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Review article

Mitochondrial quality control in the diabetic heart

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ABSTRACT

Diabetes is a well-known risk factor for heart failure. Diabetic heart damage is closely related to mitochondrial dysfunction and increased ROS generation. However, clinical trials have shown no effects of antioxidant therapies on heart failure in diabetic patients, suggesting that simply antagonizing existing ROS by antioxidants is not sufficient to reduce diabetic cardiac injury. A potentially more effective treatment strategy may be to enhance the overall capacity of mitochondrial quality control to maintain a pool of healthy mitochondria that are needed for supporting cardiac contractile function in diabetic patients. Mitochondrial quality is controlled by a number of coordinated mechanisms including mitochondrial fission and fusion, mitophagy and biogenesis. The mitochondrial damage consistently observed in the diabetic hearts indicates a failure of the mitochondrial quality control mechanisms. Recent studies have demonstrated a crucial role for each of these mechanisms in cardiac homeostasis and have begun to interrogate the relative contribution of insufficient mitochondrial quality control to diabetic cardiac injury. In this review, we will present currently available literature that links diabetic heart disease to the dysregulation of major mitochondrial quality control mechanisms. We will discuss the functional roles of these mechanisms in the pathogenesis of diabetic heart disease and their potentials for targeted therapeutical manipulation.

Contents

Abbreviations: ROS, reactive oxygen species; Mfn1/2, mitofusin 1/2; Opa1, optic atrophy 1; Drp1, dynamin-related protein 1; Fis1, mitochondrial fission protein 1; MFF, mitochondrial fission factor; MiD49/51, mitochondrial dynamics proteins 49 and 51; FCCP, p-trifluoromethoxy carbonyl cyanide phenyl hydrazone; PINK1, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; p62, sequestosome 1; HDAC6, histone deacetylase 6; BNIP3, BCL2/adenovirus E1B interacting protein 3; NIX/BNIP3L, BNIP3-like; FUNDC1, FUN14 domain containing 1; BCL2L13, BCL-2-like protein 13; NDP52, nuclear dot protein 52; PPARγ, peroxisome-proliferator-activated receptor γ; PGC-1α, PPARγ co-activator-1α; ERRα, estrogen receptor-related α; NRF1/2, nuclear respiratory factors 1 and 2; mtTFA, mitochondrial transcription factor A; PKA, cyclic AMP-dependent protein kinase; PGAM5, mitochondrial phosphatase phosphoglycerate mutase family member 5; mTOR, mammalian or mechanistic target of rapamycin; ULK, unc-51 like autophagy activating kinase; AMPK, AMP-activated protein kinase; Atg, autophagy-related; AVs, autophagic vacuoles; Vps34, vacuolar protein sorting 34; PI3K, phosphatidylinositol 3-kinase; LC3, microtubule-associated protein 1 light chain 3; STZ, streptozotocin; TOM20, translocase of outer mitochondrial membrane 20; VDAC1, voltage-dependent anion channel 1; Ub, ubiquitin; Ambra1, activating molecule in Beclin1-regulated autophagy; Miro, mitochondrial Rho-GTPase; GFP, green fluorescent protein; RFP, red fluorescent protein; Smurf1, SMAD-specific E3 ubiquitin protein ligase 1; LAMP1, lysosomal-associated membrane protein 1; GABARAP, gamma-aminobutyric acid receptor-associated protein; CK2, Casein kinase 2; Usp30, ubiquitin-specific peptidase 30; CCCP, Carbonyl cyanide m-chlorophenylhydrazone; Nrdp1, neuregulin receptor degradation protein 1; mtDNA, mitochondrial DNA.

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1. Overview

Diabetic heart damage is closely related to mitochondrial dysfunction and increased generation of reactive oxygen species (ROS) [1–6]. Clinical trials have shown that simply antagonizing existing ROS by antioxidants is not sufficient to reduce diabetic heart failure [7–12]. A presumably more effective treatment strategy may be to enhance the overall capacity of mitochondrial quality control to maintain a pool of healthy mitochondria that are needed for supporting cardiac contractile function. Mitochondrial quality control can be performed at multiple points during the mitochondrial life cycle through a group of interrelated inducible processes, ranging from protein folding and ATP production to mitochondrial dynamics and motility as well as mitochondrial degradation and biogenesis.

Mitochondria undergo constant fusion and fission (collectively termed mitochondrial dynamics) to change their shape and size to meet the metabolic demand in a cell. Fusion is controlled by mitofusin 1 (Mfn1), Mfn2 and optic atrophy 1 (Opa1), while fission is controlled by dynamin-related protein 1 (Drp1), mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (MFF), and mitochondrial dynamics proteins 49 (MiD49) and MiD51 [13]. Superfluous or injured mitochondria are removed through autophagy that specifically targets mitochondria for lysosomal elimination, a process termed mitophagy. Mitophagy achieves its selectivity and specificity through a well-established pathway composed of a serine/threonine kinase PINK1(phosphatase and tensin homolog-induced putative kinase 1) and an E3 ubiquitin ligase Parkin. The specificity is also mediated by a number of adaptors or receptors that are found in cytosol or on mitochondrial membranes, including sequestosome 1 (p62), histone deacetylase 6 (HDAC6), BCL2/adenovirus E1B interacting protein 3 (BNIP3), BNIP3-like (BNIP3L or NIX) [14,15], FUN14 domain containing 1 (FUNDC1) [16], BCL-2-like protein 13 (BCL2L13) [17,18], and Optineurin and Nuclear dot protein 52 (NDP52) [19].

Normally tightly coupled to mitophagy, the mitochondrial biogenesis is a process that generates new mitochondria to replenish the mitochondrial pool. The mitochondrial proteins are encoded by both nuclear genome and mitochondrial genome which are synchronized by PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha). PGC-1α is a master regulator that activates and coordinates mitochondrial biogenesis through its effects on multiple transcription factors including PPARγ and PPARα, estrogen receptor-related α (ERRα), nuclear respiratory factors 1 and 2 (NRF1/2), and mitochondrial transcription factor A (mtTFA) [20].

The mitochondrial damage consistently observed in the diabetic heart indicates a failure of the mitochondrial quality control. In this review, we will present currently available literature that links diabetic cardiac injury to the dysregulation of major mitochondrial quality control mechanisms including mitochondrial dynamics, mitophagy and mitochondrial biogenesis. We will discuss the functional roles of these processes in the pathogenesis of diabetic cardiomyopathy and explore their potentials for targeted therapeutical manipulation.

2. Diabetic heart disease and mitochondrial dysfunction

Diabetes is a risk factor for the development of various cardiovascular complications, which constitute the leading causes of death in both type 1 and type 2 diabetic populations. Diabetic patients are prone to heart damage due to multiple diabetes-associated risk factors or processes such as obesity, hypercholesterolemia, atherosclerosis, impaired microcirculation and hypertension. Nevertheless, diabetic cardiomyopathy, a heart muscle-specific disease independent of vascular pathology, also significantly contributes to the increased risk of heart failure and mortality in diabetic patients [1,2]. Thus, cardiac dysfunction in diabetic patients is caused by multiple pathologic mechanisms. Interestingly, all these mechanisms are associated with mitochondrial injury which has been proposed to underlie the pathophysiology of diabetic heart disease [5,6]. Indeed, numerous animal and human studies demonstrate the frequent occurrence of damaged mitochondria in the diabetic hearts [21–27]. Dysfunctional mitochondria can cause more ROS production and release pro-death factors such as cytochrome C, apoptosis-inducing factor, and Smac/DIABLO [26,28–31]. Various ROS scavengers or antioxidants are able to reduce cardiomyocyte death and attenuate diabetic cardiac injury in experimental animal models [4,31–35]. Unfortunately, the antioxidant-based therapies have been generally disappointing in diabetic patients [7–12], suggesting that simply antagonizing existing ROS by antioxidants is not sufficient to reduce diabetic cardiac injury. A potentially more effective treatment strategy may be to enhance the overall capacity of mitochondrial quality control to maintain a pool of healthy mitochondria that are needed for supporting cardiac contractile function in diabetic patients. Presumably, this could be achieved by manipulating and coordinating the major quality control mechanisms to maintain a delicate balance between mitochondrial fusion and fission and a tight coupling between mitochondrial dynamics, mitophagy and biogenesis (Fig. 1).

3. Mitochondrial dynamics in the diabetic heart

Mitochondria in most mammalian cells are highly dynamic organelles that undergo constant fusion and fission to change their shape, size and number to meet the metabolic demand of the cell. Mitochondrial morphology at any given time is determined by the net balance of fission and fusion, which are controlled by a group of dynamin-related large GTPases that include fusion proteins Mfn1, Mfn2 and Opa1 as well as fission protein Drp1 and its receptors Fis1, MFF, MiD49 and MiD51 [13]. Mitochondrial dynamics is vital for mitochondrial function and cell survival, but it is also implicated in apoptosis, necrosis and necroptosis [36,37]. Mitochondrial fusion is mediated by Mfn1/2 in the outer mitochondrial membrane (OMM) and by Opa1 in the inner mitochondrial membrane. Opa1 is processed into several isoforms including the short and long forms (S-Opa1 and L-Opa1). L-Opa1 is located in the inner membrane and is important for stabilizing mitochondrial cristae for efficient mitochondrial respiration [38]. Mitochondrial fusion events allow the mixing of the contents of different