Sohag University Sohag Medical Journal Faculty of Medicine

Role of interleukin-17 and interleukin 23R gene polymorphism and serum interleukin 17A in Rheumatoid arthritis

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ABSTRACT

The multistep process of rheumatoid arthritis (RA), a chronic autoimmune disease, includes the interaction of genetic, environmental, and behavioral risk factors that break immune tolerance and trigger autoimmune processes like the production of autoantibodies, the emergence of the first symptoms before the appearance of clinical arthritis, and finally the appearance of arthritis. In rheumatoid arthritis, the interleukin (IL)-17/IL-23 axis is a crucial pro-inflammatory mechanism (RA). IL-17 is the important factor of inflammation and is contribute to the destruction of bone by increasing the migration of cells, the gene expression of chemokines and the invasiveness of synoviocytes. There are a number of variations in the IL17A gene, and these polymorphisms may affect how IL-17 is expressed. The Th17 has been shown to be more effective than other cells in the development of autoimmune illness. In psoriasis and inflammatory bowel disease patients, IL-23 receptor gene variations were found to raise susceptibilities to autoimmune illness. Investigations also revealed that synovial fibroblasts and plasma from RA patients expressed more IL-23 than normal. Therefore, RA risk may be associated with IL-23 receptor gene variation.

Keywords: Rheumatoid arthritis; IL-17A; IL-23R

Introduction

Rheumatoid arthritis (RA) an autoimmune disease with extra-articular involvement and inflammatory arthritis. It is a chronic inflamm-atory condition with no known cause [(1)] . If left untreated, it often begins in tiny peripheral joints, progresses to involve proximal joints, and is frequently symmetric. Joint degrade-ation caused by eroding cartilage and bone occurs as a result of joint inflammation over time [(2)].

According to various research IL-23R gene variations have been linked to increased susceptibility to autoimmune illness [(3)]. Investigations also revealed that synovial fibroblasts and plasma from RA patients expressed more IL-23 than normal. Therefore, RA risk may be associated with IL-23R gene polymorphism [(3)].

IL-17 is a significant cause of inflamemation and contributes to the breakdown of bone by enhancing chemokine gene expression, and synoviocyte invasiveness [(4)] . Additionally, IL-17 has a function in a number of inflame-

mations, with higher levels found in people with conditions such axial spondyloarthritis and psoriatic arthritis [5] .

Numerous polymorphisms have been found in the IL17A gene, and these changes may have an impact on how IL-17 is expressed [8] . Th17 cells have been shown to be more potent than other cells in the development of autoimmune disease, with IL-17A serving as the primary mediator [6] .

Risk factors;

Genetic disposition: A significant Swedish study from 2013 revealed that there is a 40% genetic predisposition to RA. Their analysis states that a first-degree relative has a three times higher likelihood of getting RA than a second-degree relative [7].

smoking: is a significant risk factor for rheumatoid arthritis. Anti-citrullinated protein antibody (ACPA) positive people have an interplay between their genes and smoking that raises their likelihood of developing RA, according to studies [8]. The repetitive stimulation of innate immunity is assumed to be the mechanism underlying environment-triggered RA. Smoking increases the expression of peptidyl arginine deiminase (PAD), which results in the conversion of arginine to citrulline in the airway. The development of a "neoantigen," that causes an immune response, results in the creation of antibodies against citrullinated proteins [8].

Periodontitis (PD): Chronic inflammatory condition of the gingiva that is linked to RA and other illnesses that can cause tooth loss. According to studies, autoimmune responses may be brought on by the citrullination of host peptides during infections in gingiva [9].

Microbiome: Modifications to the makeup and functioning of the gut microbiome have also been linked to rheumatoid arthritis. The reduced diversity of the gut microbiome in rheumatoid arthritis patients compared to healthy individuals suggests that the gut microbiome of these patients undergoes changes in composition. Actinobacteria, Collinsella, Eggerthalla, and Faecalibacterium are all on the rise. Collinsella increases rheumatoid arthritis disease severity and modifies gut mucosal permeability [2].

Diet and nutrition: have been demonstrated to be important RA environmental triggers. The normal "western" diet, which is fatty, calorie-dense, and poor in fiber, raises the chance of developing RA [10].

Overweight/obesity: BMI 25 kg/m2 and BMI 30 kg/m2 raise the chance of developing RA by 15%, 21-31%, and 60%, respectively, and by 80% when paired with a history of smoking [11].

Hormonal factors: Hormonal and reproductive variables are thought to be a potential cause since women are 2-3 times more likely than males to get RA. Utilization of oral contraceptives may prevent the onset of RA [12].

Immunology of rheumatoid arthritis

Development of RA-related autoimmune disorder at mucosal sites:

Antibodies in case of RA may be found in the serum prior to synovial fluid [13] and may be linked to mucosal insults like smoking, it implies that places other than the joints may be where RA-specific immune reactions develop, especially mucosal areas such the mucosa of the mouth, throat, and/or intestine [14] . Smoking causes mucosal disequilibrium through activating macrophages and DCs, chemoattracting neutrophils, modulating TLR activity, inducing necrotic cell death with subsequent DAMP production, and impairing apoptotic cell death by macrophages, among other methods.

Smoking also modifies the respiratory microbiota in a specific way [15].

Smoking and possibly other air pollutants and airborne pathogens that activate the innate immune system cause localized inflammation and the production of neoepitopes through increased citrullination and carbamylation of proteins, which can also serve as an agonist for Damage-associated molecular patterns (DAMPs) for TLR4 [8]. Citrulline-specific T-cell activation could be caused by activated mucosal DCs presenting citrullinated neoantigens in nearby LN.

Most cases that have ACPA positive who did not smoke also showed histological alterations consistent with inflammation and local immunological activation, indicating that smokeing is not the only element contributing to the establishment of APCA immunity.

RA-related autoimmune disease with secondary localisation in the joint:

Locally produced antibodies may be found many years in advance in peripheral blood before symptoms of an illness appear because they are carried via the lymphatic system after the secondary immunity is activated at the mucosa [16].

Studies have demonstrated that ACPAs can stimulate neutrophils, stimulate the complement system, improve macrophage excitation, and stimulate osteoclast formation. Adaptive, innate accumulation and activation, and resident cell activation [such as synovial fibroblast activation] combined with immunological activation once it begins in the joint will be responsible for perpetuating inflammation. Therefore, there are a number of potential, and possibly overlapping, ways by which some people's immune responses to neoantigens produced in mucosal regions far from the joint may result in arthritis [14]. Due to their roles as phagocytes, antigen-presenting cells, and cytokine makers, an important function is played by innate immune system cells in the beginning and establishment of the illness [17]. When TLR ligands activete synovial dendritic cells, they can go to LN, where primed T cells may be more likely to exhibit the TH1 phenotype, and to inflamed synovial tissue via chemokine receptors like CCR5[17]. Following the stimulation of the primary immunity in the joint, the production of cytokines and the expression of adhesion molecules then permit the continuous entry of immune cells. Numerous immunological mechanisms connected to the numbers of the cytokines and chemokines generated by innate cells directly mediate the establishment of RA [18].

Adaptive immunity in the joint of RA:

1) **Joint-infiltrating B lymphocytes' effector roles in RA**

First, B cells in synovial fluid have the capacity to create proinfl-ammatory mediators. Another function of joint-infiltrating B lymphocytes, which are probably responsible for the pathophysiology of RA, is antigen presentation to T cells [19].

B lymphocytes that invade joints and produce antibodies in RA

Rheumatoid factor: The first auto-Abs to be reported in RA were RFs [19]. Although RF has 85% specificity for RA, it can also be identified in cancer, primary biliary cirrhosis, liver cirrhosis, various rheumatic diseases, infectious or non-infectious disorders, or even in healthy individuals' sera [20].

Anti-citrullinated protein antibodyies: Antibodies against citrullinated proteins. Citrulline is an amino acid produced by peptidyl arginine deaminases after they modify arginyl residues post-translationally [2].

Anti-carbamylated protein : post translationally modified protein known

as anti-CarP antibodies are linked to RA [8]

Anti-acetylated protein antibodies: have lately been linked to RA [8]. The relationship between RA and microbiome dysbiosis may be established by the enzymatic process of acetylation, which is assumed to be mediated by bacteria. The precise mechanism is still unknown at this moment [21].

Anti-PAD :
They are the enzymes that change citrulline from arginine. However, PADs can also act as autoantigens in addition to creating epitopes that are targeted by ACPA. Anti-PAD4 antibodies were initially identified in patients, and they were linked to a more severe disease profile. [12].

2- T Cells in patients joints:
Role of CD4 T cells in RA
CD4 T cells are involved in the pathophysiology of RA. T cells, particularly CD4 T cells, are an essential component of secondary immunity. First, RA synovium has a significant infiltration of CD4 T lymphocytes [22] .

✓ **CD4 T helper cell in RA joint:**
The delayed type hypersensitivity (DTH) reaction, a typical T cell-mediated inflammatory response, activates macrophages and protects the host from intracellular infections. The (DTH) reaction, a typical T cell-mediated inflammatory response, activates macrophages and protects the host from intracellular infections. The DTH response is mediated by T helper 1 (Th1) cells that produce IFN. RA was formerly thought to be a Th1mediated disease due to histological hallmark of RA synovitis, which involves infiltration of activated macrophages and CD4 T cells [23]

Functions of CD8 T cells in RA : has received limited attention. However, similar to CD4 T cells, CD8 T cells in the joint exhibit more activation markers than those in peripheral blood [24]. Additionally, CD8 T cells have come under scrutiny as a result of a recent thorough examination of the cells in the RA joint. Three CD8 T cell subsets were found in the RA joint, as determined by the expression pattern of cytotoxic chemicals such granzyme K (GzmK) and granzyme B. (GzmB). While HLA-DR and PD-1 expression in CD8 T cells allowed mass cytometry to separate them into four subsets, GZMK + GZMB + effector cells and GNLY + GZMB + cytotoxic T lymphocytes are two examples of PD-1-HLA-DR + cells (CTL) [25] .

Cytokines in case of rheumatoid arthritis

1- IL-23/IL-17 Pathway in RA :
It is well known that the dysregulation of this axis contributes to the occurrence of a number of autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis, Sjogren syndrome [4] .
Dendritic cells , activated macrophages release IL-23 [4] . IL-23 is primarily responsible for causing naïve T cells to differentiate into Th17 cells [4] also stimulating the release of cytokines like IL-17 from Th17 which is important regulators of autoimmunity [26] . Recent findings reveal that Th17 cells may be crucial in the establishmentt of RA. It is known that Th17 are the primary source of IL-17 [27] . IL-17 has six members ranging from IL-17A to IL-17F. [28] IL-17A and IL-17F significantly increase cartilage matrix release, reduce the production of new cartilage matrix, and control the turnover of existing cartilage matrix [29]. The major functions of IL-17 are to promote and start chemotaxis as well as to draw in and activate neutrophils in inflamed tissues. levels of IL-17 are elevated in inflammatory illnesses [4] . Both early

and advanced RA illness are affected by IL-17, which encourages the activeation of FLS, osteoclastogenesis [30] . Proinflammatory mediators such prostaglandin E2 and MMPs are produced when IL-17 and TNF work together in a synergistic manner, accelerating the progression of early inflammation into chronic arthritis[4].

Genetic polymorphisms associated with Rheumatoid Arthritis

Clinical polymorphism, which manifests as a wide range of variation in symptoms, clinical presentations, and progression rates, is a clear characterristic of RA. The causes of RA are thought to be multifaceted, including both genetic predisposition and environmental influences. Modern molecular genetics has proven this connection [31].

1- Polymophism within IL-17:

On chromosome 6, *the IL-17A and IL-17F genes are located (6p12)* [32].

The IL-17A rs2275913 (197 G > A), IL-17F rs763780 ,IL-17F rs2397084 ,IL-17A rs4711998 (A > G), and IL-17A rs3819024 (A > G) SNPs were the most frequently researched ones [33].

The IL17A gene promoter, which is essential for controlling the transcription of cytokines, has an SNP called rs2275913 A>G that explains the replacement of the guanine nucleotide base with an adenine nucleotide base. Additionally, the nuclear factor has a strong affinity for the A allele. NF-B, a transcription factor that controls the expression of several cytokines, has been linked to the occurrence of many inflammatory diseases. [33].

The NFAT protein in a T cell not only regulates regulatory function but regulate T lymphocyte proliferation, selftolerance, and T-cell differentiation[33].

Researchers' analysis revealed that the IL-17A rs2275913 SNP is strongly linked to RA risk in the populations of Norway, New Zealander[44],Chinese[45], Brazilian [46] and Pakistani people [43].

IL-17F rs763780 SNP is significantly associated with RA risk in Polish[34], Tunisian[35], and Pakistani[33] populations. whereas it was linked to a greater number of affected joints in Polish patients[36] IL-17F rs2397084 In Tunisians, SNP is highly linked to RA risk[35] and Pakistan[33]. populations. Furthermore, patients with the aforementioned polymorphism benefit more from biological therapy [35].

SNPs of IL-23R in RA

On chromosome 1 (1p31), there is a gene called the IL-23 receptor (IL-23R) . The receptor complex that mediates IL-23's actions on T-cells is composed of an IL-12R-1 and a specific IL-23R chain. Natural killer (NK) cells and activated T-cells, particularly those of the TH17 subtype, as well as monocytes, macrophages, and dendritic cells exhibit the highest levels of IL23R expression [37].

The SNP in the IL-23R chain may impact IL-23 responses. The frequency of a functional SNP is significantly higher in healthy controls than in patients in the IL-23 receptor gene (IL-23R; rs11209026, 1142 G wild-type A reduced function, Arg381Gln, R381Q), indicating a protective effect of the rare allele against immune-mediated chronic inflammation [37].

A subunit of the IL-23R gene, G1142A (rs11209026, R381Q), is found in exon 9 of the gene. The amino acid arginine at position 381 in the protein is changed into glutamine (R381Q) when the A allele, rather than the more prevalent G allele, is present at the end of exon 9's coding sequence. The functional ramifications of this amino acid alteration [38].

Therefore, the signalling and responses to IL-23 are altered by replacing arginine (Arg) with glutamine (Gln). The initial tyrosine phosphorylation site,

the JAK2 binding site, and the transmembrane domain are all positioned near to the glutamine (Gln) substitution of arginine (Arg) in the cytoplasmic region of the IL-23R protein [38].

This distinct propensity affects IL-23R's surface location or signal transduction, with functional repercussions. Therefore, the signalling and responses to IL-23 are altered when arginine (Arg) is substituted with glutamine (Gln) [39].

IBD (including CD and UC), psoriasis, ankylosing spondylitis, GVH illness following bone marrow transplantation, rheumatoid arthritis, recurrent spontaneous abortion (RSA), and asthma were all prevented by the R381Q gene. [37].

studies in Korean [40], Spanish [41] , and Polish (34) populations, revealed that IL-23R gene does not appear to be associated with RA.

Interestingly, in Hungarian [42], Egyptian [43] , and Brazilian [44] populations, RA susceptibility may be correlated with some IL-23R gene SNPs. For instance, the Egyptian population has a high frequency of the IL-23R rs11209026 (G > A) SNP [43] . Functional investigations revealed that it significantly affects IL-23's ability to attach to its receptor. [45] IL-23R rs10889677 (2199 C > A) and IL-23R rs2201841 (C > T) are other IL-23R SNPs linked to an increased risk of developing RA [42]. Furthermore, it has been shown that having the haplotypes AA of rs-10889677 and CC of rs2201841 in the same person may enhance their risk of getting RA[42] .

Conclusion:

Some SNPs in the genes for inflammatory cytokines may serve as potential biomarkers for RA patients who wish to receive so-called tailored medication. In order to enhance the effectiveness of modern pharmacology, it is crucial to identify the right patients for acertain course of treatment. Therefore, more research is needed in RA patients to determine whether there is a potential correlation between polymorphic variations of proinflammatory cytokine genes and responsiveness and prognosis to applied treatment.

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