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Intercellular Adhesion Molecule-1 in patients with Sepsis: An Updated Review

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ABSTRACT

Sepsis is a global health problem caused by infection with high morbidity and mortality and is the most common cause of death in critically ill patients of intensive care unit (ICU). Severe sepsis is characterized by systemic inflammatory response syndrome (SIRS) and is often complicated with septic shock (refractory hypotension) and multiple organ dysfunction syndrome (MODS), thereby determining the outcome of severe sepsis. Both pro-inflammatory and anti-inflammatory path- ways are activated in severe sepsis, and their imbalance can determine the probability of septic shock and MODS. Therefore, new biomarkers are highly needed in the early phase of sepsis to aid diagnosis and stratification of severe sepsis patients**[1].**

Intercellular adhesion molecule 1 (ICAM-1) is a glycoprotein member of the immunoglobulin superfamily and acts as one adhesion molecule that stimulates leukocyte adhesion and transmigration across the endothelium. ICAM-1 is constitutively expressed on endothelium and its expression can be significantly up-regulated by a variety of mediators, such as proinflammatory cytokines, cellular stresses, hormones and virus infection**[2].**

Circulating sICAM-1 is up-regulated in neonatal sepsis and associated with disease severity and systemic inflammation. However, the relationship between circulating sICAM-1 and adult sepsis is complex and in whether sICAM-1 concentration is associated with se- verity and mortality of severe sepsis is not well established**[3]**.

This article reviews the association between serum sICAM-1 and clinical severity, mortality and inflammatory response of severe sepsis.

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1. Sepsis

Sepsis is a medical emergency that describes the body's systemic immunological response to an infectious process that can lead to end-stage organ dysfunction and death. Despite significant advancements in the understanding of the pathophysiology of this clinical syndrome, advancements in hemodynamic monitoring tools, and resuscitation measures, sepsis remains one of the major causes of morbidity and mortality in critically ill patients. The annual incidence of severe sepsis and septic shock in the United States is up to 300 cases per 100,000 people. Sepsis is also the most expensive healthcare problem in the United States, accounting for more than 20 million $ (about 5.2% of the total hospital cost in 2011)**[4].**

Various definitions have been proposed. While these definitions differ in detail, the fundamentals are essentially the same all seek to identify patients with severe infection, and thus require evidence of both infection (or suspected infection) and illness severity. The tools differ in how severity is defined all are imperfect. They nevertheless provide both practical tools to aid rapid identification of sepsis in clinical practice, and case definitions for research **[5].**

The global epidemiological burden of sepsis is difficult to ascertain. although a recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deathsin 2017, almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under five years of age **[6]**.

Significant regional disparities in sepsis incidence and mortality exist; approximately 85.0% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries. This difference however disappeared when adjusted for disease severity. This implies that the mortality in sepsis varies according to patient characteristics. A multicenter study in Australia and New Zealand that included 101,064 critical patients showed that the mortality rate in sepsis has decreased over the years from around 35% in 2000 to about 20% in 2012 **[7].**

Pathophysiology of Sepsis

There has been a marked evolution in our understanding of the molecular pathobiology and immunology of sepsis. Previously it was felt that hemodynamic manifestations of sepsis were primarily related to the hyperimmune host response to a particular pathogen. However, a large body of work on the molecular basis of sepsis has revealed a far more nuanced and complex interplay between the infectious agent and host that together produce the heterogeneous manifestations of sepsis **[8].**

Innate Immunity and Inflammatory Mediators

The first step in the initiation of the host response to the pathogen is the activation of innate immune cells, an innate immune response, also called natural, which recognizes pathogen-associated molecular patterns (PAMPs). These PAMPs are

recognized by pattern recognition receptors (PRRs), mainly expressed in the innate immunity cells. PRRs can also recognize host molecules containing damage-associated molecular patterns (DAMPs), molecules that are often released from necrotic cells damaged by invading pathogens.The innate immune system is composed mainly of physical barriers, such as skin and mucous membranes, chemical barriers, through the action of antimicrobial peptides and reactive oxygen species, innate immune cells, and soluble mediators such as the complement system, innate antibodies, and associated cytokines **[9].**

Dysregulation of Hemostasis

In sepsis, there is an intersection between the inflammatory and hemostatic pathways, with the simultaneous activation of both the inflammatory and the coagulation cascades. The spectrum of this interaction can vary from mild thrombocytopenia to fulminant disseminated intravascular coagulation (DIC). The etiology of the dysregulation of coagulation in sepsis is multifactorial. The hypercoagulability of sepsis is thought to be driven by the release of tissue factor from disrupted endothelial cells (other sources include monocytes and polymorphonuclear cells). In fact, in vitro experimental models of endotoxemia and bacteremia have shown a complete inhibition of inflammation-induced thrombin production with the blockade of tissue factor. Tissue factor then causes the systemic activation of the coagulation cascade resulting in the production of thrombin, activation of platelets, and formation of platelet– fibrin clots. These microthrombi can cause local perfusion defects resulting in tissue hypoxia and organ dysfunction **[10].**

In addition to the procoagulant effect described above, there is a depression of the anticoagulant effects of protein C and antithrombin that would normally temper the coagulation cascade. Protein C is converted to its active form (activated protein C) by thrombomodulin which itself is activated by thrombin. Activated protein C then exerts an anticoagulant effect by degradation of factors Va and VIIIa acting in concert with activated protein S. It is also known to have potent anti-inflammatory effects via the inhibition of TNFα, IL-1β, and IL-6 and limiting of neutrophil and monocyte adhesion to endothelium. In patients with severe systemic inflammation, such as in sepsis, there are decreased plasma levels of protein C, downregulation of thrombomodulin, and low levels of protein S thus allowing for the unregulated propagation of the coagulation cascade **[11]**.

In addition to the hypercoagulability described above, a reduction of fibrinolysis is also observed as a result of sepsis. As TNFα and IL-1β levels increase, tissue plasminogen activators are released from vascular endothelial cells. The resultant increase in activation of plasmin is blunted by the sustained increase in plasminogen activator inhibitor type 1 (PAI-1). The net effect is diminished fibrinolysis and fibrin removal, which contributes to the perpetuation of microvascular thrombosis**[12]**.

Immunosuppression

Interestingly, the initial proinflammatory state of sepsis is often superseded by a prolonged state of immunosuppression. There is a decrease in the number of T cells (helper and cytotoxic) as a result of apoptosis and a decreased response to inflammatory cytokines. Postmortem studies of ICU patients who died of sepsis demonstrated a global depletion of CD4+ and CD8+ T cells, most notably found in the lymphoid organs such as the spleen. Studies have also demonstrated decreased production of crucial cytokines such as IL-6 and TNF in response to endotoxin. In septic patients, neutrophils were found to have expressed fewer chemokine receptors, and there was diminished chemotaxis in response to IL-8 **[13]**.

The above findings suggest that the immune system in a septic individual is unable to stage an effective immune response to secondary bacterial, viral, or fungal infections. Based on a study that showed that a low lymphocyte counts early in sepsis (day 4 of diagnosis), it has been postulated that early leukocytosis with relative lymphopenia can serve as a biomarker for immunosuppression in sepsis **[14].**

Cellular, tissue, and organ dysfunction

The underlying mechanism behind tissue and organ dysfunction in sepsis is the decreased delivery to and utilization of oxygen by cells as a result of hypoperfusion. Hypoperfusion occurs due to the cardiovascular dysfunction that is seen in sepsis. The incidence of septic cardiomyopathy varies from 18% to 60% in various studies. It is thought to be related to circulating cytokines, such as TNFα and IL-1β among others, which can cause depression of cardiac myocytes and an interference with their mitochondrial function. The most important feature of septic cardiomyopathy is that it is acute in onset and reversible. also, the low left ventricular ejection fraction is accompanied by normal or low left ventricular filling pressures (unlike in cardiogenic shock) with increased left ventricular compliance. Multiple studies have shown both systolic and diastolic dysfunction with decreased stroke volumes and increased end-diastolic and end-systolic volumes in sepsis **[15].**

A definite effect on mortality as a result of myocardial depression, because of the arterial and venous dilation (induced by inflammatory mediators) and consequent reduced venous return, a state of hypotension and distributive shock is produced by sepsis. There is dilation of all three components of the microvasculature arterioles, venules, and capillaries. This is exacerbated by the leakage of intravascular fluid into the interstitial space as a result of loss of endothelial barrier function induced by alterations in endothelial cadherin and tight junctions. All the above changes in the body's hemodynamics in conjunction with microvascular thrombosis can result in hypoperfusion of tissues and organs. Consequently, there is increased anaerobic glycolysis in cells resulting in the production of lactic acid. In addition, (ROS) produced by the inflammatory response cause dysfunction of mitochondria and a drop in ATP levels. These mechanisms cause damage at the cellular level. The broader

alterations that occur in the tissue and organs collectively and cumulatively contribute to much of the morbidity and mortality of sepsis **[16]**.

There are significant alterations to the endothelium with disruption of its barrier function, vasodilation, increased leukocyte adhesion, and the creation of a procoagulant state. This results in accumulation of oedema in the interstitial spaces, body cavities, and subcutaneous tissue. In the lungs, there is disruption of the alveolar–endothelial barrier with accumulation of protein-rich fluid in the interstitial lung spaces and alveoli. This can cause a ventilation–perfusion mismatch, hypoxia, and decreased lung compliance producing acute respiratory distress syndrome (ARDS) in extreme cases. In the kidneys, a combination of reduced renal perfusion, acute tubular necrosis, and more subtle defects in the microvasculature and tubules together produce varying degrees of acute kidney injury. In the gastrointestinal tract, the increased permeability of the mucosal lining results both in bacterial translocation across the bowel well and autodigestion of the bowel by luminal enzymes. In the liver, there is a suppression of bilirubin clearance producing cholestasis. Altered mentation is commonly noted in sepsis and is indicative of CNS dysfunction **[17]**.

The endothelial changes described above undermine the blood–brain barrier, causing the entry of toxins, inflammatory cells, and cytokines. The ensuing changes of cerebral edema, neurotransmitter disruption, oxidative stress, and white matter damage give rise to a clinical spectrum of septic encephalopathy that varies from confusion to delirium and coma. Sepsis is known to produce a catabolic state. There is a rapid and significant breakdown of muscle to produce amino acids for gluconeogenesis that will fuel the immune cells. In addition, increased insulin resistance can result in a state of hyperglycemia **[18]**.

2. Soluble Intercellular Adhesion Molecule-1 (sICAM-1)

Soluble intercellular adhesion molecule-1 (sICAM-1) represents a circulating form of ICAM-1 (CD54) that is constitutively expressed or is inducible on the cell surface of different cell lines. Structurally ICAM-1 belongs to the immunoglobulin superfamily. It mostly serves as a counter-receptor for the leukocyte integrin, lymphocyte function-associated antigen (LFA-1). Interaction between ICAM-1, present on endothelial cells, and LFA-1 facilitates leukocyte adhesion and migration across the endothelium, however sICAM-1 binding to LFA is capable of inhibiting lymphocyte attachment to endothelial cells **[19]**.

Soluble ICAM-1 has been found in such body fluids as serum, cerebrospinal fluid, synovial fluid, and sputum. It has also been detected in urine and in bronchoalveolar lavage fluid, demonstrating that sICAM-1 is also released into the pulmonary tract **[20]**.

The release of soluble ICAM-1 is modulated by several cytokines and various factors. The mechanism or mechanisms allowing sICAM-1 generation to have not been completely elucidated. In vitro studies using cultured endothelial cells established that sICAM-1 simply reflects ICAM-1 expression on these cells. Therefore, ICAM-1 shedding from the cell membrane via proteolytic cleavage facilitated by specific proteases has been proposed. However, other studies report on the presence of messenger RNA transcripts coding in cells, specific for soluble ICAM-1. Therefore, at least two mechanisms must be involved in sICAM-1 generation **[21]**.

Structure and Features

ICAM-1 consist of five extracellular domains, numbered from the N terminus in a sequence, with the C terminus attached to the cell membrane, a transmembrane domain, and a short cytoplasmic domain. ICAM-1 shed from the cell surface is built of the extracellular domains. Structurally monomeric sICAM-1 is a slightly bent rod of 18.7 nm in length and 2-3 nm in width. The characteristic bend occurs between third and fourth domain. The molecule is built of 453, mainly hydrophobic, amino acids, with about 90 amino acids coming into each domain. The molecular weight of monomeric sICAM-1, approximately 90 kDa, relates to that of ICAM-1, since the transmembrane and cellular domains are built of only 24 and 28 residues respectively. Soluble ICAM-1 is a glycoprotein. The sICAM-1 molecules from various cell lines are glycosylated differentially. Therefore, molecular weight of monomeric sICAM-1 can be variable. Moreover, circulating ICAM-1 molecules form complexes consisting of two or more monomers. Complexed forms exceeding 500 kDa have been detected **[22]**.

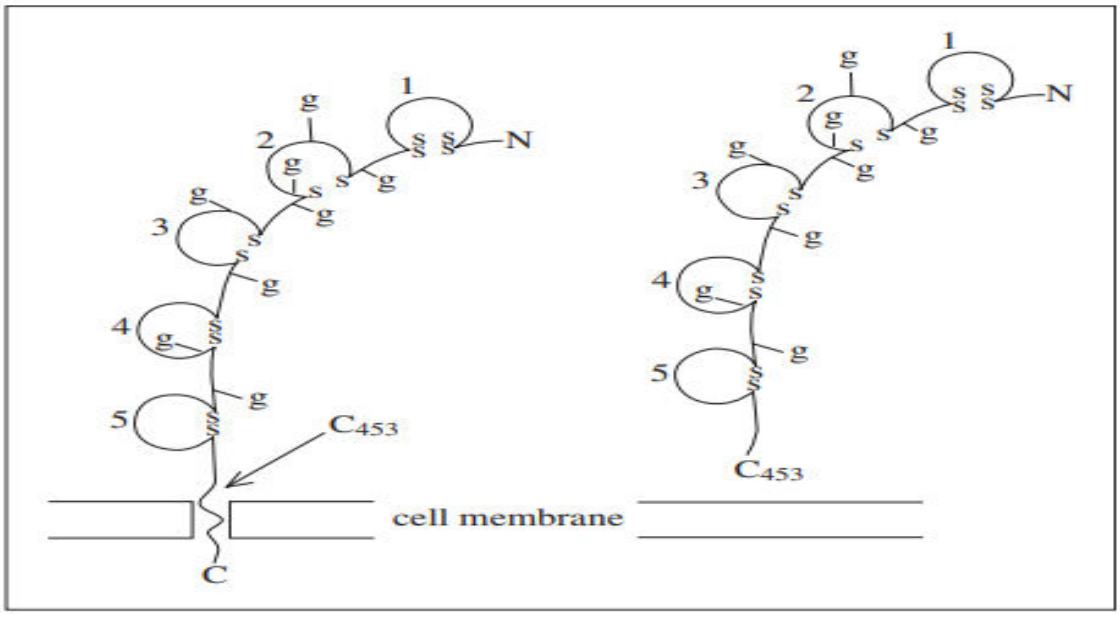

Figure 1 Structures of ICAM-1 and sICAM-1. 1-5, extracellular domains. S, sulphur atom in disulphide bonds stabilizing the domains. g, potential sites of glycosylation **[23].**

Clinical Significance

ICAM-1 and its circulating form have been implicated in the development of any number of diseases. ICAM-1 present on endothelial cells allows transendothelial leukocyte migration to sites of inflammation initiating angiogenesis. An in vitro study by Gho et al. provided information that sICAM-1 may promote angiogenesis by stimulating the chemokinetic endothelial cell migration, endothelial cell tube formation and vessel sprouting from aortic rings. In vivo it induced neovascularization in chicken eggs. Recently, the same researchers have established that human sICAM-1 stimulates tumor cell growth in mice injected with tumor cells. These findings are a step forward in the understanding of the pathogenesis of angiogenesis-dependent diseases, such as cancers and rheumatoid arthritis **[24]**.

Viral Infections

Many upper respiratory tract infections are caused by rhinoviruses, which penetrate epithelial cells after interaction with ICAM-1, which serves as a membrane receptor for these viruses. Following cell invasion, rhinoviruses are capable of modulating the two distinct messenger RNA transcripts coding for membranous ICAM-1 and soluble ICAM-1 in bronchial epithelial cells with subsequent ICAM-1 expression on the cell surface and downregulation of sICAM-1 release at the same time. This mechanism appears to promote epithelial cell infectivity. Interestingly sICAM-1 has been found to prevent cellular infection and replication of viruses, thus constituting a defense mechanism for cells **[25].**

Autoimmune Diseases

In rheumatoid arthritis (RA), soluble isoforms of several types of cellular adhesion molecules (sCAM) have been described. As with other adhesion molecules, sICAM-1 levels were found to be elevated in RA, however numerous reports showed no association between the molecule and disease activity. In RA synovial tissue, the main sources of sICAM-1 are endothelial cells. Moreover, in RA complicated by vasculitis, sICAM-1 concentrations rise markedly as compared to patients without symptoms of vasculitis. These findings suggest that higher sICAM-1 levels in RA reflect vascular involvement. Elevated concentrations of sICAM-1 have also been observed in other vasculitis syndromes such as polyarteritis nodosa, systemic sclerosis, and Wegener's granulomatosis **[26]**.

Atherosclerosis and Coronary Heart Disease (CHD) risk

Elevated sICAM-1 levels are associated with cardiovascular risk factors such as hypertension, smoking and frequent alcohol consumption. The fact that high blood pressure may contribute to development of atherosclerosis has been known for years. Hypertension stimulates inflammation, which is critical for the pathogenesis of atherosclerosis. Soluble ICAM-1, considered as one of the proinflammatory factors, and therefore, as a possible marker of inflammatory events, was found to be related to increasing systolic blood pressure. Angiotensin II (Ang II), a potent vasoconstrictor, stimulates ICAM-1 expression in a direct or indirect manner, and increases sICAM-1 release in vivo. It was found that Ang II type 1 receptor antagonists lower sICAM-1 levels in patients with congestive heart failure by decreasing TNF-α and IL-6, which are capable of stimulating ICAM-1 shedding in vitro**[27]**.

Cancers

Human melanoma and prostatic carcinoma cells are capable of expressing ICAM-1, and release sICAM-1 from their surface. This sICAM-1 release from melanoma cells is inducible by the proinflammatory cytokines IFN-γ and TNF-α. However, the ICAM-1 positive cells were not the sources of sICAM-1 in cancers, ICAM-1 negative tumour cells were also found to induce ICAM-1 shedding mediated by IL-1α in cultured endothelial cells. Interestingly, circulating forms of ICAM-1 were found to inhibit the interaction between T cells and tumours, and block NK cell-mediated toxicity. These findings are a possible explanation for tumour escape from immunosurveillance**[28].**

Neurological Disorders

In the central nervous system (CNS) ICAM-1 is expressed on cerebral endothelial cells, astrocytes, and can be induced on microglial cells. Therefore, these cells in the CNS are sources of circulating ICAM-1. About one-third of the sICAM-1 detected in normal cerebrospinal fluid (CSF) is brain-derived. In inflammatory diseases of the CNS however, the elevated sICAM-1 levels in the CSF come mainly from this fraction. Meningeal infections of bacterial or viral origin bring about an increase in sICAM-1 release into the CSF. The release however is more spectacular in bacterial

infections. Elevated sICAM-1 levels in CSF and serum were also found in multiple sclerosis (MS). The serum levels correlated with disease activity **[29]**.

Transplantation and Draft Rejection

It has been well documented that heart transplant recipients show high sICAM-1 titres. These elevated sICAM-1 levels in one study were related to the subsequent development of transplant-associated vasculopathy. However, other researchers have not confirmed these findings. The low number of study participants may possibly account for the lack of significance in the second study. In transplant coronary artery disease (CAD), serum sICAM-1 levels above 308 ng/ml seem to reflect ICAM-1 expression on arterial and arteriolar endothelium. Therefore, the authors conclude that sICAM-1 can be useful for assessment of transplant CAD, posttransplant ischemic events, and cardiac graft failure**[30]**.

Physical Activity

Physical stress must be taken into account as a factor of sICAM-1 influence. Normally, sICAM-1 levels rise insignificantly after training, however in patients with peripheral arterial disease and claudication this elevation is prominent **[31].**

Nutritional Aspects

Nutrition is of great importance to the immune system. It has been well documented in several nutritional surveys that the expression of CAMs on vascular cells can be induced by abnormalities in lipid metabolism **[32].**

Fat is one of the most significant dietary factors involved in the effects of sICAM-1. The alterations in sICAM-1 levels depend on the origin of the fat, its level in food, and the presence of other nutrients. It was found that saturated fatty acids and high-fat meals stimulate sICAM-1 release. No similar effects were observed after high-carbohydrate or high-fat meal combined with vegetables such as tomatoes, carrots and peppers, rich in vitamin antioxidants. In pathological states associated with an impairment in the lipid metabolism, high sICAM-1 levels were observed.

Although the role and functions of soluble ICAM-1 have not yet been completely elucidated, the evidence suggests its implication in disease progression, or at least its

elevated levels may inform the clinician about pathological processes associated with vascular wall inflammation. Therefore, its measurement would be helpful for:

identification of subjects at risk of CHD, hypertension or graft failure,detection of hematogenous metastases, detection of vasculitis syndrome in the course of rheumatoid arthritis.

Further studies are necessary to establish its value in certain pathological states. However, one must bear in mind that for numerous diseases it is of rather limited diagnostic significance, although it may be helpful for monitoring disease progression and staging **[33].**

3. ICAM-1 Signaling in Endothelial Cells

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 **[34].**

Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in large arteries, and it increasingly threatens human health worldwide. 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. All of these risk factors can influence endothelial cell function resulting in their increased permeability, the increased adhesion of leukocytes and the expression of procoagulant molecules **[35].**

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. The “response to injury” hypothesis first proposed by Ross and Glomset, and the more recent “response to retention” hypothesis both propose that the earliest events in atherogenesis are part of an inflammatory response. 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) that leads to the activation of the endothelium and to elevated levels of adhesion molecules. 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 **[36].**

ICAM-1

ICAM-1 is a type I transmembrane protein with a molecular weight of 80–114 kDa depending on its level of glycosylation. Unglycosylated ICAM-1 has a molecular weight of 60 kDa. 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 -sheet structure, which is stabilized by disulfide bonds. The cytoplasmic tail lacks classical signaling motifs, but has one tyrosine residue, which may be important for signaling. 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 (**Figure 2**). **[37]**.

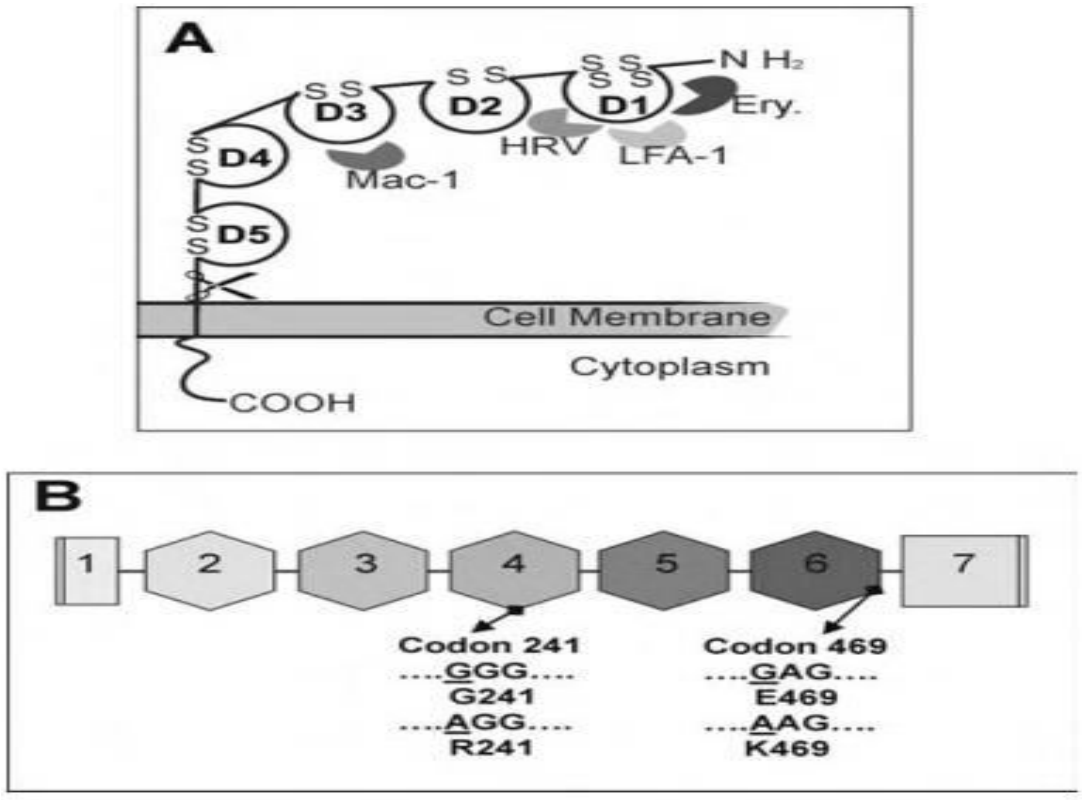

Figure 2: A cartoon depicting (A) ICAM-1 with its five Ig-domains (D1-D5) and ligands LFA-1, Mac-1, Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP-1) and human rhinovirus (HRV). The scissors represent the generation of sICAM-1 by cleavage of ICAM-1's extracellular domain from the cell surface, 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 **[38]**.

Two single nucleotide polymorphisms have been described within the exons that encode the extracellular domains of the ICAM-1 gene. 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. 2**). 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. The substitution from glutamic acid to lysine has been associated with coronary heart disease, myocardial infarction and peripheral artery disease. These results need to be confirmed by larger studies **[39]**.

Several ligands for ICAM-1 have been identified, including the membrane bound 2 integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) on leukocytes, fibrinogen, rhinoviruses and Plasmodium falciparum-infected erythrocytes **[40]**.

ICAM-1's Function

ICAM-1 plays an important role in both innate and adaptive immune responses. It is involved in the transendothelial migration of leukocytes to sites of inflammation, as well as interactions between antigen presenting cells (APC) and T cells (immunological synapse formation) **[41]**.

Trans-endothelial migration can be divided into four sequential, but overlapping steps summarized in **Figure3[42]**.

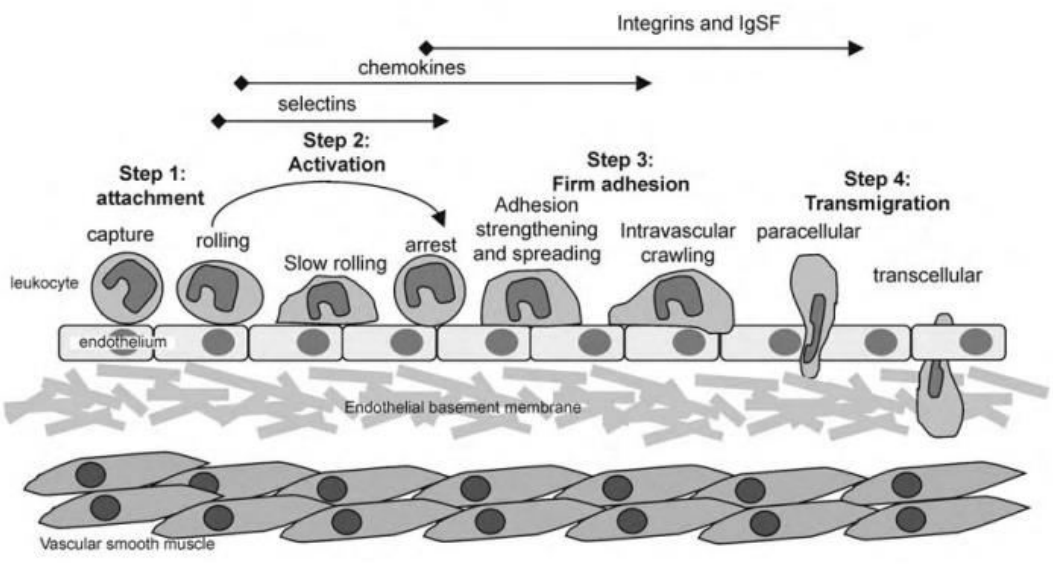

Figure3: A cartoon depicting the transendothelial migration of leukocytes into sub-endothelial space **[43]**.

Step 1: involves the rolling and tethering of leukocytes, facilitated by interactions between selectins and the sialylatedcarbohyrate portion of E- and P-selectin, both of which are present on the endothelium, and bind to carbohydrate structures closely

related to sialyllewisx 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 sialyllewisx 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-1α/β **[44]**.

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 **[45].**

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 α4β7/MAD 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 antiICAM-1 antibodies or an ICAM-1-deficient endothelium **[46].**

Step 4: Leukocytes migrate through the endothelial cell barrier into the sub-endothelial space. 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. 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 **[47].**

4. 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. 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. 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 **[48].**

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 but refuted by others. The potential of sICAM-1 as a biomarker to predict secondary cardiovascular disease in patients with coronary artery disease has also been investigated. Levels of sICAM-1 have also been assessed in cardiac allografts

with contradictory results. Studies of ApoE$^{-/-}$ mice have shown a correlation between increased sICAM-1 levels and the progression of atherosclerotic lesions **[49]**.

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, and human rhinovirus, 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 proinflammatory cascades and causes angiogenesis. These results suggest sICAM-1 may be involved in the progression of atherosclerosis and other chronic inflammatory diseases **[50]**.

The production of MIP-1α, TNF- α, IFN- and IL-6, MIP-2 has been noted in different cell types following incubation with sICAM-1, while the activation of NF-$_k$B src tyrosine kinase and Erk-1/-2 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. The presence of sICAM-1 has also been shown to contribute to the migration of VSMC. 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 **[51]**.

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. 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. In contrast, higher sICAM-1 concentrations are required to inhibit the ICAM-1/LFA-1 interaction in vitro (greater than 20 μM for 50% inhibition **[52]**.

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**[53]**.

(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.

Soluble Adhesion Molecules as Markers for Sepsis

Sepsis, due to its detrimental sequelae and limited therapeutic options, continues to be responsible for many deaths amongst all age groups. Growing evidence indicates that aberrant leukocyte activation and recruitment into host tissues plays a pivotal role in causing breakdown of the vascular endothelium, which in turn leads to organ failure and death. Inflammatory leukocyte recruitment is initiated by soluble mediators (for example, cytokines or bacterial-derived lipopolysaccharide (endotoxin), which upregulate adhesion molecule expression on both leukocytes and the endothelium. This upregulation results in a multistep adhesion cascade whereby circulating immune cells sequentially roll on, firmly adhere to, and transmigrate across the endothelium **[54]**.

During the progression of inflammatory responses, soluble isoforms of the leukocyte recruitment adhesion molecules are shed from cell surfaces and accumulate within the circulating blood plasma. These soluble isoforms have been considered promising prognostic biomarkers of severity of inflammation but the clinical utility of monitoring such changes remains poor **[55]**.

One reason for the thus far limited clinical utility of these soluble isoforms is the fact that shedding in general is neither a passive nor an inevitable consequence of upregulated expression/cell activation. Most shedding is an active process, which is discretely regulated by diverse proteolytic enzymes, although cell damage can also variably contribute to soluble adhesion molecule levels.

Refernces:

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