Introduction

Absolute or relative insulin insufficient functions will produce abnormal glucose homeostasis that can induce consequence of a complex metabolic disorders. After overnight fasting times, blood glucose elevated over 126 mg/dL, or random postprandial level excess 200 mg/dL, or glycated hemoglobin concentration higher than the threshold of 6.5 gm%, diabetes mellitus can be diagnosed with or without clinical characteristics [1]. The pathogenesis, triggering factors and underlying mechanisms behind the development of diabetes and its complications remain elusive.

Mitochondrion contains double-membrane organelles with multiple essential cellular functions. The mitochondria-specific proteins are encoded and con-trolled by both the nuclear and mitochondrial genomes [2]. Mitochondria are always recognized for the role in generating cellular adenosine 5’-triphosphate (ATP) via oxidative phosphorylation (OXPHOS). The other metabolic functions include the generation by the tricarboxylic acid (TCA) cycle of numerous metabolites that function in cytosolic pathways, oxidative catabolism of amino acids, ketogenesis, ornithine cycle activity (“urea cycle”) are also important for cells living and fuel supporting. All of these related to cell energy production and utility, therefore, mitochondrion is the power plant of cells. The primary or secondary alterations in mitochondria related signaling pathways could be explained multiplicity of organelle functions and va-riability in the pathophysiology [3].

Mitochondrial diabetes was initially described as maternally inherited diabetes and deafness syndrome (MIDD). The origin of MIDD is primary defects in mitochondria mutation with dysfunction. The clinical presentation of MIDD is similar to that of type 1 or type 2 diabetes but accompany with hearing impairment, poor vision, and seizure disorders [4]. The clinical phenotype of MIDD is heterogeneous, even within the same family. Some patients may present with isolated diabetes or impaired glucose tolerance but no overt hearing loss, whereas others have early-onset diabetes and deafness and yet others have MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). This phenotypic variability has been ascribed in part to differences in the amount of mutant mitochondria deoxyribonucleic acid (mtDNA) relative to wild-type
mtDNA, which may vary across tissues [5]. We will not focus on this primary type of mitochondrial defects in this article. We will discuss about issues of the following sections as mitochondrial dysfunction and diabetes, diabetes with mitochondrial dysfunction, and hyperglycemia with mitochondria.

**Mitochondrial dysfunction and diabetes**

When mitochondria produce ATP for cellular energy sources, reactive oxygen species (ROS) sustain with ATP synthesis. Overloading of ROS will injury the mitochondria especial in pancreatic beta cells by fragmented DNA then activates a consequent stress pathway [6]. ROS appear to be produced in larger amounts by islets from T2DM patients than by those from non-diabetic subjects [7,8,9]. Type2 diabetes subjects’ beta islet exhibit mitochondrial morphologic abnormalities. A hypertrophic, round shape and higher density compare to a slim, elliptical and low density in normal control that had been revealed [10]. Pancreatic beta cells’ mitochondrial membrane potential are regulated by uncoupling protein-2 (UCP2). UCP2 can facilitate proton trickle that will reduce the mitochondrial membrane potential then diminished the synthesis of ATP. UCP2 also can down regulates insulin secretion. While mitochondrial ROS over-production particular superoxide (O•−2 ) that could enhance UCP2 activation results in beta cell dysfunction [11].

Type 2 diabetes is following with progressive decrease in β-cell mass due to marked increase beta cell apoptosis [12]. It’s well known that mitochondria play a pivotal role in regulating cell apoptotic death [13]. Proapoptotic stimulating agents are released from mitochondrial cytochrome c into the cytoplasm. By the way, cytochrome c participates in apoptosome formation which can conduct a series of caspase reaction and subsequent activation then demolished the cell apoptosis.

Insulin resistance was defined as a diminished responsive ability of cells or tissues in normal physiological insulin concentrations. Genetic and environmental factors, including aging, obesity, lack of exercise, and stress are considered to causes of insulin resistance. The molecular and cellular mechanisms of insulin resistance are relevant to the pathogenesis of type 2 diabetes [14, 15]. The major sites of insulin resistance are the target tissue of insulin actions e.g. liver, skeletal muscle and adipose tissues. A possible mechanism may explain the impaired mitochondrial function which contributes to insulin resistance due to altered metabolism of fatty acids. Increased tissue lipid load would lead the accumulation of fatty acyl coenzyme A (CoA), diacylglycerols, ceramides, products of incomplete oxidation, and RO. These will conduct to experimentally reduced insulin signaling and action [16, 17]. The other possible mechanisms linking between impaired mitochondrial oxidative function and insulin resistance persisted. Diminished ATP synthesis is insufficient for energy requiring functions such as insulin-stimulated glucose uptake. Therefore, insulin cannot perform whole functions [18].

About the relationship between mitochondrial and pancreatic beta cells, we can make a picture as figure1.
Diabetes with Mitochondrial Dysfunctions

The biopsies of type 2 diabetes subjects’ skeletal muscle demonstrated that size of mitochondria became smaller size and number per unit volume are relatively dense [19]. The size of mitochondria appears with positive correlate with whole-body insulin sensitivity. Moreover, mitochondria of offspring of diabetic subjects are lower in density compared with those of controls [20]. It is clear that morphological changes in mitochondria occur in diabetic states. These changes will reduce NADH oxidoreductase and decline citrate synthase activity in the mitochondria of the diabetes and obese subjects compared with lean subjects.

Besides mitochondrial number and morphology, mitochondrial metabolism also depends on the dynamic movement and distribution of the this organelles, such as fusion or fission, which is essential to maintain the mitochondrial function of ATP synthesis [21]. As mitochondria move within cells, they undergo both fission, needed for distribution and networking, and fusion, needed for mixing of the mitochondrial genome. Evidence indicates that obesity in both humans and rodents is associated with reduced ability of fusion [22]. That means losing the capacity of change mtDNA. Moreover, polymorphisms of presenillin-associated rhomboid-like (PARL) protein which also one kind of fusion protein in humans is associated with insulin resistance [23].

About 30-40% decrease in oxidative phosphorylation measured by magnetic resonance spectroscopy (MRS) in insulin resistance related subjects including type 2 diabetes, lean to normal glucose-tolerant elderly individuals, and offspring of patients with type 2 diabetes when compare with normal healths [24]. The defect in oxidative phosphorylation in lean, NGT, insulin-resistant offspring of patients with type 2 diabetes is associated with a decreased metabolic flux through the tricarboxylic acid (TCA) cycle under basal conditions. [25]. Type 2 diabetes subjects easy have impaired recovery of intracellular phosphocreatinine concentration following exercise [26,27]. This suggests a mitochondrial defect in oxidative phosphorylation possible contributes to the impairment in exercise capacity in these insulin-resistant individuals.

From above mentions, diabetes subjects have decreased variety of mitochondrial activities compared with healthy individuals. We can make a summary as figure 2.
Hyperglycemia and Mitochondria

Hyperglycemia will increase the response of oxidative stress then enhance mitochondrial damage [28]. The fasting blood glucose and hemoglobin A1c (HbA1c) have been shown to be correlated to phosphocreatinine recovery half-time [27]. It’s possible that hyperglycemia could have adverse effects on mitochondrial biogenesis and/or function in patients with type 2 diabetes. Significant improvement of diabetes glycemic control does not affect skeletal muscle mitochondrial respiration and contents [29]. Skeletal muscle mitochondrial respiration was approximately 20% lower in patients with type 2 diabetes compared with age- and BMI-matched control subjects. The differences were eliminated when data were normalized to citrate synthase activity. Mitochondrial respiration and content was not improved after significant improvements in glycemic control. Severe hyperglycemia inhibited respiration reversibly due to block electron transport via increased ROS production. The dynamic changes in mitochondrial morphology are associated with high glucose-induced overproduction of ROS. Mitochondria became fragmentation rapidly with a concomitant increase in ROS formation after exposure to high glucose concentrations [30].

Chronic persisted hyperglycemia will induce tissue damage by different mechanisms, include: activated protein kinase C (PKC) isoforms synthesis as the second messenger diacylglycerol (DAG), increased hexosamine pathway flux, increased advanced glycation end product (AGE) formation, and increased polyol pathway flux. Hyperglycemia also induced superoxide over-production and inhibited glucose-6-phosphate dehydrogenase which is the causal link between high glucose and the pathways responsible for hyperglycemia's damage [31]. Diabetes is typically accompanied by increased production of free radicals and/or impaired antioxidant defense capabilities, indicating a principal contribution for ROS in the onset, progression, and pathological complications of diabetes [32]. Mutations in mtDNA and decreases in mtDNA copy number have been linked to the pathogenesis of type 2 diabetes [33]. The relationship between mtDNA and type 2 diabetes has revealed the influence of the mitochondria of nuclear-encoded glucose transporters, glucose-stimulated insulin secretion, and nuclear encoded uncoupling proteins in β-cell glucose toxicity.

Therefore, hyperglycemia could affect mitochondria continuously. We can make a summary as figure 3.
Conclusion

The relationships between mitochondria and diabetes are complex. Reciprocal causation and interaction make a vicious cycle. Mitochondria over produce ROS will create pancreatic beta cells damages including apoptotic changes and loss normal function. Beside beta cell, mitochondria also play the roles on the insulin classic target tissue such as skeletal muscle, liver and adipocytes. Insulin resistance will be provoked especial mitochondria loss its regular function.

Diabetes will generate mitochondrial deviation including small and dense morphological alternation, diminished fusion ability and oxidative phosphorylation. That will illuminate the reason of diabetes patient with fatigue and exercise intolerance. Chronic and acute hyperglycemia also deteriorate the mitochondria's defense ability and increase free radicals. Poor compensatory reaction including copy numbers and mutant mtDNA, accompany by low respiratory contents, which will cause exacerbation of mitochondrial function. Day by day, chronic complications will be developed.

This article can provide a little knowledge as a bridge between mitochondria and diabetes. Further literatures survey and laboratory trials still needed.

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Conflicts of interest statement

There are no competing interests and none to declare.

References