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The crosstalk between cardiomyocyte calcium and inflammasome signaling pathways in atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most frequent arrhythmia in adults. The prevalence and incidence of AF is going to increase substantially over the next a few decades. Because AF increases the risk of stroke, heart failure, dementia, and others, it severely impacts the quality of life, morbidity and mortality. Although the pathogenesis of AF is multifaceted and complex, focal ectopic activity and reentry are considered as the fundamental proarrhythmic mechanisms underlying AF development. Over the past 2 decades, large amount of evidence points to the key role of intracellular Ca^{2+} dysregulation in both initiation and maintenance of AF. More recently, emerging evidence reveal that NLRP3 (NACHT, LRR, PYD domain-containing 3) inflammasome pathways contribute to the substrate of both triggered activity and reentry, ultimately promoting AF. In this article, we review the current state of knowledge on Ca^{2+} signaling and NLRP3 inflammasome activity in AF. We also discuss the potential crosstalk between these two quintessential contributors to AF promotion.

Keywords

atrial fibrillation; calcium; NLRP3 inflammasome; delayed afterdepolarization; ryanodine receptor type-2; SERCA; sodium-calcium exchanger

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia. It is associated with an increased risk of stroke, heart failure, dementia and death, thereby substantially influencing morbidity and mortality [81]. Current strategies for AF treatment include rate control by reducing the activation rate of the ventricles and rhythm control by converting the rapid and irregular atrial activation into sinus rhythm [123]. AF ablation is commonly used as a rhythm control strategy; however, the recurrence rate of AF is high in patients after successful AF ablation [52,113]. On the other hand, the conventional anti-arrhythmic drugs targeting cardiac ion channels yield modest benefits in converting AF to sinus rhythm and are often proarrhythmic [32,36]. The translational challenges to prevent AF are largely attributed to our limited ability to detect AF, the complex pathophysiology of the underlying AF-promoting atrial cardiomyopathy [53], and the progressive nature of AF leading to arrhythmia persistence and therapy resistance [66,68,157]. Mounting evidence demonstrate that aberrant calcium (Ca^{2+}) handling in cardiac cells plays a central role in the development of AF [69]. Moreover, recent work also points to the involvement of sterile inflammatory signaling in the pathogenesis of AF [129]. In this article, we first review the pathophysiology of AF; then, we assess the specific roles of abnormal Ca^{2+} homeostasis and inflammatory signaling in AF paradigms; finally, we elaborate on the potential crosstalk between these two pathways that may support the progression of AF to more persistent forms.

1. Pathophysiology of AF

In a healthy heart, the electrical impulses are generated by a cluster of pacemaker cells located in the sinoatrial node (SAN). These electrical impulses travel through the cardiac conduction system and cause the sequential depolarization of atria and ventricles [29]. To date, two types of arrhythmic events are being recognized as main determinants of AF - ectopic (triggered) firing and reentry [110]. Ectopic firing refers to the state where the SAN is no longer the sole source for initiating electrical impulses, which could be attributed to enhanced automaticity or focal triggered activity. Reentry refers to events where the impulse waves activate a rotating entry path, forming a circus movement or a rotor generates spiral waves [114].

1.1) Enhanced Automaticity

Haissaguerre et al. first discovered that focal triggers at the base of the pulmonary veins (PVs), near the superior vena cava and the posterior wall of the left atrium, could fire spontaneously and initiate AF [60]. These triggers from PVs are now widely accepted as a major source of ectopic firing in AF (almost 90% cases) [44]. This report laid foundation and rationale for the modern AF ablation technology by applying either high energy (radiofrequency ablation) or cold temperature (cryoablation) to destroy the tissues surrounding PVs and isolating the spontaneous firing from PVs, thereby eliminating fibrillatory conduction to the atria [3]. However, recent studies revealed that approximately 1/3 of ectopic firings could come from the right atrium, suggesting that other regions also could initiate and maintain AF [128].

1.2) Triggered activity

Triggered activity (TA) refers to spontaneous membrane voltage oscillations during or after an action potential (AP). TAs could be induced by either early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). Both events are heavily influenced by the altered functions of Ca^{2+}-handling proteins in cardiomyocytes. EADs are generated as a result of prolongation of the AP duration (APD). When APD is abnormally prolonged, it allows the reactivation of voltage dependent inward Ca^{2+} currents during phase 2 of the AP [83,110]. EADs can be also linked with APD shortening, occurring late in phase-3 of the AP. During the late phase-3 of APD, Na^+/Ca^{2+} exchanger (NCX) can be activated by large amplitude Ca^{2+} transients from sarcoplasmic reticulum (SR), particularly when the APD is abbreviated, which produces a depolarizing transient inward current (I_{ti}) that could cause late phase-3 EADs [18,83]. In contrast, DADs occur after the AP repolarization is completed and are primarily associated with the enhanced activation of the NCX due to increases in spontaneous Ca^{2+} release from SR [110,152].

1.3) Reentry

Ectopic firing is a frequent initiator of AF-maintaining reentry, but it could also sustain AF by itself by producing fibrillatory conduction even in the absence of a proarrhythmic atrial substrate. Reentry is considered the main mechanism that maintains AF. Circus movement reentry was found in jellyfish for the first time in 1906 [145]. This concept was then translated to arrhythmias by studies on cardiac tissue that exhibited circular electrical pathways. The formation of reentry can be a consequence of anatomical and functional substrates. The anatomical substrate has a prominent anatomical structure where the non-excitable scars (e.g. necrotic tissue or fibrosis) are surrounded by a circular pathway. A functional substrate could develop due to heterogeneities in excitability or conduction, whereby abbreviated refractoriness and slow conduction both promote reentry [153]. The effective refractory period (ERP) is determined by the cardiomyocyte APD, and conduction velocity (CV) is determined by the cellular excitability that is influenced by the amplitude of Na^+ current (I_{Na}), the state of cell-to-cell communication via gap junctions, and the heterogeneity of tissue composition. Conceptually, the product of ERP and CV determines the wavelength (WL = ERP x CV) of a circuit. When ERP is abbreviated or CV is slowed, often referred as electrical remodeling, the WL of a circuit decreases [31]. The smaller the circuit is, the more circuits the atria can accommodate. ERP shortening, as a consequence of APD abbreviation, is associated with the increases in repolarizing K^+ currents carried by the slow delayed rectifier K^+ currents I_{Ks} [19] inward rectifier K^+ current I_{K1} , the constitutively active G-protein coupled inward rectifying K^+ current $I_{K,ACh}$ [35,151], and 2-pore-domain K^+ currents I_{K2P} [126], and the reduction in depolarizing L-type Ca^{2+} current ($I_{Ca,L}$) [28]. Reduced CV could be the result of impaired I_{Na}[135], reduced expression or altered distribution of connexins, and increased local extracellular volume due to interstitial fibrosis and local inflammation [73]. Atrial enlargement or hypertrophy also support the formation of an increased number of wavelets. Thus, shortened ERP, reduced CV, and atrial enlargement are the best-established factors supporting the evolution of proarrhythmic substrates for AF.

2. Ca^{2+} dysregulation and AF development

Ca^{2+} is a second messenger and plays an essential role in several fundamental biological processes, including muscle contraction, synaptic transmission, membrane trafficking, cardiac contractility, gene transcription, and cell division [21,27,49,51,61]. The association between the increased frequency of spontaneous SR Ca^{2+} release events (SR Ca^{2+} leak), which frequently underlie triggered activity, and AF was first reported by Hove-Madsen and colleagues in 2004 [72]. Since then, substantial amount of evidence collectively supports the notion that enhanced SR Ca^{2+} leak likely plays a causative role in AF development. In this section, we focus our discussion on 1) the role of Ca^{2+} homoeostasis in normal cardiac electrophysiology, and 2) the role of abnormal function of Ca^{2+}-handling proteins in the promotion of triggered activity and in the evolution of the reentrant substrate associated with AF development (Figure 1).

2.1) Ca^{2+} homeostasis in cardiomyocytes

Ca^{2+} is a key contributor of excitation–contraction coupling (ECC) in cardiomyocytes [9]. When an AP starts due to the rapid activation of voltage-gated Na^{+} channel (Nav1.5), the related membrane depolarization activates the voltage-dependent Ca^{2+} channel (also known as L-type Ca^{2+} channel, LTCC) located on the sarcolemma, allowing a small influx of Ca^{2+} into the cytosol. The Ca^{2+} entry via LTCC triggers the intracellular Ca^{2+} channel located on the SR – ryanodine receptor type-2 (RyR2) to open and release a much larger amount of Ca^{2+} from SR into the cytosol, a process known as Ca^{2+}-induced Ca^{2+}release (CICR). Since activated RyR2 channels can activate neighboring RyR2 channels, the rapid rise of intracellular Ca^{2+} concentration from about 100 nM during diastole to about 1 μM during systole creates the systolic Ca^{2+} transient. Ca^{2+} binds to troponin C, leading to crossbridge of the myofilaments and cardiomyocyte contraction [9,46]. Following contraction, Ca^{2+} dissociates from the myofilaments, and cytosolic Ca^{2+} begins to decrease due to removal from cytosol via several mechanisms, thereby initiating relaxation. The decline in cytosolic Ca^{2+} concentration during diastole is primarily due to the SR Ca^{2+} uptake carried out by sarcoplasmic reticulum Ca^{2+}/ATPase type-2a (SERCA2a), and Ca^{2+} removal from cytosol via NCX type-1 (NCX1) and plasma membrane Ca^{2+} ATPase (PMCA). Recent studies suggest that cytosolic Ca^{2+} can also be taken up into the mitochondria by the mitochondria Ca^{2+} uniporter (MCU) located on the outer membrane of mitochondria [40]. However, the relative contribution of mitochondrial Ca^{2+} transporters to the overall Ca^{2+} homeostasis remains to be quantitatively determined. The complex interplay between Ca^{2+} signaling from the SR and mitochondria has been discussed in details elsewhere [40].

2.2) Abnormal Ca^{2+} handling promotes triggered activity

Ca^{2+}-handling abnormalities and cellular DAD-mediated triggered activity are critical events in atrial cardiomyocytes of patients with paroxysmal (pAF) and long-standing persistent (chronic) AF (cAF), as well as patients developing postoperative AF (poAF) [37,67,111,148–150]. Abnormal Ca^{2+} release can be estimated as alteration in frequency of Ca^{2+} sparks and spontaneous Ca^{2+} waves (SCaWs) [156]. Ca^{2+} spark is generated by the spontaneous Ca^{2+} release via a cluster of RyR2 channels located within 2-4 μm vicinity [23]. Increased Ca^{2+} spark frequency (CaSF) and SCaWs activate NCX1 [11], which is

electrogenic. In its forward mode, NCX1 brings 3 Na^+ ion into the cell for each Ca^{2+} ion pumped out of cell, which produces a transient depolarizing inward current that can potentially cause a DAD. Development of DADs increases the propensity for TAs. Simultaneous recording of membrane APs and intracellular Ca^{2+} signals of cardiomyocytes by combined patch clamping and Ca^{2+} imaging techniques have demonstrated that the SCaWs can directly evoke DADs and TAs in atrial cardiomyocytes [11,50,91,149]. The potential specific contributions of individual Ca^{2+}-handling proteins to TA are discussed below.

RyR2—RyR2 is a tetrameric channel, first cloned from rabbit cardiac muscle in 1990 [108,112]. Since then, multiple mechanisms have been identified that can regulate the opening of this main intracellular Ca^{2+}-release channel [39]. The stoichiometry of the RyR2 macromolecular complex is a key to maintain the normal RyR2 activity. Several binding partners of RyR2 affect the opening and closing states of this macromolecular complex. The most known RyR2-binding partner is FK506-binding protein 12.6 (FKBP12.6), and the lack of FKBP12.6 enhances the opening of RyR2 channel, increases CaSF, and promotes AF inducibility in FKBP12.6−/− knockout mice [91,134]. Similarly, junctophilin-2 (JPH2), a tethering protein that can help to maintain the optimal distance between sarcolemma and SR membrane at the junctional SR, is another important binding partner of RyR2. Beavers et al. showed a reduction of JPH2 levels in pAF patients and a mutation of JPH2 that reduces binding of JPH2 to RyR2 channels enhances SR Ca^{2+} leak via RyR2 and the susceptibility to inducible AF in the $JPH2^{E169K}$ knockin mince [8]. Conversely, RyR2 protein levels are strongly increased in pAF patients, which likely results from an impaired posttranscriptional regulation of *RYR2* due to the reduced level of the microRNA (miR)-106-25 cluster [25]. Genetic ablation of miRNA-106b-25 in mice recapitulated the increase of RyR2 protein seen in pAF patients, and increased CaSF and SCaWs [25]. Interestingly, the amount of RyR2-bound JPH2 was reduced in the miR-106-25−/− mice, suggesting that JPH2-deficient RyR2 channels might be overactive, contributing to the SR Ca^{2+} leak.

Post-translational modifications (PTMs) are known to affect activity of RyR2 channels. Despite many controversies, PTMs of RyR2 appears to play a critical role for RyR2 dysfunction in AF [38]. Phosphorylation, oxidation, and nitrosylation are the best known PTMs associated with RyR2 activity. RyR2 channels can be phosphorylated by protein kinase A (PKA) at Serine-2808 (S2808), Ca^{2+}/calmodulin kinase II (CaMKII) at Serine-2814 (S2814), and striated muscled preferentially expressed protein kinase (SPEG) at Serine-2367 (S2367) [20,148,155]. Some studies also suggest that PKA phosphorylates RyR2 at Serine-2030 (S2030) [75]. Phosphorylation of S2808 or S2814 enhances open probability of RyR2, thereby increasing Ca^{2+} release from SR [21,148,155]. Vest et al. demonstrated that the increase in S2808 phosphorylation of RyR2 enhances AF susceptibility [148]. Following this, several studies from different groups revealed that levels of Threonine-287 autophosphorylated (active) CaMKII and S2814-phosphorylated RyR2 are unaltered in pAF patients, but both are increased in cAF and poAF patients [21,92,111,149,150]. Disease modeling with a phosphomimic mutation of RyR2-S2814 (S2814D) in a knockin mouse model recapitulated the enhancement of SR Ca^{2+} leak and resulted in increased AF inducibility [149]. In addition to the canonical activation

mechanism, oxidation of CaMKII at Methionine-281/282 in mice infused with angiotensin II enhances its activity and triggers AF, mediated by the hyperphosphorylated and hyperactive RyR2 [117]. Opposite to the effects of PKA and CaMKII, SPEG-mediated phosphorylation of RyR2-S2367 stabilizes RyR2 channel [20]. A recent study showed that the level of SPEG and RyR2-S2367 phosphorylation was reduced in pAF patients and the loss of SPEG inhibitory modulation of RyR2 increases CaSF and AF susceptibility in mice [20]. However, the steady-state phosphorylation of the RyR2 channels is also affected by channel dephosphorylating protein phosphatases [43,65]. Defective regulations via protein phosphatase type-1 (PP1) and PP2A might contribute to the enhanced phosphorylation of RyR2 at both S2808 and S2814, respectively [43,141,173]. Additionally, spinophilin-1 (Sp1), functioning as a regulatory subunit of PP1 holoenzyme, facilitates the PP1-mediated regulation of RyR2. The loss of Sp1 in mice (Sp1−/−) leads to hyperphosphorylation of RyR2 at S2814, promoting atrial ectopy and pacing-induced AF [26]. A recent study by Alsina et al. revealed that PPP1R3A, a newly discovered PP1-regulatory subunit, also regulates RyR2 channel and is downregulated in AF patients. The reduced PPP1R3A levels impairs PP1 targeting to both RyR2 and PLB, causing hyperphosphorylation of both proteins and the loss of PPP1R3A in mice enhances SR Ca^{2+} leak and increases AF susceptibility [2].

RyR2 is also regulated by luminal Ca^{2+} levels of the SR. Calsequestrin type-2 (CSQ2) is a Ca^{2+}-buffering protein located inside the SR. When SR Ca^{2+} is low, CSQ2 becomes monomeric Ca^{2+}-free form, and interacts with the accessory proteins such as triadin (TRDN) and junctin (JCN) to prevent RyR2 from opening. As the SR luminal Ca^{2+} increases, CSQ2 form dimers and polymers, dissociate from RyR2 complex, relieving the RyR2 inhibition [22,145]. Csq2 loss-of-function mouse model displays SCaWs and DADs, and are more susceptible to inducible AF [45,169]. Collectively, these studies demonstrate multiple mechanisms of altered RyR2 function that are all potential contributors to AF development.

SERCA2a—The activity of the SERCA2a pump is tightly regulated by the micropeptides phospholamban (PLB) and sarcolipin (SLN) [5,161]. PLB and SLN directly bind to and serve as endogeneous inhibitors of SERCA. Phosphorylation of PLB by PKA at Serine-16 (S16) or CaMKII at Threonine-17 (T17) relieves SERCA2a inhibition, allowing larger SR Ca^{2+} reuptake, which increase SR Ca^{2+} content [76,82]. SPEG may also regulate atrial SERCA2a function, with loss of SPEG resulting in reduced SR Ca^{2+} reuptake [121]; however, the latter is not a consistent finding [20] and requires further validation. In pAF patients and cAF patients with heart failure, although the expression of SERCA2a is reduced in pAF patients, the overall SERCA2a function increases in both AF populations due to the enhanced phosphorylation of PLB by PKA and CaMKII or reduced SLN level [111,130,144,150]. In cAF patients with preserved ejection fraction, the hyperphosphorylation of PLB is also attributed to the enhanced inhibition of PP1 by hyperphosphorylated (hyperactive) Inhibitor-1 (I-1) [43]. Genetic ablation of SLN in mice (SLN1−/−) enhances SERCA2a activity and promotes DADs [5,161]. Because both SR Ca^{2+} release and Ca^{2+} uptake are augmented, AF patients likely experience a faster Ca^{2+} cycling. The latter could more frequently activate NCX1, thereby causing membrane depolarizations

that ultimately lower the threshold for DADs and related TAs in AF patients. As mentioned above, the CaMKII expression and activity are increased in cAF patients and promote arrhythmogenesis through phosphorylation of multiple targets (RyR2, PLB, and LTCC), proving CaMKII as a critical nodal point in AF pathogenesis. For more detailed overview on the CaMKII-mediated regulation of Ca^{2+}-handling proteins and its relationship with AF development, we refer to a recent review article [69].

NCX1—The most known pathological consequence of augmented NCX1 function is the promotion of DADs and TAs. As a result of enhanced RyR2 activity or SR Ca^{2+} overload due to increased SERCA2a activity, SR Ca^{2+} leak can over-activate the forward mode NCX1 and generate the transient inward current I_{NCX}, which causes a membrane depolarization potentially producing DADs. Once the depolarization reaches the threshold to activate the fast sodium channel, a premature AP will be triggered [50,115,147]. Increased NCX1 function has also been linked to the development of late phase-3 EADs [18,42,139]. The level of NCX1 has an impact on the APD. NCX1 overexpression in transgenic mice prolongs APD, and knockout NCX1 in mice shortens APD [116]. Of note the enhanced NCX1 function in cAF patients appears to involve an upregulation of protein expression, which should amplify the consequences of increased SR Ca^{2+} leak [150]. However, the molecular mechanism underlying the upregulation of NCX1 in AF remains elusive. Because NCX1 is a membrane protein, the enhanced function of NCX1 in cAF could also be associated with an enhanced trafficking. Under normal condition, a considerable amount of NCX1 is present in the cytoplasm [59]. Thus, it raises the possibilities that the fast trafficking of NCX1 from cytoplasm to the plasma membrane might be enhanced in the context of cAF, which warrants direct demonstration. In ventricular myocytes, EHD3 (Eps15-homology-domain-containing gene produce 3) modulates NCX1 trafficking [58]. Whether this mechanism holds true in atrial myocytes remains to be determined. Moreover, some studies also suggest that NCX1 can be phosphorylated by either PKA or PKC [171]. Further studies are needed to elucidate the relationship between the phosphorylation of NCX1 and AF. Of note, the intracellular Na^+ level ($[Na^+]_i$) appears to be reduced in a rabbit model of AF induced by rapid atrial pacing. Greiser et al. reported that the resting $[Na^+]_i$ in rabbit atrial myocytes might decrease as a consequence of the rapid-pacing induced reduction of $I_{Ca,L}$ and APD shortening [56]. The reduced $[Na^+]_i$ level may favor the forward-mode NCX activation in atrial myocytes, which requires further validation and detailed analysis.

2.3) Abnormal Ca^{2+} handling promotes a reentrant substrate

Although large amount of data pointing to the causative role of abnormal Ca^{2+} handling in the formation of TA, there are also evidence that abnormal Ca^{2+} handling can promote reentry by a reduction of APD/ERP, a slowing in atrial conduction, or promoting atrial structural remodeling (hypertrophy and fibrosis), which is detailed below.

2.3.1) LTCC & reduced ERP—

Decreased function of LTCC is a hallmark of cAF. In cAF patients and the rabbit model of rapid atrial pacing, mimicking the rapid atrial rhythm during AF, amplitude of $I_{Ca,L}$ is reduced due to the downregulation of Cav1.2, the α-subunit of LTCC [10,28,119]. Increased LTCC dephosphorylation due to enhanced activity of PP1

and PP2A also contributes to the lower $I_{Ca,L}$ [10,28,119]. The reduction in $I_{Ca,L}$ shortens the APD, and thus ERP, allowing the formation of AF-maintaining reentry in patients with cAF [28].

The downregulation of Cav1.2 is attributed to a number of mechanisms. First, Luo et al. reveal that the enhanced microRNA (miR)-328 mediated posttranscriptional regulation of CACNA1C (encoding Cav1.2) is associated with cAF in patients and in a canine model of AF [98]. They also showed that overexpression of miR-328 through adenovirus infection in canines and transgenic mice decreases $I_{Ca,L}$ and APD in atrial myocytes, increasing the vulnerability to AF. Conversely, inhibition of miR-328 by antagomiR reversed these alterations [98], suggesting that miR-328 could be a target to prevent AF progression [62]. A loss of transvers tubule (T-tubules) can also lead to a loss-of-function of LTCC channel [86]. The autophagosome-mediated degradation of Cav1.2 has been linked to the increased incidence and burden of AF in cAF patients and rabbit model of atrial rapid pacing [167]. Overexpression of autophagy gene 7 (Atg7) facilitates targeting of the ubiquitin-binding proteins RFP2 and p62 to Cav1.2, accelerating Cav1.2 degradation [167].

In addition to reduced expression of Cav1.2 protein, the open probability of LTCC is directly regulated by the cytosolic Ca^{2+} concentration. When the level of intracellular Ca^{2+} increases in the microdomain of Cav1.2, Ca^{2+}-bound calmodulin interacts with Cav1.2 and inactivates the channel [170]. The enhanced SR Ca^{2+} leak in AF might cause a stronger inactivation of LTCC, a hypothesis that needs experimental verification. Notably, the calmodulin-mediated inactivation of Cav1.2 serves as a self-protecting mechanism that can prevent cells from Ca^{2+} overload in the early stage of AF and is usually reversable. When the arrhythmia transitions into more persistent forms of AF, additional mechanisms involving transcriptional and posttranscriptional regulations and protein-degradation process as described above become more important causing a downregulation of Cav1.2, often associated with electrical remodeling in cAF patients.

2.3.2) Abnormal Ca^{2+} handling and structural remodeling—Structural remodeling is a key factor for the maintenance of AF. Ca^{2+} signaling also plays a role in structural remodeling. When cytosolic Ca^{2+} levels rise, this can activate the Ca^{2+}-sensitive phosphatase calcineurin (CaN) [17,33,140]. Active CaN dephosphorylates nuclear factor of activated T-cell (NFAT)-c3 and NFAT-c4, and subsequently promotes the translocation of these transcription factors into the nucleus, thereby initiating the transcription of multiple hypertrophic and profibrogenic genes associated with structural remodeling (Figure 1). The enhanced activity of CaN-NFAT pathway correlates with both the enlargement of the left atrium and the maintenance of AF in cAF patients and the canine model of AF [93,100]. Fibrosis, another important feature of structural remodeling associated with AF, could also be affected by the dysregulated Ca^{2+} signaling in cardiac fibroblasts. For example, the expression of transient receptor potential canonical type-3 (TRPC3) channels, which permeate Ca^{2+}, was increased in AF patients. The increased Ca^{2+} entry via TRPC3 channels promotes fibroblast proliferation and their differentiation to collagen-secreting myofibroblasts by activating the extracellular signal-regulated kinase (ERK) signaling [63]. For a detailed review on the diverse Ca^{2+}-handling systems in fibroblast and their potential roles in fibrosis, please refer to recent review articles [68,109].

Another important aspect of Ca^{2+}-related structural remodeling is occurring within the specialized t-tubule system [143]. Although earlier studies suggested that the t-tubule system is rudimentary in small animals like rats and mice [80,158], there are t-tubules in the atria of large animals and the human [122]. Of note, recent studies with improved methodology in sample preparation and imaging system have revealed that large networks of axial tubule (AT) structures consistently exist in atrial myocytes of the human, large and small animals, with ATs facilitating rapid Ca^{2+} release at axial junctions [13,14]. While the t-tubule system tends to run perpendicular to the long axis in ventricular myocytes, ATs predominantly run along the long-axis in atrial myocytes. Lenaerts et al. first reported the loss of atrial tubular structure in a sheep model of persistent AF [86]. The decreased atrial tubular density is associated with increased cell volume and hypertrophy, decreased $I_{Ca,L}$, reduced coupling between LTCC and RyR2, and increased NCX1 activity in atrial myocytes of sheep with persistent AF [86,143]. However, whether AF-related remodeling of the atrial t-tubule system is a cause or bystander of AF development requires further extensive examination. One possibility is that the remodeled atrial t-tubule system could promote AF via re-distribution of NCX1 thereby increasing the propensity for DADs. Alternatively the related decrease in $I_{Ca,L}$ causes an abbreviation of APD and ERP, promoting reentry. Given the presence of ATs across species, it would be important to identify the mechanisms of AT development and study how dysfunction in AF formation could promote AF in animal models and perhaps patients with AF.

3. Inflammasome and AF development

Inflammasome refers to the multimeric molecular platform responsible for the activation of pro-inflammatory caspases, which in turn lead to the processing and secretion of pro-inflammatory cytokines [15,127,129]. Over the past 20 years, inflammasomes have been recognized for their roles not only in the host defense against invading pathogens but also in the development of auto-inflammatory, cancer, and metabolic diseases [34,103]. In recent years, inflammasome, particularly the NLRP3 (NACHT, LRR, PYD domain-containing 3) inflammasome, has been linked to the pathological progression of several cardiovascular diseases including atherosclerosis, hypertension, cardiomyopathy, ischemic heart disease, and arrhythmias [89,94]. Inflammatory cytokines have been associated for a long time with the onset and maintenance of AF, as well as the outcome of AF ablation [89], and recent studies suggest that inflammasome activation may play a causative role in AF development, partially via the dysregulation of Ca^{2+} handling.

3.1) NLRP3 inflammasome

Among various forms of inflammasomes identified so far, the NLRP3 inflammasome is the best characterized and most extensively studied inflammasome complex [127,129]. NLRP3 inflammasome is unique in a way that it responds to a diverse stimuli [57]. The NLRP3 inflammasome is composed of the sensing subunit NLRP3, the adaptor protein ASC, and the effector subunit pro-caspase-1 [127]. NLRP3 protein contains a N-terminus pyrin domain responsible for the recruitment of ASC, a central nucleotide-binding oligomerization domain that enables the activation of the inflammasome signaling platform, and a C-terminus leucine-rich repeat (LRR) functioning in ligand sensing and autoregulation [142]. Basal

level of NLRP3 is relatively low and insufficient for active inflammasome formation [7]. Meanwhile, NLRP3 is kept in an inactive ubiquitinated state until a priming signal evokes de-ubiquitination [118]. It is well-known that the activation of the NLRP3 inflammasome requires two processes: priming and triggering (Figure 2). The priming stimuli, such as ligands of toll-like receptors (TLRs), NLRs and cytokine receptors, can induce the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)-mediated transcription of the inflammasome component genes *Nlrp3, Asc, pro-caspse-1*, as well as the effector genes *pro-Il-1b* and *pro-Il-18* [96,165] . Activation of NF-κB also leads to de-ubiquitination of NLRP3 through the deubiquitinating enzyme BRCC3 [118,120]. As the second step to the NLRP3 inflammasome, triggering stimuli promotes the assembly of NLRP3, ASC, and pro-caspase-1 proteins, facilitating the autocleavage of caspase-1 [138]. To date, a wide range of trigging stimuli have been identified, including ATP, nigericin, silica, uric acid, ionic flux (i.e. K^+ efflux, Ca^{2+} flux, Na^+ influx, and Cl^- efflux), mitochondrial dysfunction, the production of reactive oxygen species (ROS), and cathepsin B released from the damaged lysosome [54,71,105,172]. In addition to the triggering stimuli, the activation of NLRP3 requires spatial arrangement driven by the microtubule network [101,106]. Active caspase-1 is an aspartate-specific cysteine protease that proteolytically cleave the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. Furthermore, active caspase-1 also cleaves gasdermin D (GSDMD), which results in fragmentation of GSDMD. The N-terminus fragment of GSDMD (Nt-GSDMD) form pores on the plasma membrane, which facilitates the release of IL-1β and IL-18. In some cases, pore-forming action by Nt-GSDMD may also trigger a lytic, pro-inflammatory form of cell death, known as pyroptosis [48,77,97,131] (Figure 2).

3.2.) Overactive NLRP3 inflammasome promotes AF

Clinically, inflammation is frequently detected in patients with pAF, cAF and poAF. Several inflammatory markers including IL-1β and IL-18 correlate with the progression of AF, and can also predict the recurrence rate of AF after ablation [47,88,89,99,159]. Because the production of IL-1β and IL-18 is partially attributed to the activation of NLRP3 inflammasome, it suggests that NLRP3 inflammasome may play a role in AF pathogenesis. Recent studies have demonstrated that the NLRP3 inflammasome activity is increased in atrial samples of pAF, cAF, and poAF patients, as well as in diabetic patients who are at increased risk for AF [47,67,164]. An increased activity of the NLRP3 inflammasome was also noted in animal models of AF including the dogs with atrial tachypacing-induced AF and the CREM transgenic mouse model with spontaneous AF development [79,90,164]. Although NLRP3 inflammasomes exist in multiple cell types including cardiomyocytes, cardiac fibroblasts, macrophages, and adipocytes, etc.[129,146], direct comparison of the NLRP3 inflammasome components in human atrial myocytes versus human atrial fibroblasts revealed that cardiomyocyte NLRP3 inflammasome activation strongly contributes to the overall increase of NLRP3 activity in atrial tissues of AF patients [164]. Additionally, in the macrophage specific *Atg7* knockout mice, the increased activity of macrophage NLRP3 inflammasome exerts minimum impact on AF susceptibility [132,164]. These data underscore that cardiomyocytes are key drivers of increased inflammasome activity in atria. However, it is currently unknown whether and how the NLRP3 inflammasome activation is altered in atrial adipocytes, particularly in the epicardial adipose

tissue (EAT) of AF patients. Since obesity is a known risk factor of AF and EAT is considered as an important local source for the paracrine modulation of cardiomyocytes [6,55,102], subsequent work should specifically address the role of adipocyte NLRP3 inflammasome in EAT and its potential involvement in AF pathogenesis.

To demonstrate the potential causality between the cardiomyocyte NLRP3 activity and AF pathology, a mouse model with cardiomyocyte-restricted expression of a constitutively activated NLRP3 was recently developed (αMHC:NLRP3$^{A350V/+}$). The A350V mutation can facilitate the inter-domain interaction between NLRP3 and other inflammasome components, thereby promoting its activation [16]. αMHC:NLRP3$^{A350V/+}$ mice exhibit atrial ectopic activity, shorter atrial ERP, enlarged atria, and atrial hypertrophy and fibrosis, all of which predispose to AF development. Despite the lack of spontaneous AF, αMHC:NLRP3$^{A350V/+}$ mice are very susceptible for rapid pacing-induced AF. Selective blockade of NLRP3 by the inhibitor MCC950 or a short-hairpin RNA-mediated knockdown of Nlrp3, both prevent the AF induction in αMHC:NLRP3$^{A350V/+}$ mice. Consistently, the genetic ablation of NLRP3 in CREM transgenic mice prevented the development of spontaneous AF [164]. Combined these findings support a causative role for NLRP3 in AF development. Nevertheless, many important questions that need clarification remain: 1) how is the inflammasome activated in AF; 2) what are the specific effects of IL-1β, caspase-1, and GSDMD on atrial function in AF; and 3) whether NLRP3 inflammasome has IL-1β independent functions in cardiac cells.

3.3) Inflammasome activation amplifies other inflammatory signaling pathways associated with AF

Activation of NLRP3 inflammasome can potentially boost the activity of other prominent inflammatory cytokines linked to AF development, such as IL-6 and tumor necrosis factor alpha (TNFα). IL-1β, the effector of NLRP3 inflammasome activation, can trigger the expression of IL-6 and TNFα via IL-1 receptor (IL-1R) activation and the formation of active NF-κB. Clininical studies have shown that the increased levels of IL-6 and TNFα associate with AF development in patients and with adverse outcome of AF ablation [1,24,87,136]. In a rat model of sterile pericarditis, the development of poAF is accompanied with increases in IL-6 and TNFα, and atrial fibrosis [74], and the anti-AF effect of colchicine in this model is partially attributed to inhibition of IL-1β-induced expression of IL-6 [160]. The AF-promoting effects of IL-6 and TNFα are largely associated with their ability to promote hypertrophy and fibrosis in AF patients and mouse models [73]. Studies in cardiomyocytes also reveal that TNFα directly reduces $I_{Ca,L}$, CaTs, and SERCA2a and can induce DADs perhaps because of increases in I_{NCX} [85,124]. Cardiomyocyte-specific overexpression of TNFα in mice also lead to downregulation of Cx40 and enhances AF susceptibility [125]. Since NF-κB is a master transcription factor controlling the expression of many inflammatory cytokines, and NF-κB activation is likely the consequence of the several cytokine receptors including IL-1R and TNFα receptor (TNFR), a deleterious inflammatory signaling circle involving multiple cytokines may exist in atrial tissue supporting the development of AF substrates.

4. Crosstalk signaling linking altered Ca^{2+} handling and NLRP3 inflammasome activation

Although previous studies have dealt with the role of altered Ca^{2+} signaling and NLRP3 inflammasome activity in AF development, emerging recent work suggest these two systems may have common nodal points of mutual regulation. Here, we discuss some potential crosstalk possibilities between Ca^{2+} handling and NLRP3 inflammasome that could exist in the context of AF (Figure 3).

4.1) Intracellular Ca^{2+} may activate the NLRP3 inflammasome

Ca^{2+} has multiple and indispensable roles in cellular life [30]. Earlier studies revealed the mobilization of intracellular Ca^{2+} during the process of NLRP3 inflammasome activation in macrophages and that Ca^{2+} signaling is required for NLRP3 inflammasome activation [107]. Multiple sources of Ca^{2+} may lead to the increase of intracellular Ca^{2+} that contributes to NLRP3-inflammasome activation. In immune cells, where the Ca^{2+} sensing receptor (CaSR) exists, CaSR can be sensitized by elevated extracellular Ca^{2+} to cause influx of Ca^{2+}, which activates the NLRP3 inflammasome [84]. In non-excitable cells, the IP_3 receptor (IP_3R) is the main Ca^{2+} release channel from the endoplasmic reticulum (ER). Inhibition of IP_3R by 2-aminoethyl diphenylborinate (2-APB) reduces intracellular Ca^{2+} and prevents IL-1β secretion in macrophages [84,154]. Although there is a correlation between intracellular Ca^{2+} and inflammasome activation, the precise mechanisms linking Ca^{2+} fluxes with NLRP3-inflammasome activation remain elusive. In macrophages Ca^{2+} could facilitate the interaction between NLRP3 and ASC as recently suggested [84]. Alternatively, the elevation in cytosolic Ca^{2+} can lead to mitochondrial Ca^{2+} overload, generation of mitochondria-derived reactive oxygen species (ROS), and subsequent activation of the NLRP3 inflammasome [70,95,107]. ER stress might also activate the NLRP3 inflammasome, and in many occasions, ER stress is influenced by dysregulations of the Ca^{2+} homeostasis [104]. Furthermore, the Ca^{2+}-sensitive phosphatase CaN is also involved in the inflammasome activation. In a mouse model with cardiac-specific heterozygous overexpression of CaN, increased inflammation is attributed to the upregulation of *Nlrp3,* increased mature Casp-1, and elevated serum level of IL-1β [12]. Conversely, the CaN inhibitor cyclosporine reduced IL-1β production due to the decreased mRNA and protein levels of IL-1β in macrophages, positioning active CaN as an important contributor to both priming and triggering of the NLRP3-inflammasome [154]. Since increased SR Ca^{2+} release and elevated diastolic Ca^{2+} are common in AF, it would be interesting to elucidate whether and how the abnormal SR Ca^{2+} release events and mitochondrial Ca^{2+} signaling contribute to NLRP3-inflammasome activation in atrial cardiomyocytes of AF patients.

It is worth highlighting that ROS and reactive nitrogen species (RNS) signaling modulates the activity of CaMKII and several Ca^{2+} handling proteins in cardiomyocyte independently [166]. It is well documented that the elevated level of atrial ROS/RNS is associated with AF [4,41,78,133]. The sources for the increased ROS/RNS production in atria has been linked to the increased expression of NADPH oxidase 2 (NOX2) and the enhanced mitochondrial function [4,41,78]. The increased ROS level can activate CaMKII by oxidation at Methionine-281/282, which should phosphorylate RyR2 and PLB, as discussed above

[117,166]. In parallel, ROS/RNS can directly cause the oxidation or s-nitrosylation of RyR2, which enhances the RyR2-mediated SR Ca^{2+} leak [162]. All of these actions lead to an elevated intracellular Ca^{2+} level, which could contribute to the activation of NLRP3 inflammasome [163].

Recent studies demonstrate that histone deacetylase 6 (HDAC6) plays an indispensable role for the microtubule transport and assembely of inflammasome in macrophages [101,106]. Coincidentally, earlier work have shown that increased HDAC6 activity is a key component of AF-related atrial remodeling in both patients and HL-1 cells subjected to high frequency *in vitro* pacing [89]. HDAC6 activity contribibutes to atrial tachycardia remodeling-induced decreases in LTCC current and Ca^{2+} transient amplitudes, and sacromere contractility [168]. Subsequent work should address whether HDAC6-mediated inflammasome activation requires activation of Ca^{2+} signaling and delinieate the underlying mechanisms.

4.2) NLRP3 inflammasome activation enhances SR Ca^{2+} leak

Because the enhanced NLRP3 inflammasome activity in cardiomyocytes promotes aberrant SR Ca^{2+} leak, a crosstalk between these two systems likely occurs. In the αMHC:NLRP3$^{A350V/+}$ mouse model, where NLRP3 was specifically activated in cardiomyocytes only, CaSF was increased and RyR2 protein was upregulated, which was associated with enhanced atrial ectopic firing [164]. In atrial cardiomyocytes of poAF patients, the more frequent occurrence of SCaWs was associated with a pre-existing low-grade local inflammatory state [67]. Acute application of IL-1β to mouse atrial-cardiomyocytes (HL-1 cells) significantly increased phosphorylation of RyR2-S2814 and PLB-T17, suggesting that the increases of CaMKII and RyR2 activities seen in atria of poAF patients might be a direct consequence of IL-1β signaling. Indeed, inhibition of CaMKII by the inhibitor KN-93 reversed the IL-1β induced hyperphosphorylation of RyR2 and PLB [67]. Similarly, in a heart failure model induced by transverse aortic constriction, the activation of NLRP3 inflammasome and inflammation in ventricular tissue could be attenuated by cardiomyocyte-specific knockout of CaMKII [137]. Together, these recent studies suggest that a self-amplifying feed-forward loop via a NLRP3/CaMKII nexus exists and could play an important role in the pathophysiology of AF and heart failure. Clearly further work is needed to dissect the precise interaction patterns between Ca^{2+} signaling and NLRP3-inflammasome activation in cardiomyocytes, which is expected to lead to the discovery of novel potential drugs targets to treat cardiovascular diseases.

Conclusion

Aberrant Ca^{2+} homeostasis due to versatile mechanisms is essential in promoting the formation of ectopic (triggered) activity and a reentrant substrate for AF promotion. NLRP3 inflammasome has emerged as a novel mechanism associated with AF pathogenesis. Dysregulated Ca^{2+} and NLRP3-inflammasome activation may crosstalk creating a feed-forward loop of joint amplification in AF. Basic science discoveries are key guides for the development of novel anti-AF therapeutics [64]. Thus, identifying the nodal points of crosstalk signaling between these two systems may allow to develop strategies to halt their deleterious interaction potentially preventing AF induction and its perpetuation.

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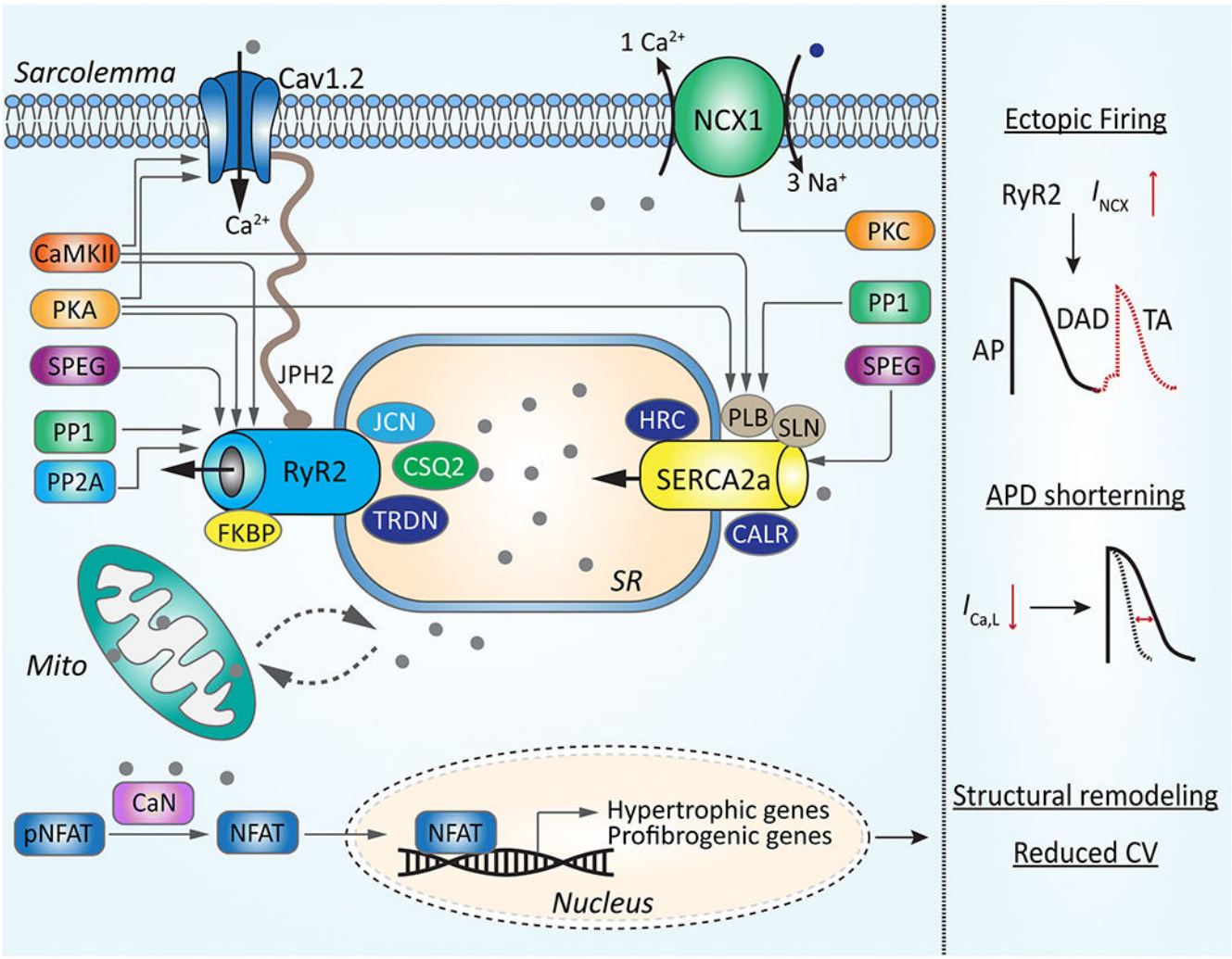

Figure 1. Putative molecular mechanisms contributing to abnormal Ca^{2+} handling associated with atrial fibrillation (AF).

Focal ectopic firing due to the delayed afterdepolarization (DAD)-induced triggered activity (TA), APD shortening, and atrial enlargement as a result of the upregulation of hypertrophic and profibrogenic genes are key events associated with dysregulated Ca^{2+} handling in atrial cardiomyocytes during AF. DAD-inducing sarcoplasmic reticulum (SR) Ca^{2+} release (SR Ca^{2+} leak) is higher due to the enhanced activity of ryanodine receptor type-2 (RyR2). The latter could be a consequence of an impaired interaction with FKBP (FK506-binding protein 12.6) or junctophilin-2 (JPH2), altered phosphorylation by CaMKII, PKA, and SPEG, or a combination of both. The SERCA2a-mediated SR Ca^{2+} uptake could be increased in pAF because of a reduction of sarcolipin (SLN) or a hyperphosphorylation of phospholamban (PLB). In cAF, the hyperphosphorylation of PLB is associated with the enhanced Inhibitor-I (I-1) mediated inhibition of protein phosphatase type-1 (PP1). These alterations lead to the enhanced SR Ca^{2+} leak, which can activate the Na^{+}/Ca^{2+} exchanger 1 (NCX1) and promote DADs. The shortening of APD is partially due to the reduced level of Cav1.2 (α-subunit of L-type Ca^{2+} channel, LTCC) or increased LTCC dephosphorylation due to enhanced activity of PP1 and PP2A. Together with structural remodeling involving Ca^{2+}-induced calcineurin

(CaN)-mediated activation of NFAT (nuclear factor of activated T-cell), a transcription factor associated with the hypertrophy and fibrosis, AP shortening promote AF-maintaining reentry.

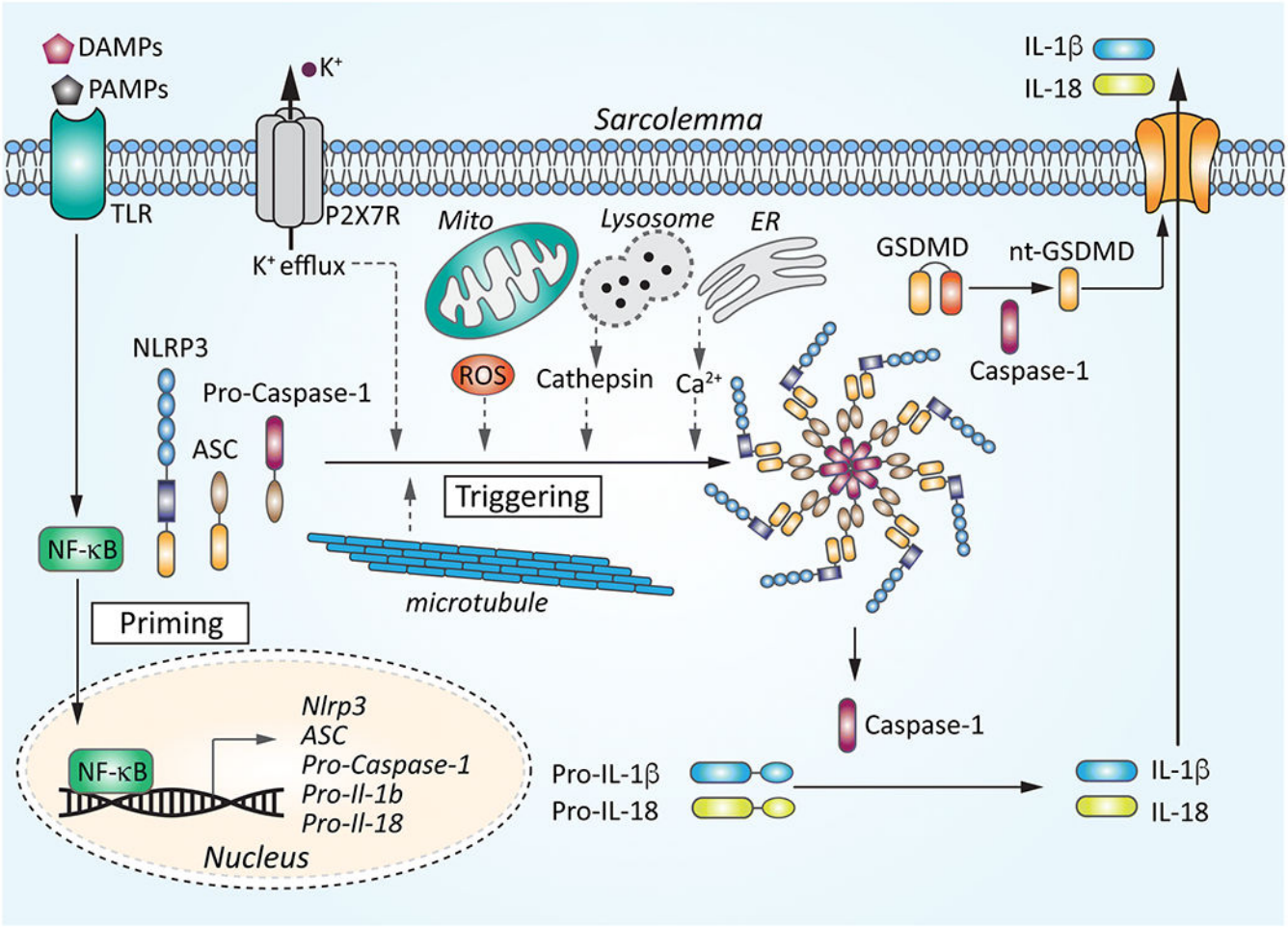

Figure 2. Potential mechanisms underlying NLRP3 inflammasome activation.

Activation of NLRP3 involves two major processes: *priming* and *triggering.* Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) activate toll-like receptor (TLR), and subsequently induce NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)-mediated transcription of inflammasome components (NLRP3, ASC, and pro-Caspase-1) and effectors (pro-IL-1β and pro-IL-18). A wide array of triggering signals may promote the inflammasome assembly. To date, the most established triggering stimuli include 1) K^+ efflux via the purinergic receptor P2X7R, 2) increased intracellular Ca^{2+} levels, 3) ER stress, 4) enhanced cathepsin-B release by lysosome rapture, and 5) increased ROS generation. Spatial arrangement organized by the microtubule network is also essential for the inflammasome assembly. The activation of inflammasome promotes the autocleavage of caspase-1. Mature caspase-1 activates IL-1β, IL-18, and gasdermin-D (GSDMD). N-fragmented GSDMD (Nt-GSDMD) creates membrane pores and facilitate the release of mature IL-1β and IL-18.

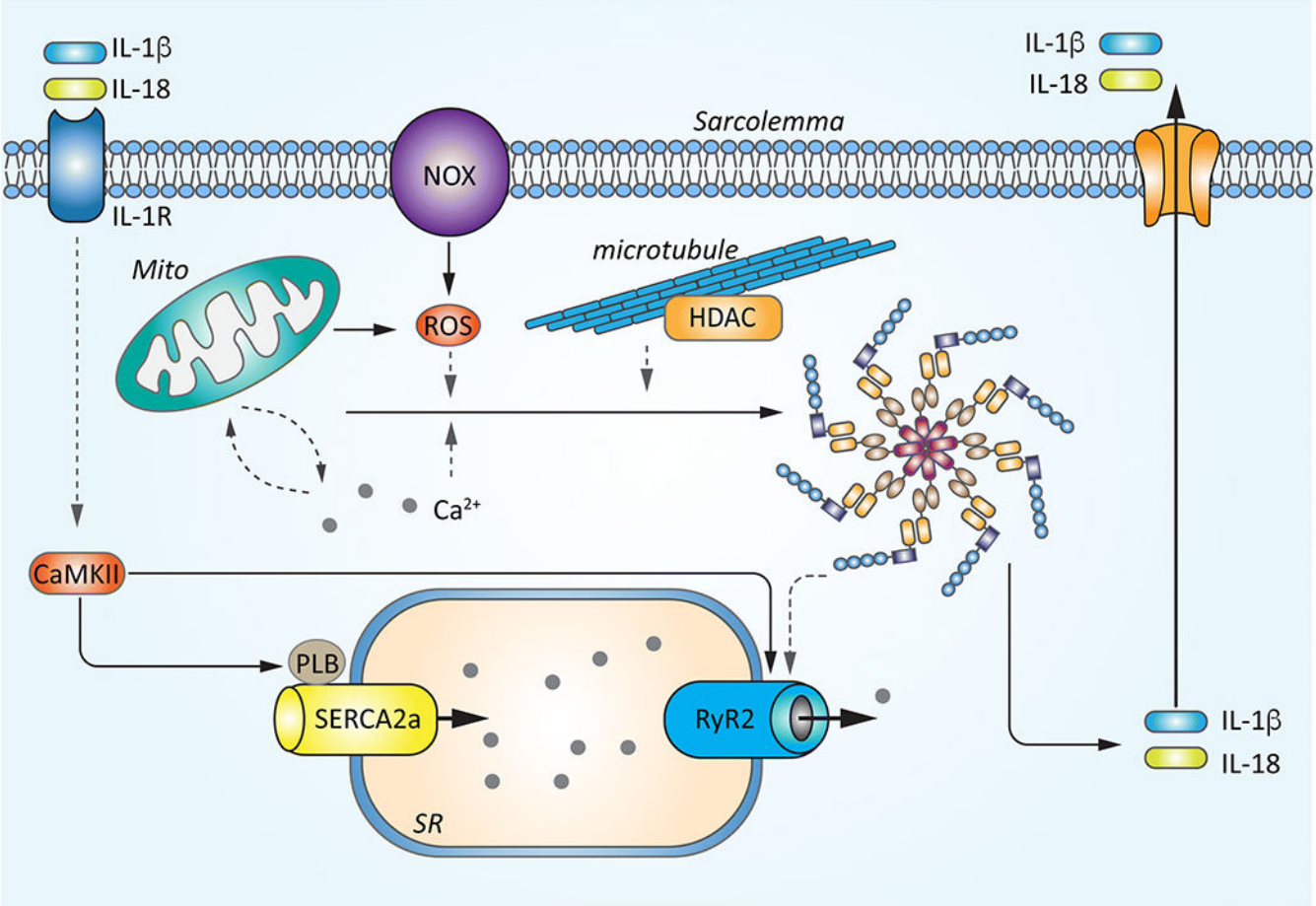

Figure 3. Crosstalk signaling between altered Ca^{2+} handling and NLRP3 inflammasome signaling in atrial fibrillation (AF).

The increase in sarcoplasmic reticulum (SR) Ca^{2+} release (SR Ca^{2+} leak) in cardiomyocytes may directly activate the NLRP3 inflammasome by facilitating the inter-domain interactions between inflammasome components or may have indirect effects by promoting the mitochondria (mito)-derived ROS production. Increased levels of ROS due to the enhanced function of mitochondria or NADPH oxidase type-2 (NOX2) can activate CaMKII and RyR2, perpetuating the Ca^{2+}-induced activation of the inflammasome. Abnormal Ca^{2+} signaling might also trigger the HDAC6-mediated inflammasome activation. Conversely, the enhancement of the NLRP3 inflammasome could amplify the CaMKII-mediated augmentation in SR Ca^{2+} handling via abnormal IL-1β signaling or elevate RyR2 protein level and RyR2-mediated Ca^{2+} release via IL-1β or caspase-1 independent mechanisms. Solid lines indicate established regulation patterns, dash lines indicate putative mechanisms that require direct demonstration.