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Mitochondrial dynamics and morphology in beta-cells

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Mitochondrial dynamics contribute to the regulation of mitochondrial shape as well as various mitochondrial functions and quality control. This is of particular interest in the beta-cell because of the key role mitochondria play in the regulation of beta-cell insulin secretion function. Moreover, mitochondrial dysfunction has been suggested to contribute to the development of Type 2 Diabetes. Genetic tools that shift the balance of mitochondrial fusion and fission result in alterations to beta-cell function and viability. Additionally, conditions that induce beta-cell dysfunction, such as exposure to a high nutrient environment, disrupt mitochondrial morphology and dynamics. While it has been shown that mitochondria display a fragmented morphology in islets of diabetic patients and animal models, the mechanism behind this is currently unknown. Here, we review the current literature on mitochondrial morphology and dynamics in the beta-cell as well as some of the unanswered question in this field.

Mitochondrial dynamics

Mitochondria are dynamic organelles that function as heterogeneous networks. They move from one location to another and undergo continuous fusion and fission events, together termed mitochondrial dynamics. As such, this process regulates mitochondrial morphology, number, location, and function.[1,2] Mitochondrial dynamics have been demonstrated to contribute to mitochondrial function in a number of systems including pancreatic beta-cells, muscle, and neurons. It has been established that mitochondrial dynamics can influence various aspects of mitochondrial biology including mitochondrial biogenesis, bioenergetics, heterogeneity and elimination.[3]

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Proteins that regulate mitochondrial fusion and fission have been identified. In mammals, fusion is regulated by at least three mitochondrially localized GTPases: mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy protein 1 (Opa1).[4,5] Mfn1 and Mfn2 are localized to the outer mitochondrial membrane, while OPA1 is an inner mitochondrial membrane protein. Mitochondrial fusion is a two-step process where inner and outer membrane fusion occurs as separate events, with fusion of the outer membranes occurring first, which is subsequently followed by inner membrane fusion. Fission is mediated by the transmembrane protein Fis1 and the cytosolic GTPase dynamin related protein 1 (Drp1/DNM1L); with Fis1 as the rate-limiting factor for fission in some models.[3,6,7] Drp1 translocates from the cytosol to scission sites (Fis1 sites) on the outer mitochondrial membrane to initiate fission events.[8] In addition to Fis1, another outer mitochondrial membrane fission factor has recently been identified, Mff.[9] It is a mitochondrial fission factor that also serves in the recruitment of Drp1 to mitochondria. Mff-dependent mitochondrial fission has been shown to be independent of Fis1.[10] Interestingly, it has been recently shown that contact between mitochondria and endoplasmic reticulum (ER) identifies sites of mitochondrial fission.[11]

Mitochondrial dynamics facilitate the maintenance of a metabolically efficient mitochondrial population and disruption of either fusion or fission alters mitochondrial morphology and functionality. Manipulation of mitochondrial dynamics proteins and the balance between mitochondrial fusion and fission have been shown to contribute to a number of diseases. There is strong evidence correlating the dysfunctional glucose-stimulated insulin secretion (GSIS) in models of type 2 diabetes with mitochondrial dysfunction, including changes in respiratory chain activity.[12–15] Mitochondrial dynamics and morphology have been shown to be regulators of mitochondrial function in a number of cell types.[3] These observations gave rise to the hypothesis that an impaired balance between fusion and fission contribute to the deterioration of beta-cell function in the progression of diabetes. The aim of this review is to examine the current literature describing mitochondrial morphology and dynamics in the beta-cell under normal physiological conditions as well as under high nutrient conditions and in type 2 diabetes. Emphasis will be placed on how changes in the fusion/fission balance disrupt both mitochondrial and beta-cell function. We will also address unanswered question and future directions of study in the field of beta-cell mitochondrial dynamics.

Characteristics of beta-cell mitochondria

Mitochondria are essential for beta-cell function. Mitochondrial metabolism serves to integrate nutrients and generate signals necessary for insulin secretion. The mitochondrial generation of ATP in response to glucose is integral to the downstream closure of ATP-sensitive K^+ channels, consequently leading to plasma membrane depolarization, opening of voltage-gated Ca^{2+} channels, and insulin exocytosis.[16] GSIS occurs in two distinct phases, the first a triggering phase, which is followed by a secondary amplifying phase. Mitochondrial metabolism has been shown to contribute to both phases of insulin secretion.[16,17] Beta-cell lines depleted of mitochondrial DNA (mtDNA) are unable to secrete insulin in response to stimulatory glucose levels.[18] This demonstrated that mitochondria, specifically electron transport chain activity (ETC), are required for normal beta-cell function. The role of mitochondria in the beta-cell can be further appreciated when examining mitochondrial membrane potential ($\Delta\psi_{mt}$) in response to elevated glucose concentrations. Heart et al. demonstrated that beta-cell mitochondria respond to increasing glucose concentrations with a corresponding increase in $\Delta\psi_{mt}$.[19] This increase in $\Delta\psi_{mt}$ is positively correlated with an increase in insulin secretion.

The morphology of beta-cell mitochondria has been characterized in both human and animal islets. Beta-cell mitochondria exhibit tubular networks that vary in size depending on the source of the beta-cells and experimental conditions (i.e. nutrient levels). Park et al. measured mitochondrial length and quantified morphology in primary human pancreatic beta-cells and the rat beta-cell line, INS-1 cells. They observed that in both beta-cell types, mitochondria formed tubular networks throughout the cytosol. The mean length of mitochondria in human beta-cells was measured at 3.5 μm.[20] INS-1 cells were found to have a more elongated mitochondrial network with an average mitochondrial length of approximately 7.5 μm.[20] Molina et al. also found that mitochondria in INS-1 cells exhibited a more tubular network than in primary beta-cells. In that study, mitochondrial length and architecture were examined in primary mouse islets with mitochondrial-targeted photo-activatable GFP (PA-GFPmt),