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Review Article

Review of interleukin-6 polymorphisms in rheumatoid arthritis: a genetic implications

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ABSTRACT

The objective review is to inspect the involvement of Interleukin-6 (IL-6) in rheumatoid arthritis (RA) and to highlight the role of IL-6 and its variants in the pathogenesis of RA and response to anti-IL-6 agents. Several genetic and environmental risk factors and infectious agents contributed to the development of RA. Interleukin-6 is engaged in self-targeted immunity by modifying the equilibrium between T regulatory (T_{reg}) and T helper-17 (T_h-17) cells. The evidences reported that IL-6 participated in RA pathogenies including synovitis, angiogenesis, joint damage, and dislocations of bone. IL-6 induces peripheral and central pain sensitization that provokes chronic pain development. Many IL-6 loci contribute to the risk of RA development. Several IL-6 gene variants were studied, which included; -174, -572, -597, and -622 in the 5-flanking region (Promotor). The current data demonstrates the significant role of IL-6 promoter Single Nucleotide Polymorphisms (SNPs), particularly G (-174) C, in the susceptibility and pathogenesis of RA. The C allele linked with the risk, the genotypic and allelic frequencies were higher in Asian and Indian RA patients. Elevated serum IL-6 levels are observed in mutant homozygote CC carriers at the -174 locus, which could explain the impact of this SNP on RA. It seems that age, ethnicity, geographic region, and lifestyle impact the effect of the IL-6 variant in RA. In conclusion; because IL-6 plays a central role in the pathogenesis of RA and its symptoms, it can be speculated that IL-6 promoter SNP (rs1800795) could be a risk agent for RA.

Keywords: Rheumatoid arthritis, Interleukin-6, Genetics, Polymorphism, Pharmacogenetics

Introduction

Rheumatoid arthritis is a generalized autoimmune and chronic inflammatory disorder. Various organs and tissues could be affected, with the synovium of the joints being particularly impacted [1]. Rheumatoid arthritis affects approximately 0.5-1% of the global population, including 0.8% in the UK, the chronic synovial inflammation from RA can result in joint destruction and disability [2]. Several factors contribute to RA; including genetics, environmental influences, and autoimmunity, all of which can lead to synovitis and the progression of RA [3]. Additionally, gender (male), age, and other chronic diseases correlated with the disease activity score [4].

Although the onset and progression of RA remain unclear, many therapeutic strategies are available. Rheumatoid arthritis is initially triggered by synovitis, where inflammatory cells such as lymphocytes and macrophages infiltrate the synovium [5]. This is followed by angiogenesis and synovial hyperplasia, along with excessive production of synovial fluid, leading to joint swelling accompanied by stiffness and pain [6]. Consequently, the articular cartilage in the joint becomes damaged, leading to bone erosion, osteoporosis, and, in some patients, eventual permanent disability [7].

Chronic inflammation in RA can lead to various systemic and general symptoms in patients, including anorexia, anemia, weight loss, fatigue, muscle weakness, fever, and cardiovascular disease [8]. Nowadays, the primary goals of therapeutic strategies are to reduce symptoms and relieve pain in RA patients, as well as to alternate the disease progress [9]. Many cytokines

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(inflammatory mediators) like IL-6 play a significant role in the development of RA. Excessive production of IL-6 in the blood and synovial fluid has been observed in RA patients and is correlated with the disease pathogenesis [10]. IL-6 stimulates the production of auto-antibodies such as Rheumatoid Factor (RF), which then triggers several intra-articular events, including synovial inflammation, bone and cartilage damage, as well as extra-articular manifestations [11].

Several soluble anti-IL-6 agents and TNF-α inhibitors, such as tocilizumab and etanercept, work to slow the progression of rheumatoid arthritis (RA) by blocking IL-6 and TNF-α activity, respectively [12, 13]. This review aims to present current evidence on the genetic role in rheumatoid arthritis (RA), the pathological role of IL-6 in RA development, and the association between variants in the IL-6 gene and the incidence, development of RA, and response to therapy.

Data collection and examination

A systematic review was conducted to investigate the interplay between RA incidence, IL-6 signaling pathway, and genetic polymorphisms of IL-6. A comprehensive search strategy utilizing the keywords "RA," "genetic polymorphism," "IL-6," "IL-6 receptors," and "biological effect" was employed across, Scopus, Google Scholar, PubMed, and Research databases. Eligible articles published between 2010 and December 2024 meeting pre-defined criteria were thoroughly examined and incorporated into this review.

The biology of IL-6

Interleukin-6 is a major multifunctional pro-inflammatory cytokine, that is involved in the immune response process, hematopoiesis, and inflammation [14].

Interleukin -6 is part of a broad cytokine family that includes many pro-inflammatory agents, like Cardiotrophin-like Cytokine Factor 1, Neurotrophic factor, Oncostatin, Leukaemia Inhibitory Factor Cardiotrophin and IL family (L-11, IL-27, IL-31 [15].

It has several pro-inflammatory characteristics, including promoting chemokine production and lymphocyte adhesion molecules. Additionally, during inflammation, IL-6 plays a crucial role in neutrophilia and granulocytic cell migration [16], it also has a principal role in both adaptive and innate immunity.

It also plays an endocrine role by regulating the secreting state of the hypothalamus-pituitary-adrenal axis, while also increasing cortisol and adrenocorticotropic hormone levels [17].

The types of inflammation and the infection could induce IL-6 production [18]. In fact, IL-6 is produced principally by macrophages in response to inflammation or pathogenic agents. It exerts a protective activity by eliminating infectious causes and repairing damaged tissues through stimulation of immune responses and activation of acute phase pathways [19]. At sites of inflammation, many cell types contribute to IL-6 production such as T-lymphocytes, monocytes, endothelial cells, and fibroblasts [20].

Interleukin-6 impacts both the acquired and innate immunity. At the site of inflammation, IL-6 acts as a chemoattractant by stimulating the infiltration of mononuclear cells and the neutrophils migration, while also serving as a chemoreceptor for monocytes [17].

Impact of IL-6 on the pathogenesis of RA

The exact cause of RA remains unclear, it has been proven that IL-6 contributes to the onset and progress of the disease. The clinical analysis showed that higher IL-6 levels were noticed in the blood and synovial fluid of RA patients [10], they inferred that related to the disease activity. Although many factors could impact RA pathogenesis, several studies pointed out that there is a correlation between the IL-6 blood level and RA [18]. However, the sIL-6R expression level in the blood does not differ between RA patients and healthy individuals. On the opposite, the upregulation of sIL-6R is observed in the synovial fluid of RA patients compared to OA patients [19]. The lymphocytes and monocytes that infiltrate into synovial fluid are considered the origin of sIL-6R [20].

• Roles of IL-6 in synovitis

The synovitis is maintained and supported by the inflammatory cells' infiltration from the newly formed blood vessels and the growing synovial cells. Many cytokines and growth factors are involved in RA pathogenesis; however, the Vascular Endothelial Growth Factor (VEGF) is the primary factor due to its angiogenic activity [21]. The VEGF plays a specific role in the pathogenesis of RA, particularly in the formation of inflammatory vascular tissue (pannus). There is a significant rise in VEGF circulatory concentration in RA patients [22]. Additionally, clinical trials have shown that anti-VEGF antibodies suppress IL-6-induced angiogenesis by preventing IL-6 from inducing Fibroblast-Like Synoviocytes (FLS) in RA patients [23].

Furthermore, IL-6 improved the Monocyte Chemotactic Protein-1 and FLS production and increased monocyte adhesion to endothelial cells by stimulating the production of endothelial adhesion molecules (ICAM) like ICAM-1 [24].

Large amounts of IL-6 are expressed by synovial fibroblastic cells through TAK1/NF-κB/HIF-1α signaling in response to some pro-inflammatory mediators such as IL-1, IL-17, and TNFα that finally IL-6 amplified synovial fibroblastic cells [25]. Some IL-6R inhibitors inhibit the biological activities of IL-6 and significantly improve synovitis in RA patients [26].

• Impact of IL-6 in joint damage

Irreversible joint damage, dislocations, and bone disintegration is a distinctive trait of RA. The Pro-inflammatory cytokines activate osteoclasts, resulting in localized bone erosion and subsequent destruction [27].

The internal layer lining the bone marrow, which contains FLS-A and FLS-B, contributes to tissue damage. FLS-A and FLS-B primarily produce TNF, IL-6, and other cytokines [28]. Local

arthritic signs arise from the combined effects of TNF, IL-6, and cytokines derived from FLS [29].

Both osteoblasts and osteoclasts expressed IL-6R [30], therefore, IL-6 is considered a potential mediator of osteoclast function which triggers the immune response and exacerbates the deterioration of RA [31].

In RA patients, osteoclasts have been determined at the cartilage destruction sites [27]. Additionally, IL-6 and IL-6R increase bone resorption; the IL-6/sIL-6R ligand straightaway stimulates osteoclastogenesis [32]. Interleukin-6 regulates the inflammatory process by promoting pannus development and bone resorption through osteoclast activity. This leads to the autoimmune production of antibodies (IgM and IgG), RFs, and citrullinated peptides (dysregulated citrullination) [32].

Additionally, clinical evidence has shown that IL-6 signaling affects bone resorption and osteoclastogenesis, blocking osteoclast activity occurs directly through the use of an IL-6R inhibitor [33].

Furthermore, by influencing TNFα and IL-1, IL-6 mediates bone resorption inflammation and thickening of the synovial membranes, which is accompanied by cartilage, bone erosion, and pannus formation [34]. These events occur due to IL-6 stimulates neutrophils infiltration into the joint, promotes angiogenesis, and alters the differentiation of both B and T cells [35], as well as, stimulation of Matrix metalloproteinase (MMP)-1, 3, and 13 from synovial cells and chondrocytes [36].

Moreover, the synthesized IL-6 that originates from the inflamed joint reaches the liver through systemic circulation, which in turn stimulates adaptive immunity by prompting hepatocytes to secrete serum Amyloid A, Fibrinogen, and C-reactive Protein (CRP). These mediators contribute to the persistence of chronic inflammation and joint disruption [37].

Genetic contribution to RA

Several autoimmune disorders are influenced by hereditary [38-41]. The hereditary potential of RA has been assessed between 50 to 60 % [38]. The risk of developing RA increases approximately 3 to 5 times in families with a history of the disease [38]. Genetic factors such as Major Histocompatibility Antigens (class II), Human Leukocyte Antigens (HLA), and non-HLA genes have been involved in the pathogenesis of RA [42, 43].

Many studies find a linkage between the SNPs with certain loci and RA. Large-scale cohort studies have permitted the simultaneous estimate of dozens of genes, leading to a comprehensive finding of genetic relevance [44]. For instance, certain genes are associated with some disease's development and/or prognosis [45-50]. While some gene screening is related to nonresponse or response to treatment, and also to the degree of response (good or bad) to therapy [51]. In Iraq, numerous recent reviews and studies have reported on genetics, including genetic SNPs in various genes like TNF and ILs, which influence the response of RA patients to biological therapies such as Adalimumab and Etanercept [52-56].

Based upon the clinical trials on animal models for RA, both B and T immune cells participated because it contributed directly to the risk and pathogenesis of this disease particularly in the inflammation synovial joint [57].

About 31 confirmed genetic loci in non-HLA genes contributing to RA risk, the loci of PTPN22 and IL23R genes demonstrated a strong association with RA [58]. Farago *et al*. (2009) [59] also the outcomes demonstrated a linkage of some gene's loci with RA in Hungarian RA patients.

For instance, because the peptidyl arginine-deiminase 4 (PADI4) enzyme that encodes with the PADI4 gene has a main role in the information of protein citrullination, it participates in RA pathogenesis of RA [60]. The PADI4 haplotype correlation with RA was speculated in Asian populations but could not be verified in Caucasian population cohorts [61] and a lack of association was recorded in European patients [62]. Other important genetic loci include TRAF1, CD40, FCGR2A, TNF-α, IL-4, and IL2RA/IL2RB genes have been the most powerful correlation [63-67].

It has been shown that several distinct HLA alleles (called HLA-DRB1*01) correlated with RA susceptibility [68]. Some alleles in HLADRB1 can stimulate citrullinated protein through particular T cell reactions by the presence of citrulline in its own antigens anchoring pockets [69]. Often, HLA-DRB1 alleles are intensely connected with the anti-citrullinated protein antibodies seropositive RA [70]. It also confirmed that genetic loci in this gene were relevant with RF and anti-citrullinated protein antibodies seropositive-RA group along with RA severity and bad prognosis [71].

IL-6 polymorphisms and RA

Several IL-6 gene variants were studied and determined the association with RA including four located at positions −174 (rs1800795), -572 (rs1800796), -597, and − 622 in the 5-flanking region [72].

Ren *et al*. (2023) [72] first recorded the G>C SNP in the 5-untranslated region (flanking region) at a locus (174G > C) (promotor region), it made the G to C substitution and could make in-vitro changes in transcriptional reaction to the stimuli of HeLa cells. The connection between the IL-6 variant (174 G>C) and the risk of RA susceptibility was studied; Shafia *et al*. (2014) [73] studied the IL-6-174 SNP in the north Indian population; they reported that G allele frequency was 82.5% in the patient cohorts in comparison to the control group 90%, In contrast, C allele was recorded 17.5% compared to 10% in the same group. Additionally, a significant variance was reported in the genotypic frequency of CC (10% Vs 0%) and GG (75% Vs 80%) in both RA patient and control groups. Hence, it can be concluded that the IL-6-174 locus is strongly related to RA susceptibility in north Indian cohorts. Subgroup analysis also detected that the IL-6-174 G>C locus demonstrated a significant connection with the susceptibility to RA in the Asian population [74]. While the case-control studies that have been done on Caucasian RA patients did not show a significant correlation between the allelic distributions of IL-6-174G>C variant and the risk of developing RA [75-77].

For Middle Eastern countries, there is a potential heterogeneity for all the genetic prototypes; The heterozygous, dominant, allelic genetic models and increase the risk to RA exhibited a significant correlation for the −174 locus [78, 79]. While the −572 variant did not demonstrate a degree of significance for heterogeneity except in Asian people carriers. Additionally, the susceptibility and risk of RA development increased in the CC genotype (C allele) [80, 81]. Unexpectedly, the −174 polymorphism was related to some benefits, it correlated with some protective impact for Latin populations [82].

Although, the −597 SNP is not responsible for developing RA; however, the −572 polymorphism could raise the risk of susceptibility to RA, particularly in Middle Eastern and Asian populations [78, 79].

Several pieces of evidence reported the effect of IL-6 -174 polymorphism on IL-6 plasma concentration. Some clinical trials explained the effect of the variant on IL-6; In vivo, the serum levels of IL-6 elevated among RA patients with IL-6 -174 mutant homozygote allele (CC genotype) and also in heterozygote GC genotypes than that with wild homozygote allele (GG genotype), therefore, it has been related with elevation of IL-6 levels [83] in the general population. Another study finds that there is a significant increase in the circulatory IL-6 level in RA patients that have wild allele and genotypes (GG+GC genotypes) in comparison with the mutant homozygote CC carriers [84].

The existence of repetitive inflammatory stimulants in RA patients may be correlated with a more significantly impact of the -174C allele on IL-6 blood concentrations in the serum and synovial fluid, in this context, the high IL6 concentrations in the C allele patients could be deteriorated the RA consequences and raised prevalence of cardiovascular disease in RA patients by triggering and intensified the inflammation condition [85].

Since the IL-6 variant is effected by many confounding factors; It has shown that IL-6 level is also influenced by circadian rhythm, stress, diet regime, adipose tissue density (obesity), smoking and elderly considered an additional triggering agent for IL-6 formation and rising plasma IL-6 levels in the RA patients that possess -174C allele [86, 87]. Although it seems that the promoter SNP tended to rise of IL-6 production [88], the prevalence and effect of this variant were significantly geographic and ethnicity different and with significant heterogeneity in the genetic models.

It is possible that age also impacts in the effect of IL-6 variant in RA; there is a statistical difference ($P<0.05$) in average ages of healthy controls and RA patients (47 Vs 50 years), the finding concluded that age and IL-6 gene SNP-RA have a risk connection [89].

Based on ethnicity, Li *et al.* (2016) [79] reported that the dominant homozygous IL-6-174 C allele is significantly related with 4.5-fold, 1.8-fold and 4.7-fold raised the susceptibility of RA in Asian RA carriers for IL6-174 C allele, while, under three genetic models; there is non-significant relation was recorded in Europeans RA patients.

The statistical distribution according to the geographic region that the significant differences only appeared in eastern China RA patients, additionally, the risk of RA was significantly rise in people that have -174C allele [90]. The genotype distributions showed that these Asian populations and Middle Eastern carriers had the minimum allelic frequencies (1-10%) [72, 73]. In contrast, it was higher in European carriers (40%) [91, 92]. As the G allele is connected with lower serum IL-6 concentration [92], they inferred that a majority of Europeans have a minor circulatory IL-6 concentration.

The quality of life and lifestyle choices play a significant role in modulating the impact of the −174 variant on the progression of rheumatoid arthritis (RA). An unhealthy lifestyle, particularly one characterized by a diet rich in unhealthy carbohydrates, can elevate circulatory levels of interleukin-6 (IL-6), thereby exacerbating inflammatory responses and contributing to the development and progression of RA [93]. This suggests that poor dietary habits may enhance the responsiveness of the immune system to inflammatory conditions, leading to increased IL-6 levels and a heightened risk of RA. Indeed, autoimmune diseases such as RA are influenced by genetic polymorphisms, including those affecting cytokine regulation [94]. Among these cytokines, IL-6 is particularly notable due to its central role in inflammatory processes and its association with disease severity. Thus, both genetic factors and lifestyle choices interact to shape the immune response and influence the course of autoimmune conditions like RA.

Conclusion

In summary, the data revealed that IL-6 influences the pathogenesis of RA and in its symptoms, it can be inferred that IL-6 promoter SNP (rs1800795) could be a genetic predisposing factor for RA. The relationship between IL-6 SNPs could assist physicians in identifying individuals at higher risk for developing RA in the future and in predicting their response to RA treatment.

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