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Review article

Mitochondrial dynamics in type 2 diabetes: Pathophysiological implications

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ABSTRACT

Mitochondria play a key role in maintaining cellular metabolic homeostasis. These organelles have a high plasticity and are involved in dynamic processes such as mitochondrial fusion and fission, mitophagy and mitochondrial biogenesis. Type 2 diabetes is characterised by mitochondrial dysfunction, high production of reactive oxygen species (ROS) and low levels of ATP. Mitochondrial fusion is modulated by different proteins, including mitofusin-1 (MFN1), mitofusin-2 (MFN2) and optic atrophy (OPA-1), while fission is controlled by mitochondrial fission 1 (FIS1), dynamin-related protein 1 (DRP1) and mitochondrial fission factor (MFF). PARKIN and (PTEN)-induced putative kinase 1 (PINK1) participate in the process of mitophagy, for which mitochondrial fission is necessary. In this review, we discuss the molecular pathways of mitochondrial dynamics, their impairment under type 2 diabetes, and pharmaceutical approaches for targeting mitochondrial dynamics, such as mitochondrial division inhibitor-1 (mdivi-1), dynasore, P110 and 15-oxospiramilactone. Furthermore, we discuss the pathophysiological implications of impaired mitochondrial dynamics, especially in type 2 diabetes.

1. Introduction

Hyperglycemia and type 2 diabetes are directly related to oxidative stress. In fact, a high production of reactive oxygen species (ROS) and a subsequent change in redox state and cellular homeostasis has been described in type 2 diabetes. Mitochondria are one of the main sources of ROS and the major site of ATP production. When levels of glucose are high, mitochondria enhance ROS production and induce oxidative stress and tissue damage as a result [1].

Mitochondrial impairment can also contribute to the development of age-dependent insulin resistance [2]. Mitochondria biogenesis contributes to modulate the energy balance, and an enhanced production of ROS by the electron transport chain under hyperglycemic conditions is thought to exacerbate pathological pathways, leading to diabetic microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (stroke, myocardial ischemia) complications [3].

All of the aforementioned characteristics suggest that mitochondria play a key role in insulin resistance in general and in type 2 diabetes in particular. Therefore, mitochondrial quality must be very well controlled. Different mechanisms have been used by mitochondria to control their homeostasis; for example, mitochondrial fusion and fission are key to the repair of mitochondrial damaged components, allowing the exchange of material between damaged and non-damaged mitochondria via the fusion process, or segregation of damaged components via the fission process [4,5]. Other mechanisms for maintaining mitochondrial homeostasis are the proteolytic system, the proteasome, and the formation of mitochondria-derived vesicles under oxidative stress conditions which can be degraded by lysosomes.

Abbreviations: AMPK, AMP-activated protein kinase; ATF6, activating transcription factor 6; BNIP3, BCL2/adenovirus E1B 19 kDa interacting protein 3; CHOP, C/EBP homologous protein; DRP1, dynamin-related protein 1; FIS1, fission protein 1; GRP78, 78 kDa glucose-regulated protein; IMM, inner mitochondrial membrane; LC3, 1 A/1B-light chain 3; mdivi-1, mitochondrial division inhibitor-1; MFF, mitochondrial fission factor; MFN1, mitofusin 1; MFN2, mitofusin 2; MiD49, mitochondrial dynamics proteins of 49; MiD51, mitochondrial dynamics proteins of 51 kDa; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; Nox 4, NADPH oxidase-4; OMM, outer mitochondrial membrane; OPA1, optic atrophy 1; p38 MAPK, p38 mitogen-activated protein kinase; PINK1, (PTEN)-induced putative kinase 1; ROS, reactive oxygen species; S3, 15-Oxospiramilactone; SIRT1/3, sirtuin 1/3; SOD, superoxide dismutase; sXBP1, spliced X-box binding protein 1; TGF-β1, transforming growth factor-β1; TRX2, thioredoxin 2; TXNIP, thioredoxin interacting protein; p62/SQSTM1, ubiquitin and sequestosome-1; UCP-1, uncoupling protein-1; ΔΨm, mitochondrial membrane potential

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Damaged mitochondria can also form autophagosomes to trigger their degradation into the lysosomes via mitophagy [6–8]. All of these aspects suggest that mitochondria may play a critical role in the pathophysiology of diabetes. It is important to take into account that mitochondria are not static; in fact they are highly dynamic and constantly changing in shape, size and location within the cells, which confers them high plasticity.

In type 2 diabetic patients, high levels of glucose can induce glucose oxidation, thereby generating pyruvate and NADH. Furthermore, ROS are released from mitochondrial complex I and III. In these conditions different antioxidant systems are triggered, such as manganese superoxide dismutase (SOD) or uncoupling protein-1 (UCP-1), to prevent ROS production and inhibit the formation of advanced glycation end products or nuclear factor kappa beta (NF-κB) activation [9], thus impeding a chronic proinflammatory state.

In this context, it is important to highlight the concept of mitochondrial hormesis in type 2 diabetes [10], which involves a reduction of ROS production and ATP synthesis in different tissues in response to high levels of glucose or excess of nutrient intake, constituting a compensatory response to overnutrition. This effect can activate sirtuin 1/3 (SIRT1/3), AMP-activated protein kinase (AMPK) and PGC-1α, therefore restoring mitochondrial function and increasing insulin sensitivity in β-cells, liver and muscle, which, in turn, prevents vascular complications [10].

In summary, mitochondrial function depends on their quality control, and an essential characteristic of this quality control is the high level of plasticity in their dynamic structures, which allows them to constantly change by fusion and fission processes [11]. Mitochondrial dysfunction, on the other hand, can play a critical role in the development of type 2 diabetes and insulin resistance-related diseases.

In the present review, mitochondrial fusion and fission dynamics, their alteration in type 2 diabetes, and the targeting of mitochondrial dynamics will be discussed, in addition to the pathophysiological implications of these aspects.

2. Mitochondrial fusion and fission dynamics

During physiological conditions mitochondria undergo morphologic changes in order to adapt to cellular energetic demands. These changes can occur through the continuous cycles of mitochondrial fusion and fission that allow an adequate distribution of mitochondria within the cells. Therefore, mitochondria are not static organelles; they change their shape and location depending on physiological stimuli. Mitochondrial fission produces small individual mitochondria, whereas large interconnected networks of mitochondria are generated through fusion. The morphology of mitochondria varies widely across different cell types; hepatocytes, for example, have small spherical or oval mitochondria, whereas fibroblast mitochondria are long filaments [12,13].

Several dynamin-related GTPases constitute the core machinery of mitochondrial fusion/fission processes. Mitofusin (MFN) 1 and 2 are responsible for outer mitochondrial membrane (OMM) fusion. MFN1 proteins can interact intermitochondrially, tethering two opposing mitochondria through their HR2 domains [14]. As for MFN1, MFN2 proteins interact among themselves, but they also heterooligomerize with MFN1 to promote mitochondrial fusion (Fig. 1) [15]. MFN2 also participates in the physical interaction between endoplasmic reticulum and the mitochondria, which is essential for Ca^{2+} signalling [16]. Whereas mitofusins mediate fusion of the OMM, fusion of the inner mitochondrial membrane (IMM) is orchestrated by optic atrophy 1 (OPA1) protein, which is also involved in maintenance of the mitochondrial cristae structure [17]. On the other hand, fission proteins include dynamin-related protein 1 (DRP1) and fission protein 1 (FIS1). DRP1 molecules assemble into a ring-like structure to constrict mitochondrial membranes in a GTP-dependent manner, while FIS1 is anchored to the OMM and seems to participate in the recruitment of DRP1 through its cytosolic domain [18]. Other OMM proteins that mediate the recruitment of DRP1 are mitochondrial fission factor (MFF) and the mitochondrial dynamic proteins of 49 (MiD49) and 51 kDa (MiD51), the latter two being sufficient to mediate fission in the absence of FIS1 and MFF [19] (Fig. 1).

Fusion and fission processes are essential for the maintenance of important cellular functions such as mitochondrial respiratory activity, mitochondrial DNA (mtDNA) distribution, apoptosis, cell survival or calcium signalling. ATP production is modulated by mitochondrial networks generated by fusion and this pathway is controlled by transmitting the membrane potential from areas of high O_2 availability to those with low availability, thus allowing the dissipation of energy [12]. Whereas this pro-fusion state is typical in situations of increased energy efficiency due to starvation or acute stress, the opposite occurs when cells are subjected to a large nutrient supply such as in obesity or type 2 diabetes. Exposure to an excess nutrient environment promotes mitochondrial fission and decreases mitochondrial fusion, which is related to uncoupled respiration [20]. In addition, mitochondrial fission is crucial for the removal of damaged mitochondria by mitophagy [21], as discussed later.

Therefore, the regulation of mitochondrial dynamics is a complex process involving different dynamin-related GTPases that maintain a balance between mitochondrial fusion and fission. Any alteration of this balance can involve oxidative stress, mitochondrial dysfunction and metabolic alterations, eventually promoting the development of mitochondria-related diseases, such as insulin resistance and type 2 diabetes. In this sense, several studies suggest that genetic ablation of fusion proteins alters glucose homeostasis and promotes insulin resistance and obesity in mice [22,23]. In addition, recent evidence shows that genetic ablation of *Drp1* or *Mfn1* in the liver protects mice against HFD-induced obesity and insulin resistance [24,25]. These findings highlight the important role of mitochondrial dynamics in the regulation of glucose metabolism and insulin signalling, and, in turn, in the development of obesity and type 2 diabetes.

2.1. Mitochondrial dynamics and mitophagy

The maintenance of a healthy mitochondrial population is essential for cell survival. Cells employ the mechanism of autophagy to remove defective organelles and recycle their essential components through their encapsulation by a double-membrane structure known as the autophagosome. In the case of mitochondria, this mechanism is known as mitophagy [26]. The importance of a proper regulation of mitophagy lies in the fact that when a damaged mitochondrion fuses with a healthy one, the result is not a larger healthy organelle, but rather a larger damaged mitochondrion, which could expand the damage by releasing high amounts of ROS [27]. In this sense, mitochondrial fission plays a central role, since mitophagy is preceded by mitochondrial division, which generates individual mitochondrial fragments of manageable size for encapsulation [8] (Fig. 2). To achieve this pro-fission state, the fusion proteins MFN1 and MFN2 are degraded by the ubiquitin proteasome system during the induction of mitophagy, whereas OPA1 is degraded by the IMM zinc metalloprotease OMA1 and AAA proteases [28]. The main orchestrators of the process of mitophagy are (PTEN)-induced putative kinase 1 (PINK1), the ubiquitin ligase PARKIN, ubiquitin and sequestosome-1 (p62/SQSTM1). PINK1 and PARKIN are both indispensable for mitophagy, since loss of any of these proteins results in failure of selective mitochondrial clearance [29]. Upon malfunctioning of a mitochondrion, it suffers a depolarization, which interrupts normal proteolytic processing of PINK1, leading to PINK1 accumulation in the mitochondrion and phosporylation of its targets, which include ubiquitine and PARKIN. Afterwards, PARKIN mediates the ubiquitination of the OMM, tagging it for p62 binding, which is linked to the autophagosomal microtubule-associated protein 1 A/1B-light chain 3 (LC3), leading eventually to the