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Diabetes and Mitochondrial Fission and Fusion Dynamics

Tania Bagga*

Department of Pharmaceutics, DIT University, Dehradun, India

Abstract

Mitochondria are biosynthetic, bioenergetics and signaling organelle that regulates cellular and organism homeostasis in variety of ways. Mitochondrial dysfunction, a high generation of reactive oxygen species (ROS), and low level ATP are all symptoms of type 2 diabetes. Mitofusion-1, 2 and optic atrophy regulate mitochondrial fusion, whereas Mitochondrial fission 1, dynamic related protein 1 and mitochondrial fission regulate mitochondrial fission. PARKIN and PTEN-induced putative Kinase 1 are involved in the mitophagy process. In this review, we discuss about molecular pathways of mitochondrial dynamics in type 2 diabetes.

Keywords: Biosynthetic; Bioenergetics; Mitochondrial fusion; PTEN- induced putative Kinase 1

Introduction

Mitochondria plays a very important role in maintaining cellular energy metabolism, also regulates cell life and death. Membrane bound cell organelles with high plasticity and also involves in dynamic process in mitochondrial fission and fusion, biogenesis. Type 2 diabetes characterized by hyperglycemia, related to oxidative stress. Mitochondrion locates at intersection of critical cellular pathways i.e. Reactive oxygen species (ROS), apoptosis and important source of ROS, also prime spot of ATP production. When glucose levels are high, Mitochondria increase ROS production, causing oxidative stress and tissue damage.

Mitochondrial dysfunction play a role in the development of age related insulin resistance. Mitochondrial biogenesis regulates energy balance and boost productivity. Under hyperglycemia conditions, electron transport cycle produces ROS. Mitochondria playing a important role in insulin resistance and also on type 2 diabetes. For example, Mitochondrial Fission important to repair damaged mitochondrial components, segregation of damaged components via fission process. Proteolysis system and mitochondria derived muscles are the methods for maintaining homeostasis [1].

High glucose level in type 2 diabetes can cause glucose oxidation, thereby production of pyruvate and NADH. ROS also released by mitochondrial complexes I and III. Different antioxidant systems such as superoxide dismutase and uncoupling protein, activated to prevent ROS production and inhibit formation of advanced glycation end products, thereby preventing a chromic proinflammatory state.

Mitochondrial homesick in type 2 diabetes, which decreases ROS production and ATP synthesis in various tissues in response to high glucose level or excess of nutrient intake. Mitochondrial morphological changes are linked to variety of diseases, including neurodegeneration and ageing. Apoptosis followed by mitochondrial fragmentation [2]. The role of mitochondrial fission/fusion in pancreatic cell functions as well as hyperglycaemic consequences. The great amount of plasticity in their dynamic structures, which allows them to constantly change by fusion and fission processes, crucial characteristic of mitochondrial quality control. Mitochondrial malfunction, on the other hand has been linked to the development of type 2 diabetes and insulin resistance.

Mitochondrial Fusion and Fission Dynamics

The dynamic related outer mitochondrial membrane proteins mitofusion1 and 2 form homonymic (MFN1-MFN1 and MFN2-MFN2) or heterotypic (MFN1-MFN2) complexes after close contact between mitochondria established. Mitofusion 1 and 2 are in charge of outer mitochondrial fusion. Inner mitochondrial membrane fusion mediated by ocular atrophy 1 after tethering and dependent on inner membrane potential. By allowing the dilution of superoxide species and altered DNA, as well as repolarization of membrane. Fusion process preserves mitochondrial capacity and metabolic uniformity. Fission which forms one or more daughter mitochondria necessitates the presence of cytosolic dynamic related protein1 [3]. ER membrane linked with mitochondria, these ER mitochondrial interaction sites become important participants in lipid metabolism, calcium signaling, mitochondrial dynamics. At ER interaction locations, mitochondria constriction and division occur. Four localized adaptor proteins, mitochondrial fission factor, mitochondrial dynamics proteins of 49 and 51kDa and fission 1 all recruit DRP1 to mitochondria. DRP 1 hydrolyses GTP and divides mitochondria by constriction.

Mitochondrial Dynamics and Mitophagy

Autophagy is a technique used y cells to eliminate faulty organelles and recycle their vital components by encasing them in a double membrane structure called an autophagosome. Mitophagy is the name given to this mechanism in case of mitochondria. The need of good mitophagy control stems from the fact that when a damaged mitochondrion merges with a healthy one, the outcome is not a larger healthy organelle, but larger damaged mitochondrion which can exacerbate damage by producing enormous level of ROS. Mitophagy is preceded by mitochondrial division, which yields individual mitochondrial fragments of manageable size for encapsulation, hence mitochondrial fission plays important role in this regard [4].

The fusion proteins MFN1 and MFN2 are degraded by ubiquitin proteasome system during mitophagy induction where OPA1 is degraded by IMM zinc metalloprotease OMA1 and AAA proteases to achieve profession state. PTEN induced putative Kinase 1, ubiquitin

***Corresponding author:** Tania Bagga, Department of Pharmaceutics, DIT University, Dehradun, India, Tel: +91 6284623573; E-mail: tv36912150@gmail.com

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ligase PARKIN, ubiquitin and sequestosome1 are major orchestrators of mitophagy. Both PINK1 and PARKIN required for mitophagy, as absence of either of these proteins causes mitochondrial fail. When a mitochondrion malfunctions, it experiences depolarization which disrupts normal PINK1 accumulation in the mitochondrion and phosphorylation of its targets. The OMM is then ubiquitinated, marking it for p62 binding, related to the autophagosome microtubule associated protein 1A/1B light chain, finally leading to mitochondrion being targeted for mitophagy (Figure 1).

Changes in the expression of some of the proteins have an impact on mitochondrial dynamics and mitophagy recycling which can lead to the development of certain illness. Mutations in PARKIN, induce early onset familial Parkinson's disease due to abnormalities in mitophagy and the loss of function of pink1, which causes an extension of mitochondrial filaments in a recessive familial type of Parkinson's disease Both types of genetic mutation cause neuronal changes that contribute to the onset of parkinsonism.

Mitochondrial dynamics in Type 2 diabetes

Hyperglycemia, dyslipidaemia, insulin resistance and abnormalities in pancreatic beta cell insulin production just a few of the clinical consequences of Type 2 diabetes. Hyperglycemia increases the formation of mitochondrial ROS, which is a primary cause of clinical problems. Increased fragmentation is a frequent hallmark of mitochondrial morphology in T2D, which is medicated by activation or up gradation of DRP1 and down regulation of MFN2 levels. HG-induced overproduction of ROS and insulin secretion in human islets were associated to enhanced fission and fragmentation of mitochondria. Most importantly, blocking DRP-1 induced fission prevented both HG-induced ROS and insulin secretion. In liver- specific MFN-2 knockout, defective mitochondrial fusion has been linked to insulin resistance in skeletal muscle as well as glucose intolerance and increased hepatic glucogenesis.MFN2 deficiency resulted in increased ROS generation, JNK activation and the stress response of the endoplasmic reticulum [5]. MFN2 over expression increased insulin sensitivity and decreased insulin sensitivity and decreased lipid intermediates in muscle and liver in ear models. MFN2 expression in the liver in rat models. MFN2 expression in the liver was linked to increased expression of the insulin receptor of the insulin receptor and the glucose transporterGLUT2 as well as activation of the P|3K/AKT2 pathway. Furthermore, T2D dyslipidaemia models demonstrate an increase in mitochondrial fission. In differentiated muscle cells, excess palpitate caused mitochondrial fragmentation and raised mitochondrion associated DRP1 and FS1 levels. PA also caused mitochondrial depolarization, decreased ATP synthesis, increased oxidative dress and inhibited insulin- stimulated glucose absorption. Mitochondria fission is linked to a number of events that lead to atherosclerosis in T2D, including endothelial dysfunction, vascular smooth muscle cell motility and proliferation.

In Type 2 diabetes and its vascular consequences, mitochondrial dynamics are critical. Indeed, mitochondria are master controllers of insulin secretion, and mtDNA alterations have been linked to type 2 diabetes development. In reality, diabetes mellitus and hyper gonadotropic hypogonadism have been linked to a new mutation in MT-ATP6/8 subunits of mitochondrial ATP synthesis. Study showed that this mutation causes mitochondrial ATP synthase assembly to be hindered and ATP generation to be reduced biochemically. Also, mitochondria are a major source of ROS and play a role in cellular apoptosis and cell death (Figure 2).

Discussion

In the schematically depicted Diagram, Mitophagy and mitochondrial fission, Mitophagy is preceded by mitochondrial diving, which produces small enough mitochondrial pieces for encapsulation. When mitochondrion malfunctions, it experiences depolarization which prevents normal PINK1 proteolysis processing, resulting in PINK1 accumulation in the mitochondrion and phosphorylation of its targets, such as PARKIN and ubiquitin. PARKIN then causes ubiquitination of the OMM, marking it for p62 binding, which is related to the autophagosome LC3 protein, resulting in the mitochondrion being targeted for mitophagy [6]. LC3, micro tube- associated protein 1A/1B- light chain 3, p62, ubiquitin- binding protein 62, DRP-1, dynamic- related protein-1,F1S1, fission1 protein1, PINK1,(PTEN)-induced putative kinase 1.

Insulin is produced by β cells and its secretion is primarily influenced by blood glucose levels. In cells, increased glucose stimulates oxidative phosphorylation, raising theta/ADP ratio and blocking K+ channels, which can depolarize the plasma membrane and increase Ca2+ levels inside the cells. This effect causes insulin to be secreted into

The bloodstream in order to keep glucose levels stable. As a result, bioenergetics status of mitochondria influences insulin secretion. Insulin resistance is a prevalent symptom of type 2 diabetes and it has been linked to mitochondrial dysfunction. In the skeletal muscle of insulin resistant patients, an impairment of mitochondrial function and an increase in lipid peroxidation have been observed. Also, type 2 diabetes has been linked to a down regulation of genes involved in mitochondrial biogenesis and oxidative phosphorylation.

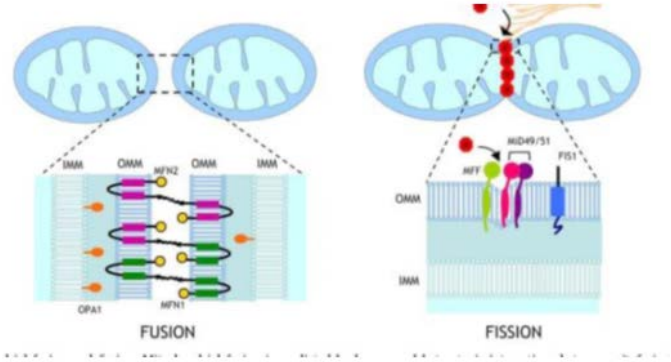

Figure 1: Mitochondrial Fusion and Fission.

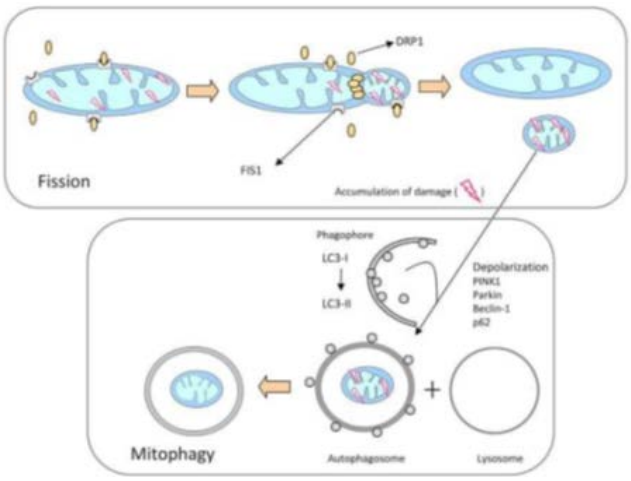

Figure 2: Mitophagy and mitochondrial fission.

Diabetic individuals and animal models have shown changes in mitochondrial structure and size. Type 2 diabetic patients, mitochondria are smaller than healthy controls and hyperglycemia causes mitochondrial fragmentation in a variety of cell types, including the heart, liver, circulatory system [7].

Under hyperglycaemic circumstances, mitochondrial dynamics are linked to ROS generation, In reality, high glucose levels cause the creation of ROS and fragmentation of mitochondria, which is reversed when ROS levels fall, Also mitochondrial changes in mitochondria are an upstream cause of ROS production in the context of high glucose levels, emphasizing the importance of mitochondrial dynamics as a regulator of mitochondrial function. The process by which mitochondrial morphology disrupts ROS in hyperglycemia remains, however, unknown.

Conclusion

Regardless of Body Mass Index, found that type 2 diabetes is linked to mitochondrial dysfunction, increased contraction impairment, and increased cardiac oxidative stress, Type 2 diabetes was linked to myocardial mitochondrial network fragmentation and a significant drop in MFN1 expression. Schultz et al. demonstrated that FIS1 is a crucial regulator in pancreatic cells in another investigation. Also, discovered that both glucose- stimulated insulin secretion and mitochondrial dynamics were clearly tailored to create precise Fission expression levels.

Acknowledgement

None

Conflict of Interest

None

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