

Review

Cell-cell interactions in synovitis Endothelial cells and immune cell migration

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Abstract

Leukocyte ingress into the synovium is a key process in the pathogenesis of rheumatoid arthritis and other inflammatory conditions. In this review, the role of endothelial cells in leukocyte extravasation will be discussed, including the role of the most relevant cellular adhesion molecules. These molecules play an important role in mediating leukocyte–endothelial interactions. It is likely that different adhesive pathways are involved in different steps of leukocyte adhesion to and migration through endothelia. Targeting of pathological endothelial function, including leukocyte–endothelial adhesion, may be useful for the future management of inflammatory arthritis.

Keywords: Adhesion molecules, endothelium, leukocyte migration, rheumatoid arthritis

Introduction

Leukocyte extravasation through the endothelial barrier is important in the pathogenesis of inflammatory disorders such as rheumatoid arthritis (RA). Endothelial cells line the lumina of vessels, thus separating and also connecting the blood and the synovial tissue. It has become clear that, in inflammation, endothelial cells are not only passive bystanders but are active responders to various stimuli (state of activation of leukocytes, exogenous cytokines, endogenous endothelial mediators, and crosstalk between adhesion molecules). Thus endothelia are targets for inflammatory leukocytes and their mediators. In return, endothelial cells themselves produce a number of inflammatory mediators, express cellular adhesion molecules (CAMs) and therefore directly influence the action of leukocytes and the outcome of the inflammatory response [1,2].

Endothelial cells are involved in a number of mechanisms underlying arthritis. Various inflammatory mediators, primarily pro-inflammatory cytokines including tumor necrosis factor (TNF)- α and IL-1 β , activate endothelial cells. In response, there is an upregulation of endothelial CAMs in RA, leading to increased leukocyte–endothelial interactions [2–4].

In this review we discuss the role of endothelial cells, as well as that of leukocyte–endothelial adhesion and migration in synovial inflammation. First we describe the general characteristics of leukocyte–endothelial adhesion. Then the role of the most relevant CAMs, as well as that of the most important adhesive pathways determined by these CAMs in arthritis is introduced. Finally we discuss potential strategies of targeting these mechanisms.

CAMs = cellular adhesion molecules; CLA = cutaneous leukocyte antigen; ESL = E-selectin ligand; HEV = high endothelial venule; ICAM = intercellular adhesion molecule; IL = interleukin; LFA = lymphocyte function-associated antigen; PECAM = platelet–endothelial adhesion molecule; PSGL = P-selectin ligand; RA = rheumatoid arthritis; TGF = transforming growth factor; TNF = tumor necrosis factor; VAP = vascular adhesion protein; VCAM = vascular cell adhesion molecule.

Leukocyte–endothelial interactions in synovitis

The ingress of leukocytes into the synovium is an active process mediated by a number of CAMs. The cascade of events begins with the adhesion of neutrophils, lymphocytes and monocytes to the specialized, fenestrated synovial endothelium [4,5]. High endothelial venule (HEV)-like microvessels, similar to HEVs in the primary lymphoid organs, are present in the rheumatoid synovial tissue [2,4,5]. Thus the process of leukocyte extravasation into the synovium closely resembles physiological lymphocyte ‘homing’. After adhesion, leukocytes transmigrate through the vessel wall into the synovium [6**,7**,8,9].

CAMs have been classified into a number of superfamilies. However, most CAMs involved in endothelial adhesion belong to three supergene families, the integrin, selectin and immunoglobulin families [6**,7**,8,9]. Leukocyte adhesion to endothelial cells occurs in four distinct steps [9,10] (Table 1):

1. Primary, relatively weak adhesion termed ‘rolling’ occurs within the first 1–2 h. It is mediated by E-, P- and L-selectins and their counter-receptors.
2. Leukocyte activation and triggering occurs next and is due to the interactions between chemokine receptors on leukocytes and proteoglycans on endothelial cells. Platelet–endothelial adhesion molecule (PECAM)-1 (or CD31) and the soluble platelet-activating factor (PAF) are also involved in this step.
3. Activation-dependent, firm adhesion occurs within 4–6 h. This interaction is mediated mostly by $\alpha_4\beta_1$ integrin–vascular cell adhesion molecule (VCAM)-1 and $\alpha_L\beta_2$ integrin [or lymphocyte function-associated antigen (LFA)-1]–intercellular adhesion molecule (ICAM)-1 interactions.
4. Transendothelial migration or diapedesis occurs when secreted chemokines bind to endothelial heparan sulphate glycosaminoglycans. Chemokines attract endothelium-bound neutrophils and/or mononuclear leukocytes preferentially. Integrins recognizing fibronectin and laminin enable leukocyte extravasation [9,10**]. Leukocyte adhesion to and migration through the vascular endothelium result in the formation of inflammatory infiltrates within the synovium [2,4,5].

Cellular adhesion molecules and pathways in the rheumatoid synovium

Selectins contain an extracellular N-terminal domain related to lectins, an epidermal growth factor-like domain and moieties related to complement regulatory proteins [6**,7**,8,9]. This superfamily of CAMs includes E-, P- and L-selectin. Among these CAMs, E- and P-selectin are present and cytokine-inducible on endothelial cells; they are therefore markers of endothelial activation in inflammation [4,6**,7**,11]. E- and P-selectin ligands, such as E-selectin ligand (ESL)-1, P-selectin ligand (PSGL)-1 and

Table 1

Distinct steps during leukocyte emigration into the arthritic synovium

Step	Factors on endothelium	Factors on leukocytes
Rolling	P-selectin	PSGL-1
	E-selectin	ESL-1
	L-selectin ligand ?	Sialyl Lewis-X, CLA, L-selectin
Activation	Chemokines (IL-8, MCP-1), PAF PECAM-1 E-selectin	Cytokine and chemokine receptors PECAM-1 PSGL-1, ESL-1
Firm adhesion	ICAM-1, VCAM-1	β_1 , β_2 and β_7 integrins
Diapedesis	ICAM-1 VCAM-1 PECAM-1	β_1 , β_2 and β_7 integrins PECAM-1

MCP-1 = monocyte chemotactic protein-1.

cutaneous leukocyte antigen (CLA), contain sialylated glycan motifs [12–14]. E-selectin mediates the adhesion of neutrophils and, to a smaller extent, eosinophils, monocytes and some memory T cells to endothelia [15]. E-selectin has been associated with dermal and pulmonary inflammation in animal models [16,17]. We and others found an abundant expression of E-selectin in the synovial tissues [18*,19]. P-selectin is constitutively present on the membrane of endothelial Weibel–Palade bodies and is involved in neutrophil and monocyte adhesion to endothelium [6**,7**,20,21*]. Because the upregulation of P-selectin expression on endothelia occurs within seconds, this CAM is thought to be involved in the very early phases of adhesion [22]. We demonstrated P-selectin expression on RA synovial endothelial cells [23].

Integrins are $\alpha\beta$ heterodimers and are classified into families with respect to their common β subunits (β_1 – β_8) [6**,7**,8,9]. Among these CAMs, β_1 and β_3 integrins are expressed on endothelial cells. These integrins ($\alpha_{1-9}\beta_1$, $\alpha_V\beta_3$) mediate cell adhesion to ECM components, including various types of collagen, laminin, fibronectin, fibrinogen, tenascin, vitronectin and thrombospondin [6**,7**,8]. Not only are integrins involved in endothelial cell adhesion to ECM, but sometimes they are able to mediate cell–cell contacts. In the latter situation, integrins bind to CAMs belonging to the immunoglobulin superfamily. The two most relevant receptor–counter-receptor pairs are $\alpha_4\beta_1$ integrin recognizing VCAM-1 and β_2 integrins (LFA-1 and Mac-1) binding to ICAM-1 and ICAM-3 [6**,7**,24]. We and others have demonstrated the abundant expression of endothelial integrins in synovial inflammation [4,5,23–26].

Table 2**The most important leukocyte–endothelial adhesion pathways in rheumatoid arthritis**

Adhesion molecule superfamily	Receptor on endothelium	Ligand(s)
Integrin	β_1 integrins (most)	Extracellular matrix components (laminin, fibronectin, collagen, vitronectin, etc.)
	$\alpha_4\beta_1$ integrin	VCAM-1, fibronectin
	β_2 integrins (LFA-1, Mac-1)	ICAM-1, ICAM-3
	$\alpha_V\beta_3$ integrin	Extracellular matrix components (fibronectin, fibrinogen, thrombospondin)
Immunoglobulin	ICAM-1, ICAM-3	β_2 integrins: LFA-1, Mac-1
	VCAM-1	$\alpha_4\beta_1$ and $\alpha_4\beta_7$
	LFA-3	CD2
	PECAM-1 (CD31)	Homophilic, $\alpha_V\beta_3$
	CD66a–e	?
Selectin	E-selectin	ESL-1, PSGL-1, CLA
	P-selectin	PSGL-1
Other	CD44	Hyaluronic acid
	Endoglin	TGF- β
	VAP-1	?

VCAM-1, a ligand for the integrins $\alpha_4\beta_1$ and $\alpha_4\beta_7$, is constitutively expressed on resting endothelial cells but its expression is markedly upregulated by IL-1, TNF- α and IL-4 [4,27]. Abundant VCAM-1 expression has been associated with inflammatory infiltrates [28]. We and others have reported the expression of VCAM-1 on synovial endothelial cells, and also on macrophages in RA [4,18*,29].

ICAM-1 serves as a ligand for the β_2 integrins LFA-1 ($\alpha_L\beta_2$), Mac-1 ($\alpha_M\beta_2$) and p150,95 ($\alpha_X\beta_2$) [6**,7**,8,9]. ICAM-1 shows basal expression on endothelial cells; however, its expression can be further stimulated by IL-1, TNF- α and interferon- γ [30*]. *In vitro*, the maximal expression of ICAM-1 on endothelia is observed later (more than 24 h) than that of E-selectin or VCAM-1 [1]. ICAM-1 is highly expressed on endothelial cells in inflammatory sites such as the inflamed synovium *in situ* [4,16,18*].

Other CAMs mediating endothelial cell adhesion to cells in the inflamed synovium include LFA-3, PECAM-1 (CD31), CD44, CD66, vascular adhesion protein (VAP)-1, endoglin, ICAM-3 and possibly others [4,5,6**,7**,8,31–34]. LFA-3 and its counter-receptor CD2 are members of the immunoglobulin superfamily. Whereas CD2 is a T cell marker, LFA-3 is present on endothelial cells. The CD2/LFA-3 adhesion pathway is involved in various inflammatory responses including synovitis [4,31]. PECAM-1, another member of the immunoglobulin supergene family, mediates homotypic adhesion by binding to PECAM-1, and heterotypic adhesion by recognizing the

$\alpha_V\beta_3$ integrin [6**,7**,8,35]. PECAM-1 is a marker of activated endothelium; we found it in large quantities in the RA synovium [23,33]. CD44 is a receptor for hyaluronate [6**,7**,8] and is present on activated endothelial cells in inflammation including RA [23,36]. VAP-1 was originally isolated from synovial endothelial cells. The expression of VAP-1 is increased in RA [32]. Endoglin is a receptor for transforming growth factor (TGF)- β_1 and TGF- β_3 , and is involved in endothelial adhesion. We have detected endoglin on most endothelial cells in the RA synovium [34]. ICAM-3 is a leukocyte CAM that is a known ligand for LFA-1. It is absent from resting endothelial cells. However, we could detect ICAM-3 on a portion of RA synovial endothelial cells [24,37], which suggests the possible role of endothelial ICAM-3 in synovitis. Thus a number of CAMs might have a role in leukocyte–endothelial interactions underlying inflammatory synovitis.

In RA, the most important adhesive interactions between leukocytes and endothelial cells are determined by $\alpha_4\beta_1$ –VCAM-1, β_2 integrin (LFA-1, Mac-1)–ICAM-1 and CD2–LFA-3 interactions, as well as E- and P-selectins, CD44, PECAM-1 and their ligands. These adhesion pathways are summarized in Table 2.

Leukocyte–endothelial adhesion: a possible target for antirheumatic therapy

There have been several attempts to therapeutically block leukocyte adhesion to endothelium, and thus to control inflammation. Adhesion and the expression of CAMs can

be targeted with currently used antirheumatic agents, specific monoclonal antibodies, purified protein or carbohydrate ligands, soluble adhesion molecules, gene therapy or other methods [4]. Leukocyte–endothelial adhesion and adhesion molecules have been targeted *in vitro*, in animal models of arthritis, and recently in humans.

With regard to studies *in vitro*, dexamethasone (a glucocorticoid compound) and bucillamine (a D-penicillamine derivative) inhibit T cell adhesion to cultured synovial fibroblasts [38*,39]. Corticosteroids can also suppress TNF- α -induced ICAM-1 expression on these fibroblasts [40]. Gold sodium thiomalate inhibits cytokine-induced VCAM-1 and E-selectin expression on endothelia [41]. Clarithromycin markedly suppresses the upregulated expression of ICAM-1, VCAM-1 and LFA-3 on human synovial fibroblasts [42]. Purified CAM ligands such as integrin-binding peptides block cartilage chondrolysis [43*]. Antisense oligonucleotides block ICAM-1, VCAM-1 and E-selectin expression on endothelial cells [44**].

In animal models, methotrexate blocks leukocyte–endothelial adhesion and leukocyte extravasation [45]. Antibodies against ICAM-1 and the β_2 integrin subunit (CD18) inhibited leukocyte ingress into the synovium in rats, and also the development of arthritis in rats and rabbits [46,47*,48]. Anti-ICAM-1 antibody also inhibited murine collagen-induced arthritis [49]. Anti- $\alpha_4\beta_1$ integrin antibodies suppressed leukocyte migration to joints and diminished adjuvant-induced arthritis in rats [48,50*,51]. Anti-CD44 antibodies markedly decreased the severity of murine proteoglycan-induced arthritis [52,53*].

In humans, oral methoxypsoralen combined with intra-articular UV-A irradiation downregulated ICAM-1, VCAM-1 and E-selectin expression in the RA synovium [54]. Gold salts inhibited synovial E-selectin expression in RA [55]. In a recent series of studies, 32 patients with longstanding RA that had been resistant to conventional therapy were treated with anti-ICAM-1 monoclonal antibody; there was a transient improvement in the status of these patients [56**]. An even greater effect of this antibody was observed when treating 10 patients who had early or indolent RA [57]. Anti-cytokine targeting in RA might also influence the production of synovial adhesion molecules. For example, treatment of RA patients with monoclonal antibody against TNF- α resulted in decreased serum levels of soluble ICAM-1 and E-selectin in these patients [58*].

Summary

Leukocyte–endothelial adhesion has a central role in leukocyte extravasation, a key feature of inflammation including arthritis. A number of adhesion molecules, among which are integrins, selectins and immunoglobulins, act in concert and regulate the sequence of distinct steps. According to the four-step model of leukocyte–

endothelial interactions, the selectin-dependent leukocyte rolling is followed by integrin-dependent leukocyte activation, firm adhesion and then transmigration. The most important adhesive pathways are determined by receptor–ligand pairs including endothelial E- and P-selectin and their respective sialylated ligands; $\alpha_4\beta_1$ integrin and VCAM-1; and LFA-1 or Mac-1 integrin and ICAM-1. The presence of various CAM pairs and the existence of distinct steps of rolling, activation, adhesion and migration account for the diversity and specificity of leukocyte–endothelial interactions. There have been several attempts to interfere therapeutically with the cellular and molecular mechanisms described above. Most studies have been performed with animal models of various types of inflammation. A limited number of human clinical trials, such as that with anti-ICAM-1 antibody in RA, have given promising results. Specific targeting of pathological endothelial function might be useful for the future management of inflammatory arthritis.

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