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# **Mitochondrial Dysfunction in Insulin Insensitivity and Type 2 Diabetes and New Insights for Their Prevention and Management**

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Additional information is available at the end of the chapter

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## **1. Introduction**

There are two major types of diabetes mellitus. Type 1 diabetes is caused by the loss of insulin-secreting  $\beta$  cells of the pancreas, which leads to a deficiency of insulin in the human body. Type 2 diabetes, known as non-insulin-dependent diabetes mellitus (NIDDM), is characterized by insulin resistance of insulin-responsive tissues, such as the muscle and adipose tissues. Inability of glucose disposal in these tissues after a meal leads to the elevation of glucose level in the blood circulation of the patients. Subsequently, the long-term effect of hyperglycemia may induce inflammation and oxidative damage to other organs and result in many complications such as cardiovascular disease, blindness, amputations and renal failure [1]. Unfortunately, type 2 diabetes has high prevalence compared to type 1 diabetes in modern societies because the pathogenesis of this disease is quite complicated, multi-factorial, and is strongly associated with lifestyle, dietary habits, and environmental toxins. In light of these findings, many biomedical researchers and clinicians have made great efforts to better understand the pathophysiology of insulin resistance and to explore new avenues for the therapy of type 2 diabetes [2].

## **2. Mitochondrial role in the regulation of cellular metabolism**

### **2.1. Overview of mitochondria**

Mitochondria play important roles in energy metabolism, apoptosis and biosynthesis of heme and pyrimidine nucleotides because many vital biochemical reactions take place in the organelles. They are also called the powerhouse of mammalian cells because they generate a majority of ATP required by the cells. Mitochondria contain key enzymes involved in the

tricarboxylic acid (TCA) cycle,  $\beta$  oxidation of fatty acids and the electron carriers of the respiratory chain. Metabolic intermediates generated from catabolism of carbohydrates and lipids by TCA cycle and  $\beta$  oxidation provide reducing equivalents (NADH and FADH<sub>2</sub>), which are funneled into the electron transport chain that consists of a series of respiratory enzyme complexes I, II, III and IV. The proton gradient generated from the electron transport chain across the inner membrane is then utilized by Complex V to drive the phosphorylation of ADP to produce ATP in mitochondria to meet the energy need of the cell [3]. Mitochondrion has its own genome, mtDNA, which is a 16.6 kb circular double-stranded DNA. Mammalian mtDNA encodes 2 rRNAs, 22 tRNAs and 13 polypeptides required for the assembly of respiratory enzymes. Each mammalian cell contains several hundreds to more than a thousand of mitochondria, and each mitochondrion contains 2-10 copies of mtDNA to meet different energy needs of the cells. Most importantly, mtDNA is naked, compact, and has no efficient DNA repair systems, which renders it prone to free radical attack and oxidative damage, and thereby increases its risk of acquiring DNA mutations. More than one hundred mutations in mtDNA have been reported to be associated with human diseases [4].

## 2.2. Regulation of mitochondrial biogenesis

The mitochondrial biogenesis of the human cells is controlled by extracellular stimuli such as low temperature, thyroid hormone, fasting, and exercise through up-regulation of the master control, peroxisome proliferator-activated receptor gamma co-activator 1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  can promote nuclear respiratory factor 1 (NRF-1) and NRF-2 to transcribe their target genes that produce many nuclear DNA-encoded mitochondrial proteins and mitochondrial transcription factor A (mtTFA), which is a key transcriptional factor for the expression of genes encoded by the mitochondrial genome. A great majority of the nuclear DNA-encoded proteins are translocated from the cytosol to mitochondria and are assembled with mtDNA-encoded proteins to form functional respiratory enzyme complexes on the inner membrane. Because mitochondrial biogenesis is a complicated process involved with the expression of genes in the two genomes, the communication between mitochondria and the nucleus is essential for the proper functioning of mitochondria under different physiological conditions [5, 6].

## 2.3. ROS and antioxidant enzyme system in mitochondria

Mitochondria are also the major source of intracellular reactive oxygen species (ROS). Within mitochondria, the superoxide anions (O<sub>2</sub><sup>•-</sup>) are produced in the reaction between O<sub>2</sub> and the electrons leaked out from Complex I and III of the respiratory chain. Subsequently, the O<sub>2</sub><sup>•-</sup> can be converted to lipid-permeable hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) by the Mn-dependent superoxide dismutase (MnSOD), and further changes to more reactive hydroxyl radicals (OH<sup>•</sup>) via Fenton reaction. There is a set of enzymatic and non-enzymatic ROS-scavenging system to protect cells from the assault by ROS. The H<sub>2</sub>O<sub>2</sub> can be reduced to H<sub>2</sub>O by catalase (CAT), glutathione peroxidase (GPx) or a group of small cysteine-containing

proteins such as thioredoxins (Trx) and peroxiredoxins (Prx) [7-9]. Nevertheless, overproduction of ROS by defective mitochondria and inefficient antioxidant enzyme system may cause oxidative damage to cellular components such as DNA, especially mtDNA, proteins, and lipids of target tissues in aging and age-related diseases [10]. It has been reported that mitochondrial defects caused by mtDNA mutation or oxidative stress also play a role in insulin resistance or diabetes [11-13].

### **3. Mitochondrial dysfunction contributes to insulin resistance and type 2 diabetes**

In the early 1990s, diabetes has been discovered to be one of the symptoms associated with some of the mitochondrial diseases such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and maternally inherited diabetes and deafness (MIDD) syndrome, and patients with these syndromes frequently harbor an A to G transition at nucleotide position 3243 of mtDNA [11]. However, until recent years diabetes has been usually thought as a secondary effect of aging or age-related diseases in patients with an mtDNA mutation. Several recent studies provided the linkage between mitochondrial dysfunction or defects in mitochondrial biogenesis and the pathogenesis of insulin resistance or type 2 diabetes [12-22]. These studies showed that the tissues of mice and human subjects with insulin insensitivity or type 2 diabetes displayed lower expression levels of the genes encoding subunits constituting respiratory enzymes, decrease in the activities of respiratory enzyme complexes, decreased expression of genes involved in mitochondrial biogenesis, mutation or deletion of mtDNA, decrease in the bioenergetic capacity, or defects in  $\beta$  oxidation of fatty acids. In summary, impairment in the mitochondrial OXPHOS function was a common observation in insulin-responsive muscle and adipose tissues of diabetic mice or patients. Most importantly, the amplitude of the decline of mitochondrial function was found to be related to the severity of diabetic symptoms and insulin resistance. These findings support the notion that mitochondrial dysfunction is one of the major etiological factors for insulin resistance and type 2 diabetes.

### **4. Mitochondrial DNA alteration causes insulin resistance and type 2 diabetes**

In order to prove the concept that mitochondrial dysfunction is involved in the development of insulin resistance, chemical treatments and genetic manipulation have been used to impair mitochondria by alteration of the quantity or quality of mtDNA. Park and Lee [23] observed a decrease of insulin sensitivity and impaired activation of insulin signaling in mtDNA-depleted muscle cells after chronic treatment with a low dose of ethidium bromide (EtBr). Moreover, repletion of mtDNA by removal of EtBr revealed that the defects in insulin response could be recovered [23]. Besides, Pravenec et al. [24] demonstrated that sequence variations in mtDNA could directly lead to metabolic dysregulation that includes glucose intolerance and insulin insensitivity in the conplastic

strains of rats. In addition, defects in oxidative phosphorylation caused by treatment of oligomycin A, an inhibitor of Complex V, also resulted in a decline of insulin-stimulated glucose uptake and inactivation of Akt and IRS-1 in the insulin signaling pathway in murine C2C12 myotube cells [25]. The above two lines of experiments clearly demonstrated a relationship between mtDNA alteration-induced mitochondrial dysfunction and insulin insensitivity.

#### **4.1. Overproduction of ROS impairs insulin signaling**

Excess ROS production from defective mitochondria has been considered as one of the possible unifying factors leading to insulin resistance. Increased concentration of glucose in the culture medium was found to significantly increase the ROS level and led to insulin resistance in mouse adipocytes and rat primary adipocytes and this effect could be prevented by pre-treatment of the adipocytes with the antioxidant N-acetylcysteine [26, 27]. After administration with ROS-scavenging enzymes, the insulin sensitivity of muscle cells was found to be improved in diabetic mice [28]. Recent studies also demonstrated that the amount of superoxide anions generated by mitochondria was increased in four different animal models of insulin resistance. Furthermore, it was reported that by addition of mitochondria-targeting superoxide dismutase mimetics to decrease the level of ROS could alleviate insulin resistance in the insulin-insensitive animals [29]. The mechanisms underlying the disruption of insulin signaling by overproduction of ROS have been extensively investigated in the past decade. It was demonstrated that, at a certain concentration range, ROS could cause an increase in the activity of multiple stress-sensitive serine/threonine kinases such as p38 MAPK, JNK, ERK, and NF $\kappa$ B and elicit subsequent phosphorylation of IRS1 and downstream signaling proteins, which may culminate in the compromise of insulin sensitivity [30].

#### **4.2. Accumulation of fatty acids impairs insulin signaling**

It is thought that impaired lipid metabolism resulted from defects in  $\beta$  oxidation of fatty acids is involved in the disturbance of insulin signaling. Accumulation of intracellular lipids by the decreased activities of carnitine palmitoyl transferase (CPT), which transports long-chain fatty acids into mitochondria, and long-chain acyl-CoA dehydrogenase (LCAD), an enzyme involved in  $\beta$  oxidation of fatty acids, led to insulin resistance in insulin-targeting cells [31]. It has been demonstrated that an accumulation of fatty acid metabolites, such as diacylglycerol, fatty acyl-CoA and ceramides, could induce activation of serine/threonine protein kinases such as PKC $\beta$  and PKC $\delta$  in human tissues [32]. In turn, the activation of PKCs phosphorylates IRS-1 and IRS-2 on serine/threonine residues to inhibit their enzymatic function and activate the downstream PI3K/Akt signaling pathway. The above-mentioned observations suggest that ROS overproduction and lipid accumulation elicited by mitochondrial dysfunction may play a role in the dysregulation of insulin signaling pathway, which then leads to an attenuation of insulin response in affected tissues.

### **4.3. Loss of mild stress-induced AMPK $\alpha$ activation may lead to insulin resistance**

Low concentration of ROS is a normal byproduct of cellular functions and is known as the secondary messenger in the regulation of intracellular signaling to adapt to the extracellular environment. But prolonged exposure to oxidative environment may lead to oxidative damage to tissue cells and development of diseases. Recent studies revealed that activation of AMPK by low dose of ROS is involved in the activation of antioxidant defense system, the influx of glycolysis and lipid metabolism [33, 34]. The activation of the downstream targets of AMPK, including GLUT4, PFK2, and ACC, enhances the  $\beta$  oxidation of fatty acids and the basal and insulin-stimulated glucose uptake. Besides, activated AMPK can directly phosphorylate the forkhead transcription factor 3a (FOXO3a) to promote its nuclear translocation and formation of a transcription complex, which in turn up-regulates the expression of thioredoxin and peroxiredoxin [35]. It has been shown that activation of the AMPK-FOXO3a pathway via AICAR or metformin, an antidiabetic drug, can decrease the intracellular ROS level to improve insulin sensitivity in epithelial cells [35, 36]. These findings indicate that mild oxidative stress-elicited activation of AMPK and FOXO3a may safeguard glucose homeostasis and redox status in healthy subjects. Taken together, the decrease in the sensitivity and capacity of the response to low-level oxidative stress may play a role in insulin insensitivity and type 2 diabetes.

## **5. The roles of sirtuins in the maintenance of glucose homeostasis and their defects in insulin resistance and type 2 diabetes**

### **5.1. Introduction of sirtuins**

Sirtuins are a highly conserved family of proteins that exhibit NAD<sup>+</sup>-dependent protein deacetylase and ADP-ribosyltransferase activities. Mammals contain seven sirtuins that are confined in different subcellular compartments and regulate diverse functions, such as intermediary metabolism, energy homeostasis, and oxidative stress. SIRT1, SIRT6 and SIRT7 are primarily localized to the nucleus, SIRT2 is a cytosolic protein, and SIRT3, SIRT4 and SIRT5 are all located in mitochondria. Sirtuins can regulate the function of enzymes or transcription factors by deacetylation of target proteins to cope with nutrient deprivation or metabolic stress. In addition to getting involved in the regulation of aging and longevity, some of the sirtuins have emerged as important regulators of glucose homeostasis. Sirtuins may regulate the activities of some of the regulatory proteins or enzymes involved in the insulin-mediated signaling pathways and regulation of mitochondrial function, which in turn determine the sensitivity and acuity of biochemical response to high blood glucose of the muscle and other peripheral tissues in the human body.

### **5.2. SIRT1 and type 2 diabetes**

Accumulating evidence has established that SIRT1 contributes to the pathogenesis of type 2 diabetes through its effect on oxidative metabolism of the liver, skeletal muscle, adipose



tissue, and pancreatic  $\beta$  cells, which indicate that mammalian sirtuins play an essential role in the pathogenesis of diabetes and aging-associated metabolic diseases [37]. Increasing evidence has suggested that SIRT1 provides overall protection against type 2 diabetes. SIRT1-overexpressing transgenic mice showed significant protection from the adverse effects of high-fat diet, including hepatic inflammation and impaired insulin sensitivity [38, 39]. In addition, administration of resveratrol and SIRT1-activating compounds was found to improve glucose homeostasis and insulin sensitivity in diet-induced and genetically-predisposed type 2 diabetic mice [40, 41]. It has been reported that certain sequence variations of the SIRT1 gene is strongly associated with type 2 diabetes and obesity in a Dutch population [42]. Taken together, these findings suggest that SIRT1 plays a role in the pathogenesis of type 2 diabetes and its manipulation has great potential in the prevention and treatment of type 2 diabetes in animals and the human.

### 5.3. SIRT3 and type 2 diabetes

In recent years, it has become increasingly clear that reversible lysine acetylation is an important posttranslational modification of mitochondrial proteins for the regulation of their proper function [43]. A number of proteomics studies have revealed that many key metabolic enzymes are acetylated in mitochondria and that their enzymatic activities are regulated by changes in acetylation in response to environmental stimuli [44]. Among seven members of the sirtuin family, three sirtuins (SIRT3, SIRT4 and SIRT5) are primarily located and exert functions in mitochondria. It is a remarkable fact that SIRT3 is the most important one regarding the regulation of mitochondrial function because it is responsible for deacetylation of the majority of mitochondrial proteins [45]. SIRT3 has been shown to control multiple key metabolic pathways through its deacetylase activity in response to nutrient deprivation. For example, SIRT3 can deacetylate and activate the mitochondrial enzyme acetyl-CoA synthetase 2 (AceCS2). The oxidation of acetate is required for the generation of ATP and heat under low-glucose or ketogenic condition [46, 47]. Besides, SIRT3 has been shown to deacetylate long-chain acyl-CoA dehydrogenase (LCAD) during fasting and thereby promotes  $\beta$ -oxidation of fatty acids in the liver mitochondria [48]. Recently, some studies provide critical insights into the connection between SIRT3 and the pathogenesis of type 2 diabetes and metabolic syndrome. It has been demonstrated that the SIRT3 expression in skeletal muscle is reduced in animal models of type 1 and type 2 diabetes and that results in the decrease of mitochondrial bioenergetic function and overproduction of ROS, which in turn disturbs insulin signaling pathway leading to insulin insensitivity [49]. These findings suggest that decreased SIRT3 expression and activity could contribute to the metabolic abnormalities in skeletal muscle and pathogenesis of diabetes mellitus. On the other hand, mitochondrial dysfunction induced by SIRT3 deficiency in pancreatic  $\beta$  cells might contribute to the defects in insulin secretion upon stimulation with various insulin secretagogues [50]. In a recent study, Hirschey and coworkers [51] showed that loss of SIRT3 and resultant mitochondrial protein hyperacetylation contribute to obesity, hyperlipidemia, insulin resistance, and steatohepatitis. In addition, they identified a single nucleotide polymorphism in the human SIRT3 gene, which causes a loss of the

enzyme activity of SIRT3 and is highly associated with the prevalence of metabolic syndrome. Abundant evidence has been accumulated to show the importance of reversible acetylation/deacetylation of mitochondrial proteins through the action of SIRT3 and its potential role in the development of insulin resistance and metabolic disorders. Thus, site-specific acetylation of mitochondrial proteins and the development of new SIRT3-targeted drugs may serve as therapeutic tools to regain normal cellular redox status and energy homeostasis in the patients with diabetes and insulin resistance, as well as some of the mitochondrial diseases.

## **6. Defects in the secretion or function of adipokines as an important contributor to insulin resistance or type 2 diabetes**

### **6.1. Regulation of glucose homeostasis by adipocyte-derived adipokines**

The adipose tissue has traditionally been considered as the site for lipid storage in the human body. In recent years, a growing number of studies have revealed that adipose tissues can perform endocrine function in secreting several adipokines, which can modulate the intermediary metabolism and glucose homeostasis in the peripheral tissues. Adipocyte-derived adipokines can be divided into two groups according to their action in the regulation of glucose metabolism in the mammals. One group is called as “anti-hyperglycemic adipokines”, which include leptin, adiponectin, omentin, and visfatin. They enhance insulin sensitivity in the peripheral tissues to increase glucose utilization and decrease the glucose level in blood circulation. Another group of adipokines is termed “pro-hyperglycemic adipokines” or “pro-inflammatory adipokines”, which include resistin, TNF- $\alpha$ , and RBP4 since they tend to result in an increase of blood glucose and systemic inflammation. The imbalance of these two groups of adipokines in blood has been frequently observed in patients with insulin resistance [52, 53].

### **6.2. Adiponectin improves insulin sensitivity**

Adiponectin has been considered the most important adipokine due to its higher concentration in blood than the others and a decrease in its level is highly correlated with type 2 diabetes [54]. Several clinical studies demonstrated that the plasma level of adiponectin in obese subjects or patients with type 2 diabetes was significantly lower compared with those of normal subjects, and that blood glucose was higher and insulin sensitivity was largely decreased in mice with adiponectin deficiency [55, 56]. Besides, administration or overexpression of adiponectin in mice can enhance insulin sensitivity and glucose utilization to ameliorate the symptoms of insulin resistance [57-59]. This indicates that dysregulation of secretion of adipokines from adipose tissues is an important contributor for the pathogenesis of type 2 diabetes. Thus, adiponectin has become the most attractive adipokine and its function has been gradually unraveled. The underlying mechanism of adiponectin in improvement of insulin sensitivity and fatty acid  $\beta$  oxidation in skeletal muscle has been demonstrated by Yamauchi and his colleagues [60]. They showed that the phosphorylation and activation of AMPK is stimulated when adiponectin



binds to adiponectin receptor 1 (AdipoR1), which is a seven-transmembrane receptor specifically expressed in the skeletal muscle. In turn, AMPK can induce GLUT4 translocation to the plasma membrane for the increase of glucose uptake. On the other hand, the phosphorylated AMPK also activates acetyl-CoA carboxylase to increase the oxidation of fatty acids through independent pathways.

### **6.3. Bi-directional regulation of the biogenesis and function of mitochondria by adiponectin**

Because the decrease of adiponectin expression and the biogenesis and function of mitochondria have been observed concurrently in adipose tissues of diabetic mice and human subjects [22], some researchers made an effort to elucidate the connection between these two cellular events. Koh and coworkers demonstrated that the biogenesis and function of mitochondria are important for the maintenance of the adiponectin level in adipocytes [61]. They found that adiponectin expression and the mitochondrial content in adipose tissues were both reduced in obese mice, and these changes could be reversed by the administration of rosiglitazone, a mainstay drug used for treatment of diabetes. Induction of mitochondrial biogenesis via adenoviral overexpression of nuclear respiratory factor-1 (NRF-1) in cultured adipocytes increased the expression of adiponectin. Besides, they found that inhibition of mitochondrial function by a respiratory inhibitor or uncoupler decreased the level of adiponectin in plasma through activation of ROS-dependent kinase such as JNK. This finding suggests that mitochondrial function is linked to adiponectin synthesis in adipocytes, and explain the observation that mitochondrial dysfunction is associated with the defects of secretion and function of adiponectin, which may lead to systemic insulin resistance in obesity and type 2 diabetes.

On the other hand, a recent study also showed that adiponectin can increase the activity of PGC-1 $\alpha$  and enhance the biogenesis and respiratory function of mitochondria in muscle cells [62]. The study provided evidence that adiponectin induces extracellular Ca<sup>2+</sup> influx through binding to AdipoR1, which is essential for subsequent activation of Ca<sup>2+</sup>/calmodulin-dependent protein kinase kinase  $\beta$  (CaMKK $\beta$ ), AMPK and SIRT1. Adiponectin ultimately causes an increase in the expression of PGC-1 $\alpha$  by CaMK, a downstream target of CaMKK, and increase in the activity of PGC-1 $\alpha$  by deacetylation of SIRT1. These events may in turn elevate the biogenesis and function of mitochondria in muscle cells. This new insight into the up-regulation of mitochondrial function by adiponectin signaling accounts for the long-term effect of adiponectin on the gene expression and provides a biochemical mechanism by which adiponectin improves insulin sensitivity of the muscle.

## **7. Environmental toxins in mitochondrial dysfunction and insulin insensitivity**

Because of the increasing prevalence of type 2 diabetes and metabolic syndrome in westernized and industrialized countries, type 2 diabetes is thought as an “epidemic

disease". With this consideration in mind, scientists conjectured that one of the causative factors for type 2 diabetes is probably related to the environmental impact of industrialization. A growing body of evidence has indicated that the cause of type 2 diabetes and metabolic syndrome is strongly associated with some environmental pollutants and mitochondrial toxins. Persistent organic pollutants (POPs), which are organic compounds present in many herbicides, insecticides, rodenticides, industrial products and wastes, are resistant to photolytic degradation and other chemical or biological destruction processes. Owing to these chemical characteristics, POPs can be present for a long time in our environment and are accumulated in the human body. Thus, POPs are potential environmental risk factors that may affect the human health [63].

### **7.1. POPs cause insulin insensitivity**

By analysis of the results from National Health and Nutrition Examination Survey in 1999-2000, Lee and colleagues found that the prevalence rate of type 2 diabetes was highly correlated with the serum concentration of POPs of the American population [64, 65]. Contamination of POPs in the human diets might be a contributor to the pathogenesis of metabolic diseases including the diabetes. For example, atrazine (ATZ, 2-chloro-4-ethylamine-6-isopropylamino-S-triazine), one of the herbicides, has been extensively used in the corn fields of the United States since the early 1960s. Interestingly, the time and areas of ATZ usage are matched with the timing of increase in the incidence of obesity and other metabolic syndromes [66, 67]. In addition, long-term exposure of Australian outdoor workers to pesticides was found to associate with the disturbance of glucose homeostasis, including higher blood glucose and insulin resistance in these subjects [68]. It was demonstrated that mice fed with a high-fat diet with POPs-contaminated farmed salmon fillet would exaggerate insulin resistance, visceral obesity, and glucose intolerance [69]. However, remission of the above symptoms was observed in the mice fed with farmed salmon fillet containing low level of POPs [69]. Furthermore, the mortality rate of diabetes was positively correlated with the concentration of exposed pesticides [70]. In order to establish a cause and effect relationship in humans, Lee et al. [71, 72] approached the Nested case control study to measure the serum levels of POPs in certain population before the development of metabolic disease phenotypes. The results revealed that increased serum levels of some POPs were highly associated with the incidence of adiposity, dyslipidemia, and insulin resistance in a healthy population. This finding indicates that exposure to low dose of POP may contribute to excess adiposity and other features of metabolic syndrome.

### **7.2. Impairment of mitochondrial dysfunction by POPs**

Several studies have demonstrated that environmental toxins could cause oxidative damage to mitochondria, the organelles are most susceptible to extrinsic toxins including POPs. It has been shown that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), one of the POPs, caused a loss of mitochondrial membrane potential and increase of ROS production in mammalian

cells. The oxygen consumption rate was increased, due to the uncoupling of respiration, and the intracellular ATP content and ADP/O ratio were decreased due to defects in  $F_0F_1$ -ATPase in the affected tissues of TCDD-treated mice [73]. Recently, some animal studies revealed that POPs could result in insulin insensitivity by impairment of mitochondrial function. It was found that chronic exposure to POPs led to mitochondrial dysfunction, morphological disruption of mitochondria, decreased activities of respiratory enzymes and decreased oxygen consumption rate in the liver and skeletal muscle of mice [74]. Besides, POPs were found to down-regulate the expression of leptin in adipose tissues and inactivated insulin signaling pathway in the skeletal muscle [75]. These subsequently resulted in insulin resistance, hyperlipidemia, abdominal obesity, and hepatosteatosis in mice and the severity of these symptoms was more pronounced in the mice fed on high-fat diets. Moreover, mitochondria could be the primary organelles involved in the initiation of inflammation, leading to chronic damage in the affected cells or organs. High level of polychlorinated biphenyls (PCBs) could promote accumulation of lipids and expression of pro-inflammatory adipokines, which decreased the expression of adiponectin and the insulin-stimulated glucose uptake in the adipose tissue, leading to systemic obesity and obesity-associated atherosclerosis [76]. Taken the findings from the epidemiological survey and the above observations together, we suggest that the mitochondrial dysfunction resulted from environmental pollutants or toxins play a role in the pathogenesis and prevalence of type 2 diabetes and insulin resistance.

## **8. Improvement of the biogenesis and function of mitochondria by exercise and pharmaceutical agents for treatment of insulin resistance and type 2 diabetes**

In light of the observations of mitochondrial impairment and increased oxidative stress in the patients with type 2 diabetes, it has been thought that an increase of mitochondrial function or scavengers of ROS may be effective therapies for these patients. Biomedical researchers and clinicians have made considerable efforts in looking for possible ways to improve insulin sensitivity in target tissues through up-regulation of the mitochondrial function or antioxidant defense system. In this section, we provide experimental evidence to demonstrate increase of mitochondrial function and enhancement of the antioxidant defense by exercise, treatment of natural products or pharmaceutical agents that can effectively ameliorate the symptoms of insulin resistance and type 2 diabetes.

### **8.1. Anti-diabetic drugs**

Clinically, the thiazolidinediones (TZDs) have been commonly used to treat patients with type 2 diabetes by increasing insulin sensitivity of the muscle and adipose tissues. These drugs include pioglitazone, rosiglitazone, and troglitazone, which belong to the group of PPAR $\gamma$  agonists and can up-regulate the expression of PGC-1 $\alpha$ , a master control of mitochondrial biogenesis, and a set of genes involved in the regulation of oxidative metabolism [77]. Recent studies revealed that these drugs not only increase insulin

sensitivity of cells, but also significantly improve the mitochondrial biogenesis, function and morphology *in vitro* and *in vivo* [78, 79]. New insights in improving mitochondrial function by these anti-diabetic drugs further substantiate the idea that manipulation of mitochondrial gene expression is a feasible therapy for the patients with insulin insensitivity or type 2 diabetes.

## 8.2. Regular exercise

It is worth mentioning that mitochondrial biogenesis can be up-regulated by regular exercise through the activation of PGC-1 $\alpha$  and its downstream targets including mtTFA and nuclear respiratory factors NRF1 and NRF2 [80, 81], which regulate the expression of a number of polypeptides constituting the respiratory enzyme complexes. These molecular events culminate in the increase of the bioenergetic function of mitochondria and thereby improve the insulin sensitivity of the animals or human subjects doing regular exercise [82]. In light of these laboratory findings and the documentation that exercise can alleviate the symptoms of patients with type 2 diabetes [83], we suggest that the increase of the biogenesis and function of mitochondria is one of the key underlying mechanisms by which exercise improves the insulin sensitivity of patients with type 2 diabetes.

## 8.3. Natural products and chemicals

Resveratrol (3,5,4'-trihydroxystilbene), a polyphenol and a well-known antioxidant, has been demonstrated to be able to promote mitochondrial biogenesis and fatty acid  $\beta$  oxidation as well as insulin sensitivity in a mouse model [84]. Resveratrol treatment was found to lead to the decrease of PGC-1 $\alpha$  acetylation through activation of SIRT1 and thereby increased the activity of PGC-1 $\alpha$ . In turn, an array of oxidative metabolism-related genes was up-regulated and mitochondrial OXPHOS was also elevated in the muscle tissues of the mice that had been treated with resveratrol. Moreover, resveratrol increased insulin sensitivity in the muscle and protected mice from obesity or insulin resistance when fed on a high-fat diet [40]. Additionally, epigallocatechin-3-gallate (EGCG), which is the most effective and abundant catechin in green tea, has been reported to have the antioxidant, anti-obesity and anti-cancer activities [85]. Several studies on cultured adipocytes and animal models demonstrated that EGCG decreased intracellular levels of ROS and inhibited extracellular signal-related kinases (ERK) activation. Moreover, EGCG was found to activate the AMPK to elevate mitochondrial function and  $\beta$ -oxidation of fatty acids to decrease the accumulation of lipids [86]. All of these downstream effects of EGCG would be of great use to improve insulin sensitivity of the target tissue cells.

On the other hand, attention should be paid to the therapeutic potential of pyruvate in the treatment of diabetes. Pyruvate, an intermediate located at the key position of glucose metabolism, has been involved in anaerobic glycolysis and aerobic respiration. Some beneficial effects were reported about the administration of pyruvate to patients harboring with A3243 or A8344G mutation of mtDNA [87]. Pyruvate can not only improve the intracellular redox status by elimination of hydrogen peroxide via non-enzymatic reaction,

but also increases ATP production by oxidation of NADH to NAD<sup>+</sup> by lactate dehydrogenase (LDH). The high level of NAD<sup>+</sup> may also enhance the activity of SIRT3, an NAD<sup>+</sup>-dependent deacetylase. In addition, it was found that through the inhibition of TNF $\alpha$  production and NF $\kappa$ B signaling pathways pyruvate could ameliorate the inflammatory symptom of insulin resistance [88].

#### 8.4. Increase of antioxidant defense

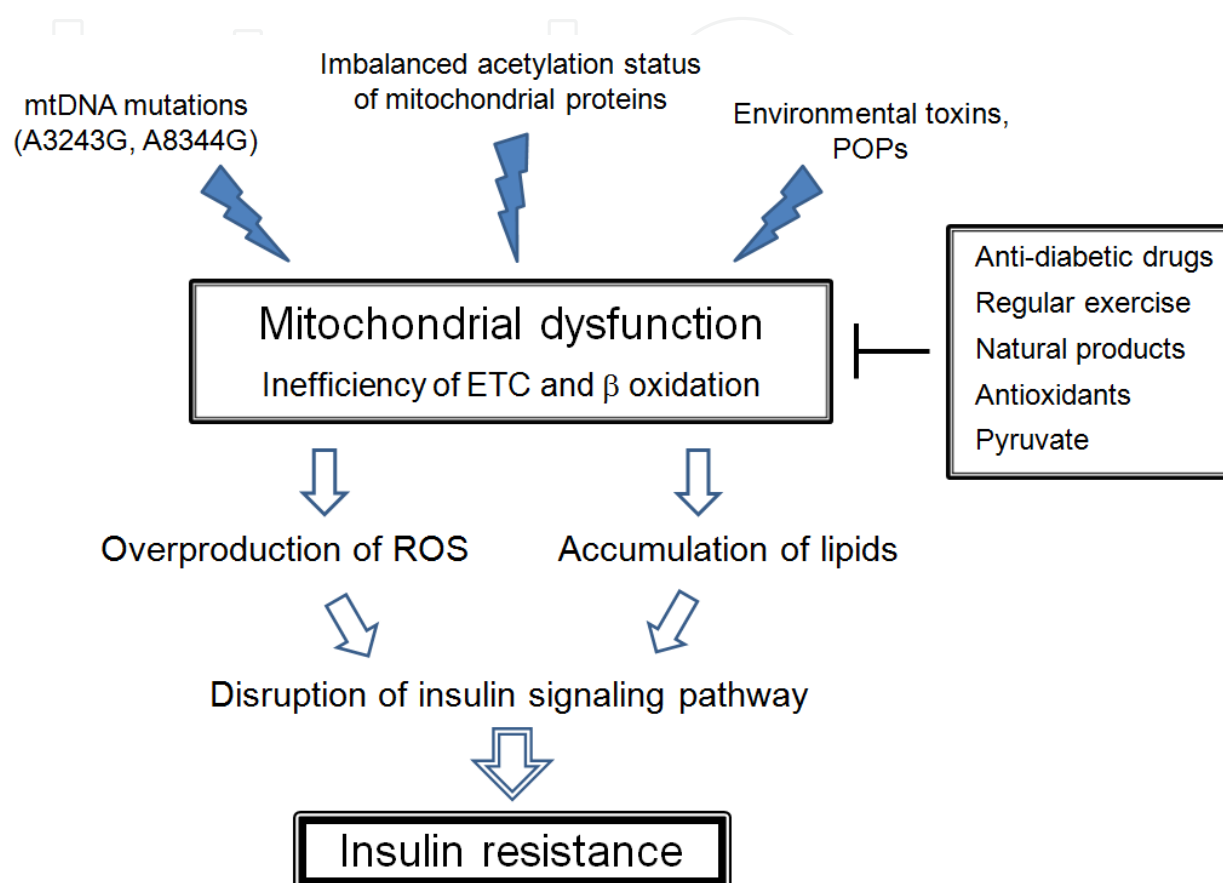
Treatment of lipoic acid, an antioxidant, could not only decrease the intracellular ROS but also enhance insulin-stimulated glucose utilization in skeletal muscle of diabetic animals with insulin resistance. Yaworsky et al. [89] demonstrated that lipoic acid significantly increased insulin-stimulated glucose uptake of adipocytes through rapid translocation of Glut1 and Glut4 to the plasma membrane *via* the activation of insulin signaling pathway, which includes an increase in tyrosine phosphorylation of IR and IRS-1 as well as activation of PI3K and Akt. In addition to its antioxidant activity, lipoic acid was found to significantly increase mitochondrial biogenesis and function, including oxygen consumption rate and  $\beta$ -oxidation of fatty acids in adipocytes [90]. All of these effects of lipoic acid were enhanced by co-treatment of cells with acetyl L-carnitine (ALCAR), another mitochondrial nutrient [91]. These findings suggest that lipoic acid improves insulin sensitivity of adipocytes through its ability to elevate the antioxidant capacity and to enhance mitochondrial function. In addition, several studies have demonstrated that increasing antioxidant capacities by addition of cell-permeabilized MnSOD [29, 30] or overexpression of catalase [92, 93] and GPx3 [94] to reduce intracellular ROS could improve insulin sensitivity in cultured cells or mice. Taken together, the above-mentioned observations clearly indicate that therapeutic agents targeting to mitochondria or antioxidant defense system could ameliorate the symptoms of insulin insensitivity in cultured cells and animals, and perhaps also in the patients. These findings also support the notion that mitochondrial function is essential for the maintenance of insulin sensitivity and glucose homeostasis in the human body.

### 9. Concluding remarks

This chapter has provided an overview of recent advances in the understanding of mitochondrial role in the insulin insensitivity and type 2 diabetes, including the clinical observations and possible mechanisms of the insulin insensitivity induced by mitochondrial dysfunction in the insulin-responsive tissues. Mitochondrial defects resulted from inheritable A3243G or A8344G mutation of mtDNA or environmental pollutants and toxins or dysregulated acetylation status of metabolic enzymes may lead to an overproduction of intracellular ROS and lipids. These events culminate in the inactivation of the insulin signaling pathway and result in insulin insensitivity in muscle and adipocytes. Improvement of insulin sensitivity and glucose homeostasis may be achieved by the strategy to up-regulate mitochondrial biogenesis, function and antioxidant defense through exercise, therapeutic agents, and dietary supplement of antioxidants or natural products



(Figure 1). These recent advances not only provide novel information for us to better understand the connection between mitochondrial dysfunction and metabolic diseases but also lead us to a new avenue in the prevention and treatment of type 2 diabetes or metabolic syndrome by the mitochondria-targeting medicine.



**Figure 1.** The scheme illustrating the role of mitochondria in the pathogenesis and therapeutic target of insulin resistance

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