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REVIEW

Association of mitochondrial dysfunction and lipid metabolism with type 2 diabetes mellitus: A review of literature

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BACKGROUND: Diabetes mellitus (DM) is one of the most prevalent chronic diseases, and its prevalence continues to increase globally. The impact of mitochondrial dysfunction and lipid metabolism on diabetes mellitus and insulin resistance (IR) has been implicated in several previous reports; however, the results of studies are confusing despite four decades of study.
METHODS/RESULTS: This review has evaluated updated understanding of the role of mitochondrial dysfunction and lipid metabolism on type 2 diabetes, and found that mitochondrial dysfunction and lipid metabolism disorder induce the dysregulation of liver and pancreatic beta cells, insulin resistance, and type 2 diabetes.
CONCLUSION: Mitochondrial dysfunction and lipid metabolism induce metabolic dysregulation and finally increasing the possibility of diabetes.

Keywords Insulin resistance, Type 2 diabetes, Mitochondrial dysfunction, Lipid metabolism

Introduction

Mitochondrial dysfunction is associated with the pathogenesis of metabolic disorders because abnormal mitochondrial function can lead to insulin resistance and lipid accumulation. To decrease the damage from reactive oxygen species (ROS), there should be a balance between mitochondrial synthesis of ATP through oxidative phosphorylation (OXPHOS) and degradation of the proton gradient.

Mitochondria are cellular organelles derived from aerobic bacteria as their ancestral cells (Ferla et al., 2013). Following integration of aerobic bacteria, the mitochondria evolved and to a great extent shared similar characteristics with bacteria, including a double cellular membrane which delimitates four different compartments: Outer Mitochondrial Membrane (OMM), Inner Mitochondrial Space (IMS), Inner Mitochondrial Membrane (IMM) and Mitochondrial Matrix (MM). IMM surrounds the MM in which major metabolic reactions take place and mitochondrial electron transfer chain (ETC) is located. This chain is formed by four different protein complexes (I, II, III and IV) that allow protons to pass across IMS to generate a proton gradient. Finally, ATP synthase or complex V uses the proton gradient to catalyze the formation of ATP (Freund-Michel et al., 2014; Koob and Reichert, 2014; Shaikh et al., 2014; Frohman, 2015; Vyssokikhet al., 2015; Zhong and Yin, 2015; Patwardhan et al., 2016). Therefore, mitochondria play an essential role in energy production through the oxidative phosphorylation pathway where the beneficial conversion of nutrients arises in the form of adenosine triphosphate (ATP). This feature powers many activities within the cells. In addition, mitochondria have been implicated in various physiologic processes, including cell signaling and cell death, production of reactive oxygen species (ROS), steroidogenesis, pyrimidine biosynthesis, lipid biosynthesis, cellular level regulation of different substrates such as amino acids, metabolites, enzyme cofactors, apoptosis regulation, metal metabolism (Fe–S cluster and heme), calcium flux and homeostasis, neurotransmitter synthesis, heat production, and insulin secretion regulation (Freund-Michel et al., 2014; Munday et al., 2014; Song et al., 2014; Garcia de la Garma et al., 2015; Morgan et al., 2015).

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Overeating and a sedentary life style decrease the combustion of food components in the mitochondria. This excess food in the body is converted to triglyceride and stored in adipocytes, muscle and liver (Yki‐Järvinen, 2005). The change in the metabolism and storage of fats is an important predisposing factor for insulin resistance and type 2 of diabetes. A study showed that the diabetes is developed during early age in patients with congenital monodystrophy, in which the synthesis and storage of triglycerides in the adipocytes is disturbed (Javor et al., 2005). Other studies revealed that protease inhibitors and nucleoside analogs cause partial lipodystrophy and damage the mitochondrial DNA (mtDNA) replication during antiretroviral therapy and result in the development of type 2 diabetes. In addition, epidemiological studies have revealed a particularly strong relationship between hepatic accumulation of fat and the development of whole-body insulin resistance (Yki-Jarvinen and Westerbacka, 2005). The mutation in mtDNA causes intracellular triglyceride droplets in patients and decreases beta-oxidation (Narbonne et al., 2004), which may increase the redistribution of body fat to lipoma (Suzuki et al., 2004). Several of these mutations are recognized to be associated with the diabetes (Maassen et al., 2005). Although scientists have classified diverse abnormalities in multiple tissues and the secondary consequences of established hyperglycemia and hyperlipidemia, it is challenging to recognize and classify the primary events that lead to the development of diabetes. To address these difficulties, it is crucial not only to define the abnormalities associated with established disease but also to classify the preceding and underlying metabolic characteristics. Therefore, herein we discuss the association of mitochondrial dysfunction and lipid metabolism with diabetes (Fig. 1).

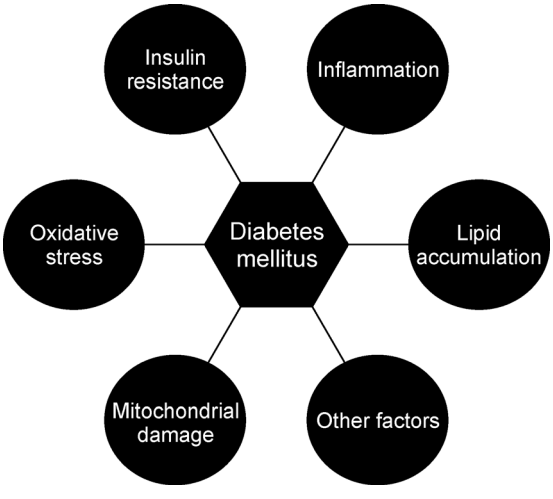

Figure 1 Diabetes mellitus pathogenesis. This disease has many pathogenesis aspects. In this literature, the association of mitochondrial dysfunction and lipid metabolism with diabetes have been reviewed.

Mitochondrial function

Formation of ATP requires two major steps: oxidation of NADH (or $FADH_2$) and phosphorylation of ADP to form ATP (oxidative phosphorylation, OXPHOS). These two reactions are coupled in mitochondria and OXPHOS is an efficient and cost-effective way of producing energy in aerobic organisms. The energy obtained from a proton gradient across the membrane is used to drive the synthesis of ATP from ADP (Venediktova et al., 2013; Antos-Krzeminska and Jarmuszkiewicz, 2014; Forkink et al., 2014; Genova and Lenaz, 2014). Furthermore, mitochondria generate heat through a mechanism called “proton leak.” Proton leak from the inter membrane space to matrix reduces proton-motive force and generates heat instead of ATP. The proton leak is a catalytic property of specific molecules termed uncoupling proteins (UCPs) that regulates both heat and Reactive Oxygen Species (ROS). UCPs belong to the mitochondrial anion carrier protein family, which are located in the mitochondrial inner membrane. Mammals have five UCP homologs. Based on genetic association studies, UCP2, UCP3, or both are reportedly associated with obesity, insulin resistance, type 2 diabetes mellitus and metabolic syndrome in humans (Udagawa et al., 2014).

Mitochondria and Metabolism

In mammalian cells, glucose, free fatty acids (FFAs) and glutamine are the three major fuels (Obre and Rossignol, 2015; Salerno et al., 2015) that are oxidized completely by several enzymatic reactions in mitochondria. Therefore, mitochondria have always been considered as important organelles in the regulation of cellular metabolism (Kuhn et al., 2015) since many processes such as β-oxidation of free fatty acids, ketogenesis, glutaminolysis and catabolism of branched chain amino acids (BCAA) take place in the mitochondria (Czibiket al., 2014; Yu et al., 2014; Lian et al., 2015).

β-oxidation of FFAs is a stepwise repetitive and alternative chain reaction which splits long carbon chains of fatty acids into acetyl-CoA by various tissues primarily in adipocytes in response to energy demands (Gogga et al., 2011). FFAs are activated to their coenzyme A (CoA) esters in the cytosol through a conversion process which is followed by transportation of long-chain fatty-acyl-CoA across the mitochondrial membrane. After being imported by the carnitine acyl-carnitine translocase system (Kathirvel et al., 2013), four separate enzymatic reactions of β-oxidation result in the removal of two carbons in terms of acetyl-CoA. These processes are repeated until the total fatty acid is converted to acetyl-CoA. Furthermore, glycolysis is the primary source of pyruvate production in the cytosol. In aerobic metabolism, pyruvate is imported into the mitochondria to be converted into acetyl-CoA. In essence, pyruvate and fatty acids are

transported from the cytosol into mitochondria and converted to acetyl-CoA to produce cholesterol or other lipids through lipogenesis, or to feed other metabolic pathways such as Krebs (tricarboxylic acid) cycle (Camoes et al., 2015). TCA cycle is a fundamental metabolic pathway of complete acetyl-CoA oxidation and an important hub for the biogenesis of building blocks used in gluconeogenesis, as well as amino acid and fatty acid anabolism. In the Krebs cycle, all the enzymes (other than succinate dehydrogenase that is tightly bound to the inner mitochondrial membrane) are found in the mitochondrial matrix. During the conversion of pyruvate to acetyl-CoA, carbon dioxide (CO_2) is a byproduct and NADH and $FADH_2$ are produced as the electron carriers. NADH is a product of both glycolysis and Krebs cycle while $FADH_2$ is only produced in Krebs cycle. Given the close proximity between TCA cycle and the oxidative phosphorylation system (electron transport), each NADH and $FADH_2$ molecule is fed into that pathway as an important source of energy that is used to generate ATP. It is noteworthy that the TCA cycle is overloaded through excessive production of acetyl-CoA from the β-oxidation, resulting in its conversion to create ketone bodies. In conditions where glucose levels are too low, the ketone bodies can serve as a fuel in times of starvation or in an uncontrolled diabetic situation when a patient cannot utilize most of the circulating glucose. In such cases, the stored fat is liberated to generate energy through the TCAs cycle, but the ketone bodies are generated in response to over accumulation of acetyl-CoA. Hence, these ketone bodies can be imported into the mitochondria of the peripheral tissues where they are degraded into acetyl-CoA to replenish the TCA cycle (Fatland et al., 2002; Hiltunenet al., 2010; Hynes and Murray, 2010; Kathirvel et al., 2013; Chen et al., 2014; Demine et al., 2014; Fukao et al., 2014; Lian et al., 2014; Ng and Tang, 2014; Smiljanic et al., 2014; Wang et al., 2014; Krivoruchko et al., 2015).

Acetyl-CoA: A crossroads compound

Another fate of acetyl-CoA is its application in cholesterol synthesis and lipogenesis (Wang et al., 2014). In fact, acetyl-CoA is utilized for biosynthesis of cholesterol as a fundamental lipid in a complicated way within the endoplasmic reticulum of hepatic cells. Mitochondria, however, are considered cholesterol-poor organelles and obtain their cholesterol from extra mitochondrial sources and trafficking within mitochondrial membranes. Mitochondria participate in steroid synthesis in terms of steroidogenesis. Anyhow, mitochondrial cholesterol has a central role in synthesis of bile acids in the liver or in the formation of steroid hormones in specialized tissues using cholesterol of different origins (Fatland et al., 2002; Hiltunen et al., 2010; Hynes and Murray, 2010; Lian et al., 2014; Zhu et al., 2014; Zhu et al., 2014; Krivoruchko et al., 2015). Moreover, acetyl-CoA has the potential to convert back to fatty acid in a sequence of several chemical reactions during a lipid formation process known as lipogenesis for subsequent storage. Various studies have proclaimed the mitochondrial ability to elongate short-chain fatty acids from acetyl-CoA precursors through a complex of enzymes known as fatty acid synthase (FAS). The mitochondrial type of FAS pathway is composed of a set of monofunctional enzymes similar to the bacterial FAS II system, which contrasts with that of the eukaryotic cytosolic multifunction. Characterization of eukaryotic cells in the dual localization of fatty acid synthesis (FAS) is indicative of the fact that they have maintained FAS in the mitochondria in addition to the "classic" cytoplasmic FAS (FAS I) (Hiltunen et al., 2010). The recently identified glutaminolysis draws our attention to another dimension of mitochondrial metabolic function of energy production by glutamine degradation. Apart from the role of glutamine in protein synthesis, the production of αKG from glutamine via double deamination of glutamate leads to α-ketoglutarate production, which is critical to replenish the tricarboxylic acid (TCA) cycle to sustain ATP levels in order to feed the TCA cycle. Interestingly, α-ketoglutarate can also be reduced to acetyl-CoA by isocitrate dehydrogenase-1 to proceed lipogenesis (Demine et al., 2014). The importance of these processes becomes evident when the lack of glutamine completely prevents cell growth (Pan et al., 2015).Under hypoxia conditions, for instance, glutaminolysis seems to be functional for cell growth, as lipogenesis seems to rely exclusively on this pathway (Carey et al., 2014; Demine et al., 2014; Carey et al., 2015).Additionally, there are three hydrophobic branched amino acids of Valine, Leucine and Isoleucine (BCAAs), the metabolism of which is coordinated with mitochondria. Branched-chain alpha-keto acid dehydrogenase complex (BCKDC) converts these three essential amino acids into acyl-CoA derivatives in humans, which finally results in the generation of either acetyl-CoA or succinyl-CoA that enter the TCA cycle. Although the metabolic disorders affecting the branched-chain amino acids lead to branched-chain ketoaciduria or maple syrup urine disease (MSUD), recent studies have shown that the impaired BCAA metabolism might occur in obesity (Lynch and Adams, 2014). However, the role of BCAAs in controlling the metabolism of carbohydrates cannot be ignored. To confirm this issue, Kadota et al. showed that BCAAs increase glucose uptake as one of the core contributors to glucose metabolism in rat skeletal muscles. These results suggest that plasma BCAAs play an important role in maintaining normal glucose tolerance in rats (Kadota et al., 2012).

Mitochondrial dysfunction and epigenetics

The term epigenetics refers to heritable changes in the expression of active versus inactive genes without any change to the underlying DNA sequence, which means a change in phenotype without a change in genotype. Although epige-

netic change is a regular and natural occurrence, it can be influenced by several factors including age, lifestyle, environment, and diseases. Epigenetic modifications can manifest as commonly as the manner in which the cells terminally differentiate to end up as skin, liver, brain and other cells, or have more damaging effects that can lead to diseases like cancer. At least three systems, including DNA methylation, non-coding RNA (ncRNA)-associated gene silencing, histone modification (acetylation, phosphorylation, sumoylation, ADP ribosylation and ubiquitination) are currently considered to initiate and sustain epigenetic changes. Continuously, new expectations and ongoing areas of research are unveiling the role of epigenetics in a variety of human disorders and fatal diseases (Egger et al., 2004).Over the last two decades, the mutation of mitochondrial DNA (mtDNA) has held a prominent place as a major cause of inherited human diseases. mtDNA is maternally inherited and has a very high mutation rate. Here, in this part of review, the potential role of epigenetic factors in the pathogenesis of mtDNA diseases will be discussed. According to the emerging evidences, mitochondria contain the machinery required to epigenetically modify mtDNA expression. In addition, the increased production of reactive oxygen species seen in several mtDNA diseases could lead to epigenetic modification of the nuclear genome, including chromatin remodeling, alterations to DNA methylation and microRNA expression. These observations could offer a glimmer of hope to investigate the role of mtDNA methylation in human diseases (Chinnery et al., 2012). Physiologically, the alteration of gene expression has various outcomes; for example, it contributes to the onset and progression of obesity, type 2 diabetes and their complications. Various studies have shown the profound role of high-fat diets in epigenome alteration which results in obesity and type 2 diabetes. Interestingly, maternal obesity and a high fat diet change DNA methylation patterns and histone modifications in utero and would increase the offspring's susceptibility to obesity (Dudley et al., 2011; Suter et al., 2011; Jacobsen et al., 2012; Ge et al., 2014). Likewise, Khalyfa et al. have shown that a high fat diet could change DNA methylation patterns in insulin sensitive patients (Khalyfa et al., 2013). However, when compared to lean individuals, different patterns of DNA methylation can be observed in skeletal muscles of obese and diabetic patients. These epigenetic modifications occur in association with altered skeletal muscle mitochondrial beta-oxidation and mitochondrial number. In insulin sensitivity, exercise can change epigenetic modifications by advancement of adiposity and mitochondrial function. Remarkably, the genes that are epigenetically regulated by fatty acids and exercise are also important regulators of mitochondrial adaptations. Collectively, skeletal muscle mitochondrial adaptations which contribute to lipid metabolism by the regulation of fatty acid oxidation may be epigenetically regulated by diet and exercise (Taylor et al., 2014).

Fatty acids and epigenetic regulation

Several studies have shown the important role of short-chain fatty acids in mitochondrial epigenetic regulation of gene expression as inhibitors of the histone deacetylase (HDAC) and as transformers of DNA methylation patterns. Butyrate, acetate, propionate, valerate and caproate are the typically short- chain fatty acids which have the ability to inhibit HDAC. In addition to short- chain fatty acids, other metabolic byproducts, such as pyruvate and lactate, can inhibit HDAC activity to epigenetically regulate gene expression. More recently, short-chain fatty acids like butyrate have been shown to act as anti-obesogenic and anti-diabetic agents. The anti-obesogenic and anti-diabetic effects of these short-chain fatty acids may be due partially to the upregulation of mitochondrial function, and more specifically to the upregulation of skeletal muscle's mitochondrial fatty acid oxidation and energy expenditure. Butyrate, acetate, propionate, valerate, and capropate have all been shown to inhibit HDAC, thereby enabling the hyperacetylation of core histone proteins (Taylor et al., 2014). Zheng et al. study on animal models and cell cultures has demonstrated that an improper amount of glucose and lipid, as well as impaired insulin signaling might lead to mitochondrial alteration. Nevertheless, molecular mechanisms of mitochondrial alterations unfortunately remain unexplored in human subjects (Dudley et al., 2011).

We will now explain four key metabolic regulators in the alteration of gene expression, namely PGC1, FOXO, SIRT-1 and PTP1B and discuss their effects on mitochondrial function, diabetic and insulin resistance in more detail.

Key metabolic regulators in alteration of gene expression of PGC-1

Peroxisome proliferator activated receptor gamma co-activator alpha (PGC-1α) was recently identified in a yeast. It interacts with PPARγ transcription factor and regulates the genes involved in energy metabolism during mitochondrial biogenesis and function. This protein is a transcriptional co-activator which strongly coordinates gene expression. PGC-1α has different functions. In brown fat tissue, it stimulates mitochondrial oxidative metabolism, in skeletal muscle, it switches fiber-type, and finally in liver, PGC-1α is involved in multiple aspects of the fasting response (Aguirre-Rueda et al., 2015; Shokouhi et al., 2015). Another remarkable role of PGC-1α in brown fat is PPARγ co-activation for powerful induction of uncoupling protein 1 (UCP1) (Carey et al., 2014). Another member of the family, PGC- 1β,was identified later based on sequence homology to PGC-1α (Villena, 2014). PGC-1α plays a central role in a variety of tissues by inducing a core program of mitochondrial biogenesis and oxidative phosphorylation (OXPHOS) (Laafi et al., 2014). Obviously, decreased levels of PGC-1α mRNA have been

verified in fat tissues of individuals with obesity and type 2 diabetes. Finally, PGC-1 α could be a target for anti-obesity or diabetes drugs according to its controlling role for energy homeostasis (Zhao et al., 2014).

FOXO

The forkhead box O (FoxO) transcription factor family members are important targets of the phosphatidylinositol 3-kinase/Akt pathway, which is a chief protein in downstream of insulin and insulin-like growth factor receptors that have been conserved in an evolutionary pathway. The mammalian FoxO family, including FoxO1, 3, 4 and 6, are highly similar in terms of structure, function and regulation. These proteins are involved in diverse physiologic and cellular mechanisms, including apoptosis response, proliferation, differentiation, longevity, cancer and regulation of cell cycle, metabolism and response to oxidative stress (Tzivion et al., 2011; Ferber et al., 2012). FoxO1, for example, is the most abundant isoform in different tissues like liver, adipose tissue and pancreatic beta cells, which is considered as a hepatic regulator of glucose and lipid production (Bandyopadhyay et al., 2015). In addition, FOXOs have been noted to have tumor suppressor function and are important for stem cell maintenance. For instance, FoxO1 was found to suppress the expression of genes involved in lipogenesis, including SREBP-1c, in the liver (Bose et al., 2014). Recent studies have suggested that FoxO1 may simultaneously regulate lipid metabolism (Cook et al., 2015).

SIRT-1

Sirtuins, silent information regulator 2 (Sir2) proteins, are an ancient but phylogenetically conserved family of nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases/ADP-ribosyltransferases. Currently, Sirtuins are classified as class III histone deacetylases (HDACs). At least seven Sirt2 homologs (Sirt1-7) have been introduced in mammalian cells. They regulate DNA repair and recombination, chromosomal stability, gene transcription, and most importantly mediate the health-promoting effects of caloric restriction (CR), which includes the retardation of aging. Mammalian Sirt1, the best-studied family member, is expressed throughout the body. It is known that Sirt1 plays an essential role in different biological processes encompassing metabolism, oxidative stress, cellular proliferation, cellular aging, endothelial functions and genomic stability. It also connects both cellular energy and redox states to multiple signaling and survival pathways. However, sirtuins increase resistance to metabolic, oxidative and hypoxic stress in different tissues according to cell type and context-specific activation (Harijith et al., 2014; Pillai et al., 2014; Roth and Chen, 2014; Stefanowicz et al., 2015). By virtue of its activity on insulin sensitivity, Sirt1 is considered to be closely connected to the development of T2DM. Wang et al. expressed that Sirt1 protein was remarkably decreased in insulin-resistant cells. Apart from this, they have shown that reduced Sirt1 level in the gastrocnemius muscle of mice results in glucose intolerance (Wang et al., 2015). Among its various functions, Sirt1 has been shown to be involved in fat metabolism and obesity. Adipose tissues of obese mice express only low levels of Sirt1. Significantly, the loss of Sirt1 in white adipose cells will induce the impairment of fatty acid mobilization (Ka et al., 2015). Recent researches have shown that Sirt1 levels in rodents will be increased in fat tissues in response to fasting and calorie restriction (CR) (Shin et al., 2014).

PTP1B (Protein tyrosine phosphatases1B)

Protein tyrosine phosphatases are a large family of enzymes that have a major role in many cellular functions. PTP1B is a negative regulator of the insulin-signaling pathway and is considered as a promising therapeutic target in the treatment of diabetes (Bakhtiyari et al., 2010).This enzyme is extensively expressed in insulin-sensitive tissues (Goldstein, 1993). In vitro studies have shown that PTP1B binds to insulin receptor and dephosphorylates it efficiently. In vivo and in vitro studies have shown that changes in the expression of PTP1B are able to induce or prevent insulin resistance in muscle, adipose and liver tissues (Elchebly et al., 1999; Dadke et al., 2000; Klaman et al., 2000; Zabolotny et al., 2004; Nieto-Vazquez et al., 2007). A recent study has reported that the hydrodynamic injection of PTP1B-shRNA, but not the scrambled shRNA plasmid, has triggered PTP1B expression and reduced its levels by up to 84% in the liver of the diabetic mice. Remarkably, plasma glucose levels remained significantly lower in the diabetic mice for five consecutive days following the injection of PTP1B-shRNA (Vakili et al., 2013). Particularly, the obese insulin-resistant and diabetic patients have demonstrated a higher expression and activity of PTP1B in their muscle and adipose tissues (Johnson et al., 2002). Besides, whole-body knockout studies of protein tyrosine phosphatase 1B (PTP1B) in mice showed that PTP1B is a major regulator of insulin sensitivity and bodyweight (Lees et al., 2015). PTP1B deficiency also has been shown to protect against Fas-induced hepatic failure (Ding et al., 2014). Moreover, PTP1B overexpression was demonstrated to induce insulin resistance (Taheripak et al., 2013) while the defective PTP1B synthesis differentiated brown adipocytes into chemical-induced endoplasmic reticulum stress (Bettaieb et al., 2012). Obviously, the tissue-specific overexpression of PTP1B in the liver and muscle has been shown to lead to a defect in insulin signaling, resulting in systemic insulin resistance in mice (Haj et al., 2005; Delibegovic et al., 2007). Furthermore, genetic variations of the PTP1B gene have been reported to be associated with

insulin resistance, type 2 diabetes and hypertension in some studies (Meshkani et al., 2007; Meshkani et al., 2007; Gu et al., 2010). Mitochondrial disease or dysfunction is an energy production problem. All cells in the body (except RBCs) have mitochondria that produce a body's essential energy (in other words, they are power plants of cells).When the power plants of the cells do not work properly, some of the body's processes will not work normally. Mitochondrial diseases are a clinically heterogeneous group of disorders emerging because of the dysfunction in mitochondrial respiratory chain. Mutation of the genes encoded by either nuclear or mitochondrial DNA (mtDNA) can cause mitochondrial dysfunction. While some mitochondrial disorders just influence on a single organ, many affect multiple organs and often present with prominent neurologic and myopathic features. According to the variety and importance of mitochondrial functions, aberrant mitochondrial structure and function disrupt the tissue homeostasis and contribute to multiple human disorders. Clinical features of mitochondrial disease include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy and diabetes mellitus. Therefore, damage to mitochondria can have widespread negative consequents (Chinnery, 2014).

Diabetes

When mitochondria produce ATP for cellular energy sources, reactive oxygen species (ROS) are generated as the byproducts of ATP synthesis in mitochondria. In return, overloading of ROS is harmful and can damage mitochondria so that they are no longer functional. The accumulation of ROS would finally lead to cellular degeneration and death (especially in pancreatic beta cells) via DNA fragmentation which subsequently activates the stress pathway (Graham and Adler, 2014). ROS appears to be produced in larger amounts by islets from type 2 diabetes mellitus (T2DM) patients compared to that of non-diabetic subjects (Mizukami et al., 2014). The beta islets of type 2 diabetes subjects exhibit mitochondrial morphologic abnormalities. Hasan NM et al. found a significantly hypertrophic, round-shaped mitochondria with higher density in patients with type 2 diabetes compared to lean controls with elliptical and low density mitochondria (Hasan et al., 2015). Uncoupling protein-2 (UCP2), a regulator of membrane potential in pancreatic beta cells, reduces the mitochondrial membrane potential through facilitating proton trickle that will subsequently diminish the synthesis of ATP. UCP2 also has the ability to downregulate insulin secretion. Intriguingly, mitochondrial ROS overproduction will increase UCP2 activation, which finally results in beta cell dysfunction. In conclusion, the beta cell mass is decreased in type 2 diabetes due to increased beta-cell apoptosis mechanism (Liu et al., 2013).

Insulin resistance

Insulin is a potent regulator of glucose metabolism, which maintains glucose homeostasis in both feeding and fasting states. It is an essential hormone that has various actions. Moreover, insulin directly controls metabolism and regulates the cell growth. Likewise, the association of insulin with cardiovascular, renal and neural functions may elucidate the relationship between insulin resistance with the risk factors for hypertension, cardiovascular disease, nephropathy, retinopathy and neuropathy (Kim et al., 2008). Scientifically, dysfunction of insulin signaling pathway and its crosstalk with other cell signaling pathways leads to insulin resistance. Insulin resistance (IR) is a condition in which the cells become resistant to the effects of insulin, or the ability of cells or tissues to respond to physiologic levels of insulin is diminished. Because the normal response to a given amount of insulin is reduced, higher levels of insulin are needed for proper insulin effects. Therefore, the pancreas fills this gap by producing more and more insulin until it can no longer produce sufficient insulin for the body's demands, and the blood sugar levels are thus increased. Actually, the syndromes of insulin resistance make up an extensive clinical spectrum, including obesity, glucose intolerance, diabetes and the metabolic syndrome, which is likewise an extreme insulin-resistant state. Various endocrine and metabolic disorders, immunological diseases, as well as genetic and environmental factors including aging, obesity, lack of exercise and stress contribute to insulin resistance. Stress, lipodystrophy, or excess energy intake would enhance circulating free fatty acid levels (FFAs). Elevated plasma FFA levels lead to the accumulation of FFAs, diacylglycerol (DG) and triglycerides in non-adipose tissues, including skeletal muscle, liver, heart and β-cells. In fact, lipid infusions and high-fat feeding in human subjects and rodents reduce insulin-stimulated glucose disposal. Therefore, perturbation in lipid metabolism results in insulin signaling impairment as a major mechanism for insulin resistance. Impaired insulin signaling not only does influence insulin-stimulated glucose metabolism in skeletal muscle, but also affects other insulin functions linked to various pathological conditions in different tissues including, liver, adipose tissue, heart and vasculature (Kim et al., 2008; Liu et al., 2014; Kowalski et al., 2015; Muthulakshmi et al., 2015; Pereira et al., 2015; Williams et al., 2015; Wuttke, 2015). Thus, molecular and cellular mechanisms of insulin resistance are pertinent to understand the pathogenesis of various diseases associated with insulin resistance (Kim et al., 2008).

Inflammation

Environmental and genetic factors have an impact on hormone secretion and body metabolism that lead to weight gain. Consequently, predominant clinical features such as

insulin resistance, type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD) will continue to indicate this fact. Adipose tissue is considered as a pathogenic site of obesity-induced insulin resistance. The secretion of chemoattractants such as MCP-1 and MIF, as well as IL-6, TNF-α, and IL-1β cytokines draw immune cells, especially macrophages, into adipose tissue. Faulty lipid metabolism and subsequent increase in circulating free fatty acids are the starting shot of inflammatory signaling cascades for the population of infiltrating cells which then exacerbate by progressive infiltration of further immune cells, secretion of cytokines and disruption of the insulin signaling cascade (McArdle et al., 2013). Inflammation is part of the complicated and cascade-based biological response of the body tissues to noxious stimuli. From a history of science perspective, inflammation in diabetes dates back to over a hundred years ago when high doses of salicylates reduced the glucose levels in diabetic patients, and the story of inflammation is still ongoing. Studies on human obesity and insulin resistance have revealed a clear association between the chronic activation of pro-inflammatory signaling pathways and decreased insulin sensitivity. For example, elevated levels of tumor necrosis factor-α (TNF), interleukin-6 (IL-6) and interleukin-8 (IL-8) have all been reported in various diabetic and insulin-resistant states. As a whole, inflammation is caused by many factors, including oxidative stress, overweight/obesity, improper oral hygiene and nutritional deficiencies (Desai and Mathews, 2014). As a last point, the inflammatory marker C-reactive protein (CRP), a non-specific acute phase protein, is elevated in human insulin resistant states (De Luca and Olefsky, 2008).

Oxidative stress

As already mentioned, oxidative stress is a major risk factor for the progression of diabetic complications. Historically, mitochondrial reactive oxygen species (mROS) were thought to cause cellular damage and loss of physiologic function. As frequently mentioned, accumulation of ROSs is linked to multiple pathologies like diabetes, cancer, premature aging and neurodegenerative diseases. Thus, mROS are considered as unavoidable "evils of oxidative metabolism." Many evidences have suggested that mROS are critical for normal cell function (Sena and Chandel, 2012). Mitochondria are a prominent site for the development of ROS in T2DM patients compared to non-diabetic subjects. Potentially, oxidative stress may alter insulin sensitivity either by increasing insulin resistance or impaired glucose tolerance, which exhibit alterations in the physiologic cellular redox system. Furthermore, oxidative stress has been implicated as the underlying cause of both macrovascular and microvascular complications associated with T2DM. The imbalanced production ratio of ROS and antioxidants results in oxidative stress. Nevertheless, a large number of clinical trials have failed to demonstrate beneficial effects of antioxidants on these pathologies. Since the role of mROS is changed under different environmental situations, antioxidant inhibition of mROS has an ambiguous outcome on cell function. Therefore, these observations open the door to identify specific molecular targets of mROS under different environmental conditions (Wright et al., 2006).

Lipid accumulation

Circulating free fatty acids' (FFAs) lipodystrophy or excess energy intake are among the parameters elevated during stress. Elevated plasma FFA levels lead to the accumulation of FFAs, diacylglycerol (DG) and triglycerides in non-adipose tissues, including skeletal muscle, liver, heart and β-cells. In fact, lipid infusions and high fat feeding in human subjects and rodents reduces insulin-stimulated glucose disposal. These data suggest that the defects in lipid metabolism leading to the impairment of insulin signaling seem to be a major mechanism of insulin resistance (Gogoi et al., 2014; Kang et al., 2014; Montgomery and Turner, 2015).

Mitochondrial damage

After recognition of the mitochondrial dysfunction in 1960s, medical scientists and researchers found a new direction toward the role of mitochondria in health and disease. Now, mitochondrial damage is understood to play a significant role in the pathogenesis of a wide range of disorders, specifically T2D and insulin resistance (Neustadt and Pieczenik, 2008). However, the way this was revealed and its effect on cell function will be discussed later. The pathophysiology of mitochondrial DNA (mtDNA) damage is due to the accumulation of mtDNA mutations along with the central role of oxidative stress in mtDNA diseases. Actually, although many other factors such as disrupted homeostasis of Ca^{2+} may contribute to the elevation of oxidative stress and defective turnover of mitochondrial proteins, there is still uncertainty about the relative importance of these damaging processes in the development of cell dysfunction and death with respect to disease phenotype. These uncertainties limit the understanding of mtDNA damages pathophysiology and the consequent ability to improve effective therapies (James and Murphy, 2002). Interestingly, in recent years, several studies have shown that the inflammation induces mitochondrial dysfunction toward the progression of insulin resistance (Bakar et al., 2014). According to the study of Martins et al., the insulin-resistant, obese and type 2 diabetic patients have impaired mitochondrial function and reduced fatty acid oxidation capacity. Predominantly, mutations, polymorphisms and epigenetics are the alterations which can be referred to in some other studies on mtDNA damages (Martins et al., 2012). Here, we outlined the role of mitochondria and the

relative complications in different aspects of diseases such as insulin resistance, obesity, T2D and metabolic syndrome and their target tissues.

Metabolic tissues

Clinical and translational approaches, as well as numerous studies on metabolic tissues and their association with mitochondrial dysfunction have been flourished recently. Skeletal muscle, adipose tissue, islet β cells and liver are considered as peripheral metabolic tissues. There are several obvious proofs on the relationship between obesity and lipid accumulation in metabolic tissues with metabolic disorders such as insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Acute lipid infusion and its accumulation, or chronic elevation of plasma FFAs, lead to hepatic insulin resistance (Ishii et al., 2015). Elevated FFAs in the plasma leads to intracellular lipid accumulation that is associated with insulin resistance. Insulin resistance has been reported to be associated with a reduced number of mitochondria, lower mitochondrial oxidative capacity, ATP production, mitochondrial density, abnormal morphology and lower levels of mitochondrial oxidative enzyme profile. To be more specific, intracellular lipid accumulation results in reduced mitochondrial oxidative capacity in skeletal muscles of individuals with T2DM (Martins et al., 2012). Similarly, studies on patients with nonalcoholic fatty liver disease (NAFLD) show mitochondrial abnormalities, including mitochondrial DNA (mtDNA) depletion, decreased activities of mitochondrial respiratory chain complexes (Tang et al., 2015), impaired mitochondrial oxidation and ultra-structural lesions (Tanaka et al., 2015). In obesity, triglycerides are overloaded in adipose tissue and dyslipidemia causes increased lipolysis. The increase in free fatty acid flux resulting from increased lipolysis causes defects in glucose metabolism and insulin resistance in non-adipose tissues. In contrast, lipodystrophy causes excessive loss of adipose tissue, which also leads to insulin resistance, T2DM and NAFLD (Ishii et al., 2015; Kim et al., 2008; Martins et al., 2012; Tanaka et al., 2015).

Conclusion

This literature review identified various potential associations between insulin resistance and lipid metabolism with mitochondrial dysfunction; however, the findings of this review suggest further investigation to address the gaps in the current literature. Once the underlying mechanisms of ROS, lipid accumulation, inflammation and other factors in mitochondrial dysfunction and their roles in insulin resistance are better understood and the proposed molecular mechanisms are described with definite mechanisms, personalized treatments and tailored therapy can be developed to improve the quality of life and even the life expectancy in the diabetic patients. Among all these proposed molecular mechanisms for insulin resistance, inflammation, oxidative stress and lipid accumulation have been the three most important mechanisms; however, a large number of clinical trials have failed to demonstrate beneficial effects of antioxidants on these pathologies. In addition, they showed the role of mROS changes under different environmental situations, and that the antioxidants' inhibition of mROS does have an ambiguous outcome on cell function. Therefore, this review paves the way to identify specific molecular targets of mROS under different environmental conditions, although additional studies needed to put an end to all those obscure myths about the role of mROS in mitochondrial dysfunction and the related sequela, especially insulin resistance and T2D. The current review revealed that mitochondria are key players in oxidative disposal of excess fatty acids and modulate the distribution of body fat. Excessive levels of fatty acids are harmful to mitochondria and mitochondrial damage in turn decreases the capacity for beta-oxidation of fatty acids, resulting in the accumulation of triglycerides in other tissues, including liver and pancreatic beta cells. These events induce metabolic dysregulation of the liver and pancreatic beta cells, and in turn induce insulin resistance and inadequate insulin secretion, finally increasing the possibility of diabetes in the patients.

Declaration of conflicting interests

The authors have no conflicts of interest.

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