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CLINICAL ARRHYTHMIA
Review Article

Major Interleukins: Role in the Pathogenesis of Atrial Fibrillation

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ABSTRACT

Interleukins (IL) are a group of cytokines with complex immunomodulatory functions, whereas atrial fibrillation (AF) is the most common cardiac arrhythmia. This review article highlights the role of major IL in the pathogenesis of AF. IL-1 had elevated levels in permanent and persistent AF patients as compared to paroxysmal AF. A study had shown a straightforward connection between the development of postoperative atrial fibrillation and IL-2 sera levels shortly after cardiopulmonary bypass graft for the first time. IL-4 has been involved in anti-inflammatory response and played no role in the contribution of AF. The elevated level of IL-6 rapidly induces atrial electrical remodeling by downregulating cardiac connexins. This change could be significantly increased the risk of AF and related complications during active inflammatory processes. Moreover, a study has shown higher IL-8 levels in permanent AF patients as compared with paroxysmal AF patients. An association was found between IL-10 gene -592A/C polymorphism and AF in Han Chinese. Recombinant human IL-11 therapy shortened atrial refractoriness and also created favorable conditions for AF by an indirect mechanism involving volume expression, stretching of atrial myocardial tissue and sodium retention. An elevated IL-12 expression was observed in the left atrial tissues of AF patients. IL-17 signaling pathway has played a significant role, and some genes could be used as potential therapeutic targets for AF. An association between the risk of AF with single nucleotide polymorphism of IL-18 and also resulted in the increased left atrial diameter and decreased left ventricular ejection fraction in AF subjects as compared to control. IL-27 genetic variants had increased the occurrence of AF. AF patients had elevated levels of IL-37 that were closely linked with AF subgroups.

KEYWORDS: Interleukins; Atrial fibrillation; Pathogenesis, homeopathic.

INTRODUCTION

Atrial fibrillation (AF) is the most important arrhythmia disease with clinical cardiovascular diseases, which increases the morbidity of arterial embolism, stroke and heart failure[1]. In adults, the prevalence of AF is about 0.4-1%, whereas in patients over 60 years AF is about 2-4%[2]. Another study reported that about 2.3 million people suffer from AF disease, and the number could be increased to 5.6 million by 2050 in the United States[3,4].

In immunity and inflammation, cytokines play an important role, as well as in immune cell differentiation and activation. The term interleukins (IL) is used to describe a group of cytokines with complex immunomodulatory functions such as maturation, cell proliferation, migration and adhesion. IL also has pro-inflammatory and anti-inflammatory properties[5].

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There are various IL. However, the current review article focused on the basic introduction of IL. Then, it found its role in the pathogenesis of AF and also highlights the pathophysiological aspects of IL in AF. For this purpose, many databases were used, such as Google Scholar, PubMed, and ScienceDirect for searching the literature.

MAIN TEXT

There are many IL. However, this review article has discussed only major interleukins (IL) such as IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-11, IL-12, IL-17, IL-18, IL-27, IL-37, which played their pathophysiological role in AF, as explained in Table 1.

Table 1. Summary of pathophysiological aspects of major interleukins in the pathogenesis of atrial fibrillation (AF).

Interleukins	Pathophysiological aspects in AF
Interleukin-1	• Pressure overload-induced sustained AF.
Interleukin-6	• Rapidly induces atrial electrical remodeling; • Persistent inflammation in the atrial myocardium; • Atrial remodeling.
Interleukin-11	• Shortened atrial refractoriness.
Interleukin-17A	• Participates in the pathogenesis of myocardial fibrosis and promotes the occurrence of AF; • Induces fibrosis and inflammation.
Interleukin-18	• Increased left atrial diameter and decreased left ventricular ejection fraction in AF subjects.

Interleukin-1

A protein that induces the fever and is called human leukocytic pyrogen is IL-1, which comprises two major proteins, IL-1α and IL-1β[6]. There are many functions of IL-1, including hematopoiesis, development of IL-10 producing Breg cells in mouse spleens, as well as mesenteric lymph nodes, differentiation T_H 17 cells, and induction of pro-inflammatory proteins[7].

The pressure overload-induced sustained AF was due to the activation of the IL-1β pathway, which is different from NLRP3 inflammasomes[8]. Moreover, the case-control study, which included 122 patients with AF and 63 non-AF control, explained the high significant relation between IL-1 and AF patients as compared to the control. Additionally, as compared to paroxysmal AF, permanent and persistent AF patients had elevated levels of IL-1[9].

In addition, multiple logistic regression analysis had shown the independent risk factor of persistent AF was due to the IL-1β and also suggested that regional IL-1β in epicardial adipose tissue was an independent risk factor of persistent AF, which may promote the persistent AF[10]. Also, Gungor et al. showed the presence of allele 2 of a variable number of the tandem repeat polymorphism of IL-1 receptor antagonist gene that might cause the increased risk for lone AF, which was due to the inadequate limitation of inflammatory reactions[11].

In human studies, AF patients had altered IL-1β, as well as gene expression of collagen type 1. Seventy-five patients were taken to draw the right atrial tissue with rheumatic heart disease and underwent heart valve replacement surgery. The authors found a significant increase in messenger ribonucleic acid (mRNA) content of collagen type 1 in the persistent AF group ($P < 0.001$) and an increase in the paroxysmal AF group ($P < 0.05$) as compared with that in the sinus rhythm group. The mRNA content of IL-1β was up-regulated in the persistent AF group ($P < 0.05$)[12].

Interleukin-2

IL-2 was discovered from the supernatants of activated T cells, which are produced by CD41 and CD81 T cell-activated dendritic cells, natural killer (NK) and NKT cells. The main functions of IL-2 are the development of Treg cells, the stimulus for antibody synthesis, the proliferation of effector T and B cells, proliferation and differentiation of NK cells, a growth factor for B cells, and proliferation and cytokine production in innate lymphoid cells[7,13].

Regulating the expression of Na/K pump in human lymphocytes and T-cell proliferation are caused due to IL-2, which is a pro-inflammatory factor and participates in inflammatory processes. Various cardiac arrhythmias such as AF and ventricular tachycardia have been associated with IL-2. Moreover, Rizos et al.[15] also observed that decreased serum IL-2 was linked with chronic stable coronary artery disease or/and hypertension and recent-onset AF. Moreover, multivariate logistic regression analysis reported lower IL-2 admission levels were a powerful independent predictor of successful cardioversion (*odds ratio* – OR = 0.154, 95% confidence interval – 95%CI 0.043–0.552, *P* = 0.004). Authors had highlighted the role of inflammation in AF and it could be further prognostic, as well as therapeutic implications[14,15].

Furthermore, a study found that a predictive factor for early postoperative AF might be an IL-2 in cardiopulmonary bypass graft (CABG) patients[16]. Later, Zhao et al. reported that IL-2 was linked with the morbidity of arrhythmias, but how IL-2 affects cardiac electrophysiology is still unknown[17]. In addition, Hak et al. demonstrated the straightforward connection between the development of postoperative atrial fibrillation and IL-2 sera levels shortly after CABG for the first time[16].

Interleukin-4

IL-4 is produced by T helper type 2 (Th2) cells, type 2 innate lymphoid cells, basophils, mast cells, and eosinophils. There are two types of IL-4Rs. The main functions of IL-4 are in tissue adhesion and inflammation, upregulation of CD23 and IL-4R, induction of TH2 differentiation, and Ig E class-switching, survival factor for B and T cells and upregulation of class II MHC expression on B cells[7,18].

Woodward et al.[19] and Wu et al.[20] have explained that IL-4 promotes wound healing, as well as tissue repair, and also suppresses the production of some inflammatory cytokines from macrophages and monocytes. So, IL-4 does not play the role in contributing to AF, because IL-4 has involved in anti-inflammatory response[19,20].

Interleukin-6

IL-6 is a member of the IL-6-type family of cytokines, which includes ciliary neurotrophic factor, leukemia inhibitor factor, and oncostatin M[21]. IL-6 is involved in the promotion of T-cell proliferation, survival and differentiation of B-cell, and plasma cell production of IgG, IgM and IgA[22]. Moreover, allergen-induced IL-6 promotes type 2 and type 17 airway inflammation[23].

The elevated level of IL-6 rapidly induces atrial electrical remodeling by downregulating cardiac connexins. This change could significantly increase the risk of AF and related complications during active inflammatory processes[24]. Moreover, Grymonprez et al. reported that chronic obstructive pulmonary disease (COPD) subjects had a 28% increased risk of developing AF which was driven by COPD subjects with an increased IL-6 plasma level[25].

In the same way, Amdur et al.[26] examined the selected inflammatory biomarkers that risk factors for AF in Chronic Renal Insufficiency Cohort study participants and found only elevated levels of IL-6 are linked with increased risk for electrocardiogram-diagnosed AF at baseline and also new-onset AF during follow-up. It is also used in risk stratification and potential therapeutic target in the management of high-risk chronic kidney disease patients[26]. Furthermore, a recent meta-analysis had shown the elevated level of IL-6 may predict a greater number of long-term thromboembolic events, bleeding events, acute coronary syndrome events, and mortality in AF patients[27].

Additionally, to modulate the inflammation response to the influence of the development of postoperative AF and surgery, the -174 G/C IL-6 promoter gene variant appears to play a significant role. It becomes complicated due to the genetic predisposition and inflammatory component of postoperative atrial arrhythmias[28].

Supraventricular arrhythmias such as AF have altered IL-6 functional expression led to elevated risks of death and cardiovascular events in AF patients[29-31]. Additionally, increased IL-6 levels have been attributed to persistent inflammation in the atrial myocardium[26,30,32].

Moreover, Psychari et al. found that inflammation plays a significant role in AF due to the elevated levels of C-reactive protein (CRP) and IL-6. The left atrial size and AF duration were related to the CRP and IL-6 before cardioversion that indicate atrial remodeling happened due to the participation of inflammation[33].

Interleukin-8

IL-8 was identified as a neutrophil-specific chemotactic factor and also categorized as a member of the CXC chemokine family[34]. The main roles of IL-8 are chemoattractant for neutrophils, NK cells, T cells, basophils, and eosinophils; mobilization of hematopoietic stem cells; and angiogenesis[7].

In the permanent AF patients, a significant elevation of IL-8 was found in the right atrium, femoral vein and coronary sinus as compared to control or paroxysmal AF. When compared to controls or patients with paroxysmal AF, they were able to show that patients with permanent AF had significantly higher levels of IL-8 in the femoral vein, right atrium, and coronary sinus. The source of IL-8 is likely extracardiac and extrapulmonary because IL-8 levels were not raised in coronary sinus flow and were lower in the pulmonary veins[35]. Moreover, Wu et al. also reported the impact of IL-8 serum levels post-CABG on the incidence of postoperative AF in CABG patients and reported higher concentrations of serum IL-8 in CABG patients with postoperative AF, suggesting that inflammation is implicated in the pathogenesis of postoperative AF following open-heart surgery[36].

Additionally, Liuba et al. revealed higher IL-8 levels in permanent AF patients as compared with paroxysmal AF patients[37], while De Gennaro et al. in a case-control study involving 48 consecutive patients with AF and 58 controls showed that patients with AF duration < six months had a higher level of IL-8 compared with AF duration > six months even after multivariable correction for age, sex, and left ventricular ejection fraction[38].

Interleukin-10

IL-10 is an anti-inflammatory IL, which is produced from T cells, B-cells, macrophages, a small fraction of NK cells, and dendritic cells. It is regulated by B-cell linker protein. In humans, the main role is in immune suppression and an increase in allergen-specific immunotherapy. IL-10 is involved in immunosuppressive effects through antigen-presenting cells as antigen-presenting cells (APCs) or direct effects on T cell subsets; suppression of IgE, and induction of IgG by B cells in human subjects[7,39-41].

Li et al. reported more elevated levels of IL-10 in persistent and permanent AF than in paroxysmal AF[42]. Moreover, Zheng et al.[43] found the association of IL-10 gene -592A/C polymorphism with AF in Han Chinese. The distribution of the IL-10 -592A/C genotypes (AA, AC, and CC) was 55, 35, and 10% in the controls, and 71.79, 23.08, and 5.13% in AF subjects, respectively ($p = 0.0335$). The frequency of the A allele in the AF group was significantly higher than that in the control group (83.33 vs. 72.50%, $p = 0.0063$). Compared with the CC genotype, the AA genotype had an increased risk of AF in both unadjusted and adjusted analyses. As a result, the A allele has increased the risk for AF in Han Chinese[43]. Additionally, Kondo et al. observed that IL-10 treatment is a potential therapeutic approach to limit the progression of high-fat diet-induced obesity-caused AF[44].

Interleukin-11

The IL-11 structure is a monomer with a molecular weight is 19 kDa. The prominent role of IL-11 is in the promotion of neuronal development, protection of epithelial cells, as well as in connective tissue, bone remodeling, by stimulation of osteoclasts and inhibition of osteoblasts, induction of acute-phase proteins, a growth factor for myeloid, erythroid, megakaryocyte progenitors and plasmacytoma cells, inhibition of monocytes and macrophage activit[y7,45,46].

IL-11 is a cytokine that has specific effects on a variety of nonhematopoietic and hematopoietic cell types. Recombinant human IL-11 as rhIL-11 has been used to alleviate side effects caused by chemotherapy in patients with neoplastic diseases and as an experimental anti-inflammatory agent. The increased frequency of AF or atrial flutter was linked to elderly patients, and rhIL-11 therapy had shortened atrial refractoriness and also created favorable conditions for AF by an indirect mechanism involving volume expression, stretching of atrial myocardial tissue and sodium retention. It is also noticed that the effects of rhIL-11 were more susceptible in old animals than in adult animals[47].

Interleukin-12

There are many functions of IL-12, such as activation of NK cells, induction of cytotoxicity, development and maintenance of T_H1 cells, and support of dendritic cell maturation. IL-12 is produced from macrophages, microglia, B cells, monocytes, neutrophils and dendritic cells[7].

AF could be closely related to the occurrence of atrial fibrosis[48,49]. Moreover, Lappegård et al. and Stein et al.'s studies reported that elevated IL-12 expression was observed in the left atrial tissues of AF patients[50,51]. Sun et al. reported that reduction of IL-12 releases and inhibition of Ang II-induced M1 macrophage differentiation could reduce the occurrence of atrial fibrosis and AF. The authors also revealed that no studies explained the mechanism and expression of the involvement of IL-23 and IL-35 in AF[52].

Interleukin-17

The structure of IL-17A is the cysteine knot, homodimer or heterodimer with a molecular weight is 35 kDa. Interleukin-17A is involved in the activation and recruitment of neutrophils, as well as the Induction of proinflammatory cytokines, chemokines, and metalloproteases[7].

In the pathogenesis of AF, the IL-17 signaling pathway has played a significant role, and some genes could be used as potential therapeutic targets for AF. IL-17 pathway has given importance in the pathology of AF, and also targeting differential genes in the IL-17 pathway could become new diagnostic and therapeutic method in the future[53].

Moreover, other studies had found that IL-17A might stimulate the release of pro-inflammatory cytokines including IL-1β, TGF-β and IL-6, which also participate in the pathogenesis of myocardial fibrosis and promote the occurrence of AF[54,55]. In the same way, Fu et al. indicated that the pathogenesis of postoperative AF was due to the IL-17A by inducing fibrosis and inflammation in rats with sterile pericarditis[56].

Interleukin-18

IL-18 is produced from macrophages, dendritic cells, epithelial cells, chondrocytes, osteoblasts, Kupffer cells, keratinocytes, astrocytes, and renal tubular epithelial cells with the structure of heterodimer, and a molecular weight with 22.3 kDa. Induction of IFN-g in the presence of IL-12, enhancement of NK cell cytotoxicity, and promoting T_H1 or T_H2 cell responses depending on cytokine milieu are the important functions of IL-18[7,57].

Wang et al. observed the association between the risk of AF and single nucleotide polymorphism of IL-18 and that it resulted in increased left atrial diameter and decreased left ventricular ejection fraction in AF subjects as compared to control. After adjusting for various confounding factors, the reduced risk of AF was linked with IL-18 single nucleotide polymorphisms. The decreased risk of AF was related to rs187238 GC genotype and C allele, rs 360719 AG genotype and G allele, and rs 549908 GT genotype and G allele[58].

A crucial substrate for the pathogenesis of AF is structural atrial remodeling. According to the previous studies, left atrial diameter (LAD) was positively related to the elevated levels of CRP and IL-18 that promote the development of AF. Moreover, IL-6, IL-10, IL-17A, and IL-21 levels were positively related to the LAD and also negatively related to the plasma level of IL-17F and left ventricle ejection fraction (LVEF) among AF subjects, which also suggested that Th 17-related cytokines could contribute to AF development through atrial remodeling. However, a small correction coefficient was found indicating the impact of these cytokines could be small[59].

Interleukin-27

The main functions of IL-27 are the promotion of T_H1 cell differentiation, Induction of T-bet, inhibition of TH17 cell response through STAT1 and production from epithelial cells, macrophages and activated dendritic cells[7,60]. Additionally, Chen et al. observed that IL-27 genetic variants, such as GG genotype and rs 153109 G, increased the occurrence of AF in the Chinese Han population[61].

Interleukin-37

IL-37 represents a new member of the anti-inflammatory cytokines. The main functions are Inhibition of IL-18 activity and innate immunity and cell source from melanomas, monocytes, tonsil plasma cells, breast carcinoma cells, some colon carcinoma cells, and lung carcinoma[62]. IL-37 might play an important role in AF development and act as a potential risk factor for AF diagnosis. Li et al. demonstrated the expression level of IL-37 is correlated with the clinical manifestations of AF and also observed that AF patients had elevated levels of IL-37 that were closely linked with AF subgroups. In the pathogenesis and therapy of AF, IL-37 could play a novel research target. The authors found this document for the first time[63].

CONCLUSION

This review article concludes a significant role of IL (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-11, IL-12, IL-17, IL-18, IL-27, IL-37) in the pathogenesis of AF. However, there is a large number of IL whose relationship with AF has not been reported yet.

AUTHORS' CONTRIBUTION

All authors contribute equally.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

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