



Review

ICAM-1 signaling in endothelial cells

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Abstract:

Intercellular adhesion molecule-1 (ICAM-1; CD54) is a 90 kDa member of the immunoglobulin (Ig) superfamily and is critical for the firm arrest and transmigration of leukocytes out of blood vessels and into tissues. ICAM-1 is constitutively present on endothelial cells, but its expression is increased by proinflammatory cytokines. The endothelial expression of ICAM-1 is increased in atherosclerotic and transplant-associated atherosclerotic tissue and in animal models of atherosclerosis. Additionally, ICAM-1 has been implicated in the progression of autoimmune diseases.

We and others have shown that the ligation of ICAM-1 on the surface of endothelial or smooth muscle cells with monoclonal antibodies, *via* its main leukocyte ligand, lymphocyte function associated molecule (LFA)-1, or with antibodies derived from patient serum, leads to the activation of several proinflammatory signaling cascades, and to the rearrangement of the actin cytoskeleton.

A circulating or soluble form of ICAM-1 (sICAM-1) has been measured in various body fluids, with elevated levels being observed in patients with atherosclerosis, heart failure, coronary artery disease and transplant vasculopathy. sICAM-1 has signaling properties in several cell types, including EC, and invokes a range of proinflammatory responses.

Thus, we propose that in addition to acting as a leukocyte adhesion molecule, ICAM-1 directly contributes to inflammatory responses within the blood vessel wall by increasing endothelial cell activation and augmenting atherosclerotic plaque formation.

Key words:

intercellular adhesion molecule-1, endothelial cells, inflammation, atherosclerosis, trans-endothelial migration, antibodies, soluble adhesion molecules, cell signaling

Abbreviations: APC – antigen presenting cell, BMVEC – bovine microvascular endothelial cells, EC – endothelial cells, ERM – ezrin/radixin/moesin, FAK – focal adhesion kinase, GDI – guanine nucleotide exchange inhibitors, HUVEC – human umbilical vein endothelial cells, HSVEC – human saphenous vein endothelial cells, ICAM – intercellular adhesion molecule, Ig – immunoglobulin, IL – interleukin, JAM – junctional adhesion molecule, LFA – lymphocyte function associated molecule, MADCAM – mucosal addressin cell adhesion molecule, MAPK – mitogen activated protein kinase, MCP – monocyte chemoattractant protein, M-CSF – macrophage colony stimulating factor, MHC – major histocompatibility complex, MIP – macrophage inflammatory protein, MMP – matrix metalloproteinase, PECAM – platelet/endothelial cell adhesion molecule, PKC – protein kinase C, PLC – phospholipase C, PSGL-1 – P-selectin-glycoprotein ligand, RANTES – regulated upon activation, normal T-cell expressed, and secreted,

SHP – Src-homology domain 2 containing phosphatase, TACE – TNF α converting enzyme, TCR – T-cell receptor, VCAM – vascular cell adhesion molecule, VLA – very late antigen, VSMC – vascular smooth muscle cells

Introduction

Intercellular adhesion molecule (ICAM)-1 is an immunoglobulin (Ig)-like cell adhesion molecule expressed by several cell types including leukocytes and endothelial cells. ICAM-1 is present in atherosclerotic lesions and is involved in their progression. A soluble

form of ICAM-1 (sICAM-1) has been found in plasma. sICAM-1 levels are elevated in the serum of patients with cardiovascular disease, autoimmune disorders, as well as cancer, and several studies have correlated serum levels of sICAM-1 with the severity of these diseases.

Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in large arteries [52], and it increasingly threatens human health worldwide [30]. Various risk factors have been identified that contribute to the pathogenesis of atherosclerosis, including hypertension, smoking, increased concentrations of plasma cholesterol, diabetes, obesity, age and male gender [52]. All of these risk factors can influence endothelial cell function [2] resulting in their increased permeability, the increased adhesion of leukocytes and the expression of procoagulant molecules.

The formation of atherosclerotic lesions is a complex process, which often proceeds over decades. A number of different factors contribute to the formation of atherosclerotic lesions [52, 73]. The “response to injury” hypothesis first proposed by Ross and Glomset [74], and the more recent “response to retention” hypothesis [79] both propose that the earliest events in atherogenesis are part of an inflammatory response [100]. Thus, the earliest fatty streak lesions are formed after an initial insult to the EC (e.g., smoking, poor diet, genetic factors, high blood pressure, or infection [82]) that leads to the activation of the endothelium and to elevated levels of adhesion molecules [13, 61, 93]. This process facilitates the infiltration of atherogenic lipoproteins, and the entry of monocytes and T-cells into the sub-endothelial space. Upon transmigration, monocytes differentiate into macrophages under the influence of macrophage-colony stimulating factor (M-CSF), which is produced by the EC and the underlying vascular smooth muscle cells (VSMC). Lipid accumulation leads to macrophage activation and foam cell formation. VSMC migrate into the developing neointima where they take on a proliferative phenotype, which expresses growth factors and adhesion molecules and contributes to the retention of migrated macrophages and T-cells in the intima.

level of glycosylation. Unglycosylated ICAM-1 has a molecular weight of 60 kDa [91]. The extracellular portion of ICAM-1 consists of 453 mainly hydrophobic amino acids, which form five immunoglobulin (Ig)-like domains. The extracellular region is attached to a single hydrophobic transmembrane region (24 residues) and a short cytoplasmic tail (28 residues). Each Ig domain has a β -sheet structure, which is stabilized by disulfide bonds [83, 91]. The cytoplasmic tail lacks classical signaling motifs [83], but has one tyrosine residue, which may be important for signaling [88]. The gene sequence of ICAM-1 consists of seven exons, which are separated by six introns. Exon 1 encodes the signal sequence, exons 2–6 each encode one of the five extracellular domains, and exon 7 encodes for the transmembrane region and cytoplasmic tail [91, 102] (Fig. 1).

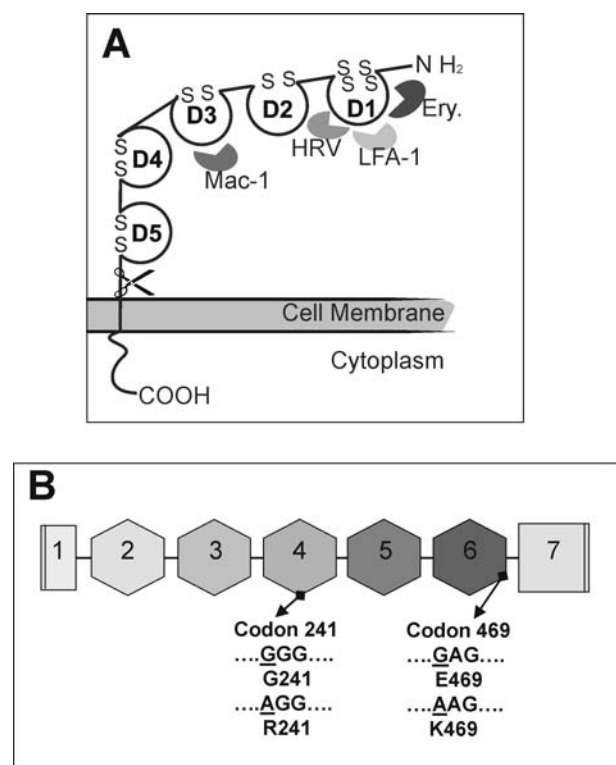


Fig. 1. A cartoon depicting (A) ICAM-1 with its five Ig-domains (D1-D5) and ligands LFA-1, Mac-1, *Plasmodium falciparum* erythrocyte membrane protein-1 (PfEMP-1) and human rhinovirus (HRV). The scissors represent the generation of sICAM-1 by cleavage of ICAM-1's extracellular domain from the cell surface, possibly by means of a matrix metalloproteinase related to TACE or an elastase. (B) A diagram of the ICAM-1 gene showing the exons that code for each Ig-like domain and the polymorphic base pairs giving rise to amino acid substitutions in the third and fourth Ig-like domains

ICAM-1

ICAM-1 is a type I transmembrane protein with a molecular weight of 80–114 kDa [91] depending on its

Two single nucleotide polymorphisms have been described within the exons that encode the extracellular domains of the ICAM-1 gene [96]. The first polymorphic residue, encoded on exon 4, substitutes the amino acid residue at position 241 from glycine to arginine (G241R), while the second polymorphic site is amino acid residue 469 on the fifth domain, which is encoded by exon 6, and changes glutamic acid to lysine (E469K) (Fig. 1). Domain 5 does not contain any known ligand binding sites. However, the fifth domain is involved in the stabilizing the structure of ICAM-1 and this substitution could influence ligand binding [35]. The substitution from glutamic acid to lysine has been associated with coronary heart disease, myocardial infarction [35] and peripheral artery disease [20]. These results need to be confirmed by larger studies.

Several ligands for ICAM-1 have been identified, including the membrane bound $\beta 2$ integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) on leukocytes [56, 80, 84], fibrinogen [39, 40], rhinoviruses [28, 57, 85] and *Plasmodium falciparum*-infected erythrocytes [62].

ICAM-1's function

ICAM-1 plays an important role in both innate and adaptive immune responses. It is involved in the trans-

endothelial migration of leukocytes to sites of inflammation, as well as interactions between antigen presenting cells (APC) and T cells (immunological synapse formation).

Trans-endothelial migration can be divided into four sequential, but overlapping steps summarized in Figure 2 (for reviews see [81, 95]).

Step 1: involves the rolling and tethering of leukocytes, facilitated by interactions between selectins and the sialylated carbohydrate portion of E- and P-selectin, both of which are present on the endothelium, and bind to carbohydrate structures closely related to sialyl lewis^x on leukocytes. P-selectin also binds to P-selectin-glycoprotein ligand (PSGL)-1. L-Selectin, which is present on all circulating leukocytes, binds to CD34, PSGL-1 and sialyl lewis^x present on EC. This step prolongs contact with the blood vessel wall and enhances exposure to chemokines including MCP-1, IL-8, RANTES and MIP-1 α/β [81].

Step 2: Chemokines are necessary for the activation of integrins on the leukocyte cell surface and to direct the migration of leukocytes. Integrins, which are present on leukocytes in an inactive form, undergo a conformational change upon cell activation, which leads to increased adhesion to their ligands [81].

Step 3: Once firmly attached, leukocytes spread and slowly migrate over the endothelium. Arrested, activated leukocytes adhere firmly to the endothelium *via* LFA-1/ICAM-1, VLA-4/VCAM-1 and $\alpha 4\beta 7$ /MAD-

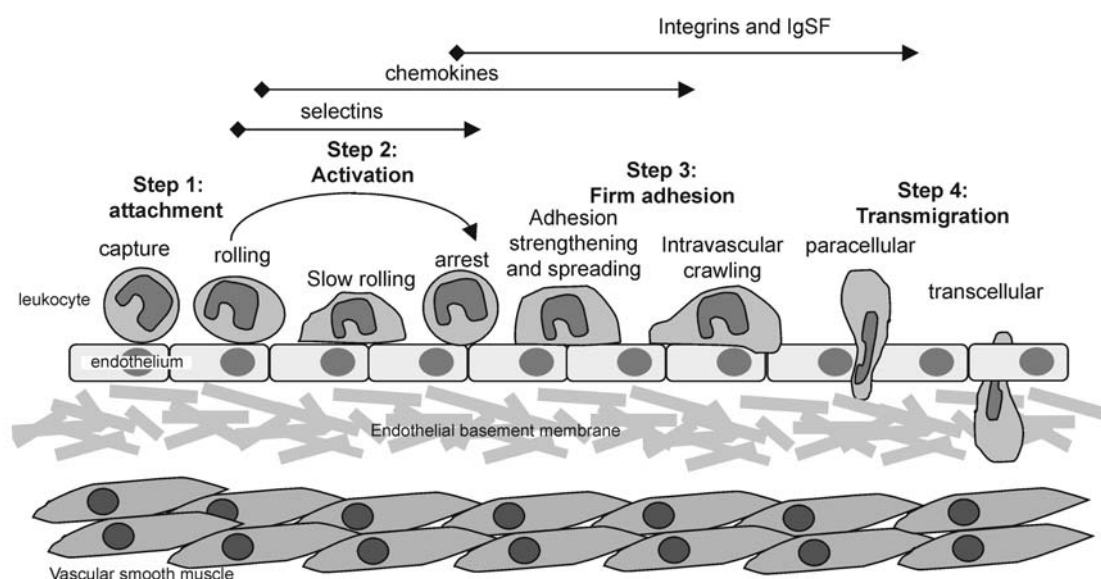


Fig. 2. A cartoon depicting the transendothelial migration of leukocytes into sub-endothelial space (adapted from [48, 81])

CAM-1. A number of studies have demonstrated the importance of ICAM-1 for the initial steps of the transendothelial cell migration process by using anti-ICAM-1 antibodies or an ICAM-1-deficient endothelium [27, 46, 69].

Step 4: Leukocytes migrate through the endothelial cell barrier into the sub-endothelial space [81]. Several junctional proteins are located at endothelial cell : cell junctions including platelet endothelial cell adhesion molecule (PECAM)-1, VE-cadherin, junctional adhesion molecules (JAMs) and CD99 (reviewed in [48]). The firm adhesion of leukocytes to the endothelium *via* ICAM-1 triggers increased intracellular Ca^{2+} , the activation of p38 and Rho, while VCAM-1 binding leads to rac1 activation. The activation of these signaling molecules is thought to facilitate transmigration by triggering EC contraction and by weakening the bonds of the junctional adhesion molecules. However, the exact mechanisms by which leukocytes migrate across the EC monolayer have not been completely delineated (reviewed in [90]).

Recent studies have identified microvilli-like projections on leukocytes called podosomes or migratory cups, which contain F-actin surrounded by a ring of $\beta 2$ and $\beta 3$ integrins, talin and vinculin that requires src-kinase activity and the presence of the GTPase regulator protein, Wiskott-Aldrich syndrome protein (WASp) to function [8, 49]. Migratory cups on EC are rich in the adhesion molecules ICAM-1 and VCAM-1, as well as ezrin/radixin/moesin (ERM), and cytoskeletal proteins [3]. These projections, which were first thought to act as “docking stations” by facilitating the firm arrest of leukocytes, are now thought to initiate the leukocytes’ transmigratory process and guide them *via* a paracellular or transcellular route [8, 9].

Immunological synapse formation is a multistage process with three major steps: junction formation, reorganization and stable immunological complex formation [25]. During junction formation the binding of ICAM-1 with LFA-1 facilitates close contact between the APC and T-cells and enables the interaction of the T-cell receptor (TCR) with the MHC-peptide complex. Following the interaction of the TCR and MHC complex, signaling events are triggered. If high affinity interactions between T-cells and APC occur, the reorganization of cell surface molecules is initiated to allow for sustained signaling. During the reorganization process ICAM-1/LFA-1 complexes move outward to form a circle around the inward moving TCR/MHC-complex. In the final stage, there is a sharp

division with all the TCR/MHC-complexes located in the center surrounded by a peripheral ring of ICAM-1/LFA-1 molecules. The polymerization of ICAM-1 on the cell surface enables not only high affinity binding to LFA-1, but also allows a ring of ICAM-1/LFA-1 molecules to form around the TCR/MHC-complexes, which concentrates the TCR/MHC-complexes inside the circle and leads to a strong APC-T-cell interaction that facilitates optimal communication [25, 102]. Recent studies also suggest that ICAM-1 functions as a costimulatory ligand during MHC class-I or MHC class-II restricted antigen presentation [21].

ICAM-1 mediated signal transduction and gene expression

The capability of ICAM-1 to transduce signals “outside in” was identified several years ago [14, 75]. As ICAM-1 signaling occurs by receptor multimerization, *in vitro* studies have used either co-cultures of EC with leukocytes, immobilized fibrinogen or antibody cross-linking to elicit a signaling response. The cytoplasmic tail of ICAM-1 is only 28 amino acids long and lacks any known intrinsic kinase activity or protein-protein interaction domains through which ICAM-1 could recruit downstream signaling molecules. However, it has a high number of positively charged amino acids and one tyrosine residue (Y512) [53]. Various signaling molecules and adapter proteins have been linked with the ICAM-1 signaling cascade *in vitro*, depending on cell lineage (i.e., the particular vascular bed from which the EC were taken) and the experimental model. In particular, molecules that link to the actin-cytoskeleton have been associated with ICAM-1 ligation, including α -actinin [10], ERM proteins [31, 87, 101], cortactin [14], β -tubulin and glyceraldehyde-3-phosphate dehydrogenase [18]. Pluskota et al. [67, 68] reported that the Src-homology domain 2 bound in a phosphotyrosine dependent manner when EC were incubated with fibrinogen. In contrast, Lyck et al. [53] showed that mutants from brain EC, which lack phosphotyrosine sites on the cytoplasmic tail of ICAM-1 are still capable of facilitating the transendothelial migration of T-cells at levels similar to wild type control cells. In

B-cells, ICAM-1 cross-linking has been shown to activate src-kinase family members p53/p56lyn [33].

One very important molecule in ICAM-1 signaling cascades appears to be the small GTPase Rho, a member of the ras superfamily of G-proteins [1, 17, 87, 101], which links the ligation of ICAM-1 on the plasma membrane to the rearrangement of the actin cytoskeleton.

Various factors tightly regulate Rho's active and inactive states including guanine exchange factors, GTPase-activating proteins and guanine nucleotide exchange inhibitors (GDI) (reviewed in [15]). Antibody cross-linking and the co-culture of HUVEC with monocytes induced ICAM-1 clustering with ERM-protein colocalization and stress fiber assembly [101]. These processes were shown to involve both the activation of RhoA, and the gene expression of RhoA and c-fos [87]. The involvement of ICAM-1's cytoplasmic tail in signaling is further supported by studies from Greenwood et al. [26] that showed antibody cross-linked ICAM-1 molecules lacking cytoplasmic tails were not capable of activating Rho proteins [26]. Mutagenesis of the cytoplasmic tail resulted in the identification of a five amino acid sequence (507RKIKK511) that seems to be essential for ICAM-1 relocalization and therefore crucial for leukocyte adhesion and transmigration [63].

In brain microvascular EC (BMVEC), ICAM-1 engagement triggered src tyrosine kinase activity and tyrosine phosphorylation on cortactin [14]. Tyrosine phosphorylation on focal adhesion kinase (FAK), paxillin and p130cas were triggered by Rho activation [17]. Furthermore, the activation of JNK has been shown to be dependent on Rho activation [17]. Upon the cross-linking of ICAM-1 on the cell surface, the formation of actin stress fibers were observed [1]. However, treatment with cytochalasin D, which disrupts actin filaments and inhibits actin polymerization, showed that stress fiber formation is not required for lymphocyte binding, but is essential for lymphocyte transmigration [1]. Furthermore, by inactivating Rho in EC transendothelial migration was also inhibited [1]. The mechanism by which ICAM-1 activates Rho is not known, but the involvement of ERM-proteins and Rho-GDI in sustaining Rho activation has been suggested [7]. The involvement and importance of src tyrosine kinase in ICAM-1 signaling was investigated by Wang et al. [99]. They cross-linked ICAM-1 with antibodies on human pulmonary microvascular EC, which resulted in the production of the

reactive oxygen species required to activate src tyrosine kinase [99]. The presence of activated src tyrosine kinase was essential for the tyrosine phosphorylation of the ERM-molecule ezrin and the p38 MAPK kinase pathway. Further studies showed the involvement of intracellular calcium signaling and protein kinase C (PKC) [16]. The cross-linking of ICAM-1 on BMVEC induced tyrosine phosphorylation of phospholipase C (PLC)- γ , which was sustained and subsequently triggered inositol phosphate production as well as increased levels of intracellular Ca^{2+} . The increase in intracellular Ca^{2+} concentration seems to be responsible for src activation, which is likely mediated by PKC, and results in the tyrosine phosphorylation of cortactin [16].

Unlike the phosphorylation of p130cas, which is completely Rho-dependent, the phosphorylation of FAK and paxillin, actin cytoskeleton rearrangement and the activation of JNK also appear to be regulated by PKC-pathways [16], since inhibitors of either pathway suppress phosphorylation and actin rearrangements. ICAM-1 ligation on HUVEC with fibrinogen resulted not only in the recruitment of ICAM-1 into lipid rafts, but also in the phosphorylation of tyrosine 512 in the cytoplasmic tail of ICAM-1 and in the subsequent recruitment of Src-homology domain 2 containing phosphatase 2 (SHP-2) [67, 68]. This alternative signaling method was further investigated by Couty et al. [12]. The cross-linking of PECAM-1 was also followed by recruitment of SHP-2. When both receptors were cross-linked at the same time, PECAM-1 dominated SHP-2 recruitment to its cytoplasmic tail and inhibits Rho and src-activation of ICAM-1 cross-linking. Couty et al. suggested that SHP-2 recruitment to PECAM-1 upon ICAM-1 signaling acts as an inhibitory influence. Furthermore, it was suggested that SHP-2 recruitment to PECAM-1 might dominate over the recruitment of ligands to ICAM-1 due to the lack of a conserved protein binding site on ICAM-1's cytoplasmic domain, which results in a reduced binding affinity of SHP-2 to ICAM-1 [12].

Depending on the experimental design and cell type investigated, the cross-linking of ICAM-1 with monoclonal antibodies may activate the MAPK kinases ERK-1/2 and/or JNK [17, 41, 76]. The activation of ERK-1 leads to AP-1 activation [41], and the ERK-dependent production and secretion of IL-8 and RANTES [76], as well as upregulation of VCAM-1 on the cell surface [41, 42] (Fig. 3). ICAM-1 cross-linking can

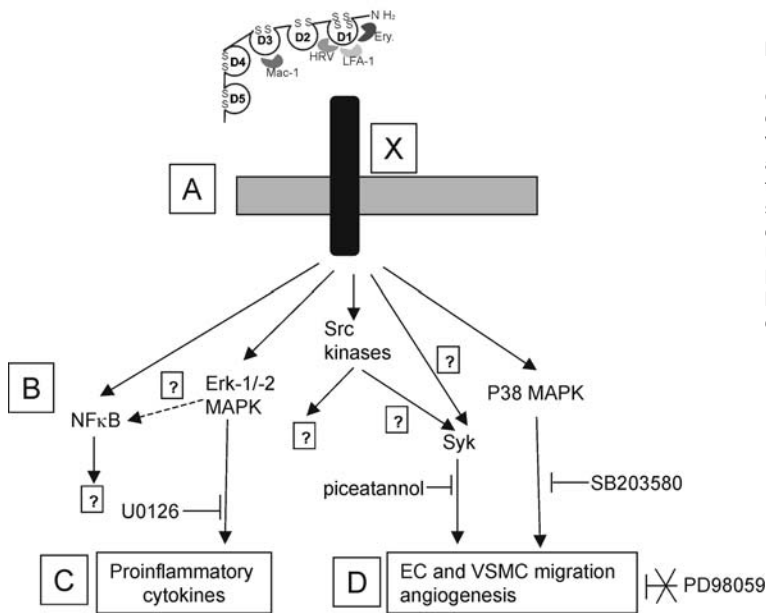


Fig. 3. The signaling cascades downstream of sICAM-1's binding to target cells have been partially elucidated. **(A)** The binding of sICAM-1 to an unidentified receptor **X** on the target cells' surface leads to **(B)** the activation of signaling pathways including NF- κ B, Erk-1/-2 and p38 MAPK, as well as Src kinases. By mechanisms that are not fully elucidated, sICAM-1 induces **(C)** the secretion of a number of proinflammatory cytokines and chemokines, possibly via Erk MAPK (inhibited by U0126, CL unpublished observations), and **D** induces EC and VSMC migration and angiogenesis via p38 MAPK (inhibited by SB203580) and Syk (inhibited by piceatannol), but not Erk (no inhibition via PD98059)

also upregulate tissue factor production [78] and pro-inflammatory cytokines including IL-1 β [37]. Patient antibodies directed against ICAM-1 also cause endothelial cell signaling [43].

ICAM-1 polymorphisms and signal transduction

We hypothesized that since the ICAM-1 gene polymorphisms described by Vora are located in exons and lead to amino acid substitutions [96] they could alter ligand binding or the stability of the multimeric ICAM-1 on the cell surface, and therefore alter signal transduction. Human ICAM-1 polymorphic variants were expressed in murine EC [43] or Cos 7 [32], and co-cultured with K562 engineered to express constitutively active LFA-1 [50] or peripheral blood mononuclear cells. Results revealed enhanced adhesion to cells expressing the G241E469 mutation [32] and increased Erk-1/-2 phosphorylation of cells expressing the G241E469 mutation compared with other genotypes (CL, unpublished observations) although the functional significance of these results has not yet been explored.

Soluble ICAM-1 (sICAM-1)

A soluble ICAM-1 molecule has been identified in serum that consists of the five extracellular Ig-domains of the membrane-bound ICAM-1-molecule, but lacks the transmembrane and cytoplasmic domains (Fig. 1). sICAM-1 is produced by a variety of different cells including HUVEC, human saphenous vein EC, human aortic SMCs, melanoma cells and hematopoietic cell lines. sICAM-1 is present in normal human serum at concentrations between 100–450 ng/ml [22]. Increased levels of sICAM-1 have been found in serum from patients with cardiovascular disease, cancer and autoimmune diseases. Several studies have correlated serum levels of sICAM-1 with severity of these diseases.

A number of studies have investigated the use of sICAM-1 as a biomarker for cardiovascular disease prognosis. A significant correlation between sICAM-1 concentrations and future coronary artery disease has been demonstrated by several groups [34, 55, 71], but refuted by others [70]. The potential of sICAM-1 as a biomarker to predict secondary cardiovascular disease in patients with coronary artery disease has also been investigated [6, 29, 98]. Levels of sICAM-1 have also been assessed in cardiac allografts with contradictory results [38, 92]. Studies of ApoE^{-/-} mice have shown

a correlation between increased sICAM-1 levels and the progression of atherosclerotic lesions [36].

The exact mechanism by which sICAM-1 is expressed has not been identified. However, a number of studies have focused on the enzymatic cleavage of cell surface ICAM-1, possibly as part of a negative feedback loop [11, 89]. Candidate proteases include matrix metalloproteinases (MMP) on astrocytes [54] and HSVEC [86], human leukocyte elastase on human myelomonocytic cell line U-937 cells [11] and TNF α -converting enzyme (TACE) on TNF α -treated HUVEC and PMA-stimulated ICAM-1 transfected 293-cells [89]. There is also some evidence that sICAM-1 could be the product of alternative splicing [97].

TNF- α , IL-1 β and IFN- γ , which are regulated through the MAPK, Src kinase and PI3K pathways [88], induce sICAM-1 to be shed off from the cell surface of various primary cells and cell lines [4, 19, 24, 45, 47, 54, 66].

Functions of sICAM-1

As might be expected, sICAM-1 binds competitively to ligands of membrane-bound ICAM-1, such as LFA-1, mac-1 [4, 5, 60, 72], and human rhinovirus [57, 58], and therefore may have potential as a therapeutic to block leukocyte : endothelial interactions. However, several studies have shown that the addition of sICAM-1 to different *in vitro* models activates pro-inflammatory cascades and causes angiogenesis. These results suggest sICAM-1 may be involved in the progression of atherosclerosis and other chronic inflammatory diseases.

The production of MIP-1 α [51, 94], TNF- α , IFN- γ and IL-6 [59, 77], MIP-2 [64, 65, 77] has been noted in different cell types following incubation with sICAM-1, while the activation of NF- κ B [77] src tyrosine kinase and Erk-1/-2 [64, 65] has also been described. sICAM-1 can also stimulate chemotactic EC migration, EC tube formation on Matrigel, sprouting in an aortic ring assay and angiogenesis in chick chorioallantonic membrane assays [23]. The presence of sICAM-1 has also been shown to contribute to the migration of VSMC [44]. A higher degree of migration was induced by sICAM-1 in VSMC obtained from spontaneously hypertensive rats than from normal Wistar Kyoto rats. Migration was blocked by the

spleen tyrosine kinase (syk)-inhibitor piceatannol and by a p38 MAPK inhibitor (SB203580), but not by inhibitors of MEK-ERK (PD98059) and Src (PP2). This data suggests that diverse signaling pathways are activated after sICAM-1 binding [44].

The exact identity of the cell surface receptor for sICAM-1 has not been identified, but cells lacking the natural ligands for ICAM-1 or detectable cell surface ICAM-1 can be activated by sICAM-1, which suggests the existence of an alternative receptor. A 49 kDa protein that may play this role has been described [64, 65]. In addition, the pro- or anti-inflammatory outcome of the sICAM-1 interactions with integrins or other receptors seems to depend on the concentration used in the experiments and on the conformation of the sICAM-1. The induction of proinflammatory mediators has been described with low nM concentrations of sICAM-1 that correlate with the normal physiological levels detected in serum [64, 65, 77]. In contrast, higher sICAM-1 concentrations are required to inhibit the ICAM-1/LFA-1 interaction *in vitro* (greater than 20 μ M for 50% inhibition [60]).

Clinical perspectives of ICAM-1 mediated signal transduction

In addition to its well known role in leukocyte emigration, ICAM-1 has now been shown unequivocally to transmit intracellular signals (i.e., outside-in signaling) that lead (1) to the rearrangement of the actin cytoskeleton, presumably to aid in leukocyte diapedesis, and (2) to activation of proinflammatory cascades that can perpetuate an inflammatory response. ICAM-1/LFA-1 interactions remain an attractive therapeutic target, but further investigations into the signaling and downstream biological effects of ICAM-1 are required in order to design suitable therapeutics that block leukocyte:endothelial interactions without contributing to ongoing inflammatory responses.

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Received:

September 25, 2008; in revised form: January 8, 2009.