sierakowski S (2008) Clinical significance of selected endothelial activation markers in patients with systemic lupus erythematosus. *J Rheumatol* 35:1307–1313
- Kwon BC, Sohn MH, Kim KW et al (2007) House dust mite induces expression of intercellular adhesion molecule-1 in EoL-1 human eosinophilic leukemic cells. *J Korean Med Sci* 22:815–819
- Langer R, Wang M, Stepkowski SM et al (2004) Selectin inhibitor bimosiamose prolongs survival of kidney allografts by reduction in intragraft production of cytokines and chemokines. *J Am Soc Nephrol* 15:2893–2901
- Lau C, Wang X, Song L et al (2008) Syk associates with clathrin and mediates phosphatidylinositol 3-kinase activation during human rhinovirus internalization. *J Immunol* 180:870–880
- Läubli H, Borsig L (2010) Selectins promote tumor metastasis. *Semin Cancer Biol* 20:169–177
- Leal EC, Avelaira CA, Castilho AF et al (2008) Müller cells do not influence leukocyte adhesion to retinal endothelial cells. *Ocul Immunol Inflamm* 16:173–179
- Lee HM, Kim HJ, Won KJ et al (2008) Contribution of soluble intercellular adhesion molecule-1 to the migration of vascular smooth muscle cells. *Eur J Pharmacol* 579:260–268
- Lefranc F, Mijatovic T, Mathieu V et al (2004) Characterization of gastrin-induced proangiogenic effects in vivo in orthotopic U373 experimental human glioblastomas and in vitro in human umbilical vein endothelial cells. *Clin Cancer Res* 10:8250–8265
- Leone M, Boutiere-Albanese B, Valette S et al (2004) Cell adhesion molecules as a marker reflecting the reduction of endothelial activation induced by glucocorticoids. *Shock* 21:311–314
- Lepenes B, Yin J, Seeberger PH (2010) Applications of synthetic carbohydrates to chemical biology. *Curr Opin Chem Biol* 14:404–411
- Levälampi T, Honkanen V, Lahdenne P et al (2007) Effects of infliximab on cytokines, myeloperoxidase, and soluble adhesion molecules in patients with juvenile idiopathic arthritis. *Scand J Rheumatol* 36:189–193
- Li Y, Wei YS, Wang M et al (2005) Association between the Ser128Arg variant of the E-selectin and risk of coronary artery disease in the central China. *Int J Cardiol* 103:33–36
- Li XX, Liu JP, Cheng JQ et al (2008) Intercellular adhesion molecule-1 gene K469E polymorphism and ischemic stroke: a case-control study in a Chinese population. *Mol Biol Rep* 36:1565–1571
- Lim HS, Blann AD, Lip GY (2004) Soluble CD40 ligand, soluble P-selectin, interleukin-6, and tissue factor in diabetes mellitus: relationships to cardiovascular disease and risk factor intervention. *Circulation* 109:2524–2528
- Lin CL, Dumont AS, Calisanelle T et al (2005) Monoclonal antibody against E selectin attenuates subarachnoid hemorrhage-induced cerebral vasospasm. *Surg Neurol* 64:201–205
- Lip GY, Pearce LA, Chin BS et al (2005) Effects of congestive heart failure on plasma von Willebrand factor and soluble P-selectin concentrations in patients with non-valvular atrial fibrillation. *Heart* 91:759–763
- Liu R, Desta T, Raptis M et al (2008) P. gingivalis and E. coli lipopolysaccharides exhibit different systemic but similar local induction of inflammatory markers. *J Periodontol* 79:1241–1247
- López-Lerma I, Estrach MT (2009) A distinct profile of serum levels of soluble intercellular adhesion molecule-1 and intercellular adhesion molecule-3 in mycosis fungoides and Sézary syndrome. *J Am Acad Dermatol* 61:263–270
- Ludwig RJ, Alban S, Bistrrian R, Boehncke WH et al (2006) The ability of different forms of heparins to suppress P-selectin function in vitro correlates to their inhibitory capacity on bloodborne metastasis in vivo. *Thromb Haemost* 95:535–540
- Ludwig RJ, Schön MP, Boehncke WH (2007) P-selectin: a common therapeutic target for cardiovascular disorders, inflammation and tumour metastasis. *Expert Opin Ther Targets* 11:1103–1117
- Lugovic L, Cupic H, Lipozencic J et al (2006) The role of adhesion molecules in atopic dermatitis. *Acta Dermatovenerol Croat* 14:2–7
- Lutters BC, Leeuwenburgh MA, Appeldoorn CC et al (2004) Blocking endothelial adhesion molecules: a potential therapeutic strategy to combat atherogenesis. *Curr Opin Lipidol* 15:545–552
- Malatino LS, Stancanelli B, Cataliotti A et al (2007) Circulating E-selectin as a risk marker in patients with end-stage renal disease. *J Intern Med* 262:479–487
- Manetti M, Neumann E, Müller A, Schmeiser T et al (2008) Endothelial/lymphocyte activation leads to prominent CD4+ T cell infiltration in the gastric mucosa of patients with systemic sclerosis. *Arthritis Rheum* 58:2866–2873
- Marazuela M, Postigo AA, Acevedo A et al (1994) Adhesion molecules from the LFA-1/ICAM-1,3 and VLA-4/VCAM-1 pathways on T lymphocytes and vascular endothelium in Graves' and Hashimoto's thyroid glands. *Eur J Immunol* 24:2483–2490
- Marschang P, Friedrich GJ, Dittbacher H et al (2006) Reduction of soluble P-selectin by statins is inversely correlated with the progression of coronary artery disease. *Int J Cardiol* 106:183–190
- Marteau JB, Sass C, Pfister M et al (2004) The Leu554Phe polymorphism in the E-selectin gene is associated with blood pressure in overweight people. *J Hypertens* 22:305–311
- Masamune A, Hakomori S, Igarashi Y (1995) N,N,N-trimethylsphingosine inhibits interleukin-1 beta-induced NF- $\kappa$ B activation and consequent E-selectin expression in human umbilical vein endothelial cells. *FEBS Lett* 367:205–209
- Mastej K, Adamiec R (2008) Neutrophil surface expression of CD11b and CD62L in diabetic microangiopathy. *Acta Diabetol* 45:183–190
- Mathieu S, Prorok M, Benoliel AM et al (2004) Transgene expression of  $\alpha$ (1,2)-fucosyltransferase-I (FUT1) in tumor cells selectively inhibits sialyl-Lewis x expression and binding to E-selectin without affecting synthesis of sialyl-Lewis a or binding to P-selectin. *Am J Pathol* 164:371–383
- Matondo Maya DW, Mewono L, Nkoma AM et al (2008) Markers of vascular endothelial cell damage and P. falciparum malaria: association between levels of both sE-selectin and thrombomodulin, and cytokines, hemoglobin and clinical presentation. *Eur Cytokine Netw* 19:123–130
- Mattsson E, Heying R, van de Gevel JS et al (2008) Staphylococcal peptidoglycan initiates an inflammatory response and procoagulant activity in human vascular endothelial cells: a comparison with highly purified lipoteichoic acid and TSST-1. *FEMS Immunol Med Microbiol* 52:110–117
- McBane RD 2nd, Karnicki K, Miller RS, Owen WG (2004) The impact of peripheral arterial disease on circulating platelets. *Thromb Res* 113:137–145
- McCafferty DM, Smith CW, Granger DN, Kubes P (1999) Intestinal inflammation in adhesion molecule-deficient mice: an assessment of P-selectin alone and in combination with ICAM-1 or E-selectin. *J Leukoc Biol* 66:67–74
- McLaren AJ, Marshall SE, Haldar NA et al (1999) Adhesion molecule polymorphisms in chronic renal allograft failure. *Kidney Int* 55:1977–1982



- Melendez MM, McNurlan MA, Mynarcik DC et al (2008) Endothelial adhesion molecules are associated with inflammation in subjects with HIV disease. *Clin Infect Dis* 46:775–780
- Mel-S Z, el-Sayed H (2009) Evaluation of microbiologic and hematologic parameters and E-selectin as early predictors for outcome of neonatal sepsis. *Arch Pathol Lab Med* 133:1291–1296
- Merlini PA, Rossi ML, Faioni EM et al (2004) Expression of endothelial protein C receptor and thrombomodulin in human coronary atherosclerotic plaques. *Ital Heart J* 5:42–47
- Merten M, Thiagarajan P (2004) P-selectin in arterial thrombosis. *Z Kardiol* 93:855–863
- Miklossy J, Doudet DD, Schwab C et al (2006) Role of ICAM-1 in persisting inflammation in Parkinson disease and MPTP monkeys. *Exp Neurol* 197:275–283
- Miller MA, Kerry SM, Cook DG et al (2004a) Cellular adhesion molecules and blood pressure: interaction with sex in a multi-ethnic population. *J Hypertens* 22:705–711
- Miller MA, Kerry SM, Dong Y et al (2004b) Association between the Thr715Pro P-selectin gene polymorphism and soluble P-selectin levels in a multiethnic population in South London. *Thromb Haemost* 92:1060–1065
- Molero L, Lopez-Farre A, Mateos-Caceres PJ et al (2005) Effect of clopidogrel on the expression of inflammatory markers in rabbit ischemic coronary artery. *Br J Pharmacol* 146:419–427
- Montoro J, Sastre J, Jáuregui I et al (2007) Allergic rhinitis: continuous or on demand antihistamine therapy? *J Investig Allergol Clin Immunol* 17(Suppl 2):21–27
- Munoz FM, Hawkins EP, Bullard DC et al (1997) Host defense against systemic infection with *Streptococcus pneumoniae* is impaired in E-, P-, and E-/P-selectin-deficient mice. *J Clin Invest* 100:2099–2106
- Musial K, Zwolinska D, Polak-Jonkisz D et al (2005) Serum VCAM-1, ICAM-1, and L-selectin levels in children and young adults with chronic renal failure. *Pediatr Nephrol* 20:52–55
- Myers DD Jr, Rectenwald JE, Bedard PW et al (2005) Decreased venous thrombosis with an oral inhibitor of P selectin. *J Vasc Surg* 42:329–336
- Nadar SK, Blann AD, Lip GY (2004a) Plasma and platelet-derived vascular endothelial growth factor and angiopoietin-1 in hypertension: effects of antihypertensive therapy. *J Intern Med* 256:331–337
- Nadar SK, Lip GY, Blann AD (2004b) Platelet morphology, soluble P selectin and platelet P-selectin in acute ischaemic stroke. The West Birmingham Stroke Project. *Thromb Haemost* 92:1342–1348
- Nonomura C, Kikuchi J, Kiyokawa N et al (2008) CD43, but not P-selectin glycoprotein ligand-1, functions as an E-selectin counter-receptor in human pre-B-cell leukemia NALL-1. *Cancer Res* 68:790–799
- Nowak M, Wielkoszyński T, Marek B et al (2008) Blood serum levels of vascular cell adhesion molecule (sVCAM-1), intercellular adhesion molecule (sICAM-1) and endothelial leucocyte adhesion molecule-1 (ELAM-1) in diabetic retinopathy. *Clin Exp Med* 8:159–164
- Nubel T, Dippold W, Kaina B, Fritz G (2004) Ionizing radiation-induced E-selectin gene expression and tumor cell adhesion is inhibited by lovastatin and all-trans retinoic acid. *Carcinogenesis* 25:1335–1344
- Ogawa N, Saito N, Kameoka S et al (2008) Clinical significance of intercellular adhesion molecule-1 in ulcerative colitis. *Int Surg* 93:37–44
- Ohkawara Y, Yamauchi K, Maruyama N et al (1995) In situ expression of the cell adhesion molecules in bronchial tissues from asthmatics with air flow limitation: in vivo evidence of VCAM-1/VLA-4 interaction in selective eosinophil infiltration. *Am J Respir Cell Mol Biol* 12:4–12
- Ohmori K, Fukui F, Kiso M et al (2006) Identification of cutaneous lymphocyte-associated antigen as sialyl 6-sulfo Lewis X, a selectin ligand expressed on a subset of skin-homing helper memory T cells. *Blood* 107:3197–3204
- Ohnishi M, Imanishi N, Tojo SJ (1999) Protective effect of anti-P-selectin monoclonal antibody in lipopolysaccharide-induced lung hemorrhage. *Inflammation* 23:461–469
- Okapcova J, Gabor D (2004) The levels of soluble adhesion molecules in diabetic and nondiabetic patients with combined hyperlipoproteinemia and the effect of ciprofibrate therapy. *Angiology* 55:629–639
- Pamuk GE, Vural O, Turgut B et al (2008) Increased platelet activation markers in rheumatoid arthritis: are they related with subclinical atherosclerosis? *Platelets* 19:146–154
- Pamuk GE, Nur Pamuk O, Orum H et al (2009) Elevated platelet-monocyte complexes in patients with psoriatic arthritis. *Platelets* 14:1–5
- Park EY, Shim JY, Kim DS et al (2008) Elevated serum soluble E-selectin levels in Korean children with measles. *Pediatr Int* 50:519–522
- Paschos KA, Canovas D, Bird NC (2010) The engagement of selectins and their ligands in colorectal cancer liver metastases. *J Cell Mol Med* 14:165–174
- Pemberton PW, Ahmad Y, Bodill H et al (2009) Biomarkers of oxidant stress, insulin sensitivity and endothelial activation in rheumatoid arthritis: a cross-sectional study of their association with accelerated atherosclerosis. *BMC Res Notes* 2:83
- Petersson H, Lind L, Hulthe J et al (2009) Relationships between serum fatty acid composition and multiple markers of inflammation and endothelial function in an elderly population. *Atherosclerosis* 203(1):298–303
- Pezzilli R, Corsi MM, Barassi A et al (2008) Serum adhesion molecules in acute pancreatitis: time course and early assessment of disease severity. *Pancreas* 37:36–41
- Phan QT, Filler SG (2009) Endothelial cell stimulation by *Candida albicans*. *Methods Mol Biol* 470:313–326
- Philpott JR, Miner PB Jr (2008) Antisense inhibition of ICAM-1 expression as therapy provides insight into basic inflammatory pathways through early experiences in IBD. *Expert Opin Biol Ther* 8:1627–1632
- Pierce JW, Read MA, Ding H et al (1996) Salicylates inhibit I $\kappa$ B- $\alpha$  phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration. *J Immunol* 156:3961–3969
- Pisella P-J, Brignole F, Debbasch C et al (2000) Flow cytometric analysis of conjunctival epithelium in ocular rosacea and keratoconjunctivitis sicca. *Ophthalmology* 107:1841–1849
- Postadzhiyan AS, Tzontcheva AV, Kehayov I, Finkov B (2008) Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and their association with clinical outcome, troponin T and C-reactive protein in patients with acute coronary syndromes. *Clin Biochem* 41:126–133
- Potapov EV, Hennig F, Wagner FD et al (2005) Natriuretic peptides and E-selectin as predictors of acute deterioration in patients with inotrope-dependent heart failure. *Eur J Cardiothorac Surg* 27:899–905
- Potenza MA, Gagliardi S, Nacci C et al (2009) Endothelial dysfunction in diabetes: from mechanisms to therapeutic targets. *Curr Med Chem* 16:94–112
- Rankin JA (2004) Biological mediators of acute inflammation. *AACN Clin Issues* 15:3–17
- Register TC (2009) Primate models in women's health: inflammation and atherogenesis in female cynomolgus macaques (*Macaca fascicularis*). *Am J Primatol* 71:766–775
- Remahl AI, Bratt J, Möllby H et al (2008) Comparison of soluble ICAM-1, VCAM-1 and E-selectin levels in patients with episodic cluster headache and giant cell arteritis. *Cephalalgia* 28:157–163
- Rho YH, Chung CP, Oeser A et al (2008) Novel cardiovascular risk factors in premature coronary atherosclerosis associated with systemic lupus erythematosus. *J Rheumatol* 35:1789–1794
- Riad A, Westermann D, Linthout SV et al (2008) Enhancement of endothelial nitric oxide synthase production reverses vascular

- dysfunction and inflammation in the hindlimbs of a rat model of diabetes. *Diabetologia* 51:2325–2332
- Riaz AA, Wan MX, Schaefer T et al (2002) Fundamental and distinct roles of P-selectin and LFA-1 in ischemia/reperfusion-induced leukocyte-endothelium interactions in the mouse colon. *Ann Surg* 236:777–784
- Riede E, Gratchev A, Foss HD et al (1998) Increased methylation of promoter region suppresses expression of MUC2 gene in colon carcinoma cells. *Langenbecks Arch Chir Suppl Kongressbd* 115 (Suppl 1):299–302
- Rodrigues SF, de Oliveira MA, dos Santos RA et al (2008) Hydralazine reduces leukocyte migration through different mechanisms in spontaneously hypertensive and normotensive rats. *Eur J Pharmacol* 589:206–214
- Rubio-Guerra AF, Vargas-Robles H, Vargas-Ayala G et al (2008) The effect of trandolapril and its fixed-dose combination with verapamil on circulating adhesion molecules levels in hypertensive patients with type 2 diabetes. *Clin Exp Hypertens* 30:682–688
- Ruth JH, Amin MA, Woods JM et al (2005) Accelerated development of arthritis in mice lacking endothelial selectins. *Arthritis Res Ther* 7:R959–R970
- Sainani GS, Maru VG (2005) The endothelial leukocyte adhesion molecule. Role in coronary artery disease. *Acta Cardiol* 60:501–507
- Saito I, Terauchi K, Shimuta M et al (1993) Expression of cell adhesion molecules in the salivary and lacrimal glands of Sjogren's syndrome. *J Clin Lab Anal* 7:180–187
- Sanada H, Midorikawa S, Yatabe J et al (2005) Elevation of serum soluble E- and P-selectin in patients with hypertension is reversed by benidipine, a long-acting calcium channel blocker. *Hypertens Res* 28:871–878
- Sarecka-Hujar B, Zak I, Emich-Widera E et al (2010) Association analysis of the E-selectin 98 G > T polymorphism and the risk of childhood ischemic stroke. *Cell Biochem Funct* 28:591–596
- Sato H, Usuda N, Kuroda M et al (2010) CA19-9 and E-selectin as markers of hematogenous metastases and as predictors of prognosis in colorectal cancer. *Jpn J Clin Oncol* 40:1073–1080
- Schnaar RL, Alves CS, Konstantopoulos K (2008) Carcinoembryonic antigen and CD44 variant isoforms cooperate to mediate colon carcinoma cell adhesion to E- and L-selectin in shear flow. *J Biol Chem* 283:15647–15655
- Selakovic V, Raicevic R, Radenovic L (2009) Temporal patterns of soluble adhesion molecules in cerebrospinal fluid and plasma in patients with the acute brain infraction. *Dis Markers* 26:65–74
- Serebruany VL, Malinin AI, Oshrine BR et al (2004) Lack of uniform platelet activation in patients after ischemic stroke and choice of antiplatelet therapy. *Thromb Res* 113:197–204
- Sfikakis PP, Mavrikakis M (1999) Adhesion and lymphocyte costimulatory molecules in systemic rheumatic diseases. *Clin Rheumatol* 18:317–327
- Shapiro NI, Yano K, Sorasaki M et al (2009) Skin biopsies demonstrate site-specific endothelial activation in mouse models of sepsis. *J Vasc Res* 46:495–502
- Shen JS, Meng XL, Moore DF et al (2008) Globotriaosylceramide induces oxidative stress and up-regulates cell adhesion molecule expression in Fabry disease endothelial cells. *Mol Genet Metab* 95:163–168
- Shimada Y, Maeda M, Watanabe G, Imamura M (2003) High serum soluble E-selectin levels are associated with postoperative haematogenic recurrence in esophageal squamous cell carcinoma patients. *Oncol Rep* 10:991–995
- Sigmundsdottir H, Johnston A, Gudjonsson JE et al (2004) Methotrexate markedly reduces the expression of vascular E-selectin, cutaneous lymphocyte-associated antigen and the numbers of mononuclear leucocytes in psoriatic skin. *Exp Dermatol* 13:426–434
- Singh K, Colmegna I, He X et al (2008) Synovocyte stimulation by the LFA-1-intercellular adhesion molecule-2-Ezrin-Akt pathway in rheumatoid arthritis. *J Immunol* 180:1971–1978
- Sjöswärd KN, Uppugunduri S, Schmekel B (2004) Decreased serum levels of P-selectin and eosinophil cationic protein in patients with mild asthma after inhaled salbutamol. *Respiration* 71:241–245
- Skiba-Choińska I, Rogowski F (1996) Adhesion molecules and their role in pathogenesis of ARDS. *Przeegl Lek* 53:627–630
- Smith CH, Barker JN, Lee TH (1993a) Adhesion molecules in allergic inflammation. *Am Rev Respir Dis* 148:S75–S78
- Smith GM, Whelan J, Pescini R et al (1993b) DNA-methylation of the E-selectin promoter represses NF- $\kappa$ B transactivation. *Biochem Biophys Res Commun* 194:215–221
- St Hill CA, Farooqui M, Mitcheltree G et al (2009) The high affinity selectin glycan ligand C2-O-sLex and mRNA transcripts of the core 2  $\beta$ -1,6-N acetylglucosaminyl-transferase (C2GnT1) gene are highly expressed in human colorectal adenocarcinomas. *BMC Cancer* 9:79
- Steinhuyl SR, Moliterno DJ (2005) The role of the platelet in the pathogenesis of atherothrombosis. *Am J Cardiovasc Drugs* 5:399–408
- Stevenson JL, Choi SH, Varki A (2005) Differential metastasis inhibition by clinically relevant levels of heparins—correlation with selectin inhibition, not antithrombotic activity. *Clin Cancer Res* 11:7003–7011
- Stewart AO, Bhatia PA, McCarty CM et al (2001) Discovery of inhibitors of cell adhesion molecule expression in human endothelial cells. 1. Selective inhibition of ICAM-1 and E-selectin expression. *J Med Chem* 44:988–1002
- Storer KP, Tu J, Karunanayaka A et al (2008) Inflammatory molecule expression in cerebral arteriovenous malformations. *J Clin Neurosci* 15:179–184
- Sukhotnik I, Coran AG, Greenblatt R et al (2008) Effect of 100 % oxygen on E-selectin expression, recruitment of neutrophils and enterocyte apoptosis following intestinal ischemia-reperfusion in a rat. *Pediatr Surg Int* 24:29–35
- Sun W, Watanabe Y, Wang ZQ (2006) Expression and significance of ICAM-1 and its counter receptors LFA-1 and Mac-1 in experimental acute pancreatitis of rats. *World J Gastroenterol* 12:5005–5009
- Svensson H, Hansson M, Kilhamn J et al (2009) Selective upregulation of endothelial E-selectin in response to *Helicobacter pylori*-induced gastritis. *Infect Immun* 77:3109–3116
- Swellam M, Ragab HM, Abdalla NA, El-Asmar AB (2008) Soluble cytokeratin-19 and E-selectin biomarkers: their relevance for lung cancer detection when tested independently or in combinations. *Cancer Biomark* 4:43–54
- Swingler S, Brichacek B, Jacque J-M et al (2003) HIV-1 Nef intersects the macrophage CD40L signaling pathway to promote resting-cell infection. *Nature* 424:213–219
- Syrigos KN, Salgami E, Karayiannakis AJ et al (2004) Prognostic significance of soluble adhesion molecules in Hodgkin's disease. *Anticancer Res* 24:1243–1247
- Takei T, Iida A, Nitta K et al (2002) Association between single-nucleotide polymorphisms in selectin genes and immunoglobulin A nephropathy. *Am J Hum Genet* 70:781–786
- Tamai R, Asai Y, Kawabata A et al (2007) Possible requirement of intercellular adhesion molecule-1 for invasion of gingival epithelial cells by *Treponema medium*. *Can J Microbiol* 53:1232–1238
- Taverna S, Flugy A, Colomba P et al (2008) Effects of *Parietaria judaica* pollen extract on human microvascular endothelial cells. *Biochem Biophys Res Commun* 372:644–649
- Telejko B, Zonenberg A, Kuzmicki M et al (2009) Circulating asymmetric dimethylarginine, endothelin-1 and cell adhesion molecules in women with gestational diabetes. *Acta Diabetol* 46:303–308

- Teoh H, Quan A, Bang KW et al (2008) Adiponectin deficiency promotes endothelial activation and profoundly exacerbates sepsis-related mortality. *Am J Physiol Endocrinol Metab* 295: E658–E664
- Thomas SN, Schnaar RL, Konstantopoulos K (2009a) Podocalyxin-like protein is an E-/L-selectin ligand on colon carcinoma cells: comparative biochemical properties of selectin ligands in host and tumor cells. *Am J Physiol Cell Physiol* 296:C505–C513
- Thomas SN, Zhu F, Zhang F et al (2009b) Different roles of galectin-9 isoforms in modulating E-selectin expression and adhesion function in LoVo colon carcinoma cells. *Mol Biol Rep* 36:823–830
- Thomson AW, Satoh S, Nussler AK et al (1994) Circulating intercellular adhesion molecule-1 (ICAM-1) in autoimmune liver disease and evidence for the production of ICAM-1 by cytokine-stimulated human hepatocytes. *Clin Exp Immunol* 95:83–90
- Tozawa K, Sakurada S, Kohri K, Okamoto T (1995) Effects of anti-nuclear factor κB reagents in blocking adhesion of human cancer cells to vascular endothelial cells. *Cancer Res* 55:4162–4167
- Tregouet DA, Barbaux S, Escolano S et al (2002) Specific haplotypes of the P-selectin gene are associated with myocardial infarction. *Hum Mol Genet* 11:2015–2023
- Tremblay PL, Huot J, Auger FA (2008) Mechanisms by which E-selectin regulates diapedesis of colon cancer cells under flow conditions. *Cancer Res* 68:5167–5176
- Tripathy NK, Chandran V, Garg NK et al (2008) Soluble endothelial cell adhesion molecules and their relationship to disease activity in Takayasu's arteritis. *J Rheumatol* 35:1842–1845
- Turunen AJ, Fernandez JA, Lindgren L et al (2005) Activated protein C reduces graft neutrophil activation in clinical renal transplantation. *Am J Transplant* 5:2204–2212
- Tuttolomondo A, Pinto A, Corrao S et al (2009) Immuno-inflammatory and thrombotic/fibrinolytic variables associated with acute ischemic stroke diagnosis. *Atherosclerosis* 203:503–508
- Uchihara JN, Matsuda T, Okudaira T et al (2006) Transactivation of the ICAM-1 gene by CD30 in Hodgkin's lymphoma. *Int J Cancer* 118:1098–1107
- Uner A, Akcali Z, Unsal D (2004) Serum levels of soluble E-selectin in colorectal cancer. *Neoplasma* 51:269–274
- Vejchapiat P, Sookpotarom P, Theamboonlers A et al (2008) Elevated serum soluble E-selectin is associated with poor outcome and correlated with serum ALT in biliary atresia. *Eur J Pediatr Surg* 18:254–257
- Vijya Lakshmi SV, Padmaja G, Kuppusamy P, Kutala VK (2009) Oxidative stress in cardiovascular disease. *Ind J Biochem Biophys* 46:421–440
- Vischer P, Telgmann R, Schmitz B et al (2008) Molecular investigation of the functional relevance of missense variants of ICAM-1. *Pharmacogenet Genomics* 18:1017–1019
- Volicik KA, Ballantyne CM, Coresh J et al (2006) P-selectin Thr715Pro polymorphism predicts P-selectin levels but not risk of incident coronary heart disease or ischemic stroke in a cohort of 14595 participants: the Atherosclerosis Risk in Communities Study. *Atherosclerosis* 186:74–79
- Vora DK, Rosenbloom CL, Beaudet AL, Cottingham RW (1994) Polymorphisms and linkage analysis for ICAM-1 and the selectin gene cluster. *Genomics* 21:473–477
- Wang K, Zhou X, Zhou Z et al (2005) Platelet, not endothelial, P-selectin is required for neointimal formation after vascular injury. *Arterioscler Thromb Vasc Biol* 25:1584–1589
- Wang JH, Kwon HJ, Lee BJ, Jang YJ (2007) Staphylococcal enterotoxins A and B enhance rhinovirus replication in A549 cells. *Am J Rhinol* 21:670–674
- Warfel JM, D'Agnillo F (2008) Anthrax lethal toxin enhances TNF-induced endothelial VCAM-1 expression via an IFN regulatory factor-1-dependent mechanism. *J Immunol* 180:7516–7524
- Wei M, Gao Y, Tian M et al (2005) Selectively desulfated heparin inhibits P-selectin-mediated adhesion of human melanoma cells. *Cancer Lett* 229:123–126
- Wei J, Cui L, Liu F et al (2010) E-selectin and Sialyl Lewis X expression is associated with lymph node metastasis of invasive micropapillary carcinoma of the breast. *Int J Surg Pathol* 18:193–200
- Wenzel K, Ernst M, Rohde K et al (1996) DNA polymorphisms in adhesion molecule genes—a new risk factor for early atherosclerosis. *Hum Genet* 97:15–20
- Wenzel K, Stahn R, Speer A et al (1999) Functional characterization of atherosclerosis-associated Ser128Arg and Leu554Phe E-selectin mutations. *J Biol Chem* 274:661–667
- West MB, Ramana KV, Kaiserova K et al (2008) L-Arginine prevents metabolic effects of high glucose in diabetic mice. *FEBS Lett* 582:2609–2614
- Woodward J (2008) Crossing the endothelium: E-selectin regulates tumor cell migration under flow conditions. *Cell Adh Migr* 2:151–152
- Wu S, Zhou X, Yang H et al (2009) Polymorphisms and plasma soluble levels of E-selectin in patients with chronic hepatitis B virus infection. *Clin Chem Lab Med* 47:159–164
- Wynn TA, Hesse M, Sandler NG et al (2004) P-selectin suppresses hepatic inflammation and fibrosis in mice by regulating interferon-γ and the IL-13 decoy receptor. *Hepatology* 39:676–687
- Xia B, Han H, Zhang KJ et al (2004) Effects of low molecular weight heparin on platelet surface P-selectin expression and serum interleukin-8 production in rats with trinitrobenzene sulphonic acid-induced colitis. *World J Gastroenterol* 10:729–732
- Xie L, Galetti A, Morris J et al (2008) Intercellular adhesion molecule-1 (ICAM-1) expression is necessary for monocyte adhesion to the placental bed endothelium and is increased in type 1 diabetic human pregnancy. *Diabetes Metab Res Rev* 24:294–300
- Xu Y, Huo Y, Toufektsian MC et al (2006) Activated platelets contribute importantly to myocardial reperfusion injury. *Am J Physiol Heart Circ Physiol* 290:H692–H699
- Yao GH, Liu ZH, Zhang X et al (2008) Circulating thrombomodulin and vascular cell adhesion molecule-1 and renal vascular lesion in patients with lupus nephritis. *Lupus* 17:720–726
- Yildirim K, Senel K, Karatay S et al (2005) Serum E-selectin and erythrocyte membrane Na + K + ATPase levels in patients with rheumatoid arthritis. *Cell Biochem Funct* 23:285–289
- Yip HK, Chang LT, Sun CK et al (2006) Platelet activity is a biomarker of cardiac necrosis and predictive of untoward clinical outcomes in patients with acute myocardial infarction undergoing primary coronary stenting. *Circ J* 70:31–36
- Yoshida M, Takano Y, Sasaoka T et al (2003) E-selectin polymorphism associated with myocardial infarction causes enhanced leukocyte-endothelial interactions under flow conditions. *Arterioscler Thromb Vasc Biol* 23:783–788
- Yoshizaki A, Yanaba K, Iwata Y et al (2010) Cell adhesion molecules regulate fibrotic process via Th1/Th2/Th17 cell balance in a bleomycin-induced scleroderma model. *J Immunol* 185:2502–2515
- Yun W, Qing-Cheng L, Lei Y, Jia-Yin M (2008) Mucosal tolerance to E-selectin provides protection against cerebral ischemia-reperfusion injury in rats. *J Neuroimmunol* 205:73–79
- Zak I, Sarecka B, Krauze J (2008) Synergistic effects between 561A > C and 98 G > T polymorphisms of E-selectin gene and hypercholesterolemia in determining the susceptibility to coronary artery disease. *Heart Vessels* 23:257–263
- Zakynthinos E, Pappa N (2009) Inflammatory biomarkers in coronary artery disease. *J Cardiol* 53:317–333
- Zaph C, Scott P (2003) Th1 cell-mediated resistance to cutaneous infection with *Leishmania major* is independent of P- and E-selectins. *J Immunol* 171:4726–4732

- Zen K, Liu DQ, Guo YL et al (2008) CD44v4 is a major E-selectin ligand that mediates breast cancer cell transendothelial migration. *PLoS One* 3:e1826
- Zhang BH, Chen H, Yao XP et al (2002) E-selectin and its ligand-sLeX in the metastasis of hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 1:80–82
- Zheng J, Bao WQ, Sheng WQ et al (2009) Serum 3'-sulfo-Le<sup>a</sup> indication of gastric cancer metastasis. *Clin Chim Acta* 405:119–126
- Zigler M, Dobroff AS, Bar-Eli M (2010) Cell adhesion: implication in tumor progression. *Minerva Med* 101:149–162
- Zimmerman T, Blanco FJ (2008) Inhibitors targeting the LFA-1/ICAM-1 cell-adhesion interaction: design and mechanism of action. *Curr Pharm Des* 14:2128–2139
- Zuccarello D, Salpietro DC, Gangemi S et al (2002) Familial chronic nail candidiasis with ICAM-1 deficiency: a new form of chronic mucocutaneous candidiasis. *J Med Genet* 39:671–675
- Zuliani G, Cavalieri M, Galvani M et al (2008) Markers of endothelial dysfunction in older subjects with late onset Alzheimer's disease or vascular dementia. *J Neurol Sci* 272:164–170