International Journal of Cardiology 287 (2019) 195–200

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Role of inflammatory signaling in atrial fibrillation

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ARTICLE INFO

Article history:
Received 2 October 2018
Accepted 3 October 2018
Available online 4 October 2018

Keywords:
Atrial fibrillation
Inflammation
Inflammasome
TNF-α
NFκB
IL-1β

ABSTRACT

Atrial fibrillation (AF), the most prevalent arrhythmia, is often associated with enhanced inflammatory response. Emerging evidence points to a causal role of inflammatory signaling pathways in the evolution of atrial electrical, calcium handling and structural remodeling, which create the substrate of AF development. In this review, we discuss the clinical evidence supporting the association between inflammatory indices and AF development, the molecular and cellular mechanisms of AF, which appear to involve multiple canonical inflammatory pathways, and the potential of anti-inflammatory therapeutic approaches in AF prevention/treatment.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, serving as a primary risk factor of stroke, which is currently the 5th leading cause of death in the U.S. and 2nd in the world [1,2]. AF prevalence continues to increase, affecting 6–12 million U.S. citizens by 2050 and nearly 18 million Europeans by 2060, which creates significant concerns as it propels toward epidemic status [3]. Despite the substantial progress that has been made in our current understanding of AF pathophysiology, the causes and perpetuators of AF including their underlying mechanisms are incompletely understood. Currently-available treatment options all have moderate effectiveness, likely because of our limited understanding of the mechanisms promoting initiation, progression, and maintenance of AF [4–6]. There is a hope that a better understanding of the molecular basis of AF will help to identify and implement safer and more efficient therapeutic approaches for AF management.

A variety of factors can increase the risk of AF including, but not limited to, genetic variants, smoking, alcohol drinking, aging, obesity, and inflammation, etc. (Fig. 1) [7,8]. Emerging evidence demonstrates that inflammatory markers such as interleukin (IL)-6, IL-1β, myeloperoxidase (MPO), and tumor necrosis factor-α (TNF-α) positively correlate with the progression of AF from paroxysmal (pAF) to persistent forms (perAF), and can predict the outcome of AF ablation [9–13]. There is an increasing evidence to suggest that inflammation is not a mere bystander of AF, but rather plays a causative role in its pathogenesis. This review discusses the clinical evidence supporting the association between inflammatory indices and AF development, the molecular and cellular mechanisms of AF, which appear to involve multiple canonical inflammatory pathways, and the potential of anti-inflammatory therapeutic approaches in AF prevention/treatment.

2. Pathophysiology of AF

The development of AF involves ectopic (triggered) activity and a reentrant substrate [6,14]. Fig. 1 summarizes the fundamental AF-promoting mechanisms (Fig. 1). Ectopic activity can maintain AF when occurring repetitively at high frequency and can act as a trigger, initiating reentry, the major AF-maintaining mechanism, in a vulnerable substrate characterized by electrical, autonomic, Ca^{2+}-handling or structural abnormalities [4,6]. Ectopic activity results predominantly from abnormal automaticity or triggered activity due to early and delayed afterdepolarizations (EADs and DADs, respectively). Extensive prior work has identified a major role for Ca^{2+}-handling abnormalities, mediated primarily by dysfunction of the major sarcoplasmic reticulum (SR) ryanodine type-2 Ca^{2+}-release channel (RyR2) in the evolution of DADs and triggered activity [6,15]. The mechanisms of reentry depend on the interaction between effective refractory period (ERP), conduction velocity and local depolarization properties of the propagating wave-fronts (the source) and the surrounding tissue (the sink) [16].

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https://doi.org/10.1016/j.ijcard.2018.10.020
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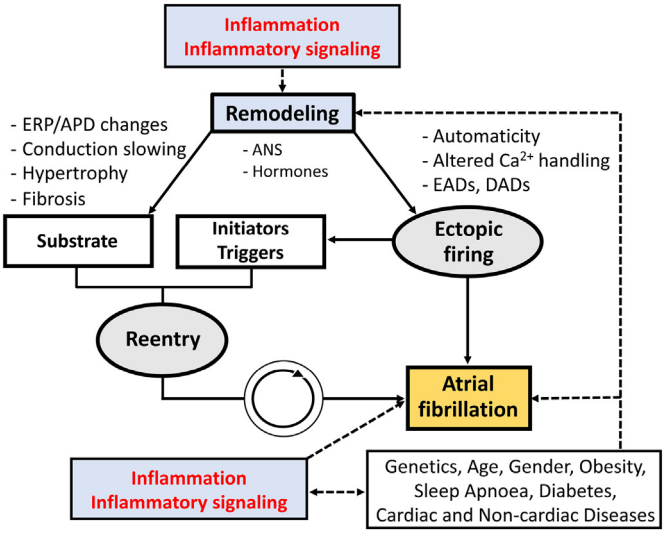

Fig. 1. Fundamental mechanisms of atrial fibrillation (AF) and potential contribution of inflammation and inflammatory signaling to the evolution of AF-promoting ectopic activity and reentry. ANS, autonomic nervous system; APD, action potential duration; EADs, early afterdepolarizations; ERP, effective refractory period; DADs, delayed afterdepolarizations.

Fibrosis is an important cause of microreentrant circuits by promoting conduction block and slow, heterogeneous conduction [17]. In addition, ERP shortening due to electrical remodeling and enlargement of the left atrium (LA) also support reentry by increasing available space for reentrant circuits [4]. In more advanced forms of AF, electrical activity becomes increasingly complex with multiple concurrent reentry circuits and ectopic foci. Any persistent change in the function and/or structure of the atria constitutes atrial remodeling, which has many forms that promote the occurrence and/or maintenance of AF by acting on the fundamental arrhythmia mechanisms illustrated in Fig. 1. Atrial remodeling increases the likelihood of ectopic firing or reentrant activity through a variety of potential molecular mechanisms, which were reviewed elsewhere [6,15]. There is emerging evidence for involvement of inflammatory signaling, particularly in atrial cardiomyocytes, in ectopic firing and reentry promoting atrial remodeling in AF, which will be discussed in detail below [18–21].

3. Inflammation & AF

Inflammation is an essential biological process that mammals utilize as a defence from injuries [22,23]. However uncontrolled inflammation might contribute to the pathophysiology of various diseases. Acute inflammation serves as the body's controlled primary physiological response to noxious stimuli, as it immediately attempts to quell effects of the identified threat [24]. To facilitate this process, the body's local vasculature is employed to administer bioactive signals and factors such as cytokines and chemokines, which encourage recruitment of innate immune cells and coordinate to intercept, confine and neutralize the targeted threat. In the event that acute inflammation persists beyond removal of the original threat, the inflammatory response may transition into a more unstable state known as chronic systemic inflammation. Because the latter is a systemic condition it ultimately leads to dysregulation of homeostatic mechanisms causing harmful tissue remodeling, which supports the perpetuation of organ damage within the whole body [22,24–27].

Growing evidence demonstrates a close association between inflammation and AF development, a trend that has been accurately verified since first reported by Bruins et al. [28,29] Inflammatory cytokines are well-recognized biomarkers that can predict the prevalence and prognosis of AF [30]. Biomarker profiling has become an important research area in AF, in hope to accurately predict the risk of AF in patients with and without history of AF, and predict the prognosis after AF ablation procedure [31,32]. Many studies demonstrated that a number of inflammatory cytokines can serve as biomarker to predict the incidence of AF and/or the outcome of AF ablation, including C-reactive protein (CRP), TNF-α, IL-6, IL-1β, IL-8, and IL-10, which are summarized in Table 1. A detailed review on the role of cytokines as biomarkers of AF is provided by Harada et al. [30].

4. Innate inflammatory signaling & AF

Innate immune cells play an important role in mediating inflammation, primarily via their ability to release pro-inflammatory cytokines. Infiltration of innate immune cells in the atrial myocardium has been observed in patients with AF. Leukocyte activation was increased in patients with perioperative AF [33], and abundance of CD45-positive cells was higher in LA and right atria (RA) of AF patients [34]. Furthermore, among these immune cells, CD68-positive macrophages are more frequently observed in the atrial myocardium than the adaptive immune cells, such as CD3-positive T-lymphocytes [35]. TNF-α, nuclear factor κB (NFκB), and the 'NACHT, LRR & PYD Domains-containing Protein 3' (NLRP3) inflammasome are the best-characterized innate inflammatory signaling pathways. Although these inflammatory signaling pathways are primarily responsible for the maturation and release of cytokines, their potential cytokine-independent functions have also been linked to AF pathogenesis. Fig. 2 summarizes the established and putative molecular mechanisms related to the innate inflammatory signaling pathways in AF pathogenesis (Fig. 2), which are outlined below.

4.1. TNF-α signaling and AF

TNF-α, first identified in 1975, is considered as an endogenous mediator of inflammation, which is involved in a variety of cellular processes including activation of genes participating in inflammatory and immunoregulatory responses, proliferation, growth inhibition, and cell death [36]. The biological effects of TNF-α are mediated by two surface receptors, TNF receptor type-1 and type-2 (TNFR1 and TNFR2, respectively), both of which are expressed in cardiomyocytes (CMs), cardiac fibroblasts (CFs), and endothelial cells. Pathogen-associated molecular patterns (PAMPs) can stimulate both TNFR1 and

Table 1
Summary of clinical studies demonstrating a correlation between inflammatory cytokines and AF development.

Biomarker	Results	Reference (PMID)
CRP	CRP increased in patients with permanent AF patients (vs. paroxysmal AF).	11739301
	CRP levels can predict patient risk for AF development.	14623805
	Elevated CRP levels in post-op surgery patients correlate with greater risk of AF reoccurrence.	29595637
TNF-α	Increase in the level of TNF-α correlates with the different stages of AF patients relative to those in sinus rhythm.	23194937; 25746525
IL-6	IL-6 activation promotes CRP production and positively correlates with persistent/permanent AF development.	25190079, 22096359, 26839066
	IL-6 serves as a risk factor and predictor of AF in patients with chronic kidney disease.	26840403
IL-1β	Increased IL-1β serum levels associated with AF patients relative to sinus rhythm patients.	22096359, 16053785, 20637189, 26283592, 20833691, 22684635, 25425976
IL-8	IL-8 levels are elevated in clinically diagnosed AF patients. And the level of IL-8 varies according to AF duration.	23194937
IL-10	IL-10 is elevated in persistent/permanent AF patients compared those with paroxysmal AF.	20153266

CRP, C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; PMID, PubMed identifier number.

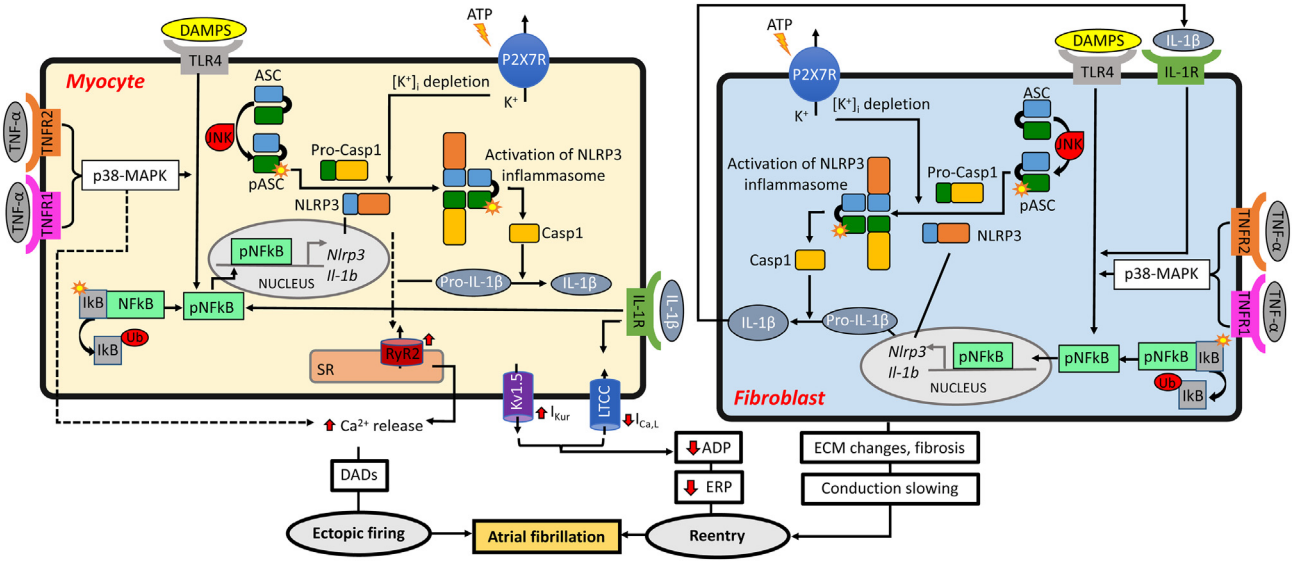

Fig. 2. Putative molecular and cellular mechanisms of atrial fibrillation pathogenesis involving inflammatory pathways. APD, action potential duration; ATP, adenosine triphosphate; EADs, early afterdepolarizations; ECM, extracellular matrix; ERP, effective refractory period; DADs, delayed afterdepolarizations; DAMPs, damage-associated molecular patterns; JNK, c-Jun N-terminal kinase; MAPK, activated protein kinase mitogen; P2X7R, P2X purinoceptor 7; SR, sarcoplasmic reticulum.

TNFR2, and subsequently lead to the activation of transcription factors such as NFκB and activating protein 1 (AP-1) [36], which are two major downstream effectors of activated TNF-α. Increased TNF-α signaling may cause arrhythmia via multiple mechanisms. It has been shown that activation of TNF-α signaling can promote atrial electrical, structural, and contractile remodeling, all of which are hallmarks of the molecular pathophysiology of AF [36]. Cardiac-specific overexpression of TNF-α in mice can enhance the susceptibility to AF induction, which is associated with abnormal Ca^{2+} handling and decreased contractile function in atrial cardiomyocytes. [37] TNF-α signaling activation is also implicated in the endurance-exercise-induced AF model via the activation of NFκB and p38-MAPK pathway [18]. It has been demonstrated that the acute application of TNF-α to the pulmonary vein (PV) CMs can produce a variety of ionic changes including smaller L-type Ca^{2+} currents and related systolic Ca^{2+} transients, larger transient outward K^+ currents (I_{to}), enhanced inward Na^+-Ca^{2+}-exchanger current (I_{NCX}), and a higher incidence of DADs, along with a transcriptional repression of sarcoplasmic reticulum ATPase (SERCA2a) expression [19,23]. In addition, elevated TNF-α levels in mice may promote atrial fibrosis, slow conduction by altering the expression of connexin-40, and alter ECM by promoting the fibroblast-myofibroblast transition, thereby enhancing secretion of collagen and metalloproteinases [18,37,38].

4.2. NFκB signaling and AF

NFκB is a transcription factor, which is inactive when it is bound to its endogenous inhibitor in cytoplasm (IκB). In response to a variety of stress signals including the damage-associated molecular patterns (DAMPs), NFκB dissociates from IκB and translocates to the nucleus, where it regulates transcription of its target genes including many inflammatory cytokines like TNF-α, IL-6, IL-8, and IL-1 [39]. The most common mechanism activating NFκB is the toll-like receptor 4 (TLR4)-myeloid differentiation factor 88 (MyD88) pathway [40,41]. The expression of TLR4, MyD88, NFκB and phosphorylated (active) NFκB are all increased in LA of AF patients compared to sinus rhythm controls [42].

Oxidative stress plays a significant role in AF pathophysiology [13,43,44], and reactive oxidative species (ROS) are major activators of key signaling pathways and transcription factors including NFκB [45]. NFκB serves as a redox-sensitive transcription factor, which in response to oxidative stress, can suppress transcription of cardiac Na^+ channels [46]. ROS detection of NFκB may also lead to modulation of other ion channels and transcription factors involved in AF development. Overall NFκB appears to serve as a nodal point in inflammatory signaling and might therefore represent a viable therapeutic target for AF treatment [44].

4.3. NLRP3 inflammasome and AF

In the innate immunity, NLRP3 inflammasome is the most extensively studied member of NOD-like receptor (NLR) family [47–49]. NLRP3 is distinguished structurally from other NLR proteins by its N-terminal pyrin domain (PYD), which interacts with the PYD domain of the ASC [apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain (CARD)] adaptor molecule. ASC facilitates recruitment of the inactive zymogen precursor caspase-1 (pro-Casp1) to complete assembly of the functional NLRP3 inflammasome complex [47–51]. Once the NLRP3, ASC, and pro-Casp1 assemble, forming the inflammasome complex, it triggers the pro-Casp1 autocleavage to produce the active form of Casp1. The active Casp1 is an IL-1-converting enzyme that consists of a 10 kDa (p10) and a 20 kDa (p20) subunit. Active Casp1 exhibits two distinct functions. It cleaves the inactive precursors of IL-1β and IL-18 (pro-IL-1β and pro-IL-18, respectively), thereby maturing the biologically active forms of IL-1β and IL-18. Macrophages and myofibroblasts can then secrete the mature cytokines, which serve as an inflammatory signaling-amplifier to perpetuate and spread the inflammatory response [47–49,52]. In addition, active Casp1 can also cleave gasdermin-D (GSDMD), releasing a 31 kDa N-terminal fragment (GSDMD-N), which forms the GSDMD-N pore through which IL-1β and IL-18 leave the cells to disseminate inflammation. If the number of pores in the plasma membrane increases above a certain threshold this can causes membrane rupture promoting a form of inflammatory cell death known as pyroptosis [53–55]. Emerging evidence points to an important role of NLRP3 inflammasome in a number of cardiovascular diseases including ischemic cardiomyopathy, atherosclerosis, etc., which is likely attributed to its dual functions promoting both abnormal cytokine release and perhaps cell death. For instance, activation of NLRP3 inflammasome can promote the development of cardiomyopathy by 1) reducing the number of working CMs due to the Casp1-mediated pyroptotic cell death, or 2) promoting structural remodeling by activation of

cardiac fibroblasts or macrophages, ultimately leading to an enhanced release of cytokines and growth factors that can further remodel the ECM [56–59].

There is clear evidence for a causal role of NLRP3 inflammasome activation in AF pathogenesis. We could recently demonstrate that the activity of NLRP3 inflammasome is increased in RA cardiomyocytes of patient with a history of pAF and perAF compared to sinus rhythm controls [77]. The activity of NLRP3 inflammasome was also enhanced in atrial samples of AF dogs and a mouse model of spontaneous AF induced by cardiac-specific overexpression of CREM-IbΔC-X [21]. Most important, the constitutive activation of cardiomyocyte NLRP3 inflammasome was sufficient to promote atrial ectopic activity and create a proarrhythmic substrate, enhancing the inducibility of AF. The cellular and molecular mechanisms underlying atrial ectopic activity and the reentrant substrate resulting from a specific activation of NLRP3 inflammasome in cardiomyocyte included 1) aberrant RyR2-mediated SR Ca^{2+} release during diastole, 2) AP shortening likely due to the augmented ultra-rapid delayed-rectifier K^+ current (I_{Kur}), 3) atrial hypertrophy, which might result from an increased level of myocyte-specific enhancer factor-2C (Mef2c), a well-known transcription activator associated with myocardial hypertrophy, and 4) atrial fibrosis. It remains to be determined whether these effects are exclusively mediated by IL-1β and IL-18 and whether pyroptosis also contributes to the evolution of the arrhythmogenic substrate. To the best of our knowledge our study is the first to demonstrate a causal link between NLRP3 inflammasome signaling and AF pathophysiology. The identification of the upstream mechanisms leading to NLRP3 inflammasome activation in AF, which need direct addressing in subsequent work, is expected to uncover novel therapeutic approaches for effective AF management.

5. Potential anti-Inflammatory therapy for AF

Despite the advancements in understanding the mechanisms of AF and improved AF patient care, this clinical condition remains an ongoing socioeconomic burden. Since AF confers a five-fold increase in the risk for stroke, many therapy regimens incorporate a variety of blood thinner and anti-arrhythmia drugs to prevent thrombus formation [60,61]. Contemporary therapeutic options for AF treatment include: 1) cardioversion and defibrillation, 2) use of anti-arrhythmic drugs with limited efficacy and substantial toxicity [5], and 3) diverse atrial ablation procedures to isolate or destroy the arrhythmic sources [60–62]. However, AF patients may still face undesirable outcomes, such as pro-arrhythmic side-effects caused by the anti-arrhythmic drugs, or severe complication due to ablation, or recurrent AF after ablation [62]. Thus there is a clear unmet need for novel anti-AF therapeutics with improved efficacy and safety profiles [62].

Frustaci et al. were the first to suggest a potential link between inflammation and AF and since then multiple pharmacological approaches targeting different inflammation signaling pathways are under evaluation in either animal studies or clinical trials [63]. Several anti-inflammatory options that have been tested in animal studies might have anti-AF effects by either modulating the cellular determinants of ectopic activity and/or by targeting the determinants of the reentrant substrate (Fig. 3). For example, in an exercise-induced AF model, TNF-α inhibition with etanercept, TNF-α gene ablation, or p38 inhibition, all prevented atrial structural remodeling and reduced AF-inducibility in response to exercise [18]. Inhibition of NLRP3 by MCC950 (a compound that can block the activation of NLRP3 inflammasome), by a shRNA (delivered by adeno-associated virus type-9), or by genetic ablation of *Nlrp3* gene, reduced the susceptibility to pacing-induced AF in mice [21]. Of note, colchicine (a microtubule delopimerizing drug with anti-inflammatory effects) and low-dose methotrexate (an anticancer agent with pronounced anti-inflammatory properties), which are used for decades to treat chronic inflammatory diseases, also inhibit the NLRP3 inflammasome [64,65]. Although colchicine appears to be effective against postoperative AF [66], the potential beneficial effects of colcichine and methotrexate against other AF forms need prospective demonstration. In addition, a variety of NFκB inhibitors are also available [67,68]. Although the effect of NFκB inhibition on AF development has not been determined, its protective role has been shown in animal models of cardiomyopathies [69,70]. Meanwhile, multiple clinical studies have been conducted to evaluate the efficacy of anti-inflammatory therapies in cardiomyopathies, which may pave the way for evaluating the therapeutic potential of anti-inflammatory strategies in AF patients. A recent clinical study (CANTOS) revealed that suppression of IL-1β, utilizing the cytokine neutralizing antibody canakinumab, can significantly reduce cardiac events in patients who are at risk [71,72]. Further investigation should address whether antibodies against IL-1β (canakinumab or gevokizumab) or IL-1α and IL-1β inhibitors such as anakinra and rilonacept can reduce the risk of AF in these patients [65,73].

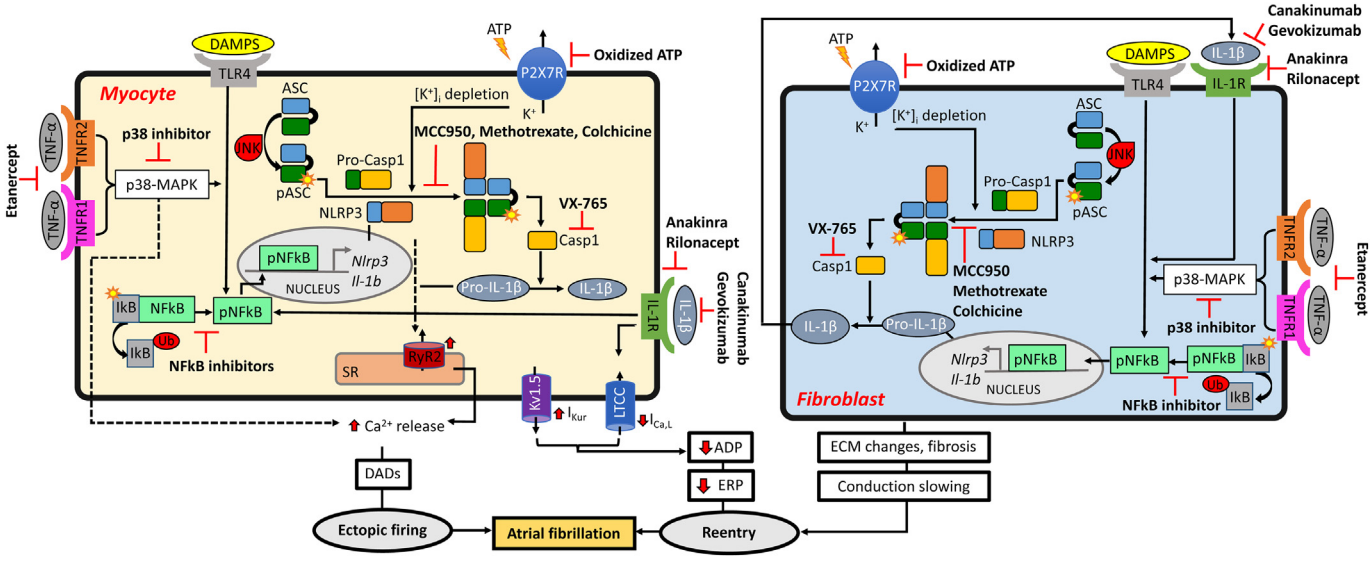

Fig. 3. Proposed therapeutic strategies for AF by targeting inflammatory pathways. APD, action potential duration; ATP, adenosine triphosphate; EADs, early afterdepolarizations; ECM, extracellular matrix; ERP, effective refractory period; DADs, delayed afterdepolarizations; DAMPs, damage-associated molecular patterns; JNK, c-Jun N-terminal kinase; MAPK, activated protein kinase mitogen; P2X7R, P2X purinoceptor 7; SR, sarcoplasmic reticulum.

As an alternative to targeting specific inflammatory regulators, some clinical studies suggest that inhibition of coagulation factors (e.g. activated factor-X; FXa), may also have anti-inflammatory effects. For example, non-valvular AF patients treated with FXa inhibitors demonstrated both reduced inflammation and coagulation relative to controls [74]. Clearly further prospective studies are needed to determine the potential anti-AF effects of oral anti-coagulants. It is possible that a three-pronged therapeutic approach utilizing anticoagulant, antiplatelet and anti-inflammatory drugs will be needed to combat AF and the related thrombogenesis in AF patients [75]. In addition, the abovementioned inflammatory signaling pathways mutually interact via transcriptional or posttranscriptional mechanisms, making it likely that inhibition of nodal points of their regulation will be required for effective treatment of AF patients. Thus, future extensive work is needed to prove and validate the causal contribution of inflammation and inflammatory signaling to AF pathophysiology and whether anti-inflammatory agents could constitute a novel therapeutic approach to treat AF patients.

Acknowledgement

This work was supported by the NIH (R01-HL136389 to N.L. and D.D., and R01-HL131517 to D.D.), the American Heart Association (17PRE33660744 to L.S.J.), and the German Research Foundation DFG (Do 769/4-1 to D.D.).

Disclosure

None.

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