Intercellular Adhesion Molecule 1 in Rheumatoid Arthritis

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Abstract

Background: Joint and extra-articular inflammation are hallmarks of rheumatoid arthritis (RA), a systemic autoimmune illness. This condition is long-lasting and mostly affects the synovial joints. Untreated, it spreads from its initial presentation in minor peripheral joints to larger proximal joints. Cartilage and bone deterioration occur as a result of chronic inflammation in a joint. Early RA is diagnosed when symptoms have been present for less than six months, while established RA is diagnosed when symptoms have been present for more than six months. Selectins, integrins, cadherins, nectins and other members of the IgSF, and other adhesion molecules such mucins are the five main classes of adhesion molecules. Some enzymes, such as vascular adhesion protein 1 (VAP-1), contribute to cell adherence alongside the more well-known adhesion molecules. Intercellular adhesion molecule 1 (ICAM-1) is a transmembrane protein in the immunoglobulin superfamily expressed on the surface of multiple cell populations and upregulated by inflammatory stimuli. It mediates cellular adhesive interactions by binding to the _2 integrins macrophage antigen 1 and leukocyte function-associated antigen 1, as well as other ligands. Many of these molecules play an important role in the mechanism of disease in rheumatoid arthritis.

Keywords: Intercellular Adhesion Molecule 1, Rheumatoid Arthritis

Introduction

RA is a systemic autoimmune disease characterized by inflammatory manifestations that involve joints as well as extra-articular sites. It is a chronic disorder that primarily involves synovial joints. It typically starts in small peripheral joints, is often symmetric, and progresses to involve proximal joints if left untreated. Joint inflammation over time leads to its destruction with cartilage and bone erosion. RA with a symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is defined as established RA. Rheumatoid arthritis is characterized by the presence of autoantibodies including rheumatoid factor (RF) **(1).**

Epidemiology:

The prevalence of RA has been rising since 1990 up to date. The largest increase was observed in the Spanish population. However, in Japan and Argentina the prevalence ratios have decreased over the years. The global prevalence ratio of RA is about 1% and it is more common in women, with small continuous fluctuations and an apparent growth from south to north, and from rural to urban areas **(2).**

In Egypt, **El-Anwar (3)** reported a female to male sex ratio of 7:1. As regards Sharkia Governorate, the prevalence rate of RA was found to be 3 per thousand in general population, as reported by Makawi **(4),**

while It Was documented that the overall female to male ratio was 6:1.

The incidence of RA varies by age and population. Studies have been conducted over years to measure the incidence in certain geographical areas and for identifying variables that have led to different results. Lower incidence rates have been reported in Japan (8 cases per 100,000 inhabitants), and France (8.8 cases per 100,000 inhabitants). The highest incidence rate has been observed in the US (44.6 cases per 100,000 inhabitants) **(5).**

Taylor-Gjevre and coworkers (6) have reported differences in incidence rates at the regional level within countries. One potential explanation for these variations may have been environmental exposure to chemicals, climatic changes, infectious diseases, and food. Furthermore, it has been reported that people with a low socio-economic background, living in rural areas during childhood, are at a higher risk of developing RA in adulthood **(6).**

Innate and adaptive immunity both contribute to the pathogenesis of RA. Genetic predisposition places individuals at risk for RA, perhaps due to abnormal T-cell selection or elevated cytokine production. Several events, such as environmental exposures, might enhance immune reactivity and permit a breakdown of tolerance. Nonspecific inflammation due to environmental exposures or endogenous ligands, such as stimulation of the toll like receptors (TLR), can also directly induce cytokine production, activate synoviocytes and macrophages that secrete chemokines, and recruit lymphocytes that can respond to local antigens. Self-antigens derived from the inflamed tissues can be processed by tissue dendritic cells, which migrate to central lymphoid organs and activate T cells. B cells and T cells activated in the central tissues can subsequently migrate back to the joint. At later stages, local cytokine networks amplify and maintain a selfsustained inflammatory loop within the joints and perhaps lead to local antigen presentation and the formation of secondary lymphoid aggregates. The activation of enzymes that degrade the matrix and osteoclasts can cause irreversible joint destruction **(7).**

Humoral adaptive immunity is integral to rheumatoid arthritis. Synovial B cells are mainly localized in T-cell–B-cell aggregates (indeed, some tissues have ectopic lymphoid follicles) that are supported by the expression of factors that include a proliferation-inducing ligand (APRIL), B-lymphocyte stimulator (BLyS), and CC and CXC chemokines (e.g., CXC chemokine ligand 14 and CC chemokine ligand 21) **(8).**

A pathogenic role for $CD20^+$ B cells is confirmed by the efficacy of rituximab (anti-CD_{20} monoclonal antibody "medication" IV) in rheumatoid arthritis. Because plasma cells are not targeted by anti-CD20 antibodies, and autoantibody levels are variably altered after treatment, these clinical observations suggest that the role of B cells and their progeny in the pathogenesis of rheumatoid arthritis goes beyond autoantibody production to include autoantigen presentation and cytokine production [e.g., interleukin (IL)-6, TNF-α, and lymphotoxin-β] **(9).**

The genetics of rheumatoid arthritis and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis. However, even though T cells are abundant in the synovial milieu, the functional role of T cells remains insufficiently understood. Direct targeting of T cells by cyclosporine or T-cell–depleting therapeutics has shown limited or no efficacy **(10-14).**

ICAM-1 is a transmembrane protein in the immunoglobulin superfamily expressed on the surface of multiple cell populations and upregulated by inflammatory stimuli. It mediates cellular adhesive interactions by binding to the 2 integrins macrophage antigen 1 and leukocyte function-associated antigen 1, as well as other ligands. Many cells exhibit basal expression of ICAM1, which is highly upregulated by a wide variety of inflammatory stimuli, including the cytokines tumor necrosis factor alpha, interleukin 1

beta, interferon gamma, and interleukin 6 (IL-6), as well as reactive oxygen species, high glucose, and shear stress **(15).**

It was discovered that ICAM-1 protein acts as a natural ligand for the cell surface lymphocyte function-associated antigen 1 (LFA1, also known as CD11a) and macrophage antigen 1 (Mac-1, also known as CD11b/CD18). **(15).**

Van Den Engel and associates **(16)** analyzed a cDNA clone of ICAM-1 gene and found its homology to the neural cell adhesion molecule (NCAM). Besides the membrane-bound protein, ICAM-1 may also be present in the blood as a soluble protein (sICAM1).

General features of ICAM-1:

The molecular weight of ICAM-1 varies from 80 to 114 Kad which mainly depends on glycosylation level but core protein having molecular weight of ~60 kDa. It contains five extracellular immunoglobulins like domains constituting ~453 amino acids with higher hydrophobicity. Every extracellular domain is stabilized by disulfide bonds.

extracellular portion is connected with short cytoplasmic tail by hydrophobic transmembrane region of around 24 amino acid residues. Single tyrosine residue at cytoplasmic tail may be significantly involved in signaling. ICAM-1 gene consists of 15 kb and is located on human chromosome 19 (cytogenetic location: 19p13.2). Extensive alternative splicing and products of spliced proteins or isoforms of ICAM-I differing in their expression and ligand binding are also observed **(17)**

The gene sequence of ICAM-1 consists of seven exons, among which exon 1 encodes the signal sequence, exons 2–6 each encodes one of the five extracellular domains, and exon 7 encodes transmembrane region and cytoplasmic tail. Various nucleotide polymorphisms have been observed in exons 4, 5, and 6. The substitution from glutamic acid to lysine in exon 6 was found to be associated with coronary heart disease, myocardial infarction, and peripheral artery disease **(18).** Structure of intercellular adhesion molecule 1:

ICAM-1 protein is a member of the immunoglobulin superfamily which also consists of antibodies and T-cell receptors. ICAM1 protein forms a dimeric structure with two amino terminals (D1 and D2), three carboxy terminals (D3–D5), a transmembrane region, and a cytosolic tail. ICAM-1 protein's extracellular domains contain multiple loops, and each loop contains disulfide bridges within loop. Further analysis of domain D1 of ICAM-I shows its relationship with "I" set of the immunoglobulin superfamily which is critical for binding to lymphocyte function associated antigen 1 (LFA-1) receptor. There are flexible FG and BC loops on the tip of domain D1, and domain D2 has conserved region in the BC loop. Domain D2 of ICAM-1 belongs to the V, C1, C2, and I set of immunoglobulin superfamily and is similar to domain 2 of the VCAM 1 and ICAM-2. Domain D3 belongs to the I-1 subset of the immunoglobulin superfamily and is made up of two b sheets similar to ICAM-I D1. Domain D4 has only five b strands, and D4 has floppy irregular region present within it **(19)**

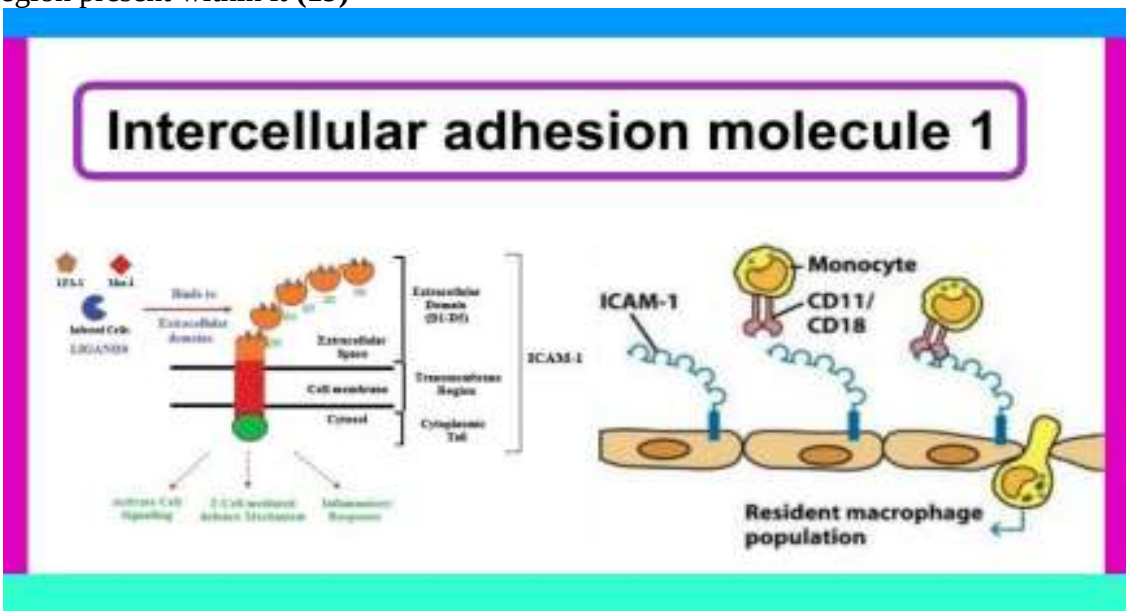

Figure (1): Intercellular adhesion molecule 1 **(19)** ICAM-1's functions:

Mac-1 and LFA-1 are expressed on endothelial cells and leukocytes. Therefore, when these proteins interact and bind to ICAM-1, transmigration of leukocytes across vascular endothelia is facilitated resulting in extravasation and endothelial inflammation. Due to these binding properties, ICAM-1 is largely implicated in intercellular adhesion. The basic function of ICAM-1 is the generation of a specific and reversible cell-cell adhesion resulting in intercellular communication, T-cell-mediated defense mechanism,

and inflammatory response **(20).**

However, the role of ICAM-1 as a simple adhesion molecule became more broadened with new discovery of ICAM-1's ability to serve as respiratory epithelial cell surface receptor of human rhinovirus, the causative agent of most common colds. It has been found that ICAM-1 binds also with Plasmodium falciparum-infected erythrocytes. This demonstrates the unique ICAM-1 role in viral and parasitic infectious diseases in addition to its role in cell surface adhesion molecule **(21).**

Sligh et al. (22) observed that surface ICAM-1 expression is not a prerequisite for survival. However, ICAM-1 deficiency caused aberrant immune and inflammatory responses such as moderate granulocytosis, impaired neutrophil migration during chemical peritonitis, and reduced contact hypersensitivity.

Gottrand et al. **(17)** demonstrated that disrupted ICAM-1 express truncated ICAM-1 isoforms lacking transmembrane domain. They further studied the effect of ICAM-I disruption, and results revealed impaired thymocyte development, peripheral T-cell distribution, T-cell activation, and T regulatory (Treg)-suppressive activity in mice containing disrupted ICAM-I which further supported vitality of ICAM-I in Treg development and suppressive function in immune response. In addition, a potential role for ICAM-1 in signal transduction is explored. Besides its classical role as an adhesion molecule, ICAM-1 is also involved in pro-inflammatory cell signaling pathways and recruits macrophages and granulocytes through cell signalling during inflammation **(18).**

Depending upon cell type, ICAM-1 has been shown to contribute in the signal transduction through outside in signaling events. ICAM-1 has also been observed to activate phosphorylation-dependent kinases resulting in activation of transcription factors, cytokine production, membrane-bound protein expression, ROS production, and cell proliferation **(18).**

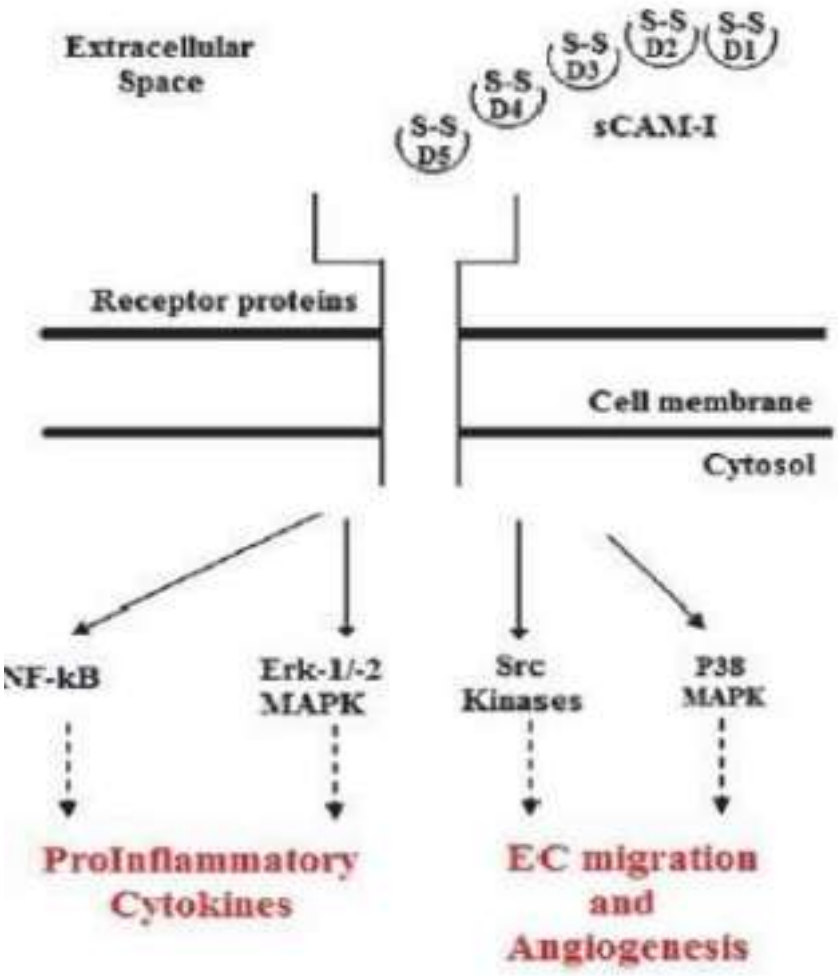

Figure (2): Schematic representation of soluble ICAM-1 mechanism **(16)**

Pathological role of intercellular adhesion molecule 1 and anti-intercellular adhesion molecule 1 in therapy:

ICAM-1 is constitutively present on endothelial cells, but its expression is increased by pro-inflammatory cytokines. The endothelial expression of ICAM-1 is increased in atherosclerotic and transplant associated atherosclerotic tissue and in animal models of atherosclerosis. A soluble ICAM-1 (sICAM-1) is elevated in the serum of patients with cardiovascular disease, autoimmune disorders, as well as various cancers. While increased level of inflammatory condition enhances ICAM-1 expression, once expressed, ICAM-1 further enhances inflammation and oxidative stress and thereby complicates various diseases. It has been found that ICAM-1 has an important role in hypersensitivity type I reaction, where ICAM-1 interacts with its receptors and thus recruits pro inflammatory lymphocytes and mast cells in ocular allergies **(23).**

In subarachnoid hemorrhagic patients, ICAM-1 level is significantly elevated as compared to control. However, ICAM-1 is not directly linked to cerebral vasospasm in these patients, but an anti-ICAM-1 antibody therapy relieved the symptoms in 70% of patients implicating the role of ICAM-1 in this disease. In addition, ICAM-1 is also involved in many complications such as cancers of myeloid and lymphoid origin, acquired immunodeficiency syndrome, and allergic asthma. In Sjogren syndrome, expression of HLA-DR antigen and ICAM-1 in human conjunctival epithelium is upregulated in patients with dry eyes **(23).**

Clinical significance:

ICAM-1 and its circulating form have been implicated in the development of many diseases. ICAM-1 present on endothelial cells allows transendothelial leukocyte migration to sites of inflammation initiating angiogenesis (development of new blood vessels) **(24).**

Gho et al. (25) 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 RA.

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 **(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 **(27).**

Bongard et al. (28) showed that soluble ICAM-1 is associated with the risk of developing at least one atherosclerotic plaque in carotid or femoral arteries. 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.

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 tumor cells were also found to induce ICAM-1 shedding mediated by IL-1a in

cultured endothelial cells. Interestingly, circulating forms of ICAM-1 were found to inhibit the interaction between T cells and tumors, and block NK cell-mediated toxicity. These findings are a possible explanation for tumor escape from immunosurveillance. Serum sICAM-1 levels correlate with tumor progression in melanoma and colorectal cancer. They are also associated with tumor size **(29).**

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 ICAM1. 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 (**30).**

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. In other neurological diseases, such as schizophrenia and migraine 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-c production and reduced lymphocyte stimulation by some antigens **(31).**

Transplantation and graft 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, **Wu et al. (32)** have not confirmed these findings.

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 **(33).**

Daniel et al. (34) 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. This significant rise can be explained either by macrophage activation and/or intensive sICAM-1 release from the tubular epithelial cells in kidneys.

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 **(35).**

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. 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 sICAM1 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 **(36).**

In a supplementation study by **Desideri et al. (37),** low dose atocopherol (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. In a study by Silvestro et al**. (35),** intravenous infusions of vitamin C (50 mg/min for 20 minutes) prevented the exercise-induced sICAM-1 rise in plasma of intermittent claudicants (cramps or sense of fatigue ion muscles of lower extremity).

Selenium is an important factor that may be involved in the regulation of sICAM-1 shedding. It has been

found that circulating ICAM-1 concentrations in healthy subjects negatively correlate with serum selenium. 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 **(38).**

Zhang et al. (39) established that cytokine-stimulated, selenium deficient endothelial cells expressed higher levels of mRNA for ICAM-1. Conversely, human TNF-α-stimulated endothelial cells treated with selenite showed significantly reduced levels of respective mRNA. Selenite might inhibit ICAM-1 expression in a dose-dependent manner.

Intercellular adhesion molecule 1 in rheumatoid arthritis

Several studies suggested a role of ICAM-1 in RA. ICAM-1 is a molecule involved in several steps of the recruitment and activation of leucocytes at the site of inflammation. In RA, the activation and recruitment of synoviocytes is partially dependent on the interaction of ICAM-1 with its counter-receptor integrins LFA-1 and MAC-1. ICAM-1 is a cell surface glycoprotein whose expression on immune, endothelial and epithelial cells is up-regulated in response to inflammatory stimuli. Its role has been best demonstrated in leukocyte transendothelial migration where it controls leukocyte rolling and adhesion with the endothelial vessel wall. It also regulates leukocyte crossing of the endothelial layer. Genetic variants affect the functional domains of the molecules that are related with leukocyte integrin binding. So, human ICAM-1 gene single base polymorphism is possible factors for RA development **(40)**

This is evidenced by that the 241-Lys/Arg substitution is located at the third domain of the ICAM-1 molecule, the counterpart of MAC-1 can modifies the functional activity of the ICAM-1 molecule leading to a different recruitment and activation of the inflammatory cells. The expression of ICAM-1 over the surface of chondrocytes induces the adhesion of T cells and eventually the death of the cells. Both the synovial and the serum soluble forms of the molecule are correlated to disease activity (Ritchie articular index and morning stiffness), erythrocyte sedimentation rate and Creactive protein, but these data have not been confirmed by Mulherin **et al. (41**).

As previously mentioned, genetic predisposition is considered an important risk factor for RA. Several genes either of the MHC or non-MHC regions have been found to be associated with the occurrence of RA in various populations. The genes of the MHC region include DR4, DR1, and DR10 and the non-MHC genes linked to the occurrence of RA are the TCR, immunoglobulin variable heavy (VH), prolactin and corticotrophin release hormone genes. The MHC region is located at chromosome 6p21 and other non-MHC genes related to the development or clinical expression of RA (namely the TCR, immunoglobulin VH, prolactin and corticotropin release hormone genes) are located at chromosomes other than chromosome 6 and a linkage with the ICAM-1 gene variants is improbable Two genes located in the MHC region were found to have a protective effect on the radiological and extra-articular (EA) manifestations of RA. The first is the HLA-DR2 gene, which was associated in one study with less severe joint damage and a lower prevalence of EAFs. The second is the TNF- alpha promoter gene, of which at least 4 allelic variants have been disclosed at positions -376, -308, -244, and -238. The -238A polymorphism was associated with less severe joint damage in a series of RA patients followed during the first 3 years of disease **(42).**

Whereas, other genes seem to be associated with the expression and severity of the disease. In particular the presence of DR4, DR1 or DR10 or the shared epitope of the third region of hypervariability of the chain of the DRB1 gene have been found to be linked to the development of more severe articular and extra-articular manifestations. The presence of the rheumatoid epitope is associated with more severe radiological disease. Among the genes located outside the MHC locus that have intimate associations with RA disease is the gene of ICAM-1 which is localized at chromosome 19. Two single base polymorphisms of the gene have been described at positions 241 (GGG or AGG) and 469 (AAG or GAG) which led to an amino acid change to the ICAM-1 protein sequence (Lys or Glu in position 241 and Gly or Arg in position 469). The polymorphism at codon 241 is located in exon 4 which codes for the Ig-like domain 3, binding site of the MAC-1 integrin, and the polymorphism at codon 469 is located in exon 6 which codes for Ig-like domain 5 whose binding activity is not yet known **(43).**

Macchioni et al. (44) have evaluated the frequency of ICAM 1 polymorphism at codons 241 and 469 in a consecutive series of 78 RA patients of Italian origin who tested positive for rheumatoid factor and who

presented an articular erosive disease. They showed that G/R ICAM-1 gene polymorphism may contribute to susceptibility to RA in the Italian population of seropositive patients and could drive the synovitis toward a less aggressive form. This analysis could confirm the protective role of ICAM-1 gene variants on the clinical severity of RA.

Navarro-Hernandez et al. **(40)** investigated the association of sICAM-1 and sVCAM-1 with ICAM1 721G>A and VCAM11238G>C polymorphisms and rheumatoid arthritis (RA) clinical activity, sixty RA patients and 60 healthy non-related subjects [healthy subjects (HS)] matched for age and sex were recruited. They showed increased levels of sICAM-1 and sVCAM-1 in RA patients (284 and 481 ng/mL) versus HS (132 and 280

ng/mL); in the RA group, significant correlations between sVCAM-1 and RF, ESR, SpanishHAQ-DI, and DAS28 were found, whereas sICAM-1 only correlated with RF. In RA patients, a significant association with the 721A allele of ICAM1 polymorphism, was found. In addition, the allele impact (G/A + A/A) of this polymorphism was confirmed. sVCAM1 and sICAM-1 serum levels reflected the clinical status in RA, independently of the ICAM1 and VCAM1 polymorphism. However, the ICAM1 721A allele could be a genetic marker to RA susceptibility.

Moreover, other genes located in the same area of chromosome 19, in close proximity to the ICAM-1 gene and found to influence the inflammatory response, are the genes of ICAM-3, MAdCAM-1, IL-11 and human heat shock protein 40. It has been suggested in an open trial on RA patients that anti ICAM-1 antibodies might have a beneficial effect on articular disease. Interestingly, during the treatment of RA patients with antiTNF antibodies, a decreased concentration of ICAM-1 has been observed in the synovial tissue. Several drugs used in the treatment of RA induce both invitro and in vivo the reduction of the expression of ICAM-1 on the cellular surface of inflammatory cells, which parallels the improvement of the indexes of clinical activity **(45).**

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