Soluble intercellular adhesion molecule-1 (sICAM-1): an overview

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Accepted for publication March 15, 2004

ABSTRACT. Soluble intercellular adhesion molecule-1 (sICAM-1) represents a circulating form of ICAM-1 that is constitutively expressed or is inducible on the cell surface of different cell lines. It serves as a counter-receptor for the 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. ICAM-1 and its circulating form have been implicated in the development of any number of diseases.

Keywords: sICAM-1; cancers; atherosclerosis; autoimmune diseases; nutrition

INTRODUCTION

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 [1-8]. 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 [9], however sICAM-1 binding to LFA is capable of inhibiting lymphocyte attachment to endothelial cells [10].

Soluble ICAM-1 has been found in such body fluids as serum [3], cerebrospinal fluid [11], synovial fluid [12], and sputum [13]. It has also been detected in urine [14] and in bronchoalveolar lavage fluid, demonstrating that sICAM-1 is also released into the pulmonary tract [15].

The release of soluble ICAM-1 is modulated by several cytokines and various factors (see *Table 1*). The mechanism or mechanisms allowing sICAM-1 generation have not been completely elucidated. *In vitro* studies using cultured endothelial cells established that sICAM-1 simply reflects ICAM-1 expression on these cells [16]. Therefore, ICAM-1 shedding from the cell membrane via proteolytic cleavage facilitated by specific proteases has been proposed [17, 18]. However, other studies report on the presence of messenger RNA transcripts coding in cells, specific for soluble ICAM-1 [2, 19]. Therefore, at least two mechanisms must be involved in sICAM-1 generation.

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 [20, 21]. 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 [22]. The characteristic bend occurs between third and fourth domain [22]. The molecule is built of 453, mainly hydrophobic, amino acids, with about 90 amino acids coming into each domain [22]. 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 [21]. 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 [3].

As the membrane-bound form, soluble ICAM-1 demonstrates avidity for leukocyte LFA-1 depending on the form of the molecule. Monomeric sICAM-1, consisting of all extracellular domains, and truncated sICAM-1 forms composed of domains 1 and 2, exhibit low affinity for LFA-1, and therefore these forms are not considered LFA-1/ICAM-1 mediated immune responses inhibitors [23]. Dimerization of immobilized sICAM-1, however, results in the 1.5-3-fold higher affinity than that of the monomeric ICAM-1 [24]. Binding to LFA-1 requires some divalent cations. Mg^{2+} and Mn^{2+} ions support high affinity adhesion to LFA-1, while Ca^{2+} ions in high concentrations compete with Mg^{2+} ions, thus decreasing the ability of sICAM-1 to bind LFA-1 [25] *(Figure 1)*.

CLINICAL SIGNIFICANCE

ICAM-1 and its circulating form have been implicated in the development of any number of diseases. ICAM-1

Table 1
Soluble ICAM-1 inducers and inhibitors

Inducers	Inhibitors
TNF-α	IL-10
IL-1	TGF β-1
IL-6	Rhinoviruses
IFN-γ	Insulin
Angiotensin II	n-3 fatty acids
Saturated fatty acids	Antioxidants
Alcohol	

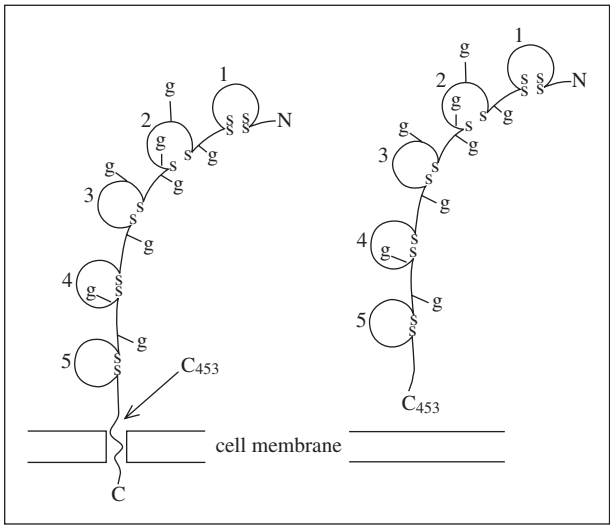

Figure 1
Structures of ICAM-1 and sICAM-1. 1-5, extracellular domains. S, sulphur atom in disulphide bonds stabilizing the domains. g, potential sites of glycosylation.

present on endothelial cells allows transendothelial leukocyte migration to sites of inflammation initiating angiogenesis [26, 27]. 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 [28]. *In vivo* it induced neovascularization in chicken eggs [28]. Recently, the same researchers have established that human sICAM-1 stimulates tumour cell growth in mice injected with tumour cells [29]. These findings are a step forward in the understanding of the pathogenesis of angiogenesis-dependent diseases, such as cancers and rheumatoid arthritis.

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 down-regulation of sICAM-1 release at the same time [2]. This mechanism appears to promote epithelial cell infectivity. Interestingly sICAM-1 has been found to prevent cellular infection and replication of viruses [30, 31], thus constituting a defence mechanism for cells.

Autoimmune diseases

In rheumatoid arthritis (RA), soluble isoforms of several types of cellular adhesion molecules (sCAM) have been described [32-34]. 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 [1, 3]. In RA synovial tissue, the main sources of sICAM-1 are endothelial cells [35]. Moreover, in RA complicated by vasculitis, sICAM-1 concentrations rise markedly as compared to patients without symptoms of vasculitis [36, 37]. These findings suggest that higher sICAM-1 levels in RA reflect vascular involvement. Elevated concentrations of sICAM-1 has also been observed in other vasculitis syndromes such as polyarteritis nodosa [38], systemic sclerosis [39, 40], and Wegener's granulomatosis [41].

In Graves' disease (GD) elevated serum sICAM-1 levels are observed compared to both normal controls [22, 42], and the toxic nodular goitre syndrome lacking autoimmunological background [42]. In a study by Wenisch *et al.* [42], a 2-month GD therapy with methimazole brought a 100 ng/ml fall in the serum sICAM-1 level, however levels of the molecule remained significantly elevated. The study also showed that sICAM-1 levels did not correlate with thyroid hormones *(Table 2)*.

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 [43, 44]. 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 [45]. 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 [46]. Angiotensin II (Ang II), a potent vasoconstrictor, stimulates ICAM-1 expression in a direct or indirect manner [47], and increases sICAM-1 release *in vivo* [48]. 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* [49].

A cross-sectional analysis of markers of systemic vascular inflammation among apparently healthy women suggests that smoking may be a factor for the development of inflammation [50], while inflammation has been recognized as crucial for the development and progression of atherosclerosis [51].

In unstable angina pectoris, the sICAM-1 concentration in peripheral blood was found to be significantly elevated as compared to stable angina and healthy controls. This observation supports possible role of sICAM-1 as a marker of ongoing inflammation in the atherosclerotic plaque [52]. In atheroma, membranous ICAM-1 is highly expressed by endothelial cells and macrophages [53]. The evidence shows that soluble ICAM-1 is associated with the risk of developing at least one atherosclerotic plaque in carotid or femoral arteries [54]. Healthy male subjects with baseline plasma sICAM-1 in the top quartile of the health-related reference interval, are at higher risk of developing myocardial infarction (MI) than those in the lowest quartile [55].

Table 2
Concentration of sICAM-1 in body fluids in diseases

Disease	sICAM-1 in disease (ng/ml)	sICAM-1 in controls (ng/ml)	Significance	Reference
Cerebrospinal fluid				
Bacterial meningitis (children)	25.9 ± 12.6 [5]	0 [22]	< 0.05	78
Viral meningitis (children)	0.44 ± 0.2 [39]	0 [22]	< 0.05	78
Neuroborreliosis (children and adults)	6.6-42.8 [11]	2.2-9.8 [11]	NC	76
Serum or plasma				
Neuroborreliosis (children and adults)	250 [11]	251 [11]	NS	76
Rheumatoid arthritis	378.9 ± 74.7 [54]	257.9 ± 43.4 [30]	< 0.001	106
Rheumatoid arthritis	309.45 ± 99.76 [22]	183.69 ± 25.27 [10]	< 0.0001	32
Rheumatoid vasculitis (women)				
Mild	271 ± 79 [10]	267 ± 45 [18]	NS	103
Moderate	391 ± 166 [18]	267 ± 45 [18]	0.0038	103
Severe	369 ± 92 [9]	267 ± 45 [18]	0.0008	103
Polyarteritis nodosa	488.5 ± 201.3 [22]	246.8 ± 65.8 [13]	< 0.0001	38
Systemic sclerosis	610 (518-745) [13]	316 (302-424) [11]	< 0.001	107
Unstable angina	373 ± 18 [15]	208 ± 13 [15]	< 0.0001	52
Angina				
Stable	126 ± 8 [19]	120 ± 10 [16]	NS	109
Unstable	217 ± 14 [20]	120 ± 10 [16]	< 0.01	109
Hypercholesterolemia	352.4 ± 57.9 [40]	114.9 ± 89.6 [20]	< 0.001	61
Hypercholesterolemia	298 ± 29 [14]	198 ± 14 [13]	< 0.01	58
Hypertriglyceridemia	342 ± 31 [13]	198 ± 14 [13]	< 0.001	58
Hypertriglyceridemia	316 ± 28.8 [39]	225 ± 16.6 [20]	0.0005	59
Schizophrenia	248 ± 95 [36]	322.9 ± 74.4 [36]	0.000	82
Melanoma				
Primary malignant	342 ± 129 (170-650) [32]	178 ± 34 (153-258) [17]	< 0.001	71
Metastatic	482 ± 314 (156-1280) [21]	178 ± 34 (153-258) [17]	< 0.001	71
Gastric cancer	222 ± 119 [224]	231 ± 73 [44]	NS	72
Gastric cancer				
Stage I-II	306.0 ± 82.3 [11]	236.9 ± 74.3 [20]	NS	70
Stage III-IV	397.1 ± 102.4 [23]	236.9 ± 74.3 [20]	< 0.05	70
Colorectal cancer	285 (195-365) [63]	203 (138-245) [51]	0.00005	69
Laryngeal cancer				
Stage II	309.6 ± 60.3 [10]	273.7 ± 63.7 [34]	< 0.05	110
Stage III	360.7 ± 94.5 [12]	273.7 ± 63.7 [34]	< 0.001	110
Stage IV	422.4 ± 96.5 [13]	273.7 ± 63.7 [34]	< 0.001	110
Graves' disease	286.6 ± 32.4 [86]	197 ± 35 [100]	< 0.001	108
Graves' disease	556 ± 131 [33]	184 ± 88 [36]	< 0.05	42
Toxic nodular goitre	386 ± 129 [34]	184 ± 88 [36]	< 0.05	42
Heart graft coronary disease	373.27 ± 183.52 [15]	235.3 ± 123.97 [10]	0.049	86
Suction blister fluid				
Systemic sclerosis				
Involved skin	83 (52-162) [13]	44 (41-64) [11]	< 0.05	107
Uninvolved skin	136 (113-199) [13]	44 (41-64) [11]	< 0.001	107

Numbers in round brackets represent ranges. Numbers in square brackets are numbers of subjects. NS: not significant. NC: not calculated.

In one study, each 100 ng/ml increase in the molecule was associated with almost a 30% increase in the risk of future coronary events [56]. All these facts taken together show that the circulating form of ICAM-1 should be considered the marker of future coronary heart disease (CHD) [55, 57].

Elevated sICAM-1 levels in hypertriglyceridemia and hypercholesterolemia are a consequence of the development of atherosclerosis [58]. Hypertriglyceridemic subjects with low HDL have markedly elevated serum ICAM-1 concentrations [59]. Positive correlation between sICAM-1 and parameters such as triglycerides, fibrinogen, tissue-type plasminogen activator antigen and total homocysteine, and negative correlation for sICAM-1 and HDL, has been also described [44]. Although cholesterol-lowering statin therapy brings about a decrease in ICAM-1 expression by macrophages [60], it does not alter sICAM-1 levels [58, 61].

Insulin-resistant subjects are specifically predisposed to developing atherosclerosis and CHD. The degree of insulin resistance correlates with plasma sICAM-1 [62]. Interestingly, insulin infusions diminish sICAM-1 titres [63]. This may be a result of insulin-suppressed ICAM-1 expression on endothelial cells [64].

Cancers

Human melanoma and prostatic carcinoma cells are capable of expressing ICAM-1, and release sICAM-1 from their surface [65, 66]. This sICAM-1 release from mela-

noma cells is inducible by the proinflammatory cytokines IFN-γ and TNF-α [65]. 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 [1]. Interestingly, circulating forms of ICAM-1 were found to inhibit the interaction between T cells and tumours [67], and block NK cell-mediated toxicity [65]. These findings are a possible explanation for tumour escape from immunosurveillance.

Serum sICAM-1 levels correlate with tumour progression in melanoma [68] and colorectal cancer [69]. They are also associated with tumour size. Liu *et al.* [70] found that those subjects who developed gastric cancer greater than 5 cm in size, had significantly elevated sICAM-1 concentration in serum as compared to those with smaller tumours.

In malignant melanoma, soluble ICAM-1 correlates with the level of another soluble receptor – sTNF-Rs [71]. Therefore, it was hypothesized that sICAM-1 and sTNF-Rs together may contribute to tumour progression [71].

Serum sICAM-1 may reflect tumour metastases [69, 71, 72]. In gastric cancer, significantly elevated sICAM-1 were observed in those patients developing hepatic and lymph node metastases [72]. Elevated preoperative levels of sICAM-1 are prognostic factors for patients survival in colorectal cancer and metastatic breast carcinoma [69, 73].

Neurological disorders

In the central nervous system (CNS) ICAM-1 is expressed on cerebral endothelial cells [10], astrocytes [4], and can be induced on microglial cells [74]. Therefore, these cells in the CNS are sources of circulating ICAM-1 [75]. About one-third of the sICAM-1 detected in normal cerebrospinal fluid (CSF) is brain-derived [76]. In inflammatory diseases of the CNS however, the elevated sICAM-1 levels in the CSF come mainly from this fraction [76, 77]. Meningeal infections of bacterial or viral origin bring about an increase in sICAM-1 release into the CSF [77, 78]. The release however is more spectacular in bacterial infections [78]. Elevated sICAM-1 levels in CSF and serum were also found in multiple sclerosis (MS) [79, 80]. The serum levels correlated with disease activity [11, 79, 81].

In other neurological diseases, such as schizophrenia [82] and migraine [83] reduced levels of sICAM-1 can be observed. Diminished sICAM-1 in schizophrenia possibly results from an impairment in the immune system function, reflected by lower INF-γ production [84] and reduced lymphocyte stimulation by some antigens [85].

Transplantation and graft rejection

It has been well documented that heart transplant recipients show high sICAM-1 titres [86]. These elevated sICAM-1 levels in one study were related to the subsequent development of transplant-associated vasculopathy [87]. However, other researchers have not confirmed these findings [88]. 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 [87]. Therefore, the authors conclude that sICAM-1 can be useful for assessment of transplant CAD, posttransplant ischemic events, and cardiac graft failure.

Infections and graft rejection are serious complications after organ transplantations. Elevated levels of serum ICAM-1 were reported in rejection syndrome after allograft transplantations of heart, liver and kidney [89, 90, 91]. Daniel *et al.* [92] found that renal graft recipients, a day before rejection, had significantly higher plasma sICAM-1 titres than those successfully treated, whereas the patients with graft infection had elevated sICAM-1 level even four to one day before infection. Urinary sICAM-1 could be also a useful parameter for screening patients at risk of renal graft rejection since an increase in the urinary sICAM-1 concentration may be observed even several days before acute rejection [14]. This significant rise can be explained either by macrophage activation and/or intensive sICAM-1 release from the tubular epithelial cells in kidneys [14].

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 [93, 94].

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 [95, 96].

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 [97], its level in food [98], and the presence of other nutrients. It was found that saturated fatty acids and high-fat meals stimulate sICAM-1 release [97, 98]. 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 [98]. In pathological states associated with an impairment in the lipid metabolism, high sICAM-1 levels were observed [59]. Hypertriglyceridemia treatment with unsaturated fatty acids, that exert beneficial effect on lipids in humans, equally seems to manifest beneficial activity on the sICAM-1 levels. The administration of ethyl esters of n-3 fatty acids to hypertriglyceridemic subjects results in markedly reduced serum ICAM-1 concentrations following triglyceride and total cholesterol reduction, and an increase in the HDL cholesterol [59]. The effect was observed after a long period of treatment that lasted for over six months. Short-term n-3 fatty acid administration proved to be inefficient.

Frequent alcohol use raises serum ICAM-1 in humans [44]. Chronic alcohol intoxication in rats intensifies ICAM-1 expression on neutrophils [99]. These findings indicate that elevated sICAM-1 levels may be a consequence of an increase in the ICAM-1 expression on cells.

Antioxidant vitamins and selenium were found to downregulate ICAM-1 expression on endothelial cells with sub-

sequent sICAM-1 reduction in serum. High vitamin E intakes, either with food or supplements, result in an accumulation of this vitamin in the cells of immune defence and endothelium [100]. Vitamin E is one of the best described dietary factors that lowers sICAM-1. In a supplementation study by Desideri *et al.* [101] low dose α-tocopherol (50 IU/day) administered for 20 weeks to healthy subjects brought a significant sICAM-1 reduction in these subjects. However, higher doses of vitamin E, 400 IU daily, taken for two years, proved to be ineffective in lowering the sICAM-1 concentration in male normolipidemic chronic smokers [102]. In a study by Silvestro *et al.* [92], intravenous infusions of vitamin C (50 mg/min for 20 minutes) prevented the exercise-induced sICAM-1 rise in plasma of intermittent claudicants.

Selenium is an important factor that may be involved in the regulation of sICAM-1 shedding. The authors of the present paper have recently found that circulating ICAM-1 concentrations in healthy subjects negatively correlate with serum selenium [103]. This finding can be linked to the modulating effect of selenium on cytokine-induced expression of ICAM-1 on endothelial cells regarded as a source for ICAM-1. Previous studies established that cytokine-stimulated, selenium-deficient endothelial cells expressed higher levels of mRNA for ICAM-1 [104]. Conversely, human TNF-α-stimulated endothelial cells treated with selenite showed significantly reduced levels of respective mRNA [105]. This latter study proved that selenite might inhibit ICAM-1 expression in a dose-dependent manner.

CONCLUSIONS

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.

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