Clinical significance of sCD163 and its possible role in asthma (Review)

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Abstract. Macrophages exert important functions in the balance and efficiency of immune responses, and participate in innate and adaptive immunity. The proinflammatory actions of macrophages are implicated in autoimmune diseases. Unlike classically activated M1 macrophages, the alternatively activated cluster of differentiation (CD)163$^+$ and CD206$^+$ M2 macrophages are involved in tissue repair and wound healing, and use oxidative metabolism to support their long-term functions. CD163 is a member of the scavenger receptor superfamily, categorized into class B, and its soluble(s) form, sCD163, is a marker of activated M2 macrophages. CD163 is selectively expressed in cells of the monocyte and macrophage lineages; however, its biological role has yet to be elucidated. The expression of sCD163 is markedly induced by anti-inflammatory mediators, such as glucocorticoids and interleukin-10, whereas it is inhibited by proinflammatory mediators, such as interferon-γ. These findings suggest that CD163 may serve as a potential target for the therapeutic modulation of inflammatory responses. The concentration of sCD163 in blood is associated with acute and chronic inflammatory processes in autoimmune disorders of connective tissue, fat metabolism and cardiovascular diseases, and it can be used for the assessment of cancer prognosis. A role for sCD163 in the pathogenesis of asthma has also been proposed. The present review serves to present the available knowledge concerning the implication of sCD163 in the pathophysiological mechanisms of asthma, and evaluate its potential as a biomarker and possible therapeutic target for asthma.

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Contents

1. Introduction

Macrophages are involved in several pathological conditions, including severe sepsis, autoimmune disorders, cancer and low-grade inflammatory disorders, such as metabolic syndrome, atherosclerosis and asthma. Macrophages are essential in regulating the activation and resolution of immune responses, and can influence the progression of a disease (1). Cluster of differentiation (CD)163 is a monocyte/macrophage-associated antigen that has been identified as a hemoglobin (Hb) scavenger receptor with anti-inflammatory and immunoregulatory properties. This surface receptor undergoes ectodomain shedding, triggered by an inflammatory stimulus, generating the soluble(s) form, sCD163, in plasma (2). CD163 is a scavenger receptor for the endocytosis of Hb and haptoglobin (Hp)-Hb complexes (3). It is almost exclusively expressed on monocytes and macrophages, and participates in the modulation of inflammatory responses (3,4). sCD163 is a novel marker associated with states of low-grade inflammation characteristic of conditions such as diabetes, obesity, liver disease and atherosclerosis (5).

The proteolytic cleavage of monocyte-bound CD163 by matrix metalloproteinases (MMPs), which is triggered by exposure to oxidative stress or an inflammatory stimulus, releases sCD163 (6-8). Oxidative stress pathways, induced by prostaglandin F2α (PGF2α) and 8-iso-PGF2α, enhance the expression of tumor necrosis factor (TNF)-α and CD163 (8). Lipopolysaccharide (LPS) can also increase the levels of sCD163 and TNF-α, via stimulation of a disintegrin and metalloproteinase metallopeptidase domain 17 (ADAM17), which is known to mediate the shedding of the extracellular domains of CD163 and TNF-α (9). The significant negative correlation,

which was revealed between membrane CD163 expression and sCD163 levels, suggests that plasma sCD163 may be derived from circulating monocytes, in addition to being secreted by tissue macrophages (10). sCD163 is constitutively being shed from the cell surface into the circulation, and it is stable and easily detectable in serum. The present review focuses on examining the role of sCD163 in various inflammatory disorders, including inflammatory disorders of the airways, and specifically in the pathogenesis of asthma.

2. Characteristics of M2 macrophages

Classically activated M1 macrophages are the first line of defense against bacterial infections and obtain energy through glycolysis. Cell-surface markers of classically activated macrophages are not well defined; however, CD40 is predominantly used (11,12). Conversely, alternatively activated M2 macrophages, which are $CD163^+$ and $CD206^+$, are involved in tissue repair and wound healing, and use oxidative metabolism to fuel their long-term functions. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferons (IFNs) can enhance the macrophage lineage, and modulate macrophage differentiation and function. M1 macrophages can be produced *in vitro* by culture and subsequent differentiation of human peripheral blood monocytes. The cytokines M-CSF, interleukin (IL)-4 and IL-10 stimulate monocyte differentiation into M2 macrophages (13). M1 macrophages secrete proinflammatory cytokines, such as IL-12 and TNF-α, and also have antigen-presenting capacity and promote Th1 immune responses.

Conversely, M2 macrophages secrete anti-inflammatory mediators, such as IL-10, and have poor antigen-presenting capabilities and stimulate the generation of regulatory T cells (13-15). The activation of M2 macrophages is primarily triggered by T helper (Th) 2 cytokines, such as IL-4, IL-13 and IL-10, as well as anti-inflammatory mediators, such as glucocorticoids (16). $CD163^+$ M2 macrophages reduce M1 populations through the release of anti-inflammatory cytokines, such as IL-10. Macrophage mannose receptor (MRC)-1, IL-13, IL-1 receptor antagonist (IL-1RA) and CD163 serve important roles in M2 differentiation (17). Monocyte-derived macrophages, classically activated via IFN-γ priming and LPS stimulation, demonstrate a decreased CD163 expression; however, the alternative activation route, involving IL-4/IL-13 priming, does not affect the expression of CD163 and calprotectin on macrophages (18). The presence of IFN-γ, indicative of Th1 inflammation, or a prolonged exposure to IL-4, promotes apoptosis of macrophages and suppresses M2 differentiation, which leads to a reduction in the clearance of apoptotic neutrophils, increased accumulation of apoptotic cells and persistent inflammation (19). Conversely, in the presence of IL-17, indicative of a Th17 response, macrophage apoptosis is prevented and M2 differentiation is stimulated, which ensures that apoptotic neutrophils are cleared efficiently and anti-inflammatory conditions are restored (Fig. 1) (19). Following IL-4 or IL-13 stimulation, M2 macrophages derived from peripheral blood mononuclear cells exhibit markedly increased mRNA expression levels of thymus activation regulating chemokine (CCL) 11, CCL17, CCL24 and CCL26, and the production of CCL17 and CCL24 is also potentiated (20).

3. CD163 structure

CD163 is a 130-kDa, type I transmembrane protein, which belongs to class B of the cysteine-rich scavenger receptor family, and was first identified in 1987 (21). The expression of CD163 on circulating monocytes and most tissue macrophages is constitutive and/or induced by some stimuli (22). CD163 has been reported to bind human pathogenic bacteria (10,23) and TNF-α-like weak inducer of apoptosis (TWEAK) (24). Using western blot analysis of CD163 variants, a panel of 10 monoclonal antibodies was mapped to scavenger receptor cysteine-rich (SRCR) domains 1, 3, 4, 6, 7 and 9 (25). Four of the SRCR domains of CD163 (domains 2, 3, 7 and 9) have conserved consensus motifs for Ca^{2+} binding, whereas domain 5 has a potentially/semi-conserved Ca^{2+} binding site. The other four SRCR domains have at least one non-conservative mutation of an essential residue in the consensus Ca^{2+} binding sequences (26).

Only the two antibodies targeting SRCR domain 3 can effectively inhibit ligand binding. This is an exposed domain and a critical factor regulating the Ca^{2+}-sensitive coupling of Hp-Hb complexes (25). Since CD163 is a scavenger receptor on the surface of macrophages, its extracellular region, consisting of nine SRCR domains, can be stimulated by inflammation or other stimuli, resulting in the release of its soluble form, sCD163, in the plasma (22,25). Ligands of Toll-like receptors (TLR) 2, 4 and 5 can stimulate ectodomain shedding of CD163, thereby releasing sCD163 (3). CD163 and pro-TNF-α are transmembrane proteins subjected to hydrolytic cleavage by the inflammation-responsive proteases ADAM17 (23,27) and ADAM10 (23) from the monocyte surface. This results in the release of sCD163 and bioactive TNF-α in the circulation. A sequence comparison of their juxtamembrane region identified similar palindromic sequences in human CD163 (1044Arg-Ser-Ser-Arg) and pro-TNF-α (78Arg-Ser-Ser-Ser-Arg) (Fig. 2) (27).

sCD163 and immunoglobulin G interact with the free Hb in plasma, leading to the endocytosis of the sCD163-Hb-IgG complex via the Fcγ receptor (FcγR) into monocytes. The endocytosed sCD163 is recycled to restore the homeostasis of CD163 on the monocyte membrane, whereas the internalized Hb is catabolized (28). Paracrine transactivation of endothelial cells is mediated by the shed sCD163, which detoxifies and clears residual Hb. Circulating sCD163 only weakly competes with membrane CD163 for the uptake of Hp-Hb complexes, and Hp-Hb saturation of sCD163 in serum can only be achieved with a large surplus of Hp-Hb complex. These findings indicated that the Hp-Hb complex may be harder to dissociate from the membrane form of CD163 (Fig. 3) (29).

4. sCD163 expression

CD163 is expressed only on cells of the monocytic-macrophage lineage, and its expression increases as monocytes mature into macrophages. CD163 expression is particularly high on macrophages in the liver (Kupffer cells), red pulp of the spleen, lungs and bone marrow (21). sCD163 is a marker of activated macrophages (30). Following an inflammatory stimulus or oxidative stress, sCD163 is released from the cell surface by proteolytic cleavage of monocyte-bound CD163 through

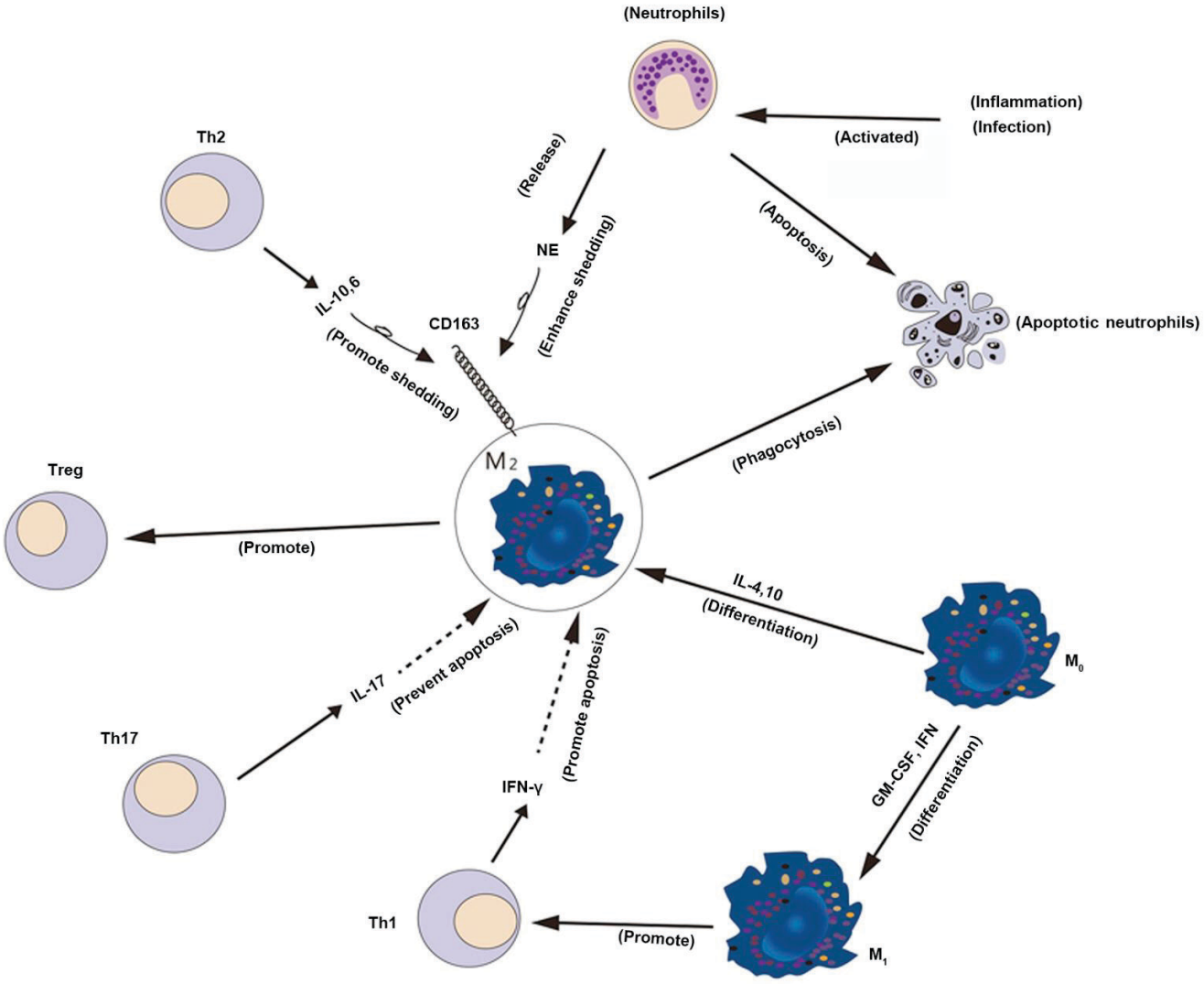

Figure 1. Macrophages serve a key role in regulating the activation and resolution of immune responses. The induction of M0 macrophages by inflammatory mediators, such as IL-4 and IL-10, results in the differentiation of M2 macrophages. IL-17 (in a Th17 environment) prevents macrophage apoptosis, whereas IFN-γ (during Th1 inflammation) promotes apoptosis of macrophages. NE stimulates CD163 shedding, a marker of M2 macrophage activation. Macrophages effectively eliminate apoptotic neutrophils via phagocytosis. IL, interleukin; Th, T helper; IFN, interferon; NE, neutrophil elastase; CD, cluster of differentiation; Treg, T regulatory.

the action of MMPs (6-8) and after LPS stimulation (22,31), whereas proinflammatory cytokines, such as TNF, reduce CD163 expression (3). Furthermore, TLR7 levels have been associated with concentrations of IL-10, IL-1RA and CD163 (32).

The expression of CD163 is induced by corticosteroids (3,33-35), IL-10 (3,22,33-35), IL-6 (12,34,36), IL-12 (37), the chemokine (C-X-C motif) ligand (CXCL)-10 (37), and oxidative stress (8). sCD163 protects monocytes from hyperactivation during bacterial infections by dampening the secretion of the proinflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8 (38). The actions of sCD163 and TNF-α seem to be interconnected, and the sCD163/TNF-α ratio is higher in patients with uncomplicated malaria (39). *In vitro*, stimulation of murine monocyte-macrophage cells resulted in increased TNF-α release accompanied by elevated CD163 expression (17). In patients with cirrhosis and hepatitis C infection, sCD163 also appears significantly correlated with TNF-α (40).

5. Clinical significance of sCD163 expression

Elevated sCD163 serum levels are currently the most specific marker for distinguishing bacterial infections, such as brucellosis, or those caused by *Staphylococcus aureus* and *Haemophilus influenzae* (41,42), from non-bacterial infections, based on previously described results comparing lumbar puncture with composite reference standards (43). sCD163 expression is correlated with levels of IL-6 (21,41), IL-10 and IL-8 (44), but not with LPS-binding protein, procalcitonin (PCT) or C-reactive protein (CRP) levels (41). Plasma levels of CRP, PCT and sCD163 are increased in patients with bacterial infections (45). CRP and PCT are also valuable diagnostic tools and can be used as markers of bacterial infections. In patients with sepsis, sCD163 levels were significantly lower than in patients with severe sepsis; however, sCD163 levels in both groups were considerably increased compared with in the control group (46,47). Furthermore, higher sCD163 levels were reported in patients with sepsis who succumbed compared

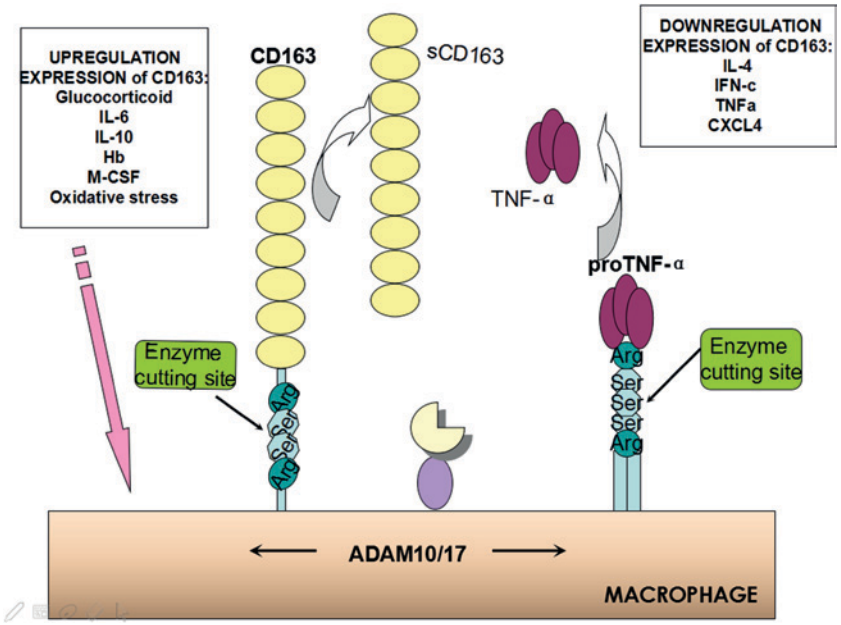

Figure 2. Shedding of sCD163. Several inflammatory signals have been demonstrated to induce ectodomain shedding of sCD163 *in vitro*. ADAM17/10 mediates shedding of CD163 and TNF-α upon stimulation by inflammatory stimuli. CD163 and pro-TNF-α are rapidly cleaved from the surface of activated macrophages by an ADAM17/10-mediated mechanism. The half-life of sCD163 is much longer than that of TNF-α. Similar palindromic sequences in human CD163 (1044Arg-Ser-Ser-Arg) and pro-TNF-α (78Arg-Ser-Ser-Ser-Arg) were identified by a comparison of the sequences of the juxtamembrane region of the proteins. s, soluble; CD, cluster of differentiation; ADAM, a disintegrin and metalloproteinase; TNF, tumor necrosis factor; IL, interleukin; Hb, hemoglobin; M-CSF, macrophage-colony stimulating factor; IFN, interferon; LPS, lipopolysaccharide; CXCL, (C-X-C motif) ligand.

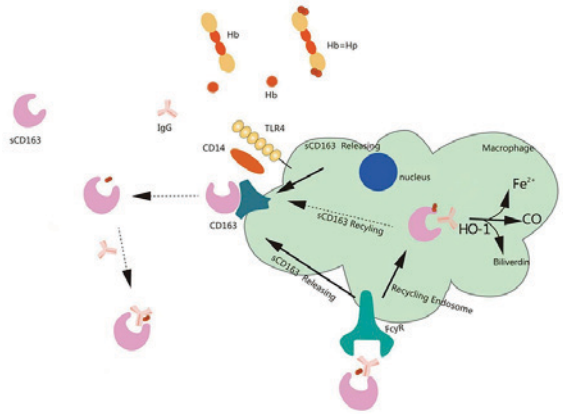

Figure 3. A hypothetical model of Hp-independent intravascular detoxification and clearance of cell-free Hb by CD163. Hb induces shedding of CD163 into the plasma and the produced sCD163 captures and quenches the residual redox-reactive Hb. Subsequently, IgG interacts with the sCD163-Hb complex. The sCD163-Hb-IgG complex then elicits an autocrine loop of endocytosis via FcγR on monocytes and subsequent recycling of the internalized sCD163 via endosomes to restore CD163 homeostasis in the membrane, whereas the internalized Hb is catabolized by HO-1. Hp, haptoglobin; Hb, hemoglobin; CD, cluster of differentiation; s, soluble; Ig, immunoglobulin; FcγR, Fcγ receptor; HO, heme oxygenase; TLR, Toll-like receptor.

with in surviving patients (46-48). MRC and sCD163 expression is markedly increased in septic patients compared with in non-septic patients and healthy controls (48). Increases in serum sCD163 levels were delayed in animals that were infected with virulent strains of *Haemophilus parasuis* (44).

sCD163 serum levels are elevated in patients with acute and chronic liver diseases. In patients with cirrhosis, sCD163 concentration is ~3 times higher compared with in healthy controls (49,50). In addition, although sCD163 is linearly associated with the pressure gradient in the portal vein, its concentration remained unaltered after a transjugular intrahepatic portosystemic shunt procedure (51). High sCD163 serum levels are considered an independent risk factor for variceal/gastrointestinal bleeding, portal hypertension and mortality in patients with cirrhosis (49,52,53). High serum sCD163 concentrations have been reported during acute liver damage, but are lower in acute hepatitis; however, in both conditions, they are higher than those reported in patients with chronic hepatitis (12,26,30). Hepatitis B infection is characterized by higher serum sCD163 levels when compared with hepatitis C, particularly when accompanied by liver fibrosis (40,54), whereas higher serum sCD163 concentrations have been associated with higher mortality (55,56).

sCD163 is also associated with obesity, insulin resistance, and the development of type 2 diabetes (57-59). In patients with type 2 diabetes, sCD163 appears strongly associated with known risk factors, such as physical inactivity, body mass index, elevated CRP levels and triglyceride content (60). High serum sCD163 levels have been associated with complications in patients with type 2 and type 1 diabetes mellitus (59,61); conversely, levels of soluble TWEAK, a cytokine that regulates inflammation, angiogenesis and tissue remodeling, follow an opposite trend (61). Serum sCD163 levels are significantly higher in obese patients compared with in lean patients, whereas efferocytosis by M2 macrophages appears to be impaired in obese patients (61-63). A low-fat diet reduced the levels of sCD163 (64,65); however, a 12-week exercise program had no such effect (66).

sCD163 has been associated with arterial inflammation, non-calcified plaque formation, perivascular fat accumulation and carotid atherosclerosis (67,68). Neutrophil elastase has been demonstrated to promote CD163 shedding, and CD163

Table I. Expression of sCD163 in different diseases and its clinical significance.

Disease	sCD163 concentration	Clinical significance	(Refs.)
Acute respiratory distress syndrome (mean)	>1,020 ng/ml	Associated with increased risk of mortality	(2)
Cirrhosis (mean ± SD)	4.7±2.5 mg/l	Associated with gastrointestinal bleeding, hepatic venous pressure gradient	(49)
Controls	1.6±0.5 mg/l		
Systemic sclerosis	984±420 ng/ml	Associated with greater skin involvement	(70)
Controls (mean ± SD)	823±331 ng/ml		
Early rheumatoid arthritis [median (IQR)]	1.69 (1.42-2.10) mg/l	Associated with disease activity	(76)
Epithelial ovarian cancers	3,220 ng/ml	Used in diagnosis; associated with poor prognostic factors	(81)
Controls (mean)	2,488 ng/ml		
Type 1 diabetes mellitus [median (IQR)]	285.0 (247.7-357.1) ng/ml	Associated with cardiovascular risk	(61)
Controls	224.8 (193.3-296.5) ng/ml		
Sepsis (mean ± SD)	105.32±145.87 mg/l	Associated with poor prognosis	(46)
Severe sepsis	233.32±171.78 mg/l		
Control group	44.19±86.48 mg/l		
Obese [median (IQR)]	974 (657-1,272) ng/ml	Used as a marker for predicting the risk of insulin resistance	(58)
Normal weight controls			
Allergic asthma (serum) (mean ± SD)	599 (423-892) ng/ml		
Controls (serum)	1,030±499 ng/ml	Associated with anti-inflammatory effects of inhaled corticosteroid therapy	(33)
Allergic asthma (sputum)			
Controls (sputum)	930±334.5 ng/ml		
	4.78±3.34 ng/ml		
	1.8±0.41 ng/ml		

IQR, interquartile range; SD, standard deviation.

expression on the surfaces of macrophages was decreased, resulting in impaired of Hb clearance by macrophages. These effects may be correlated with acute coronary syndrome and stable angina pectoris, and may increase the risk of myocardial infarction (69). It has been demonstrated that CD163 can bind and neutralize TWEAK (70), whereas sCD163 functions as a decoy receptor for TWEAK. An imbalance between TWEAK and CD163 could reflect the progression of atherosclerosis. Furthermore, the CD163/TWEAK plasma ratio may have potential as a biomarker of atherosclerosis in asymptomatic individuals (71). Substantially elevated sCD163/sTWEAK ratios have been reported in patients with critical limb ischemia and peripheral artery disease (72,73).

Serum sCD163 levels were estimated in patients with systemic sclerosis (SSc) as an indicator of disease deterioration, pulmonary fibrosis and pulmonary hypertension (4,6,74,75). sCD163 levels and the sCD163/sTWEAK ratio were significantly increased in patients with SSc compared with in controls. Elevated plasma sCD163 and an increased sCD163/sTWEAK ratio were associated with a lower risk of digital ulcers in patients with SSc (70).

Early rheumatoid arthritis (RA) patients have significantly increased sCD163 plasma levels, which are reduced following treatment. Therefore it may be hypothesized that sCD163 is implicated in RA activity, although an association between sCD163 and disease activity has yet to be demonstrated (37,76). sCD163 shed from resident tissue macrophages were abundant in inflamed synovium (77). In addition, sCD163 levels have been correlated with the Systemic Lupus Erythematosus Disease Activity Index (78). Patients with elevated serum sCD163 levels exhibit significantly higher rates of anti-double-strand-DNA antibodies (79).

Macrophages serve key roles in tumor development and invasion in several types of human cancer, and sCD163 is a marker of alternatively activated M2 macrophages. High sCD163 concentrations have been detected in hepatocellular carcinoma (80), ovarian cancer (81,82), T cell lymphoma (83) and multiple myeloma (84). Furthermore, elevated sCD163 concentrations are associated with a poor prognosis in patients with cancer (40,81-83).

In conclusion, sCD163 levels in infection, liver disease, autoimmune disorders, metabolic disease and cancer are elevated, whereas the clinical significance of this elevation varies among the various diseases (Table I).

6. CD163-deficient animal model

House dust mite (HDM)-challenged $Cd163^{-/-}$ mice have been reported to exhibit increased concentrations of airway eosinophils and develop mucous cell metaplasia (85). In addition, $Cd163^{-/-}$ mice may demonstrate transiently elevated TWEAK levels, which can stimulate muscle satellite cell proliferation and tissue regeneration in ischemic and non-ischemic limbs. These results suggested a role for sCD163 in muscle regeneration following ischemic injury (86). In CD163-deficient mice, the overall clearance of Hb has been demonstrated

to be slightly impaired and follow a one-phase decaying trend (87).

7. Functions of macrophages and potential role of CD163 in asthma

Macrophages have a central role in the regulation and efficiency of the immune response, and participate in innate and adaptive immunity. Macrophages exert important functions in autoimmune disorders, including RA, Crohn's disease, psoriasis, sarcoidosis and atherosclerosis. M2 macrophages are associated with responses to anti-inflammatory stimuli and tissue remodeling (88). Since they participate in tissue repair and in the restoration of lung microenvironment homeostasis, M2 macrophages may serve a major role in asthma (89). Macrophages represent the majority of immune cells present in lungs under physiological conditions and serve to dictate the innate defense mechanisms of the airways. Pulmonary macrophage populations are heterogeneous and demonstrate notable plasticity, due to variations in their origin, tissue residency and environmental influences (90). In mice with moderately severe asthma, the population of M1 macrophages is elevated and negatively correlated with the population of M2 ($CD163^+$) macrophages. Decreased numbers of M2-like macrophages are reported after HDM exposure, and they are negatively correlated with the number of M1 macrophages (88). In addition, macrophages have been implicated in the pathogenesis of chronic obstructive pulmonary disease (COPD). Ex-smokers with COPD have a higher percentage of $CD163^+$ macrophages in bronchoalveolar lavage (BAL) than current smokers. Furthermore, the percentage of $CD163^+$ M2 macrophages is higher in BAL than in sputum (91). In ovalbumin (OVA)-sensitized mice, exposure to the airborne particulate matter PM2.5 caused a slight increase in the number of neutrophils and macrophages (92). The balance between macrophage phenotypes fluctuates, depending on the severity of allergic airway inflammation (88). This balance is regulated by cytokines, such as IL-13, which is a typical pro-M2-Th2 cytokine that has been linked to allergic diseases and asthma. MicroRNA (miR)-155 may also be involved in regulation of the M1/M2 balance via modulating the effects of IL-13. miR-155 directly targets the IL-13RA1 gene and reduces the protein levels of IL-13RA1, thus preventing the activation of the signal transducer and activator of transcription (STAT) 6 (93).

Serum amyloid P (SAP) inhibits the generation of M2 markers, such as arginase and the chitinase Ym-1, through an FcγR-dependent mechanism in cultured macrophages. This effect has been correlated with a decrease in STAT6 phosphorylation in SAP-treated M2 macrophages (94). Type 2 cytokines, i.e. IL-4 and IL-13, can drive the differentiation of macrophages into M2 macrophages. This population of macrophages is associated with allergic inflammation (95). Monocytes co-cultured with regulatory T cells display typical features of alternatively activated macrophages, including upregulated expression of CD206 (macrophage mannose receptor) and CD163, and increased production of CCL18 (96). OVA-sensitized and challenged mice exhibit a significant increase in white blood cells, eosinophilia, mucus accumulation and goblet cell hyperplasia, which were correlated with increased expression of genes associated with alternatively activated M2 macrophages, such as arginase 1, Ym-1, Ym-2, resistin like-α, and eosinophil-associated, ribonuclease A family member 11. The expression of other genes associated with asthma, including FcγRIIb, MMP-14, CCL-8, CCL-17 (20,97), ADAM-8, lymphotoxin β receptor 1 (LTβR1), aquaporin-9 and IL-7R, is also upregulated in bronchoalveolar macrophages isolated from OVA-sensitized/challenged mice compared with in macrophages from healthy controls (97).

CD163 participates in inflammatory responses and may contribute to connective tissue remodeling. CD163 may function as a pulmonary defense element, as suggested by its local expression in the lungs, and its secretion during lung infection and as part of inflammatory respiratory responses (98). Cell surface expression of CD163 on alveolar macrophages is reduced in human subjects with asthma, which suggests that CD163 may participate in the regulation of airway inflammatory responses in the lung (85). In addition, sCD163 is inversely associated with predicted forced expiratory volume in 1 sec in patients with asthma (9) and COPD, particularly in those with severe disease (94). During *Dermatophagoides pteronyssinus* (Dp)-induced bronchoconstriction, alterations in monocyte CD163 expression and sCD163 were negatively correlated with fractional exhaled nitric oxide concentrations (99). Asthma in obese adults has been associated with impaired macrophage efferocytosis. This impairment is associated with altered monocyte programming, impaired response to glucocorticoids and systemic oxidative stress (62). Obese asthmatic children exhibit increased sCD163 expression, in addition to sex-specific macrophage activation, which may impair asthma control and lung function (9). Furthermore, sCD163 concentration in sputum is significantly higher in patients with allergic asthma compared with in controls. Treatment with inhaled corticosteroids results in a significant increase in sCD163 concentrations in sputum (33). Macrophages isolated from sputum samples from patients with asthma demonstrate significantly higher CCL17 and lower CD163 mRNA expression levels compared with macrophages from healthy subjects (100). $CD163^+$ alveolar macrophages were decreased in patients with asthma (85), whereas sputum sCD163 levels were increased (33). This inverse relationship between surface and soluble CD163 has already been described (44). Therefore, we speculate that airway inflammation and some inflammatory mediators induce alveolar macrophages to release CD163 from the cell surface in patients with asthma, and sCD163 participates in the airway inflammatory response, and the phagocytosis of $CD163^+$ M2 macrophages is impaired in asthma.

8. Conclusion

Macrophages serve a key role in the regulation of immunity and tissue remodeling. CD163, which is a transmembrane scavenger receptor found on the surface of macrophages, is released in the circulation in its soluble form, sCD163, via cleavage by MMPs following oxidative stress or inflammatory stimuli. sCD163 is involved in the pathogenesis of autoimmune diseases, atherosclerosis, diabetes and cancer. Bronchial asthma is characterized by nonspecific inflammation of the airways, and the alternatively activated $CD163^+$ M2 macrophages have a key role in this pathological condition. Through phagocytosis and the subsequent release of biologically active substances, neutrophils participate in defense mechanisms of the airways. After completing their mission, neutrophils undergo apoptosis.

Macrophages effectively eliminate apoptotic neutrophils, a process critical in suppressing acute inflammation and restoring homeostasis. Neutrophil elastase has been revealed to enhance CD163 shedding, and sCD163 is a marker of macrophage activation. Neutrophil elastase serves as a neutrophil activation marker, which suggests that macrophage activation is associated with the activation of neutrophils. A Th1/Th2 imbalance has been suggested as an indicator of the pathogenesis of asthma. Th2 cytokines, such as IL-4, IL-13 and IL-10, can influence M2 macrophage activation. IL-10 and IL-6 promote sCD163 shedding from M2 macrophages, whereas release of Th17 and IL-17 can inhibit the apoptosis of $CD163^+$ M2 macrophages. In addition, M2 macrophages are associated with T lymphocytes. IL-4 and IL-13 can stimulate eosinophil activation. sCD163, a marker of M2 macrophages, is associated with the eosinophil count through several cytokines. Furthermore, sCD163 is associated with body mass index in patients with asthma, and the concentration of sCD163 in plasma or induced sputum is inversely correlated to predicted forced expiratory volume in 1 sec. Therefore, investigating the role of sCD163 may contribute to elucidating the underlying molecular mechanisms of asthma, and may represent a promising target for the development of effective therapeutic agents for the treatment of asthma.

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