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Review

The Warburg effect: A new insight into atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained arrhythmia. Atrial remodeling, including electrical/structural/autonomic remodeling, plays a vital role in AF pathogenesis. All of these have been shown to contribute continuously to the self-perpetuating nature of AF. The Warburg effect was found to play important roles in tumor and non-tumor disease. Recently, lots of studies documented altered atrial metabolism in AF, but the specific mechanism and the impact of these changes upon AF initiation/progression remain unclear. In this article, we review the metabolic consideration in AF comprehensively and observe the footprints of the Warburg effect. We also summarize the signaling pathway involved in the Warburg effect during AF—HIF-1α and AMPK, and discuss their potential roles in AF maintenance and progression. In conclusion, we give the innovative idea that the Warburg effect exists in AF and promotes the progression of AF. Targeting it may provide new therapies for AF treatment.

1. Introduction

Atrial fibrillation(AF) is the most common sustained arrhythmia. Electrical remodeling, structural remodeling, and autonomic remodeling play an important role in AF [1]. AF causes abnormalities in each of these areas and each of these can facilitate the initiation and maintenance of AF. Recently, lots of studies documented altered atrial metabolism in AF, suggesting the role of metabolic remodeling [2]. However, the specific mechanism and how these changes impact on AF initiation/progression remain largely unanswered.

In 1923, the German biochemist Otto Warburg proposed that tumor cells can strategically generate adenosine triphosphate (ATP) through aerobic glycolysis (in addition to oxidative phosphorylation), even when oxygen is abundant [3]. Metabolic intermediates can operate as signaling factors, inducing post-translational and epigenetic modifications or activating intracellular signaling cascades. In tumor, this metabolism-driven reprogramming dictates the progression of cellular functions and cellular fate, allowing it to grow aberrantly [4]. Normal cells metabolize glucose through glycolysis, and the generated pyruvate is further oxidized in mitochondria under normoxic conditions. When oxygen becomes limiting, mitochondrial oxidative metabolism is restricted, and the pyruvate is converted to lactate instead. Warburg discovered that this latter process predominates in tumor cells, even when oxygen is plentiful, a process that became known as the 'Warburg

Abbreviations: ACC, acetyl-CoA carboxylase; ADP, adenosine diphosphate; AERP, atrial effective refractory period; AERPd, AERP dispersion; AF, atrial fibrillation; AMPK, AMP-activated protein kinase; ALD, aldolase; ATG7, autophagy related 7; ATP, adenosine triphosphate; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CIA, collagen-induced arthritis; CK, creatine kinase; CoA, Coenzymy A; CPT-1, carnitine palmitoyl transferase-1; DCA, dichloroacetic acid; DPP-4, dipeptidyl peptidase 4; EAT, epicardial adipose tissue; eEF2, eukaryotic elongation factor 2; ENO-α, enolase alpha; EPO, erythropoietin; ETC, electron transfer chain; FA, Fatty acid; $FADH_2$, reduced form of flavin adenine dinucleotide; FAT/CD36, fatty acid translocase (also known as CD36); GLUT, glucose transporter; HIF-1α, hypoxia inducible factor 1α; HK, hexokinase; LAA, left atrial appendage; LDHA, lactate dehydrogenase A; LKB1, liver kinase B1; MMP, metalloproteinases; mTOR, mammalian target of rapamycin; NADH, nicotinamide adenine dinucleotide (reduced form); OXPHOS, oxidative phosphorylation; PCr, phosphocreatineA; PE, phenylephrine; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PPARα, peroxisome proliferator-activated receptor α; PFK-L, phosphofructokinase liver type; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGC-1α, peroxisome proliferator-activated receptor coactivator 1a; PGK1, phosphoglycerate kinase 1; PKM2, pyruvate kinase M2; RAA, right atrial appendage; ROS, reactive oxygen species; RyR, ryanodine receptor; SR, sinus rhythm; SNAP-23, synaptosomal-associated protein 23; TGF-β, transforming growth factor-β; Th17, T helper 17 cells; TLR2, Toll-like receptor 2; Treg, regulatory T cell; ULK1, Unc-51 like autophagy activating kinase 1; VEGF, vascular endothelial growth factor; VHL, Von Hippo Lindau tumor suppressor protein; VLCAD, very long-chain acyl-CoA dehydrogenase; WT, wild type; ZMP, 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranosyl 5′-monophosphate

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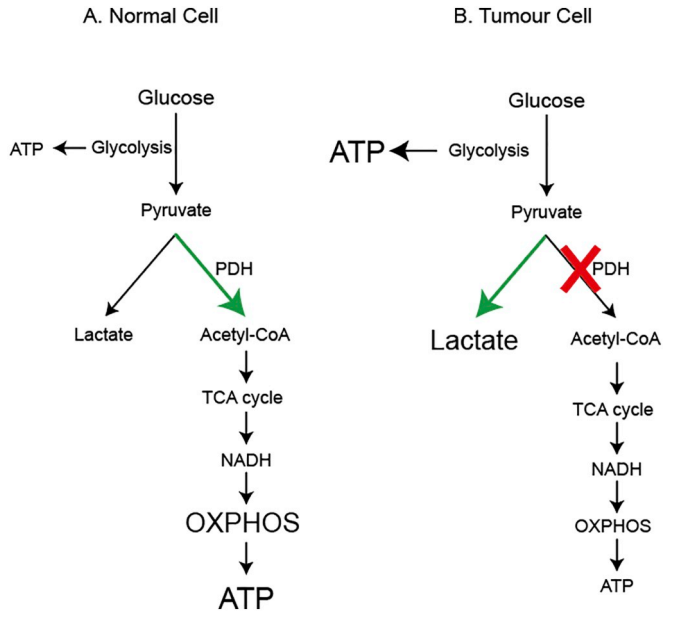

Fig. 1. The Warburg effect. A. In normal cells, glucose is metabolized to pyruvate via glycolysis. Some pyruvate is converted to lactate, but most is directed to the TCA cycle via acetyl-CoA. The TCA cycle generates NADH, which donates electrons to the mitochondrial electron transport chain so that OXPHOS can progress. B. In tumor cells, the metabolic profile switches from OXPHOS to aerobic glycolysis, known as the Warburg effect. ATP: adenosine triphosphate; PDH: pyruvate dehydrogenase; Acetyl-CoA: acetyl coenzyme A; TCA cycle: tricarboxylic acid cycle; NADH: nicotinamide adenine dinucleotide; OXPHOS: oxidative phosphorylation.

effect' or aerobic glycolysis. (Fig. 1).

Besides tumor, increasing researches show that the Warburg effect plays crucial roles in non-tumor diseases such as inflammation [4], pulmonary hypertension [5], idiopathic pulmonary fibrosis [6], and support structural remodeling in the heart [7]. In the following part, we will review the metabolic consideration in AF and present the evidence of the Warburg effect. We will also discuss the signaling pathways involved in the Warburg effect and their potential roles in AF pathogenesis.

2. Altered metabolism in AF: the existence of the Warburg effect

2.1. Energy metabolism in heart

The heart consumes large amounts of energy in the form of ATP to that is continuously replenished by oxidative phosphorylation (OXPHOS) in mitochondria and, to a lesser extent, by glycolysis [8]. Under normal conditions, the heart relies predominantly (~60–90%) on fatty acid (FA) oxidation to fuel ATP production, whereas the remaining ~10–40% of ATP is derived from pyruvate oxidation [9].

The energy supply can be divided into three stages [8]: The first stage encompasses substrate delivery, selection, uptake and oxidation, and production of acetyl-CoA and its entry into the tricarboxylic acid (TCA) cycle via citrate synthase. Fatty acid (FA:60%–90%) and pyruvate (10–40%, produced in equal amounts by glycolysis and oxidation of lactate) are the greatest contributors to acety-CoA formation. Energy is transferred from TCA cycle intermediates by electrons to the reducing equivalents $NADH/FADH_2$ and by some substrate-level phosphorylation of ADP/GDP. The second stage, oxidative phosphorylation, involves electron shuttling from cytosolic to mitochondrial reducing equivalents, transfer of energy by electrons from reducing equivalents to O_2, and generation of an electrochemical proton gradient within the mitochondrial intermembrane space. The release of this gradient is coupled to the synthesis of ATP from ADP Pi by F0,F1-ATPase (complex V), contributing 95% of ATP synthesis under aerobic conditions. The third stage, phosphotransfer, refers to the delivery of ATP from mitochondria to cellular regions of high ATP demand. Inside mitochondria, the phosphate bond of ATP is transferred to creatine by the mitochondrial creatine kinase (CK) to form phosphocreatine (PCr), which rapidly diffuses to the cytosol and the phosphoryl group is transferred back to ADP by the cytosolic CK (Fig. 2).

2.2. Ischemia/hypoxia in AF

AF is strongly associated with tissue ischemia/hypoxia. The irregular high-frequency excitation and contraction during AF will affect atrial energy demand, circulation and oxygen supply, and change the balance between energy demand and supply. In healthy atria, supply through the atrial coronary vasculature is in balance with demand by the atrial myocardium. During acute AF, the rate of electrical and contractile activity increases four-to six-fold [10], which is likely to

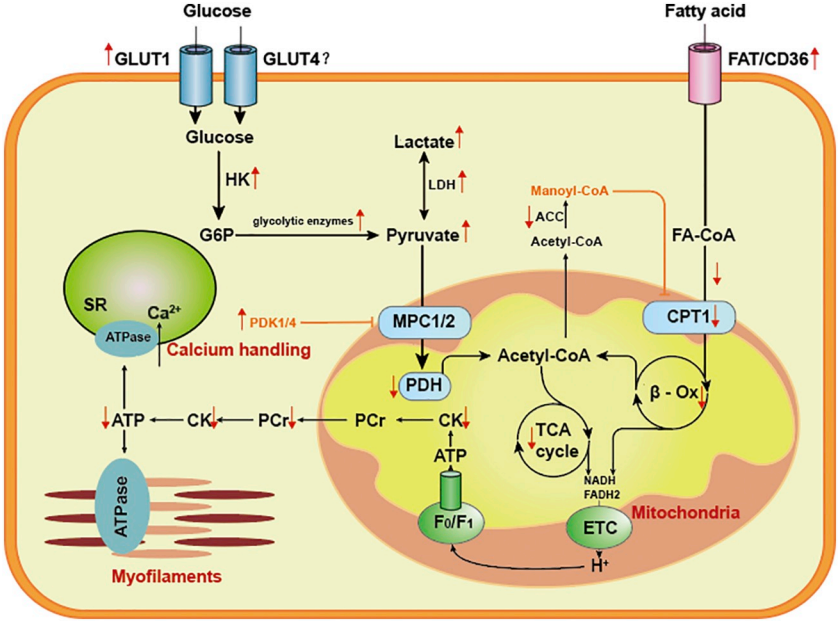

Fig. 2. Energy metabolism in heart. Red arrows indicate changes in atrial fibrillation.? indicates inconsistent datas in atrial fibrillation. GLUT1: glucose transporter type 1; GLUT4: glucose transporter type 4; G6P: glucose 6-phosphate; HK: hexokinase; LDH: lactate dehydrogenase; MPC: mitochondrial pyruvate carrier; Acetyl-CoA: acetyl coenzyme A; PDH: pyruvate dehydrogenase; FAT: fatty acid translocase (also known as CD36); FA-CoA: fatty acyl-CoA ester; CPT1: carnitine O-palmitoyltransferase 1; β-Ox: β-oxidation; ACC: acetyl-CoA carboxylase; TCA cycle: tricarboxylic acid cycle; ETC: electron transport chain; F1/Fo: F1/Fo ATP synthase; CK, creatine kinase; PCr: phosphocreatine; SR: sarcoplasmic reticulum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increase atrial energy and O_2 expenditure considerably. If this increase in demand cannot be met by an increase in supply, a state of supply-demand ischemia ensues. In anesthetized dogs, White et al. reported that the atrial blood flow increased two- to three-fold during acute AF [11]. Similarly, McHale et al. documented a 180% increase in atrial blood flow in conscious dogs during AF compared with sinus rhythm (SR) [12]. However, supply–demand ischemia still occurred in the left atrial tissue, as evidenced by increased atrial lactate production [13]. Patients with AF were found to have higher atrial lactate expression and this upregulated expression was positively correlated with regulatory indicators of atrial structural remodeling as reflected by severe oxidative stress injury and mitochondrial control of apoptosis [14]. Paroxysmal AF increased the expression of lactate dehydrogenase A (LDHA) and the production of lactate in the canine atrial myocardium [15]. Increased lactate was found in the atria of sustained atria pacing sheep in another study [16]. In a canine model of acute local atrial ischemia, changes included a strong slowing of conduction and the stabilization of reentry and promoted the maintenance of burst pacing-induced AF [17]. A case report showed that reperfusion of an atrial branch after an inferior infarction was followed by spontaneous termination of AF, further increasing evidence for the role of ischemia in AF [18]. The risk of incident myocardial infarction is increased in patients with AF [19,20] and AF is more frequent after acute myocardial infarction [21,22]. Hypoxia-inducible factor 1α (HIF-1α), the sensor that alters gene expression in hypoxic tissue, was also found increased in AF [23–27]. Altogether, these pieces of evidence prove that AF has a strong relationship with tissue ischemia/hypoxia, which is the key determinant of the Warburg effect.

2.3. Altered substrate metabolism in AF

2.3.1. Fatty acid metabolism

Circulating FAs enter cardiomyocytes via the FA transporter, FAT/CD36. Carnitine palmitoyl transferase-1 (CPT-1) then allows FA entry into mitochondria for β-oxidation, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl-CoA, NADH and $FADH_2$. Malonyl-CoA is a potent CPT-1 suppressor and is inhibited by the mitochondrial isoform of acetyl-CoA carboxylase (ACC).

FA oxidation is impaired during AF. A transcriptomic study demonstrated that patients with permanent AF have a down-regulation of enzymes controlling fatty acid oxidation [28]. Tu et al. also reported down-regulated lipid metabolism in atria of AF patients [29]. Protein expressions of CPT-1 [16,30,31] and ACC [32] were reduced in both AF patients and animal models. The decrease in FA oxidation might be explained by at least in part by suppression of peroxisome proliferator-activated receptor α (PPARα) signaling [30–32] and possibly activation of the HIF1α–PPARγ signaling axis [33,34]. Of note, a metabolic shift away from FA oxidation is not always accompanied by a concomitant decrease in FA uptake. By contrast, Matthias Lenski demonstrated that the membrane expression of FAT/CD36 and fatty acid uptake were increased in AF mice and in human atrial myocardium [35]. This is explained by up-regulated AMP-activated protein kinase (AMPK) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). Similarly, increased FAT/CD36 expression was also found in a canine model of AF which paralleled upregulated activation of AMPK [32]. And it may be the mismatch between FA uptake and FA oxidation that contributes to lipid accumulation in the fibrillating atria.

2.3.2. Glucose metabolism

Glucose is taken into the cell via the glucose transporters types 1 and 4 (GLUT1/4) and metabolized via glycolysis in the cytosol. Pyruvate is the end product of glycolysis in cells with mitochondria and an adequate supply of oxygen, which then moves into the mitochondria and is catalyzed to produce acetyl-CoA by pyruvate dehydrogenase complex (PDH complex), a key enzyme that links glycolysis and TCA. Alternatively, pyruvate is reduced to lactate in cells with mitochondrial dysfunction and limited oxygen supply.

Previous studies regarding glucose uptake in AF remain in dispute. Due to early AMPK activation, the total expression of GLUT-4 was found elevated in AF, but the membrane translocation of GLUT-4 was diminished resulting from reduced synaptosomal-associated protein 23 (SNAP-23), thereby reducing the uptake of glucose [35]. The other two studies, conversely, demonstrated down-regulation of GLUT4 expression in AF [30,31]. In the diabetic atria, GLUT-4 trafficking was impaired and can be rescued by insulin treatment [36]. Insulin-resistant animals, which had an increased vulnerability and propensity to both induced and spontaneous AF, is demonstrated to be associated with impairment in the trafficking and expression of the major cardiac isoform GLUT4 [37]. These studies implicated reduced uptake of glucose. By contrast, increased expression of GLUT1 and GLUT4 were observed in atria of sustained AF sheep in another study, thereby indicating increased glucose uptake [16]. The potential explanation may be that there is a large amount of heterogeneity in the results obtained using different models.

In regard to enzymes involved in glycolysis. Patients with permanent AF revealed up-regulation of some glycolytic enzymes [28,38,39]. A significant increase in the activity of hexokin-1,6-bisphosphate aldolase was observed in both right atrial appendage (RAA) and left atrial appendage (LAA) from AF patients [38]. The levels of intermediate metabolites of the glycolytic pathways, including 2-phosphoglyceric acid, 1,3-bisphosphoglyceric acid, and pyruvate were higher in the atria of AF sheep than in sham group [16]. Increased expression of hexokinase 1/2 (HK 1/2) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), were observed in the same study [16]. However, pyruvate dehydrogenase kinase 1 (PDK1), which inactivates the PDH complex, was up-regulated, whereas pyruvate dehydrogenase phosphatase, which reverses this inhibition, was down-regulated [15,28]. PDK4, another isoform of PDK, was also found to have an elevated expression during AF, associated with a significant down-regulation of PDH [15,40]. Similarly, reduced PDH β was found in AF patients [41] associated with increased oxidative stress. In addition, a proteomics and metabolomics analysis found that malate dehydrogenase, the α-subunit of the E1 component of PDH, were increased at 24-h and decreased at 2-week in chronic heart failure (CHF)-induced AF dog models [42]. This suggested an adaptive response (increased expression) during the onset of AF and the failure of the adaptive response (decreased expression) in the development of a molecular, metabolic and functional environment propitious to AF-maintenance. These studies indicate that even though some glycolytic enzymes are up-regulated in AF, the PDH complex, however, is reduced, thereby impairing the coupling of glycolysis to the mitochondrial, and these were accompanied by increased LDH expression and lactate production [13–16].

2.4. Mitochondrial dysfunction

Cardiac mitochondria represent a key actor of the biological systems addressed to prevent any mismatch between ATP production and utilization, and thus any major disruption in the energy available for heart function. The major function of mitochondrion is to produce ATP, which occurs at complex V using the electrochemical gradient generated by the electron transport chain (complex I to IV). A byproduct of ATP production is superoxide, which is probably generated at complex I and complex III. Superoxide can freely diffuse to cytosol and form reactive oxygen species (ROS) and can modify a variety of redox sensitive ion transporters. Altogether, mitochondrial dysfunction-associated ATP depletion and ROS accumulation can significantly affect cellular action potentials and ion homeostasis. During AF, down-regulation of electron transfer chain (ETC) activity, decreased ATP production and increased ROS production has been strongly indicated and well reviewed [43–46], which will not be deeply discussed here.

2.5. The Warburg effect in AF

The Warburg effect is attributable to tumor microenvironment hypoxia and mitochondrial dysfunction [47]. From we discussed above, AF is in relationship with hypoxia/ischemia status and mitochondria dysfunction. The fibrillating atria are likely to be more dependent on glucose instead of fatty acid, which may be explained as the energy metabolism switched to a more 'fetal phenotype' with pathological stresses [48]. Decreased fatty acid and pyruvate oxidation in mitochondria are observed during AF; Aerobic glycolysis, which generates two molecules of ATP from each molecule of glucose, is relatively augmented. This is evidenced by the significantly increased atrial lactate production, up-regulated glycolytic enzyme, and down-regulated PDH complex. These phenomena are consistent with the Warburg effect in rapidly growing tumor cells—a higher rate of glycolysis followed by lactic acid production while a much lower rate of OXPHOS. In conclusion, the existing evidence suggests that the Warburg effect does exist in AF.

3. The signaling pathways of the Warburg effect in AF

3.1. HIF-1α pathway

Hypoxia-inducible factor-1 (HIF-1) has been identified as a key regulator of the Warburg effect during cancer cell proliferation [49]. HIF-1 is a basic helix-loop-helix transcription factor made of a heterodimeric complex of alpha (α) and beta (β) subunits [47]. The α subunits are critical for the oxygen response pathway and capable of forming a complex with HIF-1β to elicit transcriptional activity. The α subunit is normally polyhydroxylated and recognized by Von Hippo Lindau tumor suppressor protein (VHL) for ubiquitination and rapid degradation. Under hypoxic conditions, the lack of oxygen prevents hydroxylation interactions with proline on HIF-1α, inhibiting the VHL tumor suppressor from binding. This allows for HIF-1α to associate with its counterpart, HIF-1β subunit, creating a heterodimeric HIF-1 transcription factor complex which is able to enter the nucleus and bind to hypoxia response elements (HREs) on specific DNA strands, targeting genes that encode for increased tumor cell survival, increased proliferative capacity and metastatic potential [50].

HIF-1α has been implicated to play important roles in AF. An analysis of altered gene expression during sustained AF in the goat suggested a role for ischemic stress in the early response of cardiomyocytes to AF via HIF-1α. In the models, HIF-1α was elevated after 1 week of AF but subsequently returned to its baseline level [51]. Felix et al. found an up-regulation of the HIF pathway in AF, followed by an increased expression of hypoxic and angiogenic markers and paralleled by fibrogenesis in atrial myocardium [24]. Ogi et al. showed that AF increased HIF-1α and vascular endothelial growth factor (VEGF) expression and upregulation of HIF-1α/VEGF is involved in the enhancement of matrix metalloproteinase-9 (MMP-9) expression under hypoxic conditions, suggesting the possibility that MMP-9 upregulation in AF is directed by activation of HIF-1α/VEGF induced by hypoxia [23]. Xu et al. reported a significantly higher level of Toll-like receptor 2 (TLR2), HIF-1α, and MMP-9 in persistent/permanent AF groups than in the control or paroxysmal AF groups, suggesting their chronic role in atrial structure remodeling [25]. Further, in an atrial fibrosis rabbit model induced with isoproterenol, angiotensin-2, HIF-1α, transforming growth factor-β (TGF-β) and MMP-9 were all highly expressed. And by inhibiting the expression of HIF-1α, the expression levels of TGF-β and MMP-9 decreased accordingly, accompanied by the reduced extent of myocardial fibrosis. This study also suggests that HIF-1α promotes the expression of TGF-β and MMP-9 protein [26]. In a recent study, MMP2 and hypoxia-inducible HIF-1α expression were found evaluated in LAA sections of patients with AF, and the results suggest that HIF is involved in the inflammatory and fibrotic alteration of epicardial adipose tissue (EAT), which is also important for AF progression [27].

The transcriptional roles for HIF-1 [47] activation are shown to upregulate PDK levels which cause the phosphorylation of PDH, thereby reducing PDH active levels and reducing the amount of acetyl-CoA formation. During AF, the PDK is increased while PDH is decreased, indicating the participation of HIF-1α. HIF-1α also up-regulate glycolytic enzymes such as HK1/2, phosphofructokinase liver type (PFK-L), aldolase A and C (ALD-A, ALD-C), phosphoglycerate kinase 1 (PGK1), enolase alpha (ENO-α), pyruvate kinase M2 (PKM2), LDH-A and PFKFB-3 [51]. Some of these enzymes are increased in AF [15,16,38,39]. HIF-1α also decreases fatty acid metabolism by inhibiting the activity of PPARα/PGC-1α pathway, which is the most important pathway in regulating lipid metabolism [48]. Decreased PPARα/PGC-1α activity along with reduced fatty acid oxidation has been demonstrated in AF models [30–32]. In addition, HIF-1α activates the expression of VEGF, which in turn stimulates angiogenesis, and this effect has been demonstrated in AF in many studies [23,24]. HIF-1α/VEGF can increase the expression of MMPs and TGF-β in AF, thereby promoting atrial fibrosis [23]. Erythropoietin (EPO) levels are also upregulated by HIF-1 transcription. Increased EPO can lead to increased O_2 and nutrient delivery, which can be considered as an adaptive response to high frequently fibrillation. An increased blood level of hemoglobin was found independently associated with AF [52], indicating the increased expression of EPO. In addition, HIF-1α directly increases GLUT-1 expression and transporter levels in the membrane, increasing the uptake of glucose, which is also indiacted in AF [16].

As we discussed above, increased expression of HIF-1α is involved in atrial fibrosis in AF. This indicates the role of HIF-1α in atrial myofibroblast. In addition, HIF-1α was found to be involved in the inflammatory and fibrotic alteration of EAT, which is also an important contributor to AF [27]. In fact, HIF-1α, the key mediator of the Warburg effect, is demonstrated to play a vital role in the execution of an optimal inflammatory response by immune cells, including innate immune cells like macrophages, neutrophils and adaptive immune cells like Treg, Th17 cells [53]. All these immune cells have been evidenced to play important roles in AF progression [54]. Similarly, HIF-1α also represents a central regulator of glycolysis energy metabolism involved in the fibrotic process [55]. The HIF-1α mediated expression of TGF-β is a key cytokine responsible for fibroblast differentiation into myofibroblasts, and this effect was documented in AF [26]. Taken together, it can be pointed out that HIF-1α plays important roles in AF, including metabolic change, atrial fibrosis and inflammatory process (Fig. 3).

3.2. AMPK pathway

AMP-activated protein kinase (AMPK) is an important sensor for cellular energy status. AMPK is activated by phosphorylation by liver kinase B1 (LKB1), and inactivated by dephosphorylation by protein phosphatases. Binding of AMP or ADP or ZMP activates AMPK by promoting phosphorylation, by inhibiting dephosphorylation and by direct allosteric activation. Once activated, AMPK activates catabolic pathways and inhibits anabolic pathways, promoting fatty acid oxidation, mitochondrial biogenesis, and the expression of genes required for oxidative metabolism [4]. This raises the intriguing prospect that AMPK activation would exert 'anti-Warburg' effects. In fact, AMPK has been demonstrated to down-regulate glycolysis by inhibiting mammalian target of rapamycin (mTOR:Raptor) and hence the expression of HIF-1α [56], thereby exerting 'anti-Warburg' effects in tumor [57].

In 2002, Gollob MH Identified a gene responsible for familial Wolff-Parkinson-White syndrome, PRKAG2 [58], which encodes for the gamma 2 subunit of the enzyme AMPK. This syndrome has a high incidence of AF (higher in the range of 40% to 50%) [59], thus indicating the role of AMPK in AF.

3.2.1. AMPK exerts protective effects in AF

AMPK exerts cardiac protective role and prevents the initiation/progression of AF. Yasumasa Ikeda found that the cardiac myocyte-

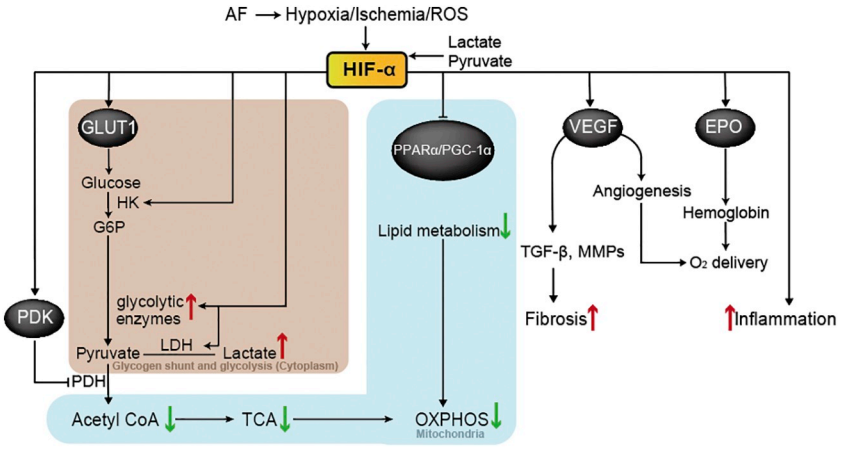

Fig. 3. The potential role of HIF-1α in AF. HIF-1α is the key regulator of the Warburg effect. Once activated, it upregulates PDK levels which cause the phosphorylation of PDH, thereby reducing PDH active levels. HIF-1α can also increase GLUT1 levels in the membrane and upregulate some glycolytic enzymes and LDH. HIF-1α decreases fatty acid metabolism by inhibiting the activity of PPARα/PGC-1α pathway. VEGF and EPO evels are also upregulated by HIF-1α transcription. HIF-1α regulates inflammatory and fibrotic progress, promoting the substrate for AF maintain. Lactate and pyruvate levels, the end products of glycolysis, can upregulate the expression of HIF-1α independent of hypoxic stimulation.

specific LKB1 knock-out mice exhibited atrial and ventricular hypertrophy, and all of them had AF eventually. In atria, the decrease of AMPK is associated with atrial enlargement, altered expression of calcium handling proteins, decreased connexin expression, increased mTOR and P70S6K expression and decreased eukaryotic elongation factor 2 (eEF2) expression [60]. Grace E. Kim demonstrated early electrophysiological abnormalities (decreased expression of ion channel and connexin) and subsequent structural remodeling (atrial enlargement and fibrosis) in mice with LKB1 deletion [61]. These findings suggested that the protective role of AMPK in AF is multifaceted. In fact, atrial alterations in LKB1-KO mice were associated with increased oxidative stress indicated by elevated H_2O_2 levels; Atrial myocardium in KO mice demonstrated significant active inflammatory processes with infiltration of lymphocytes, neutrophils, and macrophages in contrast to wild type (WT) atria [62]; In addition, inflammation was present in the tissue samples of atria before and after the initiation of AF [62]. Therefore, the decreased AMPK pathway play a potential causal role for oxidative stress and inflammation related to in atrial structural remodeling and conduction slowing, contributing to the vicious cycle of 'AF begets AF' [62]. The idea that AMPK inactivation contributes to the development or perpetuation of AF is consistent with another study, in which the AMPK phosphorylation was increased in dogs after 1 week of rapid atrial pacing and in patients with paroxysmal AF, but decreased in patients with long-standing persistent AF [63]. The activated AMPK is regarded as an adaptive response and an important contributor to maintaining atrial functional integrity by inducing metabolic compensation and offsetting the reductions in $I_{Ca,L}$, Ca^{2+} transients, and atrial contractility [63]. And it may be that enhanced AMPK activity helps to protect paroxysmal AF patients from arrhythmia persistence, whereas failure of AMPK phosphorylation may contribute to the chronicity and therapeutic resistance that characterizes long-term AF.

3.2.2. AMPK regulates metabolism in AF: anti-Warburg effect?

In heart, AMPK activation promotes the uptake and glycolysis of glucose; and is critical for facilitating both fatty acid uptake and oxidation. Studies regarding the regulatory role of AMPK in energy metabolism during AF is scarce and limited. In a AF model, irregular pacing of cardiomyocytes activated AMPK, which was associated with elevated FAT/CD36 membrane expression and increased FA uptake, increased expression of GLUT-4, and decreased levels of the GLUT-4 in the membrane. Inhibition of AMPK by compound C reverses these effects. The downregulated glucose uptake is suggested to be a result of increased uptake of fatty acids and subsequent lipid accumulation, which decrease the membrane expression of SNAP-23. SNAP-23 controls the membrane translocation of GLUT-4. Therefore, AMPK-induced GLUT-4 membrane translocation and glucose uptake are diminished [36]. Similarly, in collagen-induced arthritis (CIA) rats model, the decrease of atrial GLUT4 is also related to the decrease of AMPK while resveratrol reverses this effect [64]. As outlined above, fibrillating atria is likely to be more dependent on glucose than fatty acid. AMPK activation may reverse it. During early reperfusion of myocardial ischemia, AMPK activation helps fatty acid oxidation to predominate over glucose oxidation [65]. That may be explained by the fact that fatty acid oxidation may attenuate glucose oxidation via the Randle cycle and AMPK can down-regulate glycolysis by inhibiting mTORC1/HIF-1α pathways. Therefore, activation of AMPK may act an 'anti-Warburg effect' in AF while the failure of its activation may exacerbate it.

3.2.3. Targeting AMPK: a potential therapeutic strategy

Adiponectin, a metabolism-related protein secreted by adipose tissue that possesses potent cardioprotective effects, attenuated myocardial infarction injury and improved mitochondrial biogenesis by AMPK/PGC-1α signaling in diabetic hearts [66]. Alogliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, was found to decrease mitochondrial ROS production rate, prevent mitochondrial membrane depolarization, alleviated mitochondrial swelling, and increase mitochondrial respiration function in atria, and is associated with reduced AF inducibility. Of note, alogliptin also increased the expression of adiponectin, AMPK, and PGC-1, indicating that alogliptin can improve the mitochondrial biogenesis by adiponectin/AMPK/PGC-1α [67]. CIA induced the impairment of atrial energy metabolism by inhibiting the AMPK/PGC-1α pathway, which was reversed by resveratrol. Resveratrol protects against rheumatoid arthritis-induced atrial structural and metabolic remodeling [64]. These studies point to the protective role of the AMPK/PGC-1α pathway in AF. The use of metformin, an AMPK activator, is associated with a decreased risk of AF in patients with type 2 diabetes [68]. In a vitro study, 4 Hz-paced HL-1 atrial derived cardiomyocytes showed increased ROS production and myolysis while treatment with metformin prevented these abnormalities [68]. In a canine model of AF, metformin regulated lipid metabolism through AMPK/PPAR-α/VLCAD pathway and alleviated the abnormity of AERP and AERPd [32].

3.2.4. AMPK promotes autophagy in AF

From we discussed above, the role of AMPK in AF is more like protective. AMPK is activated due to metabolic stress caused by AF, but this adaptive effect may not last for a long time, and the failure of AMPK activation leads to multiple modifications and promotes the progression of AF, including electrical remodeling and structural remodeling. However, it must be pointed out that the actions of AMPK are not necessarily beneficial in AF. Another noteworthy role of AMPK in AF is its regulation of autophagy. AMPK induces cardiomyocyte autophagy via direct phosphorylation of the Unc-51 like autophagy activating kinase 1 (ULK1) complex and indirect inhibition of mTOR [69]. Induction of autophagy has been observed in atrial myocytes in AF

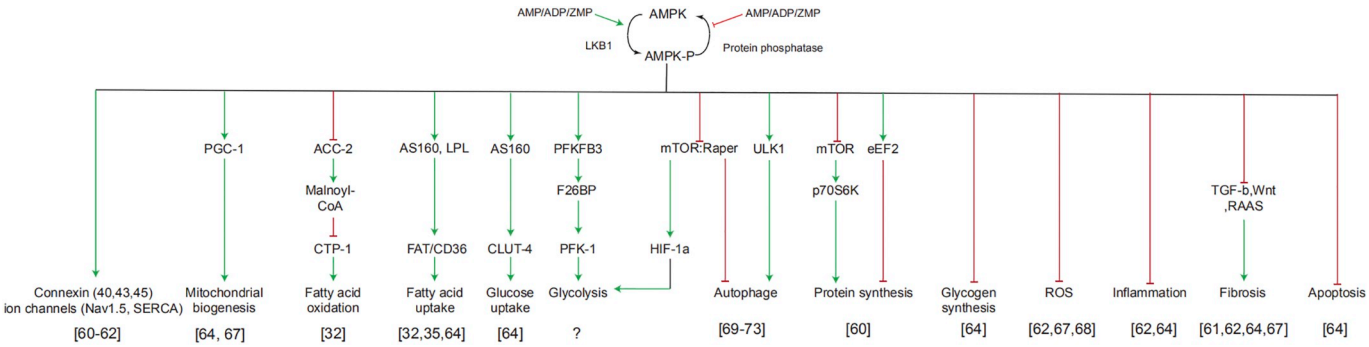

Fig. 4. The role of AMPK in AF. AMPK is activated by phosphorylation by LKB1, and inactivated by dephosphorylation by protein phosphatases. Binding of AMP or ADP or ZMP activates AMPK by promoting phosphorylation, by inhibiting dephosphorylation and by direct allosteric activation. Once activated, AMPK activates catabolic pathways (mitochondrial biogenesis,glucose and fatty acid utilization) and inhibits anabolic pathways (glycogen genesis, protein synthesis); Activated AMPK can also inhibit ROS production, inflammation, fibrosis and apoptosis while promoting autophage; Further, AMPK has been documented to regulate connexin and ion channels expression.? means no evidence in AF; [] gives the relating references that support the pathway in AF.

patients with severe mitral and tricuspid regurgitation [70]. Inhibition of endoplasmic reticulum stress was shown to attenuate autophagy and to protect against cardiac remodeling in vitro and in vivo models of AF [71]. Autophagic flux and autophagy related 7 (ATG7) protein levels were markedly increased in atria of persistent AF patients and in a rabbit model of rapid atrial pacing, and autophagy can induce atrial electrical remodeling via ubiquitin-dependent selective degradation of $Ca_{v1.2}$ [72]. A study reported that AMPK-dependent autophagy occurred in atrial cardiomyocytes after rapid atrial pacing of dogs and in persistent AF patients, indicating that activation of AMPK and downstream autophagy may be a contributor to AF [73]. These researches indicate that excessive activation of autophagy during the onset of AF may result in cardiomyocyte impairment, which may further cause AF substrate, as 'AF beget AF'. In this way, the activation of AMPK in AF may exert an adverse effect.

In conclusion, AMPK exerts multifaceted effects in AF and may be a negative regulator of the Warburg effect (Fig. 4). This anti-Warburg effect is not limited to cardiomyocyte, but also cardiac fibroblasts and inflammatory cells. Targeting AMPK (such as metformin, resevortor, adiposon, resveratrol) may provide a potential therapeutic strategy in AF.

4. Summary and perspective

The Warburg effect, as an energy shift from mitochondrial oxidative phosphorylation to aerobic glycolysis, is extensively found in tumor and non-tumor disease. For instance, the Warburg effect was discovered in the failing heart and supported the structural remodeling. Treatment of dichloroacetate (DCA) can improve cardiac function and mitochondrial oxidation in the process of heart failure and cardiac hypertrophy by suppressing the expression of PDK [74]. It should be noted that although aerobic glycolysis produces fewer ATP molecules than mitochondrial OXPHOS, aerobic glycolysis is much faster than OXPHOS, and produces more total ATP than OXPHOS in the same amount of time [75,76]. AF is characterized by irregular high-frequency excitation and contraction that affect atrial energy demands, circulation and oxygen supply, leading to a hypoxia/ischemia status. Therefore, the Warburg effect may be regarded as an adaptive response to the energy-lacking status and play a pro-survival role in the fibrillating atrial cell.

In this review, we summarize the researches related to the substrate metabolism change in AF, and observe the footprints of the Warburg effect in the fibrillating atria as evidenced by impaired mitochondrial OXPHOS, increased expression of glycolytic enzymes, decreased PDH complex expression and a significant increase of lactate level. In addition, we also summarized the role of HIF-1α in AF, the key regulator of the Warburg effect. AMPK, which exerts an anti-Warburg effect, was found to have a protective role in AF and failure of its activation can cause AF-promoting substrate. The Warburg effect also play vital roles in inflammation and fibrosis [4,55]. Therefore, it promotes structure/electrical remodeling by promoting inflammatory and fibrotic process in atria and contribute to the maintenance or progression of AF. What's more, the altered glycolysis may contribute to atrial remodeling directly. The glycolytic products pyruvate and lactate directly inhibit atrial sarcoplasmic reticulum Ca^{2+} release by reducing ryanodine receptor (RyR) activity [77]. Reduced RyR activity inhibits PDH activity and drives the cardiomyocytes to aerobic glycolysis [78]. Increased PFK

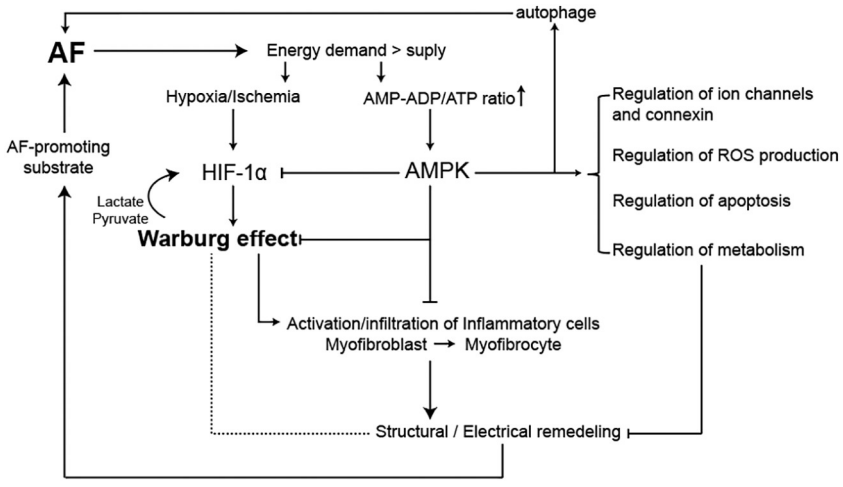

Fig. 5. Warburg effect contributing to the vicious cycle of 'AF begets AF'. Increased cellular workload during the rapid atrial activation in AF causes a energe deman-suply mismatch. The hypoxia/ischemia envrironment activates HIF-1α thereby mediating the Warburg effect. Warburg effect, the key regulator in pro-inflammatory and pro-fibrotic process, promotes the activation/infiltration of inflammatory cells and atrial fibrosis, which cause both electrical and structural remodeling, leading to the vicious cycle of 'AF-begets-AF'. The altered glycolysis may infect atrial function directly;The glycolytic end products pryruvate and laclate, can promote HIF-1α protein stability and activate HIF-1-inducible gene expression vice versa. The activated AMPK due to increased AMP/ATP ratio and its mediated cellular pathway serve as an adaptive/compensatory response and may play an “anti-Warburg effect”. Failure of AMPK activation provides substrates for AF progression.

activity induces a pathological hypertrophy heart and regulates the expression of key genes involved in cardiac metabolism and remodeling [79]. Atrial hypertrophy can be both cause and consequence of AF [80,81]. In a paroxysmal AF model, inhibiting PDH activity with phenylephrine (PE) increased atrial fibrosis remodeling and MMP-9 expression while DCA (a PDH agonist) reversed these effects [15]. The increased lactate production and lactate signaling cascade were proved to be one of the regulatory systems in the atrial structural remodeling of AF [14], including oxidative stress damage and mitochondrial control of apoptosis. Lastly, pyruvate and lactate, can promote HIF-1α protein stability and activate HIF-1-inducible gene expression vice versa [82].

Taken together, the Warburg effect may contribute to the vicious cycle of 'AF-begets-AF' (Fig. 5), targeting the Warburg effect may provide a new therapy for AF treatment. A lot of questions remain to be answered: What's the role of altered metabolic intermediates in AF? How to find a proper way to target the Warburg effect for AF treatment? As the Warburg effect plays key roles in promoting fibrosis and inflammation, can inhibiting the Warburg effect selectively (such as in myofibroblasts and immune cells) help reverse the structural remodeling in AF? Further studies are warranted.

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Declarations of interest

None.

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