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REVIEW ARTICLE

Role of Gene Polymorphism of Intercellular Adhesion Molecule 1 (ICAM 1) in Rheumatoid Arthritis

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ABSTRACT

Joint and extra-articular inflammation are hallmarks of rheumatoid arthritis (RA) that is a systemic autoimmune disease. 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. A transmembrane protein belonging to the immunoglobulin superfamily, intercellular adhesion molecule 1 (ICAM-1) is expressed on the surface of several cell types and is stimulated by inflammatory stimuli. By binding to the two integrins, leukocyte function-associated antigen 1 and macrophage antigen 1, as well as other ligands, it mediates cellular sticky connections. Numerous of these molecules are crucial to the rheumatoid arthritis disease process. ICAM-1 gene polymorphism and rheumatoid arthritis clinical activity are related, and a variety of drugs can be used to treat RA by reducing ICAM-1 expression. We aimed in this review to evaluate the role of gene polymorphism of ICAM 1 in rheumatoid arthritis.

Keywords: Intercellular adhesion molecule1, Rheumatoid Arthritis, Polymorphism.

INTRODUCTION

ICAM-1 is a transmembrane protein that is expressed on the surface of various cell types and is activated by inflammatory stimuli. It is a member of the immunoglobulin superfamily. It facilitates cellular sticky connections by binding to ligands such as leukocyte function-associated antigen 1 and macrophage antigen 1, which are both 2 integrins. Many cells exhibit basal expression of ICAM1, which is highly upregulated by a wide variety of inflammatory stimuli, including cytokines tumor necrosis factor alpha, interleukin 1 beta, interferon gamma, and interleukin 6 (IL-6), as well as reactive oxygen species, extreme hyperglycemia, and shear stress [1].A natural ligand for the cell surface antigens lymphocyte function-associated antigen 1 (LFA1, also known as CD11a) and macrophage antigen was found to be the ICAM-1 protein 1 (Mac-1, also known as CD11b/CD18) [2].

General features of ICAM-1:

The molecular weight of ICAM-1 varies between 80 and 114 kDa, mostly determined by the extent of glycosylation. The molecular weight of the core protein is approximately 60 kDa. Its five domains are similar to total immunoglobulins and extracellular immunoglobulins 453 amino acids with increased hydrophobicity. Disulfide linkages maintain the stability of every extracellular

domain. A hydrophobic transmembrane segment of about 24 amino acid residues connects this extracellular part to the short cytoplasmic tail. The cytoplasmic tail's lone tyrosine residue may play a key role in signaling. The 15 kb long ICAM-1 gene may be found at position 19p13.2 on human chromosome 19. Numerous isoforms of ICAM-I with different levels of expression and ligand binding as well as products of spliced proteins are also seen [3]

ICAM-1 has seven exons in its gene sequence, of wherein exons 2 through 6 each encode one of the five extracellular domains; the signal sequence is encoded by exon 1, the transmembrane region and cytoplasmic tail are encoded by exon 7 (figure 1). Numerous nucleotide polymorphisms have been found in exons 4, 5, and 6. It was found that the glutamic acid to lysine change in exon 6 of the gene was associated with coronary heart disease, myocardial infarction, and peripheral artery disease [4].

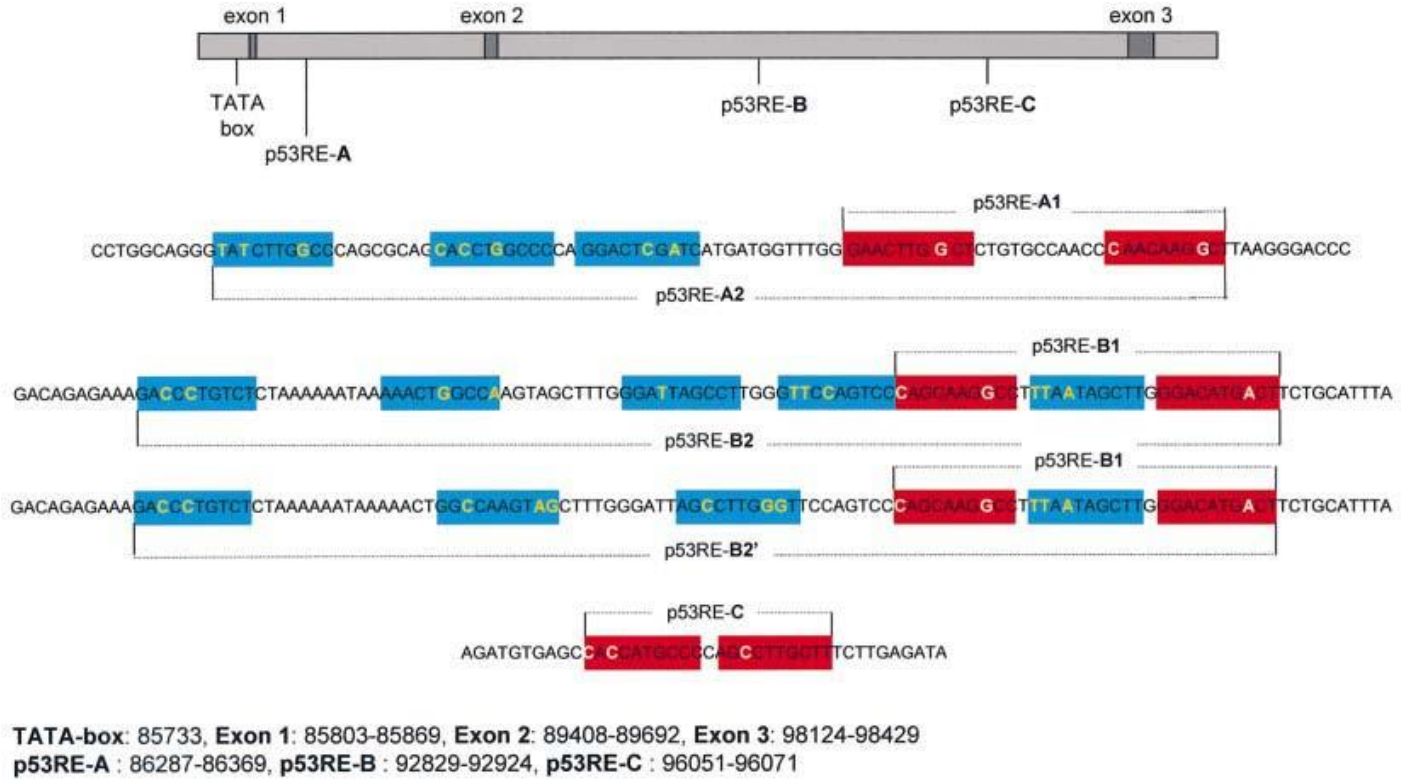

Figure 1:ICAM1 genetic structure [5].

Structure of intercellular adhesion molecule 1:

The immunoglobulin superfamily, which also includes antibodies and T-cell receptors, includes the protein ICAM-1. With two amino terminals (D1 and D2), three carboxy terminals (D3-D5) (Figure 2), a transmembrane region, and a cytoplasmic tail, the ICAM1 protein forms a dimeric structure. The extracellular domains of the ICAM-1 protein have several loops, and each loop has disulfide bridges. The link between domain D1 of ICAM-I and the immunoglobulin superfamily's "I" set, which is essential for binding to the lymphocyte function associated antigen 1 (LFA-1) receptor, is revealed through further investigation. On the tip of domain D1, there are flexible FG and BC loops, and domain D2 has a conserved area in the BC loop. Similar to domain 2 of the

VCAM1 and ICAM-2, domain D2 of ICAM-1 belongs to the V, C1, C2, and I set of immunoglobulin superfamily. ICAM-I D1-like domain D3 is composed of two b sheets and is a member of the immunoglobulin superfamily's I-1 subgroup. Only five b strands make up domain D4, which also has a floppy irregular area [6].

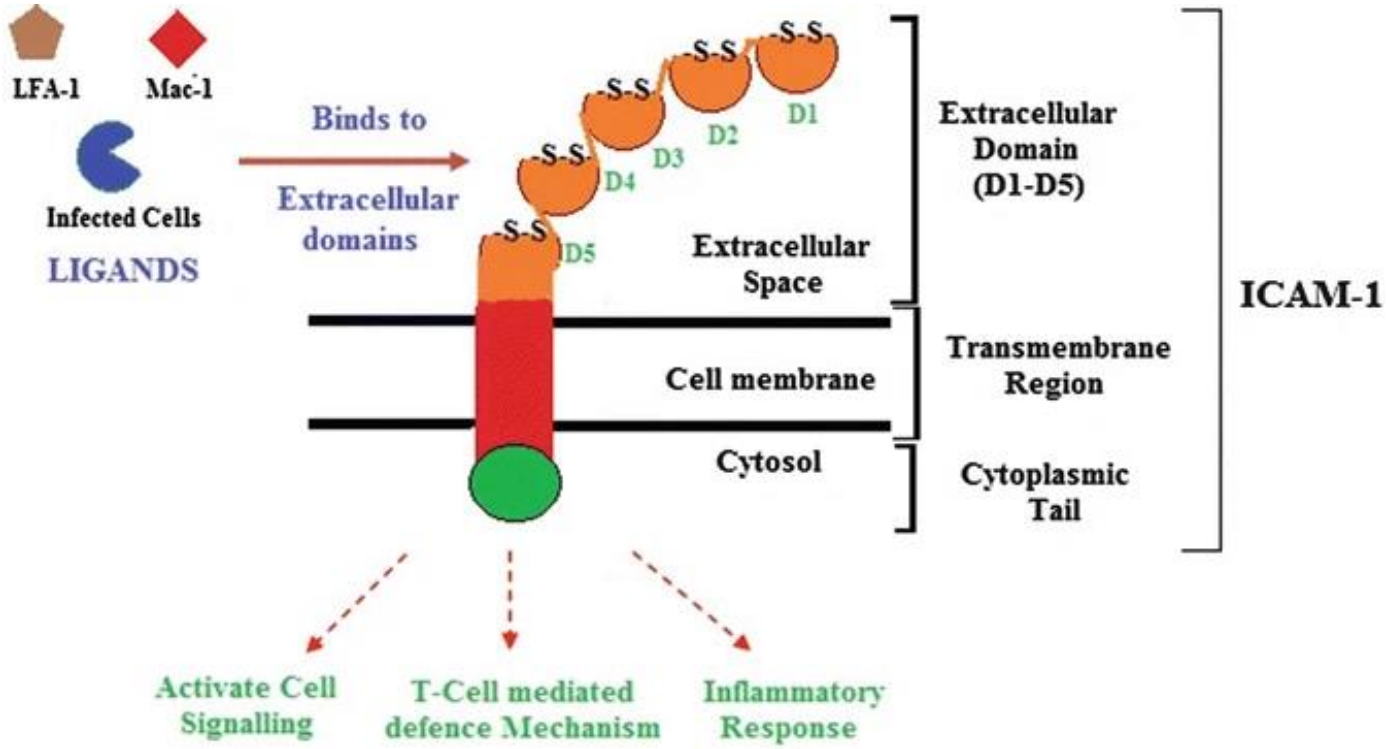

Figure (2): Intercellular adhesion molecule 1 structure [7].

ICAM-1's functions (figure 3):

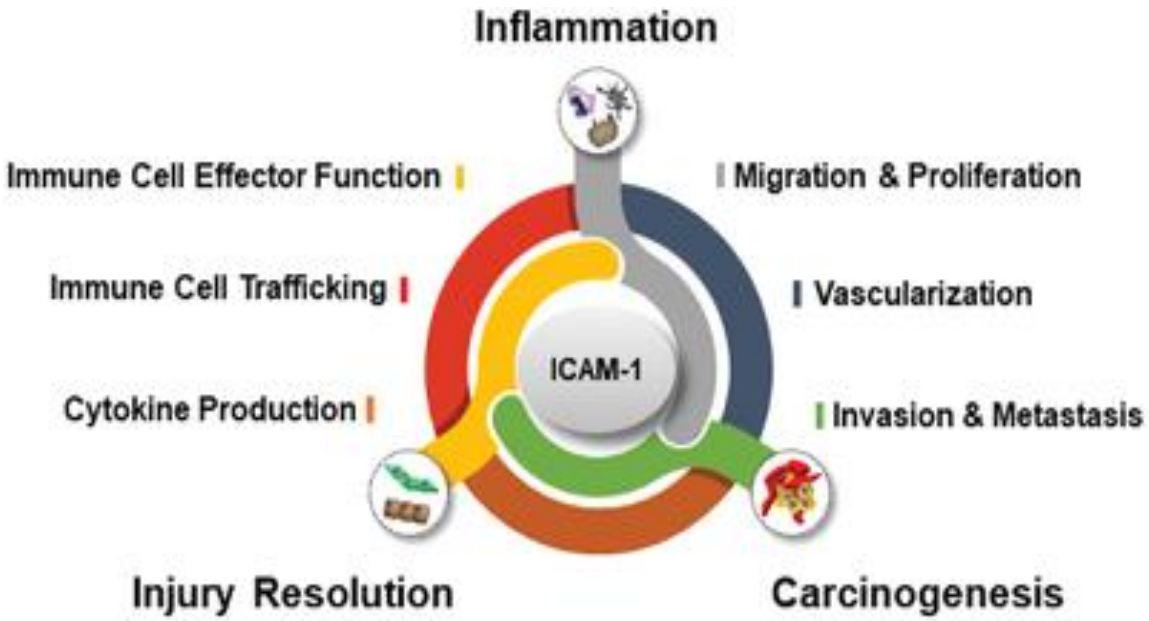

Figure (3): ICAM-1function[8].

Role of intercellular adhesion molecule 1 in cell signaling:

ICAM-1's possible function in signal transduction is investigated. ICAM-1 serves

as an adhesion and virus entry molecule in addition to its traditional functions. During inflammation, it also attracts macrophages and granulocytes and participates in pro-inflammatory cell signaling pathways. ICAM-1 plays a significant role in cell-to-cell communication due to its unique binding characteristics. Furthermore, ICAM-1 has recently been identified as the human rhinovirus's cellular receptor. ICAM-1 performs specific roles in signal transduction in addition to its unique position in immunological responses[4].ICAM-1 participates in inflammatory cell transit, antigen presentation, microbial pathogenesis, and signal transduction through external signaling events, depending on the type of cell. Moreover, it has been shown that ICAM-1 activates phosphorylation-dependent kinases, which in turn activates transcription factors, cytokines, membrane-bound protein expression, reactive oxygen species (ROS), and cell division. It's interesting to note that ICAM-I ligation increased the release of chemokines like those that are released and controlled upon activation of normal T-cell expressed and secreted (RANTES), which mediated the activation of granulocytes and macrophages[4].

Intercellular adhesion molecule 1 in rheumatoid arthritis

Several research suggested that ICAM-1 may have a part in RA. ICAM-1 is a molecule that has a role in multiple stages of leucocyte activation and recruitment at the site of inflammation. In RA, the interaction of ICAM-1 with its antagonist integrins LFA-1 and MAC-1 is necessary for the activation and recruitment of synoviocytes [7-9].Genetic variations affect the functional domains of the molecules involved in leukocyte integrin binding. Thus, single nucleotide variation in the human ICAM-1 gene may contribute to the onset of RA [10].

The presence of the 241-Lys/Arg alteration in the ICAM-1 molecule's third domain serves as evidence for this, and that the MAC-1 molecule's counterpart can alter the functional activity of the ICAM-1 molecule, changing how inflammatory cells are recruited and activated [11].ICAM-1 expression on the chondrocyte surface causes T lymphocytes to adhere, which ultimately results in cell death [9]. Erythrocyte sedimentation rate, C-reactive protein, and the molecule's serum and synovial forms are all linked to disease activity (morning stiffness and the Ritchie articular index), yet these results have not been corroborated by Bui *et al*. [8].

ICAM-1 Gene Positions 241 and 469 polymorphism

The ICAM-1 gene, which is found on chromosome 19, is one of the genes outside the MHC locus that are intimately associated with RA illness. Positions 241 (GGG or AGG) and 469 (AAG or GAG) of the gene have been identified as two single base polymorphisms that modify the amino acid sequence of the ICAM-1 protein, causing Lys or Glu in position 241 and Gly or Arg in position 469, respectively. The polymorphism at codon 469 is found in exon 6, which codes for Ig-like domain 5, whose binding activity is unknown, while the polymorphism at codon 241 is placed in exon 4, which codes for Ig-like domain 3, the binding site of the MAC-1 integrin [11].The incidence of ICAM1 polymorphism at codons 241 and 469 was examined in 78 Italian-American RA patients who tested positive for rheumatoid factor and

had articular erosive disease in a series of 78 consecutive patients. In the Italian community of seropositive patients, they demonstrated that the G/R ICAM-1 gene Polymorphism may lead to a less aggressive form of synovitis and increase vulnerability to RA. These findings may indicate that differences in the ICAM-1 gene mitigate the clinical severity of RA [12].

The association of sICAM-1 and sVCAM-1 with ICAM1 721G>A and VCAM11238G>C was investigated. A case control study illustrated 60 patients with rheumatoid arthritis (RA) and 60 healthy individuals who were matched for age and sex to examine the connection between SNPs and RA clinical activity (HS). In contrast to HS (132 and 280 ng/mL), they identified higher levels of sICAM-1 and sVCAM-1 in RA patients (284 and 481 ng/mL), and significant correlations between sVCAM-1 and RF, ESR, SpanishHAQ-DI, and DAS28 were found in the RA group, although sICAM-1 only correlated with RF. There was shown to be a strong correlation between RA patients and the ICAM1 polymorphism 721A allele. Additionally, this polymorphism's allele impact (G/A + A/A) was verified. In RA, the blood levels of sVCAM1 and sICAM-1, rather than the ICAM1 and VCAM1 polymorphism, accurately indicated the clinical condition. The ICAM1 721A allele, however, may serve as a genetic indicator of RA risk [10].In the same area of chromosome 19 as ICAM-1 are the genes for ICAM-3, MAdCAM-1, IL-11, and human heat shock protein 40, all of which have been demonstrated to influence the inflammatory response [13]. Anti-ICAM-1 antibodies may help treat articular illness, according to a hypothesis made in an open trial on RA patients. It's interesting to note that ICAM-1 levels in synovial tissue have decreased when antiTNF antibodies are used to treat RA patients [14].

ICAM-1 expression on the cellular surface of inflammatory cells is reduced by a number of medications used to treat RA both in vitro and in vivo, which coincides with an improvement in clinical activity indices [15]. These studies supported the idea that ICAM-1 plays a role in the etiology of RA. Prior research has indicated that patients with rheumatoid arthritis (RA) may benefit clinically from treatment with a murine monoclonal antibody (MAb) directed against intercellular adhesion molecule 1 (ICAM-1; CD54)[16, 17]. In an open-label experiment, 40% of RA patients with persistent, refractory illness experienced a clinical response lasting more than two months following a single 5-day course of therapy using composite evaluation criteria [16]. Patients with early-onset or slowly-progressing RA have exhibited improved clinical benefit from treatment; after just one course of medication, numerous patients experienced clinical improvement that lasted longer than six months[17]. Anti-ICAM-1 MAb therapy has been shown to cause a number of immunologic changes, which may be the basis for its therapeutic benefit. Consequently, therapy caused circulating T cells to become hyporesponsive, which was associated with a favorable clinical outcome [18]. A change in the circulation pattern of activated Thl-like T cells brought about by therapy was similarly associated with a reduction in clinical efficacy [19]. Lastly, interleukin-6 (IL-6) messenger RNA (mRNA) levels in circulating mononuclear cells were

shown to be persistently lower in patients responding to therapy one month following treatment, which supports a direct or indirect inhibitory effect on monocyte activation[20].

Declaration of interest:

The authors report no conflicts of interest.
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CONCLUSION

There is a correlation between gene polymorphism of ICAM-1 and the clinical activity of rheumatoid arthritis, and a range of medications that inhibit ICAM-1 expression can be utilized to treat RA.

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