Mitochondrial metabolism and diabetes

Soo Heon Kwak[1], Kyong Soo Park[1,2], Ki-Up Lee[3], Hong Kyu Lee[4]*

ABSTRACT

The oversupply of calories and sedentary lifestyle has resulted in a rapid increase of diabetes prevalence worldwide. During the past two decades, lines of evidence suggest that mitochondrial dysfunction plays a key role in the pathophysiology of diabetes. Mitochondria are vital to most of the eukaryotic cells as they provide energy in the form of adenosine triphosphate by oxidative phosphorylation. In addition, mitochondrial function is an integral part of glucose-stimulated insulin secretion in pancreatic β-cells. In the present article, we will briefly review the major functions of mitochondria in regard to energy metabolism, and discuss the genetic and environmental factors causing mitochondrial dysfunction in diabetes. In addition, the pathophysiological role of mitochondrial dysfunction in insulin resistance and β-cell dysfunction are discussed. We argue that mitochondrial dysfunction could be the central defect causing the abnormal glucose metabolism in the diabetic state. A deeper understanding of the role of mitochondria in diabetes will provide us with novel insights in the pathophysiology of diabetes. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00047.x, 2010)

KEY WORDS: Insulin resistance, Mitochondrial dysfunction, Type 2 diabetes mellitus

INTRODUCTION

The global figure of people affected by type 2 diabetes mellitus (T2DM) is estimated to be 220 million in 2010 and 350 million in 2025[1]. In Asian countries, where urbanization is rapidly spreading, the incidence of diabetes has reached an epidemic level[2]. This steep increase in diabetes is associated with an increased prevalence of diabetic complications, such as end-stage renal disease, cardiovascular disease and stroke. Consequently, the socioeconomic burden of the diabetes epidemic is substantial[3]. It is of major concern to better understand the pathogenesis of diabetes and develop new curative and preventive strategies.

Mitochondria are important for adenosine triphosphate (ATP) production, which is vital for all living organisms. Mitochondria are also the key regulator of glucose-stimulated insulin secretion in the pancreatic β-cells[4]. During the past two decades, a growing body of evidence has shown that mitochondrial function is closely related to various facets of diabetes – pancreatic β-cell dysfunction, insulin resistance, obesity and vascular complications of diabetes. In the present article, we briefly review the mitochondrial metabolism and focus on the etiologies of mitochondrial dysfunction and its impact on T2DM.

MITOCHONDRIAL METABOLISM: BRIEF OVERVIEW

Genome and Structure of Mitochondria

Mitochondrion is an intracellular organelle present in most of the eukaryotic cells. One eukaryotic cell contains hundreds of mitochondria[5]. It is assumed that mitochondria were first introduced to proto-eukaryotic cells by the endosymbiosis of bacteria about 2–3 billion years ago[6]. As endosymbiosis matured, mitochondria transferred most of their genes to the nucleus. Following are some characteristics of mitochondria that might help to understand their role in the pathophysiology of diabetes.

Mitochondria have their own DNA and several copies of mitochondrial DNA (mtDNA) are present per mitochondrion[5]. The mtDNA is a circular DNA with 16,569 base pairs[7]. It encodes 37 genes. Thirteen genes are coding for proteins of the electron transport chains and the rest are coding for the two rRNA and the 22 tRNA. In contrast, the majority of proteins regulating mitochondrial structure, metabolic function and biogenesis are encoded by the nuclear DNA (nDNA). For example, the transcription and replication of mtDNA is regulated by the mitochondrial transcription factor A (TFAM), which is encoded by the nDNA[8]. There is complex interplay between the nucleus and the mitochondria to ensure proper functioning of the mitochondria.

A mitochondrion is structurally divided into four compartments: (i) the outer membrane, which is capable of freely transporting ions and small molecules; (ii) the intermembranous space, where protons are accumulated and generate an electrochemical gradient; (iii) the inner membrane, which allows the transport of otherwise impermeable adenosine diphosphate (ADP), phosphate and ATP, and anchors subunit complexes of the electron transport chains; and (iv) the matrix where oxidation of pyruvate and fatty acids occur (Figure 1). The inner membrane has numerous invaginations called the cristae, which gives mitochondria its characteristic morphology. By increasing the surface area, mitochondria can increase the ATP generating capacity.

Mitochondria can change their number, size and activity within a cell through dynamic alteration of biogenesis, fusion and fission[9]. The master switch of mitochondrial biogenesis is

Departments of [1]Internal Medicine and [2]Molecular Medicine and Biopharmaceutical Sciences, Seoul National University College of Medicine, [3]Department of Internal Medicine, University of Ulsan College of Medicine, and [4]Department of Internal Medicine, Eulji University College of Medicine, Seoul, Korea
*Corresponding author. Hong Kyu Lee Tel.: +82-2-970-8458 Fax: +82-2-970-4630
E-mail address: hkleemd@eulji.ac.kr
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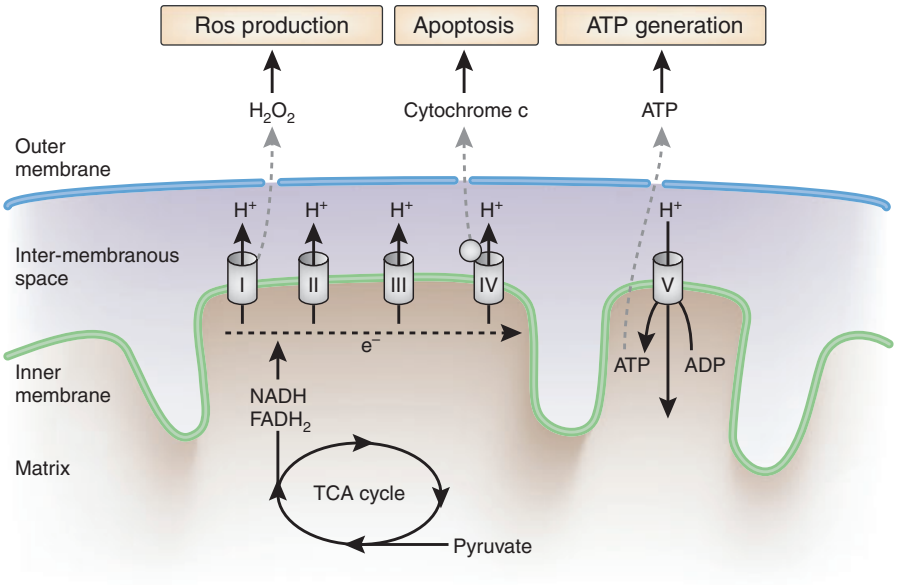

Figure 1 | Major functions of mitochondria. The three major functions of mitochondria in regard to energy metabolism include: (i) adenosine triphosphate (ATP) production; (ii) generation of reactive oxygen species (ROS); and (iii) apoptosis. The NADH and $FADH_2$, which are reducing equivalents yielded from the tricarboxylic acid (TCA) cycle, transfer the electrons to the electron transport chain through complex I and complex II, respectively. As the electrons are transported to complex III and IV, the protons are accumulated in the intermembranous space generating the electrochemical gradient. Complex V uses the proton gradient as the driving force to generate ATP. During the process of electron transport, some of the electrons can be leaked and transferred to O_2, which results in ROS generation. When the cellular ATP is depleted or in excess of ROS, mitochondrial proteins such as cytochrome c, caspases and apoptosis initiating factors are released to cytosol and initiate the process of apoptosis. ADP, adenosine diphosphate.
[Figure replaced after online publication date July 21, 2010]

the peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α and PGC-1β[10]. These are transcriptional coactivators, which activate a number of oxidative phosphorylation genes and TFAM through nuclear respiratory factor (NRF)-1[11]. PGC-1α regulates various aspects of mitochondrial function including biogenesis, adaptive thermogenesis, fatty acid oxidation and peripheral tissue glucose uptake[12]. Finally, it has been recently suggested that maintenance of mitochondrial function and repair depends on mitochondrial remodeling; that is, fusion, fission and autophagy[13]. These unique characteristics in structure and genome allow mitochondria to play a complex action in energy metabolism as well as cell fate determination.

Major Functions of Mitochondria

Adenosine triphosphate production through oxidative phosphorylation, production of reactive oxygen species (ROS) and regulation of apoptosis are the main functions of mitochondria relevant to the pathogenesis of diabetes (Figure 1). Glucose is metabolized by glycolysis to pyruvate and enters mitochondria to undergo a further metabolic pathway of the tricarboxylic acid (TCA) cycle. In contrast, fatty acids enter the mitochondria through carnitine-palmitoyltransferase (CPT)-1 and go through β-oxidation to make acetyl coenzyme A, which are further metabolized in the TCA cycle. The TCA cycle and β-oxidation yield reducing equivalents, such as NADH and $FADH_2$[14]. The electrons from NADH and $FADH_2$ enter the electron transport chain through complex I and complex II, respectively. From these two complexes, electrons are transported sequentially to complex III through the coenzyme Q and then to complex IV through cytochrome c. As the electrons are transported, the free energy released is used to pump the protons into the intermembranous space. The proton gradient formed across the inner membrane creates the electrochemical gradient, which acts as the driving force of ATP generation in complex V (ATP synthase)[14].

Aside from ATP production, mitochondria are the major source of endogenous ROS. When electron transport is impaired in the electron transport chain, it can be transferred to O_2 and generates superoxide. Complex I of the electron transport chain is the predominant site of donating electrons to O_2 and producing superoxide (O_2^-)[15,16]. Superoxide is processed to hydrogen peroxide (H_2O_2) by either superoxide dismutase 1 (SOD1) or 2 (SOD2). The decomposition of hydrogen peroxide to water is carried out by glutathione peroxidase (GPX)-1. However, in the presence of free irons or copper ions, such as in the case of mitochondria, hydrogen peroxide can be transformed to highly reactive hydroxyl radicals (OH^-)[15]. When calorie intake is in excess or the capacity of oxidative phosphorylation is limited, the electron transport is impaired in the electron transport chain and has higher chance of being converted to ROS. These ROS

can damage proteins, lipids and mtDNA of mitochondria and further increase the production of ROS. The mtDNA has no introns and has a poorly equipped repair mechanism, rendering it susceptible to oxidative damage and mutations. The mtDNA mutations accumulate with age, and these mutations might play an important role in the process of senescence and diabetes[6,17].

Mitochondria are also the prime regulators of apoptosis[6]. When confronted with cellular stress, mitochondria open the mitochondrial permeability transition pore (mtPTP)[18]. Opening of the mtPTP allows the release of mitochondrial proteins, such as cytochrome c, caspases and apoptosis initiating factor (AIF), to induce apoptosis. Oversupply of calories or physical inactivity can impair the transfer of electrons through the electron transport chain, leading to increased production of ROS and consequent apoptosis in various cells and tissues[6].

ETIOLOGICAL FACTORS OF MITOCHONDRIAL DYSFUNCTION IN DIABETES

It was only recently that mitochondrial dysfunction was shown to be an etiological factor of diabetes. In the early 1990s, a specific mutation in mtDNA was identified to be causally related to the maternally inherited form of diabetes[19,20]. A few years later, our group reported that the peripheral mtDNA copy number was decreased in subjects with T2DM even before the onset of disease[21]. Shulman *et al.* also have shown that oxidative phosphorylation was decreased in insulin resistant offspring of T2DM patients[22]. In this section, we will discuss the etiological factors of mitochondrial dysfunction in diabetes.

Genetic Factors

mtDNA Mutations

There are more than 20 mtDNA mutations that are associated with diabetes. Among these, the most frequently encountered mtDNA mutation is the A to G replacement at position 3243 (A3243G), which encodes the leucyl-tRNA$^{UUR\ 23}$. The frequency of this mutation in diabetes patients is approximately 1%[24–26]. In Koreans, the prevalence of this mutation in diabetes patients was reported to be 0.5%[27,28]. However, in patients with atypical type 1 diabetes mellitus, who showed insulin deficiency after glucagon stimulation, but had an insulin free period for more than 1 year after diagnosis, the prevalence of this mutation increased to 10%[28]. This mutation can either present as maternally inherited diabetes and deafness (MIDD)[29] or mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome[30]. A recent investigation in a French population reported that the proportion of the mutant mtDNA (heteroplasmy) is associated with age at diagnosis and increased HbA_{1c} level in MIDD patients[31]. The mechanism that links this mutation with the pathogenesis of diabetes is not quite evident yet. Most, but not all, of the studies point out that β-cell dysfunction and impaired insulin secretion is more prominent than the insulin resistance in these patients[32]. It has been shown that A3243G mutation results in decreased oxygen consumption and ATP generation[33] in the cybrid system, where the function of mitochondria carrying mutant mtDNA was studied in a neutral nuclear genomic background[34].

Nuclear DNA Mutations

Maturity onset diabetes of the young (MODY) is a specific subtype of monogenic diabetes that develops as a result of nDNA mutations associated with defects of β-cell function. It is classified into six subtypes according to the genetic defect it harbors. All the subtypes of MODY show impairment of insulin secretory function with autosomal dominant inheritance, and onset at adolescence or early adulthood[35]. Among these, MODY1, MODY3 and MODY4 are suggested to be closely related to mitochondrial dysfunction. *HNF-4α*, the gene mutated in MODY1, is a transcription factor of the nuclear hormone receptor superfamily and plays a role in hepatocyte differentiation[36]. It has been shown that genetic alteration of *HNF-4α* could result in decreased mitochondrial function, such as reduced pyruvate oxidation, decreased ATP generation and blunted glucose-stimulated insulin secretion in pancreatic β-cells[37]. HNF-4α has a close interaction with HNF-1α, which is involved in MODY3[38]. Mutations in the *HNF-1α* gene also showed defective glucose-stimulated insulin secretion, which was explained by decreased ATP generation and increased uncoupling of mitochondrial oxidative phosphorylation[39]. Mutations in *IPF-1* cause MODY4. Recently, it was reported that a deficiency in IPF-1 resulted in mitochondrial dysfunction by down-regulating the expression of *TFAM* in β-cells[40]. All of these examples highlight the contribution of nDNA mutations to mitochondrial function and pathophysiology of diabetes.

Common Genetic Variations That Alter Mitochondrial Function

T2DM is considered to be a polygenic disorder, meaning that multiple genes and environmental factors are in complex interplay. In an effort to find the relationship between mitochondrial function and diabetes, we recently reported that mtDNA 16189 T>C variant and some mtDNA haplogroups are associated with T2DM[41–43]. The mtDNA 16189 T>C variation lies in the control region of mtDNA transcription and replication[44]. We have shown that 16189C variation is associated with an increased risk of T2DM in meta-analysis of data from five Asian countries, including Korea, Japan, Taiwan, Hong Kong and China[43]. However, this association was not replicated in Europeans[45]. This could be attributed to the difference in the frequency of this variation in Asians (31.0%) and Europeans (9.2%) or ethnic difference in the nuclear or mitochondrial genetic background, such as the mitochondrial haplogroup.

The mtDNA haplogroups are geographic region specific variations thought to originate from adaptation to famine and cold[46]. We studied the association of 10 major mtDNA haplogroups with T2DM in large samples of Koreans and Japanese[41]. We noticed that haplogroup N9a was associated with a decreased risk of T2DM in both Korean and Japanese populations. In addition, haplogroup D5 and F were marginally associated with susceptibility to T2DM. Although the functional

characteristics of the N9a haplogroup are largely unknown, it is postulated that it might be associated with an uncoupling phenotype, where ATP generated from the electron transport chain is used for increased heat production[41].

Aside from the variations of the mtDNA, lines of evidence suggest that single nucleotide polymorphisms (SNP) in nuclear genes related to mitochondrial function are associated with T2DM. Among the 18 genes that have been shown to have a robust association with T2DM in recent large scale association studies or genome-wide association studies[47], at least two genes seem to have a close relationship with mitochondrial dysfunction[48,49]. These are *WFS-1* and *HNF-1β*. *WFS-1* is known to be mutated in Wolfram syndrome, which is a rare autosomal recessive disorder exhibiting diabetes insipidus, diabetes mellitus, optic atrophy and deafness[50]. *WFS-1* encodes a transmembrane protein that is localized to endoplasmic reticulum and might affect mitochondrial function through regulating calcium influx[51]. HNF-1β might control mitochondrial function in a similar manner to HNF-1α. However, it is not clear whether or how these polymorphisms alter mitochondrial function and confer risk of T2DM.

Environmental Factors Altering Mitochondrial Function

Obesity

Industrialization and westernization have dramatically changed the Korean lifestyle. Koreans are constantly deprived of physical activity and oversupplied with calories. These have led to an explosion of the obesity epidemic worldwide. It is now well-known that chronic aerobic exercise increases mitochondrial content in muscle, thereby increasing the ATP generating capacity[52]. On the contrary, chronic disuse of muscle decreases mitochondrial content and oxidative capacity leading to impaired glucose utilization[53]. In regard to energy intake, a chronic high fat diet leads to insulin resistance. In a recent report, it has been shown that a high fat diet leads to insulin resistance in rodents and humans mainly by increasing mitochondrial H_2O_2 generation[54]. Blocking H_2O_2 emission from mitochondria by targeting antioxidants to mitochondria or overexpressing catalase resulted in a marked reduction of insulin resistance in the high fat diet-fed state[54].

Intrauterine Malnutrition

Another environmental factor suggested to be linked with mitochondrial dysfunction is intrauterine malnutrition. Poor nutritional status at the fetal and infant stage can permanently alter glucose-insulin metabolism and increase susceptibility to T2DM. This 'thrifty phenotype' hypothesis was first proposed by Hales and Barker[55]. Since then, our group has investigated the role of mitochondria dysfunction as the link between protein malnutrition and T2DM[56]. We reported that liver and skeletal muscle mtDNA content was decreased in fetal and early postnatal malnourished rats, even when proper nutrition was supplied after weaning[57]. In addition, we found that protein malnutrition during fetal life resulted in decreased pancreatic β-cell mtDNA content, impaired β-cell development and impaired insulin secretion[58]. The mechanism of decreased mtDNA content during fetal malnutrition is not well understood. However, low taurine levels, low levels of methyl-donors, depletion of the nucleotide pool, and increased ROS might be the contributing factors of poor mitochondrial function[56].

Environmental Pollutants

In a certain sense, environmental pollutants, such as persistent organic pollutants (POPs) are the true environmental factor causing mitochondrial dysfunction leading to T2DM. POPs are organic compounds with characteristics of long-term persistence in the environment and bioaccumulation through the food chain[59]. The hypothesis that POPs could be the causative agent of the increasing epidemic of T2DM stemmed from the finding that serum γ-glutamyltransferase (GGT) activity is associated with T2DM, even within the normal range[60]. It has been shown that exposure to xenobiotics, including POPs, can increase the activity of GGT[61]. The most notable finding was derived from the National Health and Nutrition Examination Survey (NHANEs) dataset. By measuring the serum concentration of POPs, it was shown that there was a strong dose-response relationship between the prevalence of T2DM and the concentration of POPs[62]. Because most of the POPs are well known for their ability to inhibit mitochondrial oxidative capacity, it is suggested that mitochondrial dysfunction might be mediating these effects[63]. In accordance with this hypothesis, we have recently shown in an animal study that chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance[64]. A recent report also showed that dioxin caused depletion of mtDNA along with mitochondrial dysfunction[65].

PATHOPHYSIOLOGICAL ROLES OF MITOCHONDRIAL DYSFUNCTION IN T2DM

As described above, mitochondria play a key role in skeletal muscle oxidative phosphorylation and β-cell insulin secretion. In this section, we will discuss the pathophysiological mechanism(s) of how mitochondrial dysfunction is related to insulin resistance and β-cell dysfunction.

Insulin Resistance

Decreased mtDNA Copy Number

From the late 1990s, our group has claimed that mitochondrial dysfunction is a causative factor of insulin resistance in T2DM. To prove this hypothesis, we studied the association of peripheral blood cell mtDNA copy number with risk of T2DM and various metabolic phenotypes. In a population-based prospective cohort, we found that mtDNA copy number in peripheral blood leukocytes was significantly decreased in subjects who were converted to T2DM during a 2-year follow-up period[21]. In another cohort, we found that mtDNA copy number was also significantly associated with insulin sensitivity in non-diabetic offspring of T2DM patients[66]. Furthermore, we found that the mtDNA copy number was inversely associated with waist-to-hip

circumference ratio, blood pressure and fasting glucose[21]. Unfortunately, these findings were not always replicated in different populations[67,68]. One of the main critiques to our findings was that mtDNA copy number in peripheral blood cells might not reflect the mitochondrial function in insulin target cells.

Decreased Oxidative Phosphorylation

Shulman *et al.* proved a similar hypothesis using nuclear magnetic resonance spectroscopy studies[22,69]. First, they showed that an age-related decline in insulin sensitivity was associated with a 40% reduction in mitochondrial oxidative phosphorylation, and increased intramyocellular and intrahepatic fat accumulation[69]. Then, similar methods were used to compare the insulin sensitivity of muscle and liver in the insulin-resistant offspring of T2DM patients compared with insulin sensitive controls[22]. There was an approximately 60% decrease in insulin-stimulated glucose uptake in the muscle of insulin resistant subjects. This was associated with an 80% increase in intramyocellular fat content. Most importantly, there was an approximately 30% decrease in mitochondrial oxidative phosphorylation in the insulin resistant subjects[22]. These data strongly suggest that mitochondrial dysfunction could be an important mechanism of the insulin resistance in these subjects. Their findings were concordant with our previous report showing skeletal muscle lipolysis was decreased in high fat-fed mouse models[70,71]. Further supporting evidence that mitochondrial dysfunction is the cause of insulin resistance came from transcriptional profiling studies[72,73]. By using microarray gene expression chips, it was reported that genes involved in mitochondrial oxidative phosphorylation were coordinately down regulated in T2DM as a result of decreased *PGC-1α* expression[72,73].

Molecules Linking Mitochondrial Dysfunction to Insulin Resistance

Derivatives of fat, such as long-chain acyl-CoA (LCAC), diacylglycerols (DAG) and ceramides, mediate mitochondrial dysfunction to insulin resistance. Decreased mitochondrial fatty acid oxidation increases cytosolic LCAC, a potent inhibitor of glycogen synthase and hexokinase, and leads to insulin resistance[71]. In addition, the increased LCAC is diverted to diacylglycerols and ceramides, which are well-known for their ability to increase insulin resistance[74,75].

In a diabetes-prone obese rat model, we reported that AMPK was significantly decreased compared with normal controls[76]. AMPK is a cellular energy gauge that senses the AMP/ATP ratio[77]. Its activation inhibits acetyl-CoA carboxylase[78], therefore decreasing fatty acid synthesis in the liver and increasing fatty acid oxidation in the muscle. Interestingly, AMPK can increase the expression of *PGC-1α* and the consequent pathway of mitochondrial biogenesis[79, 80]. In contrast to obesity, physical activity and calorie restriction increase AMPK level and PGC-1α, leading to enhanced insulin sensitivity. Recently, mitofusin protein (MFN)-2 has been shown to mediate the role of PGC-1α on mitochondrial biogenesis[81]. MFN-2 is a mitochondrial membrane protein involved in mitochondrial membrane fusion and metabolism[82]. The role of mitochondrial fusion and fission in the genesis of insulin resistance awaits future research.

Finally, it should be pointed out that several recent studies raised a new possibility that mitochondrial dysfunction is a consequence of insulin resistance, rather than a cause[83–86]. Further research is required to clarify the cause-and-effect relationship between insulin resistance and mitochondrial function.

Pancreatic β-cell Dysfunction

Mitochondria and Insulin Secretion

Patients with diabetes who have mutations in mtDNA or mitochondria related nuclear DNA, largely show impaired pancreatic β-cell insulin secretory function. This is because ATP generated from mitochondria is the key factor that couples the blood glucose level with insulin secretion. When blood glucose enters the pancreatic β-cell, increased ATP/ADP ratio depolarizes the plasma membrane by closing the ATP-sensitive K channel[87]. This leads to a calcium influx by the opening of the voltage-sensitive calcium channel[87]. Increased calcium concentration stimulates the fusion of insulin containing granules with the plasma membrane and consequently leads to insulin secretion[88]. A defective mitochondrial function in any of the above processes can lead to impaired insulin secretion and T2DM.

Mitochondrial Dysfunction in β-cell Failure

Obesity and insulin resistance are well-known predispositions to T2DM. However, not all obese, insulin resistant subjects progress to T2DM. The decrease in β-cell mass and function, known as β-cell failure, is thought to be the triggering factor of this transition. Lines of evidence show that mitochondrial dysfunction is associated with β-cell failure[89]. In our previous study, we showed that in obese diabetes-prone rats, pancreatic β-cell mass is increased at an early age, but then progressively decreased[90]. Isolated islets from cadaveric donors with T2DM showed that individual islets were smaller and contained a reduced proportion of β-cells[91]. In addition, changes in mitochondrial morphology and function in human islets of T2DM, that is, swelling of mitochondria, decreased ATP level and increased uncoupling protein 2 expression[92], suggest the role of mitochondrial dysfunction in the pathogenesis of β-cell failure in T2DM.

Mitochondrial Fusion, Fission and Autophagy

A recent line of evidence highlighted the importance of mitochondria remodeling, that is, fusion, fission and autophagy, in β-cells. Through fusion, intact mitochondria can share solutes, metabolites, mtDNA and electrochemical gradients with damaged mitochondria[82]. The fission event often yields mitochondria with decreased membrane potential and reduced possibility of fusion[93]. Fusion and fission cycling is thought to be a process of segregating dysfunctional mitochondrial and rendering it for autophagy[93]. In mice, β-cell specific deletion

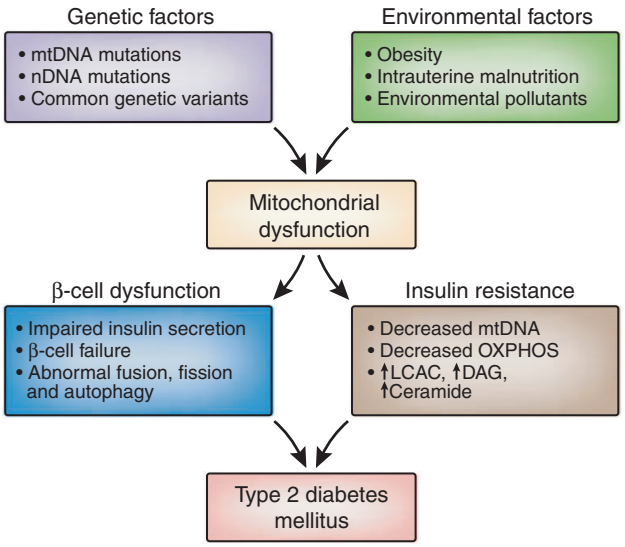

Figure 2 | Relationship between mitochondrial dysfunction and type 2 diabetes. Various genetic and environmental factors can cause mitochondrial dysfunction. Mitochondrial dysfunction is a culprit defect that leads to type 2 diabetes by affecting β-cell dysfunction and insulin resistance. DAG, diacylglycerols; LCAC, long-chain acyl-CoA; OXPHOS, oxidative phosphorylation.
[Figure replaced after online publication date July 21, 2010]

of an autophagy related gene (Atg7) resulted in decreased insulin secretion with mitochondrial abnormalities[94]. Together, fusion, fission and autophagy seem to be an integral part of maintaining homeostasis of β-cell mitochondrial function in T2DM.

Mitochondria as a Therapeutic Target for T2DM

Considering the potential role of mitochondrial function in the pathophysiology of diabetes, it would be of prime interest to increase mitochondrial function in order to prevent or treat diabetes. One of the most extensively proven methods is restricting calories. Calorie restriction is well known to reverse and prevent insulin resistance. SIRT, which are a family of NAD+-dependent deacetylases, play a central role in mediating the effect of calorie restriction on mitochondrial function[95]. In pancreatic β-cells, SIRT1 stimulates insulin secretion and provides defense from oxidative stress[96,97]. SIRT1 activates PGC-1α in muscle and liver to increase mitochondrial biogenesis[98]. It has also been reported that small molecules activating SIRT were able to increase insulin sensitivity and mitochondrial function, mimicking the effects of calorie restriction[99,100].

One of the drugs that improves mitochondrial function is thiazolidinedione (TZD), currently used as an antidiabetic drug. TZD was shown to increase mitochondrial biogenesis[101]. However, there are debates regarding the effect of TZD on mitochondrial function[102]. We have recently studied another interesting drug, alpha-lipoic acid (ALA), which is an essential cofactor of mitochondrial substrates and an anti-oxidant, in diabetes and related metabolic disorders[103]. In the diabetes prone obese rat, ALA prevented the development of diabetes[103], vascular dysfunction[104] and hepatic steatosis by increasing AMPK activity[105]. In addition, we found that ALA reduces food intake and increases energy expenditure by suppressing hypothalamic AMPK activity[106]. As more and more interest is being focused on the role of mitochondria in diabetes, it seems likely that new therapeutic agents targeting mitochondrial function will emerge in a timely manner.

To summarize, we have reviewed the roles of mitochondria in the pathogenesis of diabetes (Figure 2). ATP production, ROS generation and apoptosis are the three main functions of mitochondria. We discussed genetic and environmental factors causing mitochondrial dysfunction and pathophysiological role of mitochondrial dysfunction in T2DM in regard to insulin resistance and β-cell dysfunction. Although there is a growing body of evidence that mitochondrial dysfunction lies at the center of the pathogenesis of insulin resistance and T2DM, a causal relationship should be clarified by future studies. We hope that unraveling the roles of the mitochondria in diabetes will eventually lead us to discover new strategies to prevent and cure diabetes.

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