

Pathological basis of cardiac arrhythmias: vicious cycle of immune-metabolic dysregulation

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Abstract

Cardiac arrhythmias are a major type of cardiovascular diseases and account for high morbidity and mortality. The occurrence of cardiac arrhythmias is closely associated with abnormal neurohumoral regulation of heart rhythmicity and the pathogenesis of many cardiovascular diseases, particularly coronary artery disease (CAD). Normal immunometabolic coupling between endoplasmic reticulum (ER) and mitochondria is an essential condition for normal heart rhythm. ER stress -and mitochondrial oxidative stress-evoked immunometabolic challenges can cause inflammation, lipotoxicity and cell apoptosis, leading to CAD and the ensuing arrhythmias. These disorders are associated with activation of inducible nitric oxide synthase, excessive protein nitrosylation, malfunctioned chaperone, abnormal calcium signaling through mitochondria-associated ER membrane, disruption of oxidative phosphorylation, and activation of inflammatory and apoptotic pathways. In this review, we highlight the mechanisms underlying arrhythmias, specifically involving disorders in immuno-metabolic network and the underlying signaling process.

INTRODUCTION

As a major type of cardiovascular disease (CVD), arrhythmias account for both high morbidity and mortality. In Europe and North America, as of 2014, atrial fibrillation (AF) affects about 2% to 3% of the population; approximately 80% of sudden cardiac death results from ventricular arrhythmias [1]. According to World Society of Arrhythmias, there are 20 million patients suffering from arrhythmias including 8 million with AF and 0.54 million with sudden cardiac death/year in 2015. Thus, understanding of the regulation of cardiac arrhythmias and developing more efficient therapies are critical.

Recently, the association of immunometabolic disorders with the occurrence of arrhythmias has emerged as a new horizon of studies; however, the underlying mechanism for immunometabolic disorder-associated arrhythmias remains poorly understood. In this paper, we review current evidence supporting the involvement of vicious cycle of immune-metabolic dysregulation in the pathogenesis of arrhythmias.

CARDIAC ARRHYTHMIAS AND THE ETIOLOGY

Cardiac arrhythmia refers to irregular heart rhythm or rate due to abnormal generation or conduction of electrical impulses in the heart. The abnormal electrical activity in arrhythmias is commonly due to dysfunction and/or structural disruption of the electrical conduction system of the heart and can be classified into different types based on classifications of their pathogeneses.

Bradyarrhythmias

Bradyarrhythmias occur when action potentials fail to initiate or conduct appropriately in the rhythmic system including sinoatrial node, atrial-ventricular bundle, atrial ventricular node, and His-Purkinje fibers. Dysfunction in impulse initiation is usually due to

slowed phase 4 of action potentials in the rhythmic cells [2,3] while the underlying mechanisms are largely determined by the sources of pathological changes.

Extrinsic causes of bradyarrhythmias mainly include medications, hypothyroidism, sleep apnea, and increased intracranial pressure. In rare cases, vagal hyperactivity can also result in bradyarrhythmias, even cardiac arrest. Some of these causes may be reversible such as hypoxia, hypothermia, and those that are induced by medications [4]. In contrast, the intrinsic causes are mainly related to degenerative processes such as post-infarction myocardial fibrosis of the sinoatrial node or the conduction system, and inflammatory diseases including pericarditis, rheumatic cardiomyopathy and myocarditis [5,6].

Tachyarrhythmias

Tachyarrhythmias can result from 1) enhanced automaticity; 2) re-entry arrhythmia or, 3) triggered arrhythmia. In arrhythmias caused by enhanced automaticity, it is essential for the acceleration of spontaneous depolarization of pacemaker cells in association with

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shortening of ventricular repolarization and refractoriness [5], which often results from the activation of sympathetic activity from both the central and peripheral approaches [6].

When arrhythmias are associated with cardiac ischemia/reperfusion (I/R) injury, abnormal automaticity can lead to atrial and ventricular tachyarrhythmias, likely due to propensity of ischemic tissue to depolarize neighboring non-ischemic, healthy myocardium through either anterograde or retrograde limbs, in which re-entry arrhythmia is the most common form of tachyarrhythmia. Such arrhythmia is clinically associated with atrial ventricular re-entry, atrial flutter, and ventricular arrhythmia in post-ischemic myocardium [7].

Triggered arrhythmia occurs during after-depolarization of the action potential and frequently under cardiac ischemia and digitalis toxicity. After ischemic injury, surviving cells could spontaneously release Ca^{2+} from sarcoplasmic reticulum to evoke arrhythmias [8] through multiple approaches, such as changes in the production of microRNAs [9].

Many CVDs predispose the heart to arrhythmias, such as inflammatory cardiomyopathy, I/R injury during myocardial infarction, and metabolic CVDs [7]. Thus, the occurrence of arrhythmias is not only involving neurohumoral regulation of the rhythmic system, but also cardiac pathology. In this review, we focus on the immunometabolic basis of arrhythmias in the following section.

IMMUNOLOGICAL INJURY AND ARRHYTHMIAS

The heart shares with other organs the susceptibility to immunological injury. Many CVDs are characterized by the presence of inflammatory cells within the myocardium and autoantibodies in the sera due to immune sensitization to endogenous or exogenous cardiac antigens.

Humoral immunologic injury

The immunopathogenesis of cardiac rhythm and conduction disorders has been identified in sick sinus syndrome, bradyarrhythmias, and hypersensitive carotid sinus syndrome. For instance, cardiac autoantibodies could be detected in the sera of patients following infarction and/or cardiectomy [10]. Now it has been commonly accepted that the humoral immunological injuries are related to autoimmune disorders and non-specific humoral factors [11-13]. These facts support the proposal that autoimmunity and inflammation take part in electrical and structural remodeling of left atrium and predispose patients with autoimmune and inflammatory diseases to increased risk of arrhythmia [14].

Cellular immunologic etiology

The cellular type of immunological injury is associated with the activation of cytotoxic T-lymphocytes/cells. This has been well demonstrated in studies on the association between T cell-mediated cytotoxicity and the electric instability in those with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia [15]. In a mouse model of chronic ischemic heart failure, there were global expansion and activation of CD4^{+} T cells to induce cardiac injury and remodeling [16]. It was also reported that there are plenty of mast cells in the heart, and they are predominantly located around the coronary adventitia and in close contact with small vessels in the muscle wall. The release of mediators can influence ventricular function, heart rate, and coronary artery tone, potentially triggering arrhythmias [17]. These pieces of evidence indicate that aberrant immune reactions can

cause heart injuries through both humoral and cellular approaches; correspondingly restoration of immunologic homeostasis could potentially protect the heart from arrhythmias.

METABOLIC DISORDERS AND ARRHYTHMIAS

Normal metabolism of the cardiovascular system is the prerequisite of normal heart rhythm. Varieties of metabolic disorders such as high triglyceride, low high-density lipoprotein and obesity as well as high or low plasma glucose levels and diabetes are associated with increased risk of atherosclerosis, CAD and the resultant arrhythmias.

Dyslipidemia and lipotoxicity

Dyslipidemia in association with abnormal amounts of cholesterol, triglycerides and unsaturated fatty acids in blood increases risk of arrhythmias. This has been verified by a clinical investigation of 35232 patients in Sweden that AF in humans had substantially greater proportion of polyunsaturated diacylglycerols in the cardiac tissues [18]. Low high-density lipoprotein, a hallmark of metabolic syndrome, is closely related to AF risks by slowing atrial conduction as shown by the prolongation of P wave, PR intervals, QRS duration and corrected QT interval in mice [19]. Furthermore, very-low-density lipoproteins induced downregulation of connexin (Cx)-40 and Cx-43 at transcriptional, translational and tissue levels but impaired stability of gap junctions [19]. These facts indicate that dyslipidemia predisposes arrhythmias through cardiac lipotoxicity.

Glucose metabolism disorders

Similar to dyslipidemia, glucose metabolism disorders also promote the occurrence of arrhythmias, which is represented by diabetes cardiomyopathy and I/R heart. For example, glucose ingestion increased QT interval and aggravated the cardiac repolarization disturbances in long-QT syndrome type 2 patients [20]. Hyperglycemia can inhibit myocardial anesthetic post-conditioning, and result in oxidative stress and apoptosis in I/R condition [21]. In addition, glycated hemoglobin is a long-term measure of glucose control and has also association with AF risk [22]. Thus, both defective glucose metabolism and low tissue oxygenation may contribute to arrhythmias after acute myocardial infarction in diabetic patients. It is worth noting that reduced levels of glucose or hypoglycemia in type 2 diabetes mellitus (T2DM) can also cause arrhythmias [23]. Moreover, individuals with T2DM demonstrate greater repolarization abnormalities for a given hypoglycemic stimulus, which is related to sympathoadrenal stimulation and hypokalemia [24].

SIGNALING PATHWAY MEDIATING IMMUNOMETABOLIC DISORDER-ASSOCIATED ARRHYTHMIAS

The effect of immunometabolic disorders on atherosclerosis and the subsequent arrhythmias is closely associated with inactivation of the reperfusion injury salvage kinase (RISK) pathway, AMP-activated protein kinase (AMPK) and protein kinase C (PKC) signaling.

RISK pathway

The RISK pathway including phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-endothelial nitric oxide (NO) synthase (eNOS) cascades and extracellular signal-regulated protein kinase (ERK) 1/2 has been extensively identified in the cardioprotective effects of normal immunometabolic activity. This fact has been confirmed by studies on the cardioprotective effect of ginseng extract in rat heart [25] and estradiol-17 β treatment in high fat-fed rats [26].

In the RISK pathway, NO production is a key step in cardioprotection against myocardial I/R injury. However, NO from the eNOS but not inducible NOS (iNOS) exerts the protective effect. For example, the protective effect of adipocyte fatty-acid-binding protein deficiency did not occur in eNOS (-/-) mice but occurred in iNOS (-/-) and wild type mice [27], supporting that eNOS is required for its cardioprotection. By contrast, the PI3K/Akt signaling pathway activated by estradiol-17 β can attenuate the detrimental effects of increased iNOS expression/activity by inhibiting nitrosylation of functional proteins [26].

A key downstream target of eNOS/NO in cardioprotection is the mitochondrial ATP-dependent potassium (mKATP) channels. This has been supported by the findings of myocardial protection by hydrogen sulfate (H₂S) [28] and isoflurane-induced myocardial postconditioning under acute hyperglycemia [21]. Among them, the effect of H₂S is highly representative. H₂S is mainly converted from cyst(e)ine catalyzed by cystathionine-lyase that is activated by Ca²⁺-calmodulin and PI3K. Downstream targets of the H₂S include PI3K and ERK 1/2 [29]. Thus, H₂S can not only respond to mobilization of Ca²⁺-calmodulin signaling, but also activate RISK pathway to protect the heart through multiple layers, such as antioxidative action, preservation of mitochondrial function, reduction of apoptosis, anti-inflammatory responses, angiogenic actions, regulation of mKATP channel, and interaction with NO.

AMPK pathway

In parallel with the RISK pathway, AMPK signaling could also be an upstream enzyme of the Akt-NO pathway. This proposal is supported by the studies on vascular endothelial cells in mice [30] and human umbilical vein endothelial cells [31]. By contrast, the AMPK activity is decreased in obesity and T2DM and increased with metabolically favorable conditions and cholesterol-lowering drugs [32].

AMPK can inhibit pro-inflammatory reactions through multiple approaches. For example, AMPK activation inhibited interleukin (IL)-1 β -stimulated CXCL10 secretion, reduced IL-1 receptor-associated kinase-4 phosphorylation and downregulated MKK4/ c-Jun N-terminal kinase (JNK) and IKK/I κ B/ nuclear factor- κ B (NF- κ B) signaling [33]. In addition, AMPK can inhibit HMG-CoA reductase to reduce cholesterol synthesis and reduce inflammation [34]. Thus, the inhibition of multiple pro-inflammatory signaling pathways by AMPK can underlie the immunometabolic protection of the HR.

PKC signaling

A critical signaling event in cardioprotection is the activation of PKC. Chelerythrine, a PKC enzyme inhibitor, can block the cardioprotective effects of oxytocin in reducing infarct size, plasma levels of creatine kinase-MB and lactate dehydrogenase as well as the severity and incidence of ventricular arrhythmias in I/R rats [35]. However, different isoforms of PKC may have different, even opposite effects.

PKC- ϵ in the mitochondria is known as a modulator of cardiac cell metabolism through activation of the mKATP channel following cGMP production and subsequent activation of protein kinase G. In cardioprotection, PKC- ϵ , likely a downstream effector of PLC- β and NO generated by eNOS, has been shown in antioxidant-increased Cx-43 and suppression of ventricular fibrillation in rats [36]. In contrast, activation of PKC- α , a downstream event of PLC- β 1b that is a heart-specific signaling, leads to cardiac injury. As reported, hypoxic activation of PKC- α dramatically increased iNOS expression, concomitant to enhanced apoptotic cell percentage and molecular interaction between apoptotic protease activating factor-1 and cytochrome (Cyt) C [37].

These findings indicate that PLC- β 1b-PKC- α -iNOS signaling pathway mediates the activation of mitochondrial apoptotic pathway.

INTERACTION BETWEEN IMMUNOLOGICAL AND METABOLIC PROCESSES

In the pathogenesis of CVDs and the resultant arrhythmias, immunologic injuries and metabolic disorders occur simultaneously and are intertwined to form a malfunctioned immunometabolic network.

Metabolic influence of immune activity

Atherosclerosis is a chronic inflammatory disease that is mediated by innate and adaptive immune responses; the immune responses could be evoked by abnormal metabolic activity. As reported, high levels of circulating fatty acids and triglycerides can evoke inflammatory signaling in the heart with increased reactive oxygen species (ROS) and NF- κ B activity, mitochondrial dysfunction and insulin resistance [38]. Exposure to saturated fatty acids, such as palmitate, led to ER stress in macrophages and promoted inflammation in atherosclerotic plaques [39]. Diabetic cardiomyopathy showed oxidative stress and apoptosis in cardiac cells in rats, which could be reduced by multiple antioxidants that reduced levels of lipid peroxidation and levels of pro-inflammatory transcription factor NF- κ B as well as cytokines such as tumor necrosis factor- α (TNF- α), interferon- γ , TGF- β , and IL-10 [40]. Moreover, activated simvastatin (HMG-CoA reductase inhibitor) infusion prior to reperfusion in a pig model of I/R reduced coronary and cardiac oxidative DNA-damage, diminished neutrophil infiltration at the site of ischemia but preserved mitochondrial membrane potential [$\Delta\psi$ (m)] and reduced apoptosis in the ischemic myocardium [34]. It was also reported that sub-endothelial accumulation and modification of lipids in the artery wall trigger an inflammatory reaction in mice. This reaction can be weakened by regulatory T cells that suppress T cell proliferation and secretion of anti-inflammatory cytokines (e.g. IL-10 and transforming growth factor- β) [41]. In addition, some polysaccharide fractions were found to stimulate the production of NO and immunomodulatory cytokines (IL-1 β and TNF- α) without cytotoxicity in macrophages [42].

Immunologic influence on metabolism

On the other hand, immune reactions can cause metabolic disorders. This has been well demonstrated in studies on obesity that is generally considered a CVD-associated metabolic/inflammatory disease. In adipose tissue of high fat-fed animals, innate and adaptive immune cell responses play critical roles in the regulation of metabolic homeostasis. In the lean state, type 2 cytokine-associated immune cell responses predominate in white adipose tissue and protect against weight gain and insulin resistance through direct effects on adipocytes and elicitation of beige adipose. In obesity, these metabolically beneficial immune pathways become dysregulated, and adipocytes and other factors initiate metabolically deleterious type 1 inflammation that impairs glucose metabolism [43]. It was also reported that low-grade systemic inflammation associated with obesity leads to cardiovascular complications, caused partly by infiltration of adipose and vascular tissue by effector T cells. This change is mediated via direct exposure of CD4⁺ T cells to palmitate [44]. Clearly, metabolic disorders in the heart can result from immunologic injuries.

Together with a previous review [45], the facts presented above allow us to propose that accumulation of harmful lipids or generation of signaling intermediates can interfere with immune regulation in cardiac tissues and vice versa; they can form a vicious cycle of immune-metabolic dysregulation and in turn hurt cardiac functions.

Thus, in studying on the pathogenesis of arrhythmias and therapeutic approaches, the immune states and metabolic conditions should be considered in an intact immunometabolic network.

ROLES OF ER AND MITOCHONDRION IN ARRHYTHMIA-ASSOCIATED CELLULAR INJURIES

Immunometabolic disorders involve dysregulation of multiple organelles during cardiac injuries and the ensuing arrhythmia. ER stress and mitochondrial oxidative stress intersect immune injury and metabolic disorder, thereby highly representing malfunctions of immunometabolic network in arrhythmogenesis.

ER stress

The ER is responsible for the folding, processing and trafficking of all secretory and integral membrane proteins to the cell surface. It is also a pivotal site for the quality control of proteins, Ca^{2+} homeostasis, and biosynthesis of cholesterol and lipids. Thus, abnormal Ca^{2+} regulation, viral infection, high-fat diet, hypoglycemia, and lack of amino acids can all disrupt ER homeostasis and cause the accumulation of unfolded proteins, leading to ER stress and disruption of ER integrity. For example, palmitate-induced downregulation of sorcin, a calcium binding protein, increased levels of glucose-6-phosphatase catalytic subunit-2, which is a negative regulator of glucose-stimulated insulin secretion, leading to ER stress [46]. In contrast, statins can reduce ER stress by inhibiting cholesterol synthesis in the ER and alleviate myocardial infarction [34].

Examples of the immunometabolic disorders have been well documented in studies on saturated fatty acids-induced ER stress. Endogenous H_2S levels in serum of diabetic cardiomyopathy patients and rats, and its contents in rat heart were significantly lower, which was accompanied with cardiac lipotoxicity and the process was inhibited by ER stress inhibitor or H_2S [47]. In another example, homocysteine-evoked myocardial fibrosis can be inhibited by a paracrine/autocrine peptide intermedin-1-53 in apolipoprotein E-deficient mice and neonatal rat cardiac fibroblasts. This effect was accompanied with inhibition of the upregulation of inositol-requiring enzyme-1, an ER stress marker and inflammatory factor (e.g. $\text{TNF-}\alpha$, monocyte chemotactic protein-1, IL-6, and IL-1 β). In addition, the ER stress is also associated with rapamycin complex 1 (mTORC1) signaling [48] and its associated chaperone processes [49].

It is important to note that ER stress can propagate through inactivation of inositol-requiring enzyme-1, the key ER regulator, through nitrosylation due to excessively produced NO following increased iNOS activity [50]. This is induced by dyslipidemia-associated activation of poly(ADP-ribose) polymerase-1 in vascular dysfunction, which leads to expansion of initial event in the heart to affect the rhythmic system, resulting in arrhythmias. Together with the evidences reviewed recently [45] that ER is a critical organelle mediating both metabolic and inflammatory adaptive responses to proteotoxic, nutritional, and energy-related stresses, we propose that ER is an important immunometabolic hub in the cardiac pathogenesis and the ensuing arrhythmias.

Mitochondrial oxidative stress

Significant increase in ROS production is a primary cause of cardiomyocyte apoptosis in diabetic cardiomyopathy as well as I/R injury to the heart. ROS is a natural byproduct of the normal metabolism of oxygen including peroxides, superoxide, hydroxyl radical, and singlet oxygen. In diabetic cardiomyopathy and I/R, cardiac

production of ROS can increase dramatically, resulting in oxidative stress and significant cellular damage. The process occurs primarily in mitochondria when oxygen is prematurely and incompletely reduced during oxidative stress and superoxide anion is generated, leading to destruction of the mitochondria and cell apoptosis through Bcl-2/Bax-Cyt C/apoptotic protease activating factor 1-caspase-9 pathway [51].

Mitochondrial ROS formation during reperfusion is based on the opening of mitochondrial permeability transition pores (MPTP) and the resultant calcein release, $\Delta\text{Psi(m)}$ collapse, and disturbance of ATP recovery in isolated cardiac myocytes from adult I/R rats. During the reperfusion, Ca^{2+} oscillations occurred, mitochondrial Ca^{2+} concentration and mitochondrial ROS levels increased, cells developed hypercontracture and underwent necrosis. Suppression of the mitochondrial Ca^{2+} uptake or MPTP opening significantly attenuated Ca^{2+} oscillation, hypercontracture and necrosis. These changes were not influenced by reduced mitochondrial ROS levels since ROS scavengers had no effect on these parameters [52]. Thus, the interplay between Ca^{2+} oscillation and MPTP promotes the reperfusion-induced cardiomyocyte injury. It remains to differentiate the source of mitochondrial Ca^{2+} contributed from sarcoplasmic reticulum and from the ER. However, I/R-evoked Ca^{2+} oscillation can cause cardiac injury through mitochondrial Ca^{2+} overload and the resultant cardiomyocyte apoptosis [53].

It is worth noting that increased ROS level has dual effect on the heart, largely determined by its extent and duration. In response to sudden I/R insults, there was a burst increase in ROS production, which caused dramatic oxidative stress and myocardial injury. However, the production of ROS evoked by protective agents could protect the heart by prevention of I/R-evoked ROS burst, thereby exerting the antiarrhythmic function. For example, isoflurane upregulated ROS generation before lipopolysaccharide, but inhibited a ROS burst after lipopolysaccharide challenge [54]. Consistent finding is also present in H_2O_2 -induced cardioprotection against reperfusion injury. As reported in the Langendorff-perfused rat hearts, pretreatment of H_2O_2 significantly improved the post-ischemic recoveries in intracellular phosphocreatine and ATP levels. In isolated permeabilized myocytes, H_2O_2 accelerated the calcein leakage from mitochondria by opening the MPTP. However, H_2O_2 did not depolarize $\Delta\text{Psi(m)}$ even in the presence of ATPase but decreased mitochondrial Ca^{2+} concentration by accelerating the mitochondrial Ca^{2+} extrusion via an MPTP [55]. It is likely that stabilization of the $\Delta\text{Psi(m)}$ is critically important for maintaining normal oxidative phosphorylation and immunometabolic balance even though mild ROS challenge partially increased the leakage through MPTP and decreased mitochondrial Ca^{2+} levels.

ER-mitochondrial couplings in immunometabolic regulation

It is also important to note that there are close interactions between ER and mitochondrion in immunometabolic regulation of cardiac activity through the mitochondria-associated ER membrane (MAM) and associated proteins. MAMs in the heart are responsible for Ca^{2+} signaling between ER and mitochondria [56]. This Ca^{2+} signaling is regulated by glycogen synthase kinase-3 β (GSK3 β) protein in the ER and MAMs in the heart. Phosphorylation/activation of GSK-3 β occurs following activation of JNK induced by advanced glycation end-products in diverse pathological settings including diabetes, inflammation and acute I/R injury in the heart. GSK3 β specifically interacts with the inositol 1,4,5-trisphosphate receptors (IP3Rs) Ca^{2+} channeling complex in MAMs. During I/R, increased GSK3 β leads to enhanced transfer of Ca^{2+} from ER to mitochondria, leading cytosolic

and mitochondrial Ca^{2+} overload and subsequent cell death. Inhibition of GSK3 β at reperfusion reduced both IP3R phosphorylation and ER Ca^{2+} release, which consequently diminished both cytosolic and mitochondrial Ca^{2+} concentrations as well as sensitivity to apoptosis [57]. This finding is in agreement with a previous report that inactivation of GSK-3 β directly or indirectly by mKATP channel activation facilitates recovery of DeltaPsi(m) by suppressing ROS production and mPTP opening, leading to cytoprotection from oxidant stress-induced cell death. That is, acceleration of the DeltaPsi(m) recovery contributes to cytoprotection afforded by activation of the mKATP channel or inactivation of GSK-3 β . In addition, in H9c2 cells, opening of the mPTP with antimycin reduced DeltaPsi(m) and induced calcein leak from mitochondria, which were partially recovered by mKATP channel openers. Activation of the mKATP channel induced inhibitory phosphorylation of GSK-3 β and suppressed ROS production, LDH release and apoptosis after antimycin washout [58-60].

Another key molecule bridging the mitochondria and ER is mitofusin-2 (Mfn-2), a mitochondrial fusion protein known to be critical in regulating cardiac function. As reported, following angiotensin II and miR-106a treatment of cultured cardiomyocytes, mitochondria presented cristae defects with considerable depolarization of mitochondrial membrane and increased ROS production, which was reversed by overexpression of Mfn2, a function opposite to GSK3 β

[9]. Additionally, hyperglycemia stimulated ER interactions and mitochondrial apoptotic pathways in cardiac tissues of diabetic rats. The processes were inhibited by exogenous H_2S treatment through the regulation of Mfn-2 expression in association with inhibition of the interaction between the ER and mitochondrial apoptotic pathway, leading to decrease in the expression of mitochondrial apoptotic proteins, Cyt C, and mPTP opening [42]. These findings indicate that ER and mitochondria function like an “organelle syncytium” in the immunometabolic regulation of cardiac activity through histological and functional couplings and under the close regulation of antiarrhythmic signaling events. Figure 1 is a diagrammatic illustration of the hypothetical mechanism of immunometabolic disorders-elicited arrhythmias.

CONCLUSIONS

Immune injuries and metabolic disorders are the central risk factors for CAD, but our current knowledge of the mechanisms underlying arrhythmias is still insufficient. Full understandings of the mechanisms underlying immunometabolic disorder-associated arrhythmias, particularly vicious cycle of immune-metabolic dysregulation, will help for designing more targeted therapies to block the pathogenesis of arrhythmias by suppressing ER stress and mitochondrial oxidative stress, thereby greatly reducing the incidence of arrhythmias and the mortality from CVDs.

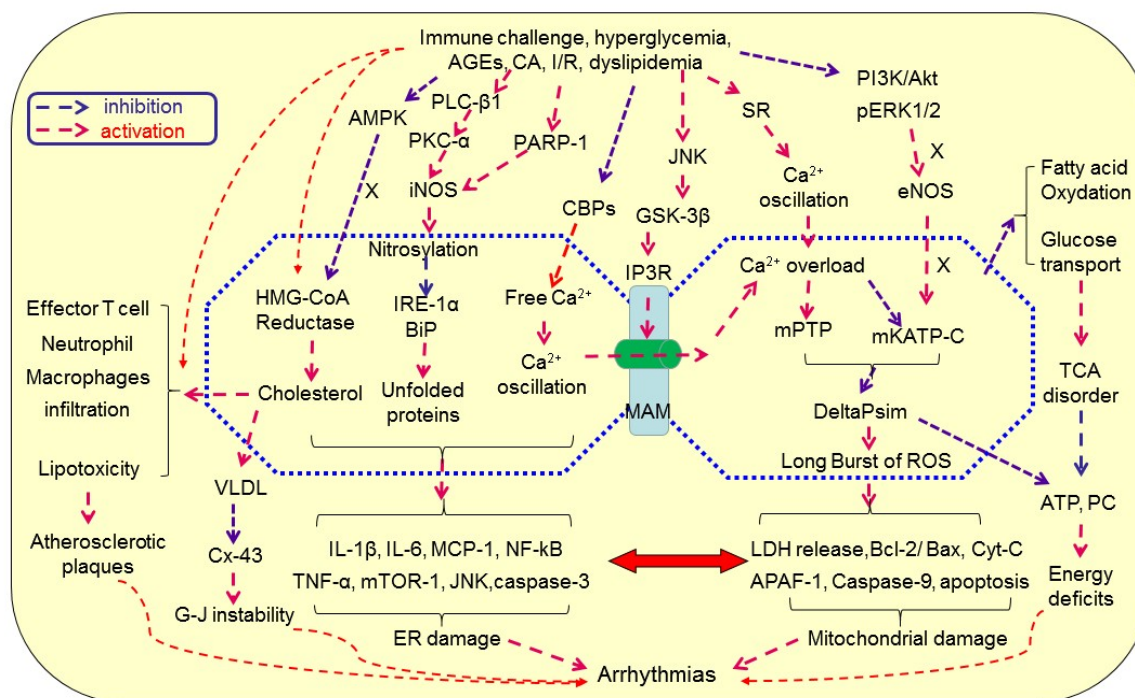


Figure 1. Hypothetical mechanism of immunometabolic disorders-elicited arrhythmias.

Immunological challenges and metabolic disorders can activate inflammation, induce endoplasmic reticulum (ER) stress, inhibit UPR and chaperone, increase the production of cholesterol and VLDL, promote the production of immune cytokine, increase ER-mitochondrial Ca^{2+} signaling through MAMs and Ca^{2+} overload, activate mitochondrial oxidative stress, disrupt TCA cycle, and activate apoptotic pathway, leading to degeneration and cell death. These processes are signaling through activating iNOS, PKC- α , JNK and GSK-3 β while inhibiting AMPK, CBPs, PI3K/Akt, pERK1/2 and eNOS. As a result, lipotoxicity, atherosclerosis and CAD occur, leading to arrhythmias once the rhythmic system is involved directly or indirectly. Abbreviations: AGEs, advanced glycation end-products; AF, atrial fibrillation; Akt, protein kinase B; AMPK, AMP-activated protein kinase; APAF-1, apoptotic protease activating factor-1; Bcl-2, B-cell lymphoma-2 protein; BiP, binding immunoglobulin protein; CA, catecholamine; CAD, coronary artery disease; CBPs, calcium binding proteins; CGL, cystathionine gamma-lyase; CVD, cardiovascular disease; Cx-43, connexin-43; Cyt C, cytochrome c; DeltaPsi(m), mitochondrial membrane potential; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated protein kinase 1/2; G-J, gap junction; H_2S , hydrogen sulfate; GSK3 β , glycogen synthase kinase-3 β ; IL, interleukin; iNOS, inducible nitric oxide synthase; IP3Rs, inositol 1,4,5-trisphosphate receptors; I/R, ischemia/reperfusion; IRE-1, inositol requiring enzyme1; JNK, c-Jun N-terminal kinase; LDH, Lactate dehydrogenase; MAM, mitochondria-associated ER membrane; mATP C, mitochondrial ATP-dependent potassium channels; MCP-1, monocyte chemoattractant protein-1; mPTP, mitochondrial permeability transition pores; PARP-1, poly(ADP-ribose) polymerase-1; PC, phosphocreatine; PI3K, phosphatidylinositol 3-kinases; PKC, protein kinase C; PLC, Phospholipase C; RISK, reperfusion injury salvage kinase; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle; TNF, tumor necrosis factor; UPR, unfolded protein response; VLDL, low-density lipoproteins.

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