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Review

Defective insulin signaling and mitochondrial dynamics in diabetic cardiomyopathy

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ABSTRACT

Diabetic cardiomyopathy (DCM) is a common consequence of longstanding type 2 diabetes mellitus (T2DM) and encompasses structural, morphological, functional, and metabolic abnormalities in the heart. Myocardial energy metabolism depends on mitochondria, which must generate sufficient ATP to meet the high energy demands of the myocardium. Dysfunctional mitochondria are involved in the pathophysiology of diabetic heart disease. A large body of evidence implicates myocardial insulin resistance in the pathogenesis of DCM. Recent studies show that insulin signaling influences myocardial energy metabolism by impacting cardiomyocyte mitochondrial dynamics and function under physiological conditions. However, comprehensive understanding of molecular mechanisms linking insulin signaling and changes in the architecture of the mitochondrial network in diabetic cardiomyopathy is lacking. This review summarizes our current understanding of how defective insulin signaling impacts cardiac function in diabetic cardiomyopathy and discusses the potential role of mitochondrial dynamics.

1. Introduction

Diabetic cardiomyopathy (DCM) is defined as the presence of left ventricular (LV) dysfunction beyond that which can be accounted for by arterial hypertension, coronary artery disease (CAD) or evidence of any other structural cardiac disease in individuals with diabetes [1,2]. From a cellular standpoint, changes in the energetics of the heart have been proposed to contribute to the development of DCM [3]. Because mitochondria are the major source of ATP to meet the energy demands of the heart, it has been proposed that mitochondrial dysfunction is an underlying cause of metabolic disorders and insulin resistance-associated heart disease [4]. Extensive experimental and clinical evidence indicates that mitochondrial dynamics (fusion, fission and mitophagy) are essential for mitochondrial quality control and sustained function in several tissues [5] including the cardiovascular system [6,7]. In addition, prolonged hyperglycemia and insulin resistance in individuals with T2DM can lead to dramatic changes in cardiac mitochondrial dynamics and function [8–10]. Studies by Battiprolu *et al.* showed that mice developed myocardial insulin resistance in response to high fat-diet (HFD) characterized by a down-regulation of IRS1 activity, decreased AKT signaling, and a shift from glucose to fatty acid (FA) utilization [11]. Mice with cardiomyocyte-selective ablation of the insulin receptor (CIRKO) showed defects in FA and pyruvate metabolism and reduced tricarboxylic acid flux associated with mitochondrial uncoupling. Thus, altered insulin signaling in the heart may contribute directly to mitochondrial dysfunction in the setting of obesity and T2DM [4]. Our group recently demonstrated a link between insulin and the regulation of mitochondrial dynamics, particularly mitochondrial fusion, in neonatal rat cardiomyocytes [12], raising new questions regarding the interplay among mechanisms affecting the architecture of

Abbreviations: DCM, Diabetic cardiomyopathy; T2DM, Type 2 diabetes mellitus; LV, Left ventricular; CAD, Coronary artery disease; HFD, High fat-diet; FA, Fatty acid; IRS1, Insulin receptor substrate 1; CIRKO, Cardiomyocyte-specific knockout of the insulin receptor; Mnf1, Dynamin-related GTPase mitofusin 1; Mnf2, Dynamin-related GTPase mitofusin 2; Opa-1, Optic atrophy protein 1; IMM, Inner mitochondrial membrane; OMM, Outer mitochondrial membrane; Fis1, Mitochondrial fission 1 protein; Drp1, Dynamin related protein 1; ROS, Reactive oxygen species; SOD, Superoxide dismutase; O-Glc-NAcylation, O-linked-β-N-acetylglucosamine modification; HF, Heart failure; mTOR, Mammalian target of rapamycin; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; Pink1, Serine/threonine kinase PTEN-induced putative kinase 1; Parkin, E3 ubiquitin ligase; AMPK, 5′ AMP-activated protein kinase; Drp1-CKO, Cardiomyocyte-specific Drp1 knockout; T1DM, Type 1 diabetes mellitus; LAMP1, Lysosomal-associated membrane protein 1; IRS2, Insulin receptor substrate 2; CIRS12KO, Cardiomyocyte-specific deletion of both IRS1 and IRS2

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the mitochondrial network in DCM. In this review, we will summarize the available evidence that links insulin signaling to DCM and discuss the potential functional roles of mitochondrial dynamics.

2. Diabetic cardiomyopathy and mitochondrial dynamics in the heart

Myocardial energy deficiency is closely related to the initiation and progression of various cardiac pathologies, such as those observed during insulin resistance and T2DM [13,14]. Under normal physiological conditions, the heart utilizes energy from substrates (FA and carbohydrates) based on metabolic demand and availability [15]; however, in the setting of insulin resistance, the myocardium's ability to use glucose as an energy source is reduced [16,17]. This change in substrate preference plays a critical role in the pathophysiology of DCM [11,18]. Mitochondria are highly abundant and represent 30% of cardiac cell volume, generating more than 90% of the intracellular ATP consumed by the heart [15,19]. Thus, many studies are currently focused on mitochondrial dysfunction as a causative factor in metabolic disorders and insulin resistance-associated heart diseases [20,21].

In mammalian cells the mitochondria are dynamic organelles that continuously change their morphology through fusion and fission events in response to intracellular circumstances, and changes in the balance of these processes have been implicated in different biological events such as cell division, apoptosis, autophagy, and metabolism [6,22]. Nonetheless, it is important to consider that evidence available in the literature about cardiac mitochondrial dynamics differs according to the type of cardiac cells analyzed. For example, mitochondria are distributed throughout the cytoplasm in a reticular network and are unrestricted in their movements in neonatal cardiomyocytes or immortal cardiac cell lines (H9c2, HL-1 cells). Conversely, in adult cardiomyocytes the mitochondria are located under the sarcolemma, around nuclei and between myofibrils, providing enough ATP for muscle contraction; however their ability to move is limited due to these cellular constraints [6,19]. Thus, mitochondrial division is estimated to only occur at an extremely low frequency in adult cardiomyocytes under physiological conditions [23]. However, despite the evidence mentioned above the proteins implicated in mitochondrial dynamics are present in the adult heart, suggesting that adult cardiac mitochondria have retained their ability to undergo fusion, fission and mitophagy (mitochondrial degradation), which are key processes associated with quality control of mitochondria, mitochondrial turnover and mitochondrial homeostasis in adult cardiomyocytes [19]. However, this is not the only task carried out by mitochondrial dynamics [5]. Recent studies have linked mitochondrial dynamics to the balance between energy demands and nutrient supply, suggesting that changes in mitochondrial morphology can act as a mechanism for energetic adaptation to changing cardiac metabolic necessities [24]. Indeed, alterations in mitochondrial structure and function have been linked to cardiovascular diseases [6] including DCM [25].

Despite the apparent correlation between the dysregulation of mitochondrial dynamics and myocardial energy deficiency, the precise mechanism of how this dysregulation contributes to the pathogenesis of DCM is still unclear. Moreover, current understanding of the importance of mitochondrial dynamics in the heart seems to contradict the long-standing paradigm in the mitochondrial field that cardiac mitochondria are relatively static [26]. Although recent *in vivo* observations support the presence of morphological changes, the question that still remains is whether these changes are cause or consequence of disease progression.

2.1. Diabetic cardiomyopathy and mitochondrial fission/fusion in the heart

In mammalian cells, the main regulators of mitochondrial fusion are the dynamin-related GTPases mitofusins (Mnf1 and Mfn2) specialized proteins localized on the outer mitochondrial membrane, and optic atrophy protein 1 (Opa-1), a protein localized on the inner mitochondrial membrane (IMM). On the other hand, the mitochondrial fission 1 protein (Fis1), localized on the outer mitochondrial membrane (OMM), and the cytoplasmic GTPase dynamin related protein 1 (Drp1) are involved in mitochondrial fission [24,27] (Fig. 1A).

Several studies have indicated that mitochondrial quality control plays a pivotal role in protecting the heart against stress, although the presence of fission and fusion has not been well documented in adult cardiomyocytes [26], extremely well organized cells in which mitochondrial movements are greatly restricted [19]. In this sense, initial studies were done with neonatal cardiomyocytes or with immortalized cardiac cell lines (H9c2, HL-1) [28,29] in which the mitochondrial network does not directly reflect that of an adult cardiomyocyte [19]. Chen *et al.* reported that the fusion/fission cycle would last 14–16 days in adult cardiomyocytes, being slower than that seen in neonatal cardiomyocytes [30], suggesting that mitochondrial dynamics is a process that depends on the cardiomyocyte cell architecture. Studies in non-cardiac cells [31–35] have shown that low expression of fusion proteins is associated with mitochondrial network fragmentation. However, Papanicolau *et al.* showed that mice harboring a cardiomyocyte-specific knockout of Mfn2 exhibited larger mitochondria [36]. This was also observed in Opa1 (+/−) mice, which accumulated large clusters of fused mitochondria with altered cristae [37]. Cardiomyocyte-specific Mfn1-null mice showed fragmentation of their mitochondrial network [38] and mice with an adult cardiomyocyte-specific conditional ablation of Mfn1/Mfn2 together developed a fragmented mitochondrial network and progressed to dilated cardiomyopathy [30]. Thus, mitochondrial dynamics is a complex process in the adult heart and may depend upon the specific cell architecture. Moreover, in terms of cardiac contractile function, increases in mitochondrial volume may directly impact the force developed by myofibrils [39], suggesting a direct link between mitochondrial morphology and cardiac contractile function. On the one hand, enhanced mitochondrial fragmentation may lead to cardiac disorders [24]; on the other hand, Ishihara *et al.* have shown that mitochondrial fission is required for neonatal cardiomyocyte development, participating in the formation of highly organized myofibrils and maintenance of uniformly active mitochondria with mitochondrial DNA (mtDNA) nucleoids in cardiomyocytes [40], suggesting that mitochondrial fission is a key process during heart development.

Studies specifically addressing the direct relationship between fission and fusion of cardiac mitochondrial and insulin resistance and T2DM are limited. However, we know that a major contributory factor linked to the onset of DCM is hyperglycemia-induced oxidative stress (Fig. 1B). In this context, *in vitro* data from Yoon's group suggest that hyperglycemia induces mitochondrial fragmentation in neonatal rat ventricular myocytes (H9c2 cells) [41]. Furthermore, in the same model Yu *et al.* also demonstrated that sustained hyperglycemia induces mitochondrial fission together with mitochondrial reactive oxygen species (ROS) production, which in turn promotes activation of a proapoptotic pathway [42]. These pathological changes could be prevented by transfecting the cells with a dominant-negative form of Drp1, DrpK38A, suggesting that mitochondrial fragmentation and dysfunction in the setting of hyperglycemia is Drp1-dependent [42]. Similarly, in a recent article, Watanabe *et al.* showed that Drp1 and ROS act synergistically to promote mitochondrial dysfunction and inhibit insulin signal transduction in H9c2 cells [43]. This effect could be partially reversed when these cells were treated with the superoxide dismutase (SOD) mimetic TMPyP [43]. In a different, but related model, Makino *et al.* showed mitochondrial fragmentation in coronary endothelial cells from murine diabetic hearts that was associated with reduced levels of Opa-1 and increased levels of Drp1 [44]. Studies in models of T2DM suggest that insulin resistance might contribute to reduced myocardial recovery after ischemia [45]. Interestingly, pretreatment of adult rat cardiomyocytes with Mdivi-1 (pharmacological inhibitor of Drp1) reduced cell death and protected the heart from ischemia/reperfusion injury [46]. Transfection of neonatal rat cardiomyocyte with Drp1K38A to inhibit fission was likewise protective [47].

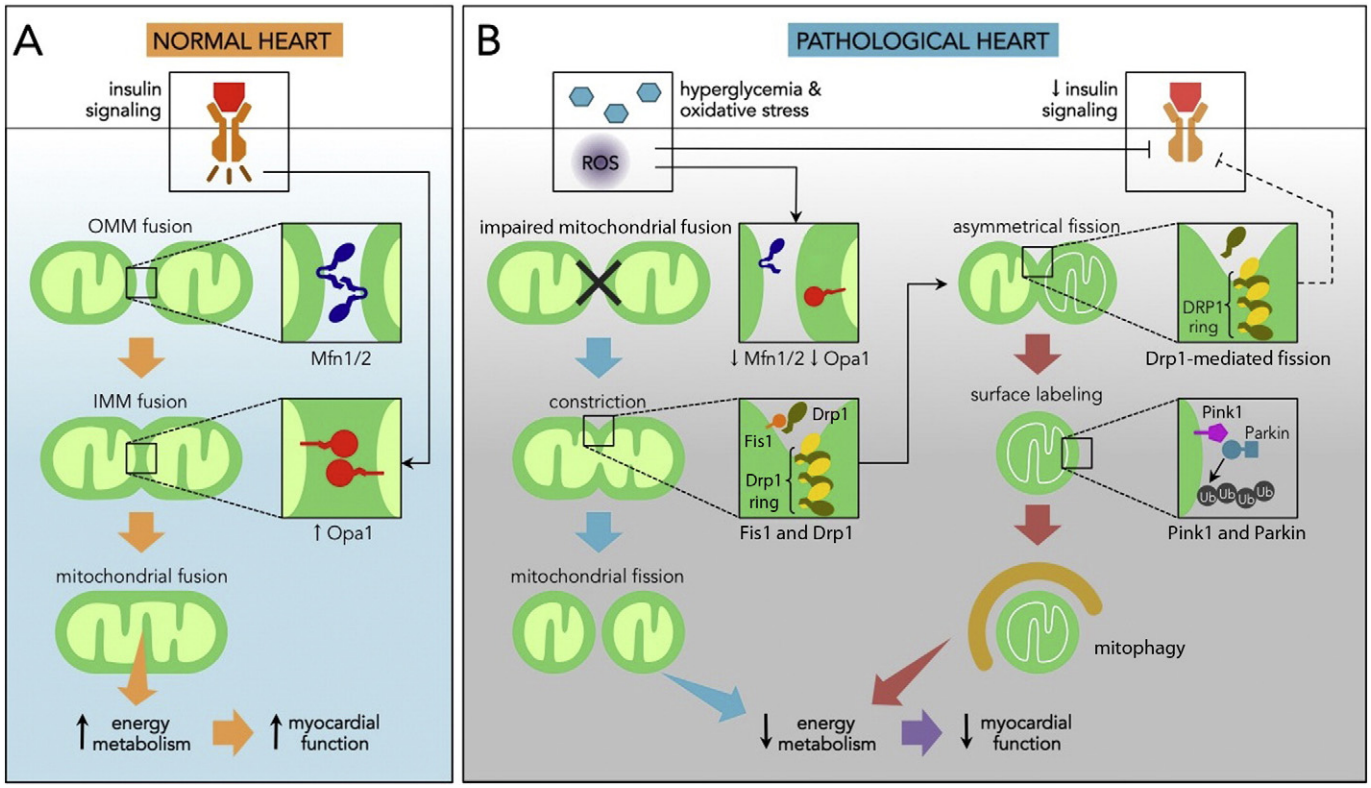

Fig. 1. Mitochondrial dynamics in the heart. A) Insulin induces mitochondrial fusion in cardiomyocytes. Fusion of the outer mitochondrial membrane (OMM) is carried out by the dynamin-related GTPases, mitofusins 1 and 2 (Mnf1/2). Optic atrophy protein 1 (Opa-1) participates in fusion of the inner mitochondrial membrane (IMM). Both processes increase cristae density, promoting mitochondrial metabolism. B) Hyperglycemia and reactive oxygen species (ROS) impair mitochondrial fusion associated with reduced levels of Opa-1 and Mfn2. These processes also promote mitochondrial fission involving the mitochondrial fission 1 protein (Fis1) and the dynamin related protein 1 (Drp1), triggering cardiac mitochondrial dysfunction. Mitochondrial damage can activate selective mitophagy that involves Drp1-mediated fission, activation of the PTEN-induced putative kinase 1 (Pink1) and the E3 ubiquitin ligase Parkin.

Whether mitochondrial fission in DCM contributes to cardiac dysfunction, and whether fusion is protective of cardiac function, both remain unclear. However, recent studies by Montaigne *et al.*, postulate that hyperglycemia may be a major driver of both mitochondrial dysfunction and mitochondrial network fragmentation in the human diabetic heart [10] (Fig. 1B). They demonstrated that declines in myocardial function in the transition from obesity to T2DM are likely related to declines in cardiac mitochondrial function rather than a direct consequence of insulin resistance, as impaired mitochondrial function and dynamics (as well as LV contractile dysfunction) are observed in diabetic patients, but not in obese patients during early stages of insulin resistance. These effects in human hearts were associated with fragmentation of the mitochondrial network and decreased expression of the Mnf1, but no significant alteration of Fis1 and Drp1 [10]. However, Montaigne *et al.*, cannot rule out the possibility that posttranslational modifications such as glycation and O-linked-β-N-acetylglucosamine modification (O-Glc-NAcylation) could modulate the function of proteins involved in mitochondrial dynamics reported in human cardiac myocytes under high-glucose conditions [48,49]. Interestingly, rat neonatal cardiomyocytes maintained under high glucose concentrations have lower Opa-1 levels and a more fragmented mitochondrial network [50] similar to the pattern observed in myocardial biopsies of T2DM patients [10]. Moreover, decreased levels of Opa-1 were also observed in biopsies of HF patients [51].

Our group recently demonstrated a link between insulin and the regulation of mitochondrial dynamics, particularly mitochondrial fusion in cardiomyocytes [12] (Fig. 1A). Insulin treatment of cardiomyocytes increased the levels of Opa-1, promoted mitochondrial fusion, increased mitochondrial membrane potential, and elevated both intracellular ATP levels and oxygen consumption in rat neonatal cardiomyocytes. However, the ability of insulin to influence metabolism was impaired in cells deficient of Mfn2 or Opa-1 [12]. Thus, these data strongly suggest that insulin stimulation enhances mitochondrial function in neonatal cardiomyocytes through a novel regulatory pathway involved in the control of Opa-1 protein levels that is mediated by AKT, mTOR, and NFκB. Taken altogether, this reinforces the concept that mitochondrial fusion is essential in cardiac homeostasis regulating different processes such as mitochondrial morphology, cardiac respiration, and contractile function in adult cardiomyocytes [30]. Whether these changes cause mitochondrial remodeling and how they affect the function of mitochondria during DCM remain to be elucidated.

2.2. Diabetic cardiomyopathy and mitophagy in the heart

Autophagy is an intracellular catabolic pathway in which proteins and organelles are delivered to and degraded in lysosomes allowing the cell to maintain energy homeostasis under conditions of starvation or nutrient deprivation [52]. Selective autophagic degradation of mitochondria is termed mitophagy [53–55]. Although mitochondria may be degraded during nonselective autophagy, it is now clear that functional status of mitochondria degraded during generalized autophagy may be very different from the functional status of mitochondria targeted for selective degradation by mitophagy [25,53]. The mitochondrial fission can facilitate removal of damaged mitochondrial components by partitioning them to a daughter mitochondrion that can then be targeted and removed by mitophagy [56]. Disruption of the mitochondrial quality control mechanisms associated with the interplay between mitochondrial dynamics and mitophagy in different tissues [56] has also been linked to various cardiac diseases [7].

Emerging key players in the regulation of mammalian mitophagy are the serine/threonine kinase PTEN-induced putative kinase 1 (Pink1) and the E3 ubiquitin ligase Parkin, which selectively promote the degradation of impaired mitochondria [57] (Fig. 1B). Parkin-deficient (Parkin $^{-/-}$) mice showed impaired mitophagy and accumulation of dysfunctional

mitochondria associated with cardiac dysfunction and reduced survival [58]. Pink1 appears to play a critical role in cardiac biology, as Pink1 knockout mice (Pink $^{-}/^{-}$) exhibit cardiac hypertrophy with defective mitochondrial function and increased myocardial injury in response to ischemia/reperfusion [59,60]. Moreover, cardiomyocyte-specific deletion of PTEN leads to the loss of Pink1-AMPK signaling, development of cardiac hypertrophy and disruption of autophagic flux in the heart [61]. Although Parkin-induced mitophagy has been shown to be dependent on the kinase activity of Pink1, the ubiquitin ligase activity of Parkin, and Drp1-mediated mitochondrial fission [62,63], a full understanding of the regulatory mechanisms involved in these processes in the heart has yet to emerge. However, recently, mitochondrial dysfunction and dilated cardiomyopathy associated with defective mitophagy [64] and autophagy [65] were reported in mice with hearts deficient for Mfn2.

In the heart, under both physiological and pathological conditions, several reports have associated mitophagy with cardiac homeostasis and myocardial protection [25,58,66–71]. Narendra *et al.* described in HeLa cells the first molecular link between mitochondrial membrane depolarization and autophagy by identifying Parkin as a mediator of mitophagy downstream of mitochondrial depolarization [57]. In the context of our current discussion, the inhibition of Parkin-mediated autophagy by cytosolic p53 was associated with mitochondrial dysfunction in the mouse heart [69]. Interestingly, a recent study showed that cardiac and mitochondrial function was normal in 3-month-old Parkin-deficient (Parkin $^{-}/^{-}$) heart. Nevertheless, Parkin $^{-}/^{-}$ mice were much more sensitive to myocardial infarction compared with wild type mice, and damages were associated with increased disorganization of the mitochondrial network [58]. However, by electron microscopy the same research group reported that 6-month-old (Parkin $^{-}/^{-}$) mice had abnormal mitochondria containing electron-dense macromolecules, suggesting that clearance occurs at a slower rate leading to an accumulation of abnormal mitochondria in cardiomyocytes with age [70].

Drp1 plays a role in mediating Parkin-induced mitophagy by Bnip3 in adult rat cardiomyocytes [72] and, as we previously mentioned, pharmacological suppression of Drp1 with Mdivi-1 attenuates myocardial injury in response to ischemia/reperfusion and reduces cell death in adult rat cardiomyocytes [46]. These results have led to a general belief that mitochondrial fusion is protective. However, a recent study carried out by Ikeda *et al.*, using an interesting model of cardiomyocyte-specific Drp1 knockout (Drp1-CKO) mice showed that downregulation of Drp1 enhanced myocardial injury in response to ischemia/reperfusion. Moreover, Drp1-CKO mice exhibited mitochondrial dysfunction, myocardial cell death, heart failure and premature death, suggesting that endogenous Drp1 plays a key role in mediating mitophagy and maintaining mitochondrial function in response to stress in the heart [73]. In parallel, Sesaki's group also reported lethal heart defects and decreased mitochondrial respiration in mice lacking cardiac Drp1. However, they described a Parkin-independent mitophagy associated with accumulation of p62 and ubiquitinated proteins in Drp1KO cardiomyocytes, highlighting the role of Parkin in mitochondrial homeostasis in the absence of cardiac mitochondrial division [74].

Several studies using models of type 1 diabetes mellitus (T1DM) [75–78] or T2DM [79–81] have suggested that the inhibition of autophagy may contribute to the development of DCM; however, its potential protective role in diabetic cardiac injury remains unclear [25]. The functional status of general autophagy may not necessarily reflect the activity of selective mitophagy. In this way, Xu *et al.* showed that autophagy is inhibited in the diabetic heart as early as 3 weeks after streptozotocin injection, while mitophagy is not reduced until more advanced stages [78]. Intriguingly, the hearts of mice deficient in Beclin 1 or Atg16 still retained mitophagic activity even under diabetic conditions, as assessed by the expression and mitochondrial localization of Pink1, Parkin, and the lysosomal-associated membrane protein 1 (LAMP1) [78]. These results suggest that in a model of T1DM reducing autophagy may be an adaptive response, whereas up-regulation of other alternative autophagic activities, such as mitophagy, may likewise help preserve cardiac function. Nevertheless, the functional role of mitophagy and the specific mechanisms regulating its activity in the diabetic heart remain to be determined.

Recent studies have suggested an important role for insulin signaling in the regulation of myocardial autophagy [82,83]. Mice with cardiomyocyte-specific deletion of both IRS1 and IRS2 (CIRS12KO) showed unrestrained autophagy in cardiomyocytes, which contributed to myocyte loss, heart failure, and premature death. Moreover, CIRS12KO mice exhibited increased apoptosis and mitochondrial dysfunction, which were not reversed when autophagic flux was normalized [83]. Moreover, insulin administration to streptozotocin-induced diabetic rats [82] and cultured cardiomyocytes *in vitro* following nutrient withdrawal [83], suppressed autophagic signaling. On the other hand, the hearts of mice with reduced PI3K/AKT signaling exhibited increased indices of autophagy and reduced accumulation of damaged organelles [84]. Conversely, constitutive activation of PI3K/AKT signaling inhibited basal cardiac autophagic flux [84,85]. However, even though this evidence provides insight into the dynamic regulation of cardiac autophagy by insulin, its role in mitophagy remains to be established.

3. Conclusion and open questions

T2DM and insulin resistance have been implicated in the pathophysiology of DCM and also increase the risk of developing cardiovascular complications [3]. Extensive evidence suggests a mechanistic link between insulin resistance and altered substrate metabolism in DCM involving a shift from glucose to FA utilization by the cardiomyocyte [11]. Mitochondria play a central role in meeting the energy demands of the heart under physiological conditions, and new insights are emerging that place mitochondrial dysfunction as a key event contributing to development of DCM [10]. Recent evidence demonstrates that insulin can promote mitochondrial fusion, increase mitochondrial membrane potential, and elevate both intracellular ATP levels and oxygen consumption in rat neonatal cardiomyocytes [12]; nonetheless, there are many open questions that remain to be addressed regarding the impact of insulin on mitochondrial dynamics in the adult heart, because differences in the cell architecture among neonatal cardiomyocytes, immortalized cell lines and adult cardiomyocytes are key for energy transfer and communication between organelles [19]. For the same reason, what is the impact of insulin signaling (protective/detrimental) on mitochondrial dynamics in DCM? Mitochondrial fission has been associated with metabolic cardiac disorders and in contrast, fusion is generally considered beneficial [24]. However, a recent study indicates that chronic downregulation of Drp1 induces elongation of mitochondria, mitochondrial dysfunction, heart failure and premature death in mice [73]. So, is there a critical balance between fusion/fission required for both preservation of mitochondrial function and maintenance of cellular homeostasis in the heart? How is this balance altered in DCM?

Recent studies have suggested an important role for insulin signaling in the regulation of myocardial autophagy [82,83]. Moreover, the inhibition of cardiac autophagy reported in different models of diabetes may contribute to the development of DCM [25]. Nonetheless, the functional status of general autophagy may not necessarily reflect the activity of selective mitophagy. A recent study carried out by Kageyama *et al.* suggests that Drp1 can promote the delivery of mitochondria to lysosomes independent of Parkin [74]. How are general autophagy and selective mitophagy differentially regulated in DCM? Answers to these questions will help elucidate the complex interplay between insulin signaling and mitochondrial dynamics in DCM and will lay the foundation for the development and application of new drugs and therapies targeted toward preventing or treating DCM.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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