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Role of mitochondrial DNA variation in the pathogenesis of diabetes mellitus

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1. ABSTRACT

Mitochondria are crucial intracellular organelles where ATP and reactive oxygen species are generated via the electron transport chain. They are also where cellular fate is determined. There is a growing body of evidence that mitochondrial dysfunction plays an important role in the pathogenesis of type 2 diabetes. Mitochondrial dysfunction in pancreatic beta-cells results in impaired glucose-stimulated insulin secretion. It is also associated with decreased oxidative phosphorylation and fatty acid oxidation in insulin sensitive tissues. Variation in mitochondrial DNA (mtDNA) quantity and quality are reported to be associated with the risk of developing diabetes. A rare variant, mtDNA 3243 A>G, is well known to cause maternally inherited diabetes. Common mtDNA variants, such as mtDNA 16189 T>C and several mtDNA haplogroups, are also associated with an increased risk of diabetes, especially in Asians. The variant load, known as heteroplasmy, in a specific tissue is thought to modulate the phenotypic expression of these mtDNA variants. In this article, we review the role of mitochondrial dysfunction in the pathogenesis of diabetes and the association between mtDNA variations and risk of diabetes.

2. INTRODUCTION: OVERVIEW OF THE PATHOGENESIS OF DIABETES

According to the recent 6th edition of the Diabetes Atlas (2013) by the International Diabetes Federation, the global burden of diabetes is estimated to be approximately 8.3% of adults (382 million people) (1). This figure is expected to increase by 55% (592 million people) within the next 25 years. In a recent analysis of the United States National Health Interview Survey, the prevalence and incidence of diabetes have doubled from 1980 to 2008 (2). Although there seems to be a plateau between 2008 and 2012, and even a decrease in the incidence of cases of diabetes, the figures are still increasing in non-Hispanic black and Hispanic populations, as well as in people with a lower educational level. The increased prevalence of diabetes is attributable to multiple factors, including reduced physical activity, increased dietary fat intake and the resulting epidemic increase in obesity (2).

Type 2 diabetes is a complex multigenic disorder where both environmental and genetic factors interact as predisposing factors (3). Several lines of evidence indicate that genetic factors play a role in the pathogenesis of diabetes, stemming from the fact that family history is a major risk factor for diabetes (4). First, it is well known that the risk of diabetes increases by two to fourfold when one or both parents are affected by diabetes (5). Although controversial, there are studies arguing that there is an excess maternal history of glucose intolerance in diabetes subjects (6). Second, evidence for a genetic predisposition to diabetes comes from the

regional/ethnic difference with regards to the prevalence of diabetes. The prevalence of diabetes is highest in the Middle East and North Africa, followed by North America and the Caribbean. More specifically, Tokelu, a territory of New Zealand in the South Pacific Ocean, has the highest prevalence of diabetes (1). In addition, Asian immigrants to the United Kingdom have markedly increased prevalence of diabetes compared with Europeans (7). This regional/ethnic difference resulted in the thrifty gene hypothesis. In this hypothesis, James V. Neel proposed that diabetogenic genes arose during evolutionary history to promote more efficient energy storage and presented selective advantages during periods of famine (8). The third evidence of genetic predisposition of diabetes is that there are monogenic forms of diabetes. Recent advances in genetic studies, accelerated by genome-wide association studies, have identified at least 70 genetic loci associated with diabetes (9, 10). However, these only explain a limited portion of diabetes' heritability (11). Mitochondrial DNA (mtDNA) variants might explain part of the missing heritability. The mtDNA is transmitted only maternally, which could explain the excess maternal association with diabetes. In addition, mtDNA could be the basis of the thrifty gene hypothesis because mitochondria are the site of most cellular adenosine triphosphate (ATP) generation and fatty acid oxidization. Finally, pathogenic mtDNA variations, such as the mtDNA 3243 A>G variant, are known to result in a specific genetic form of diabetes known as maternally inherited diabetes and deafness (MIDD).

Type 2 diabetes is characterized by variable degrees of insulin resistance and impaired insulin secretion. The relative contribution of insulin resistance and insulin secretion on the pathogenesis of type 2 diabetes has been controversial. Recently, we have reported that impaired beta-cell function and incomplete compensation for progressive deterioration in insulin resistance is crucial for the development of diabetes, at least in Asians (12). Insulin is secreted solely from pancreatic islet beta-cells. The main stimulus for insulin secretion is an increased glucose concentration. When glucose enters the beta-cell via passive diffusion and facilitated transport by glucose transporters, it is metabolized to pyruvate. Pyruvate is further metabolized in the mitochondrial tricarboxylic acid (TCA) cycle to yield ATP. The increased intracellular ATP/ADP ratio closes ATP sensitive potassium channels, resulting in depolarization and calcium influx into the beta-cell (13). The increase in cytosolic calcium stimulates fusion of preformed insulin granules with the plasma membrane and increases exocytosis (14). Mitochondria play a critical role in insulin secretion, as they are the site of ATP generation. The importance of mitochondrial function to insulin secretion is supported by the fact that most diabetes arising from pathogenic mtDNA mutation have defective insulin secretion (15).

On the other hand, insulin resistance occurs when cells and tissues do not respond adequately to insulin at physiological concentrations. The three major insulin sensitive tissues that play central roles in energy homeostasis are muscle, adipose tissue, and liver. Skeletal muscle is the largest insulin sensitive tissue and accounts for approximately 80% of insulin dependent glucose disposal (16). Skeletal muscle has a high oxidative energy demand, which is mostly supplied by mitochondria. In the fed state, mitochondria oxidize glucose, whereas during fasting, mitochondria oxidize free fatty acids to ensure an adequate energy supply (17). When there is an energy imbalance with nutrient oversupply, insulin signaling is impaired and insulin stimulated glucose transport is reduced. Mitochondrial dysfunction is thought to play an important role in skeletal muscle insulin resistance by inducing intramyocellular lipid accumulation and impaired intracellular insulin signaling (18).

The pathophysiology of type 2 diabetes implies that mitochondria can affect both insulin secretion and insulin resistance. Furthermore, the genetics of diabetes suggest that mtDNA also play a role in the development of diabetes. In the following sections, we will focus on the role of mitochondrial dysfunction in the pathogenesis of diabetes and mtDNA variations that are associated with an increased risk for developing diabetes.

3. ROLE OF MITOCHONDRIAL DYSFUNCTION IN DIABETES

3.1. Mitochondria dysfunction and insulin secretion

Mitochondrial dysfunction can lead to defective insulin secretion in three ways. First, it can impair oxidative phosphorylation and glucose-stimulated insulin secretion (19). Reduced mitochondrial mass or function leads to decreased ATP generation and consequently impaired insulin secretion (20). The nuclear DNA encoded mitochondrial transcription factor A (*Tfam*) is essential for the maintenance and transcription of mtDNA (21). A mouse model of mitochondrial diabetes, which lacked *Tfam* in pancreatic beta-cells, was shown to have early onset diabetes with severe depletion of mtDNA and decreased ATP generation (22). Importantly, there was a significant defect in glucose-stimulated insulin secretion and reduced beta-cell mass in these mice. In a genome-wide association study in humans, an intronic variant (rs950994) of mitochondrial transcription factor B1 (*TFB1M*) was associated with a reduced 30 minute plasma insulin concentration and an increased risk of type 2 diabetes (23). TFB1M, which was originally thought to be a mitochondrial transcription factor, is a dimethyltransferase that plays an important role in the biogenesis of mitochondrial ribosomes and the translation of mitochondrial proteins (24). Beta-cell specific knockout of *Tfb1m* in mice showed impaired ATP

generation by oxidative phosphorylation and defective glucose-stimulated insulin secretion, which eventually resulted in the development of diabetes (25). These data indicate that mitochondrial oxidative phosphorylation is important in beta-cell function and insulin secretion. The second way in which mitochondrial dysfunction can impair beta-cell function is through increased reactive oxygen species (ROS) production (20). Mitochondria are a major source of ROS production (26). An excess in ATP levels compared with cellular energy requirement leads to a "stagnation" in the electron transport chain and increased ROS production (27). ROS at physiological levels can participate in cell signaling and enhance glucose-stimulated insulin secretion (28, 29). However, when ROS is elevated above a certain threshold, it can impair insulin secretion (30). Superoxide ($O_2^{\cdot -}$) that is produced in mitochondria is converted to H_2O_2 primarily by the mitochondrial isoform of superoxide dismutase 2 (SOD2). It has been reported that heterozygous beta-cell specific knockout of *Sod2* in mice resulted in impaired glucose-stimulated insulin secretion in high fat fed conditions (31) and increased ROS levels in the pancreatic islets. The third way in which mitochondrial dysfunction can impair beta-cell function is through increased beta-cell apoptosis. In human studies, patients with type 2 diabetes tend to have disconnected, short, and swollen mitochondria in their beta-cells, and the islet mass is significantly decreased, suggesting that mitochondrial dysfunction is associated with apoptosis (32, 33). Mitochondria are the main regulators of cellular apoptosis (34). Glucose and fatty acid overload can lead to the loss of mitochondrial membrane potential and activation of mitochondrial permeability transition pore, resulting in beta-cell apoptosis (35). Recently, it was reported that mammalian sterile 20-like kinase-1 (MST1) is a critical regulator of beta-cell apoptosis, which exerts its effect by the mitochondria-dependent apoptosis pathway (36). Taken together, mitochondrial dysfunction resulting in defective oxidative phosphorylation, increased ROS production and apoptosis can lead to decreased insulin secretion and beta-cell dysfunction.

3.2. Mitochondria dysfunction and insulin resistance

The most important environmental risk factors of insulin resistance are obesity and physical inactivity. Both obesity and physical inactivity are associated with decreased mitochondrial mass and function in skeletal muscle (37, 38). It has been suggested that mitochondrial dysfunction in skeletal muscle impairs fatty acid oxidation and increases intramyocellular lipid accumulation, resulting in insulin resistance (18). Using nuclear magnetic resonance studies, it was reported that an age-related decrease in insulin sensitivity was paralleled by a 40% decrease in mitochondrial oxidative phosphorylation and increased intramyocellular lipid accumulation (39). Similarly, insulin-resistant offspring of type 2 diabetes patients had a 30% decrease in oxidative phosphorylation and a 38% decrease in skeletal muscle mitochondrial density compared with insulin sensitive control subjects (40). Transcriptome analysis using microarrays showed that genes involved in mitochondrial oxidative phosphorylation were coordinately down regulated in diabetic subjects as a result of decreased PGC-1alpha expression (41, 42). In a study using permeabilized muscle fibers, patients with type 2 diabetes had a decrease of approximately 20% in the oxygen consumption rate compared with normal control subjects (43). However, this difference diminished when adjusted for the mitochondrial mass, suggesting that decreased mitochondrial mass could be the major contributor. In another study using isolated mitochondria, the oxygen consumption rate was lower in mitochondria derived from obese type 2 diabetes subjects compared with that of controls, suggesting there might be qualitative difference in mitochondrial function (44). However, the causative role of mitochondrial dysfunction in skeletal muscle is still controversial (45, 46). In Asian Indians, oxidative phosphorylation capacity did not differ between diabetic and control subjects (47). In fact, compared with European Americans, Asian Indians had higher oxidative phosphorylation capacity despite being more insulin resistant. In a mouse model, targeted deletion of apoptosis inducing factor (AIF) lead to a progressive decrease in oxidative phosphorylation and resulted in increased insulin sensitivity (48). Further studies are required to clarify the role of mitochondrial dysfunction in insulin resistance.

4. MITOCHONDRIAL DNA VARIATION AND RISK OF DIABETES

Various factors, both environmental and genetic, can lead to mitochondrial dysfunction, with relevance to the pathophysiology of diabetes. Environmental factors include obesity, physical inactivity, high calorific diet, persistent organic pollutants, etc. The role of environmental factors in mitochondrial dysfunction and the pathogenesis of diabetes were reviewed in our previous articles (49, 50). Therefore, here we will mainly focus on mtDNA variations affecting mitochondrial dysfunction and diabetes.

4.1. Mitochondrial DNA variation: quantitative and qualitative

Mitochondria have their own DNA for transcription and replication (51). There are hundreds of mitochondria in a cell and each mitochondrion has 2 to 10 mtDNA copies (52). The mtDNA is a single circular double stranded DNA with 16,569 base pairs. It consists of a heavy (H) strand and a light (L) strand, which are enriched in guanine and cytosine, respectively (51). There is also a short 7S DNA strand that compliments with the L strand in the regulatory region of mtDNA resulting in a triple stranded structure. This region is called the displacement (D) loop and contains the

origin of replication for the H strand and major promoter regions (53). The D loop region also contains highly polymorphic sequences (hypervariable regions) (54). The mtDNA is unique as it does not have introns and is not equipped with histones, making it vulnerable to frequent mutations.

The mtDNA variation can have different effect according to: 1) quantitative variation in mtDNA content and/or 2) qualitative variation in mtDNA sequence. Regarding the mtDNA quantity, we investigated the association between peripheral blood mtDNA content and the risk of type 2 diabetes, and we related these factors to the metabolic phenotype (37, 55-58). In a population-based prospective cohort, mtDNA content was decreased by 25% in subjects who progressed to diabetes within two years (37). In a second study, mtDNA content was decreased by 20% in non-diabetic offspring of type 2 diabetes patients and was associated with decreased insulin sensitivity (55). The mtDNA content was inversely associated with waist to hip circumference ratio, blood pressure, fasting glucose concentration, and insulin secretion (37, 57). A study in a Chinese population reported decreased peripheral blood mtDNA content in patients with diabetes (59). However, conflicting findings have fueled a debate on whether decreased mtDNA content is a cause or a consequence of deteriorated glucose metabolism (60-62). It has been argued that mtDNA content in peripheral blood cells might not reflect the mitochondrial function in the cells or tissues that are relevant to energy metabolism.

4.2. Mitochondrial DNA 3243 A>G variation

There are number of genetic variations associated with diabetes. However, there is little knowledge about associations between mtDNA variations and type 2 diabetes. Mitochondrial DNA variations can be categorized as either rare, functional variants or common variants that increase disease predisposition. A rare, functional mtDNA variant can result in MIDD, and mtDNA variants associated with MIDD have been reviewed by Maasen et al. (15). One of the most thoroughly investigated rare mtDNA variant is the mtDNA 3243 A>G in the $tRNA^{(Leu)(UUR)}$ gene. It was first identified in a large family with MIDD (63). This variant can also result in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), which is a multisystem disorder, with typical onset during childhood (64). The frequency of this variant is relatively rare and shows ethnic difference. It is reported to be present in approximately 0.5 to 3% in Asians (65-69), while its frequency is much lower in Europeans (70, 71). The variant is more likely to be observed in particular subtypes of diabetes with maternal inheritance and hearing loss (72), early onset with family history of diabetes (66), end stage renal disease (73) and atypical type 1 diabetes (74).

Clinical presentation of the mtDNA 3243 A>G variation is heterogeneous. It can manifest as either type 1 diabetes or type 2 diabetes, depending upon the severity of the insulin deficiency (75). The age of diabetes onset is usually younger than type 2 diabetes. Diabetes patients with the mtDNA 3243 A>G variant have a lower body mass index, a progressive impairment in insulin secretion (76) and are more likely to be treated with insulin (77). The mtDNA 3243 A>G variant is associated with various conditions, such as sensory neural hearing loss, cardiomyopathy (78), macular pattern dystrophy (79), progressive kidney disease (80), gastrointestinal symptoms (81, 82), encephalomyopathy and mental disorders (83). Mechanisms for this wide variability of clinical manifestation are largely unknown. It is suggested that differences in variant load (heteroplasmy) and tissue distribution of the variant contribute to the variable phenotypic expression (84, 85). When the variant load is relatively low, it can result in MIDD (63). In contrast, when the variant load is as high as 50 to 90%, it can result in MELAS (86). Recently, it was shown that small increases in heteroplasmy level can lead to modest defects in oxidative phosphorylation and discrete changes in nuclear gene expression and cellular phenotype (87). The detection of this variant in peripheral blood samples is difficult because heteroplasmy levels in leukocytes are relatively low and decline with age (88).

Diabetes associated with mtDNA 3243 A>G variant is characterized by both impaired insulin secretion (89, 90) and insulin resistance (91). A defect in glucose-stimulated insulin secretion is a possible early primary abnormality, which might result from the progressive impairment of oxidative phosphorylation (92). Histological evaluation of pancreatic tissue from diabetes patients with this variant showed a reduction in total islet mass without evidence of insulitis or apoptosis (93). This variant can lead to dimerization of the mutant tRNA and impaired aminoacylation (94), and result in increased degradation of mitochondrial DNA encoded proteins (95). In addition, we have shown that this variant results in decreased mitochondrial oxygen consumption and increased ROS generation in cybrid cells (96). The resultant mitochondrial dysfunction activated various retrograde signaling pathways involving retinoid X receptor alpha, ROS, c-JUN N-terminal kinase, and PGC-1alpha. Among them, the retinoid X receptor alpha pathway contributed to the decrease in nuclear encoded oxidative phosphorylation gene expression and aggravated the mitochondrial dysfunction (96).

4.3. Mitochondrial DNA 16189 T>C variation

Another well-known variation is the relatively common T>C variant at the nucleotide position 16189, which produces heteroplasmic length variation of an uninterrupted poly C tract between 16184 and 16193 (97). This variant is more commonly observed in Asians with a frequency of 30%, compared with a frequency of 10%

in Europeans (98, 99). In 1998, Poulton et al. proposed that the mtDNA 16189 T>C variant is associated with insulin resistance (100). They also suggested that this variant may enhance maternal restraint of fetal growth and thereby exacerbate the subsequent risk for insulin resistance and type 2 diabetes (101). Subsequent studies reported the association of this variant with insulin resistance (102, 103), body mass index (104), metabolic syndrome (105) and cardiovascular disease (106, 107). Association with type 2 diabetes was confirmed in a large Asian population, including more than 3,600 individuals with type 2 diabetes and controls from Korea, Japan, Taiwan, Hong Kong and China (98). This study showed that the mtDNA 16189 T>C variant was significantly associated with an increased risk for type 2 diabetes (odds ratio [OR] 1.26, 95% confidence interval [CI] 1.08 – 1.46, P = 0.003) (98). Studies of Europeans showed conflicting results due to a lower frequency of this variant in European populations that required a large number of subjects for adequate statistical power (99, 108, 109). It is noteworthy that in a recent meta-analysis involving more than 26,000 European type 2 diabetes cases and controls, this variant was modestly associated with an increased risk of diabetes (OR 1.10, 95% CI 1.01 – 1.20, P = 0.03) (109).

The functional significance of this variant is not fully understood. It might play an important role in mtDNA replication because it is located at the hypervariable region of the D loop, which contains the origin of replication for the H strand (100). We found that the mtDNA 16189 T>C variant decreases the binding affinity of the mitochondrial single-stranded DNA-binding protein (mtSSB) (98). The mtSSB is known to be involved in stabilizing the D loop and maintaining the mtDNA content (110). Consistent with this finding, subjects with mtDNA 16189C variant had a lower mtDNA content compared with those with 16189T variant (111).

4.4. Mitochondrial DNA haplogroup

The mtDNA haplogroups are geographical region-specific variations that might have originated from natural selection pressures, such as cold climate or famine (112). It has been suggested that mtDNA haplogroup might affect human longevity and diseases associated with energy metabolism in modern times (113). It has also been proposed that common mtDNA haplogroups might be associated with susceptibility of type 2 diabetes. However, in a study involving 6,600 Europeans, there were no significant association between common mtDNA variants (frequency > 1%) and susceptibility to diabetes or related metabolic phenotypes (114). In contrast, in a combined analysis of 4,300 diabetes cases and controls from Korea and Japan, we observed that haplogroup N9a was significantly associated with protection against type 2 diabetes (OR 0.55, 95% CI 0.40 – 0.75, P = 0.0002). On the other hand, haplogroups F (OR 1.34, 95% CI 1.07 – 1.67, P = 0.0114) and D5 (OR 1.33, 95% CI 1.00 – 1.76, P = 0.0475) were associated with an increased risk for diabetes (115). In a Chinese population, haplogroup B4 (OR 1.54, 95% CI 1.18 – 2.02, P < 0.001) was associated with increased risk of diabetes (116). Some mitochondrial haplogroups are reported to be associated with diabetic complications (117-120) and post-transplantation diabetes mellitus (121). Gene expression studies of cybrid cells harboring diabetes-susceptible mitochondrial haplogroup F showed down-regulation of oxidative phosphorylation and up-regulation of glycolysis compared with the diabetes resistant N9a haplogroup (122).

4.5. Epigenetic factors affecting mitochondrial function

We previously showed that mtDNA content in peripheral blood is decreased in subjects with diabetes and even in offspring of diabetes patients. Fetal and early postnatal malnutrition cause long-term decreases in mtDNA content in skeletal muscle and in the liver (123). A maternal high-fat diet during pregnancy also reduced mtDNA content and decreased PGC-1alpha expression in liver (124). Mitochondrial dysfunction and the resultant mitochondrial stress can regulate both nuclear-encoded and mtDNA encoded mitochondrial genes by epigenetic mechanisms. In patients with type 2 diabetes, hypermethylation of the PGC-1alpha gene promoter was observed in skeletal muscle (125). The methylation level was negatively correlated with PGC-1alpha expression and mtDNA content. The mtDNA itself can also be epigenetically regulated. DNA methyl transferase 1 (DNMT1) binds to the mtDNA, and methylation is modulated in response to oxidative stress (126, 127). Indeed, epigenetic modulations including DNA methylation are a way of retrograde signaling for mitochondria-nucleus communication and can affect insulin signaling and metabolic pathways (128). These findings suggest that epigenetic factors are important in modulating the phenotypic expression of pathogenic mtDNA variations in addition to the level of heteroplasmy, as well as the mtDNA haplogroup.

5. SUMMARY

We have reviewed the pathophysiologic role of mitochondrial dysfunction in type 2 diabetes and the association between mtDNA variations and the development of diabetes (Figure 1). Mitochondrial dysfunction can lead to beta-cell dysfunction and impaired insulin secretion. It is also associated with insulin resistance, but whether it is a cause or consequence is unclear. A relatively rare functional variant, mtDNA 3243 A>G, is causative of mitochondrial diabetes and affects both insulin secretion and insulin resistance to varying degrees. A common mtDNA 16189 T>C variant is associated with an increased risk of type 2 diabetes, especially in Asian populations, in which there is a higher

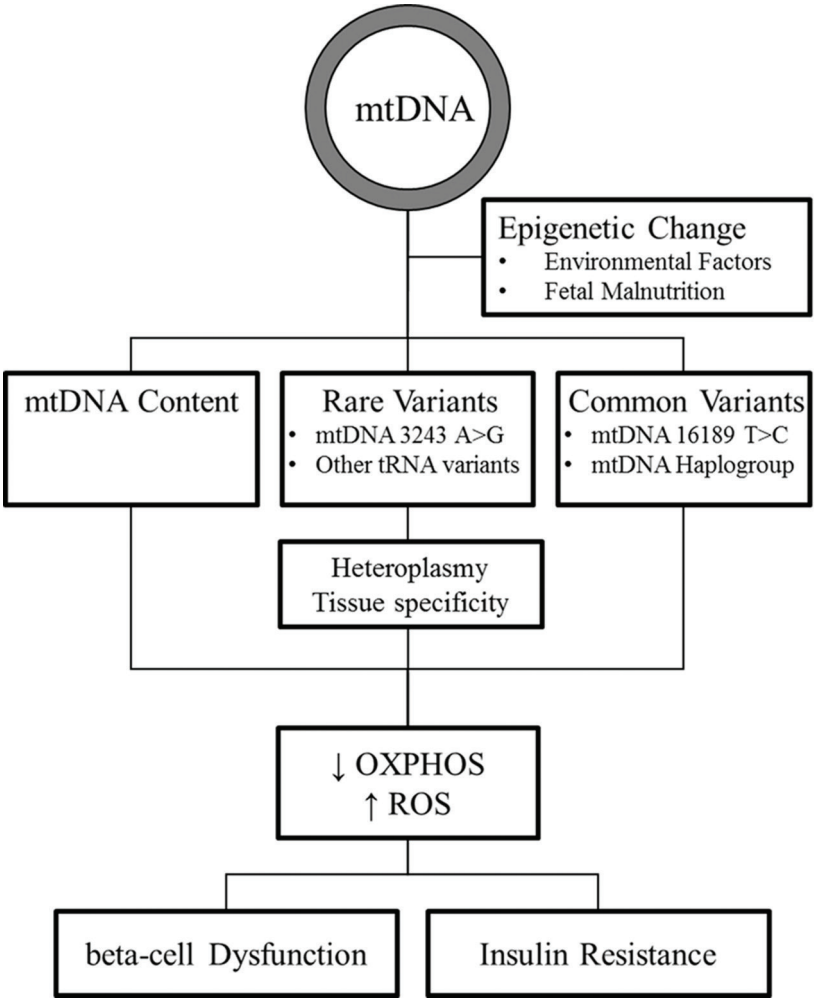

Figure 1. Genetic variants in mtDNA can affect both insulin secretion and insulin resistance. Variants in mtDNA include mtDNA content, rare functional mtDNA 3243 A>G variant, common mtDNA 16189 T>C variant, and mtDNA haplogroups. Tissue specificity and the level of heteroplasmy modulate the phenotypic effect of these variations. These variants are thought to affect both insulin secretion and insulin resistance. OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

frequency of this variant. The mtDNA haplogroup also modulates the risk of diabetes. However, as mtDNA variants exist in heteroplasmy, their level and tissue distribution might explain the variability in related phenotypes. Mitochondria are at the center of cellular energy metabolism. Therefore, further understanding of their role in the pathogenesis of diabetes and the functional consequences of mtDNA variations will improve our chances of overcoming the increasing epidemic of diabetes.

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in muylti-Ethnic Samples (T2D-GENES) Consortium, A. Mahajan, M. J. Go, W. Zhang, J. E. Below, K. J. Gaulton, T. Ferreira, M. Horikoshi, A. D. Johnson, M. C. Ng, I. Prokopenko, D. Saleheen, X. Wang, E. Zeggini, G. R. Abecasis, L. S. Adair, P. Almgren, M. Atalay, T. Aung, D. Baldassarre, B. Balkau, Y. Bao, A. H. Barnett, I. Barroso, A. Basit, L. F. Been, J. Beilby, G. I. Bell, R. Benediktsson, R. N. Bergman, B. O. Boehm, E. Boerwinkle, L. L. Bonnycastle, N. Burtt, Q. Cai, H. Campbell, J. Carey, S. Cauchi, M. Caulfield, J. C. Chan, L. C. Chang, T. J. Chang, Y. C. Chang, G. Charpentier, C. H. Chen, H. Chen, Y. T. Chen, K. S. Chia, M. Chidambaram, P. S. Chines, N. H. Cho, Y. M. Cho, L. M. Chuang, F. S. Collins, M. C. Cornelis, D. J. Couper, A. T. Crenshaw, R. M. van Dam, J. Danesh, D. Das, U. de Faire, G. Dedoussis, P. Deloukas, A. S. Dimas, C. Dina, A. S. Doney, P. J. Donnelly, M. Dorkhan, C. van Duijn, J. Dupuis, S. Edkins, P. Elliott, V. Emilsson, R. Erbel, J. G. Eriksson, J. Escobedo, T. Esko, E. Eury, J. C. Florez, P. Fontanillas, N. G. Forouhi, T. Forsen, C. Fox, R. M. Fraser, T. M. Frayling, P. Froguel, P. Frossard, Y. Gao, K. Gertow, C. Gieger, B. Gigante, H. Grallert, G. B. Grant, L. C. Grrop, C. J. Groves, E. Grundberg, C. Guiducci, A. Hamsten, B. G. Han, K. Hara, N. Hassanali, A. T. Hattersley, C. Hayward, A. K. Hedman, C. Herder, A. Hofman, O. L. Holmen, K. Hovingh, A. B. Hreidarsson, C. Hu, F. B. Hu, J. Hui, S. E. Humphries, S. E. Hunt, D. J. Hunter, K. Hveem, Z. I. Hydrie, H. Ikegami, T. Illig, E. Ingelsson, M. Islam, B. Isomaa, A. U. Jackson, T. Jafar, A. James, W. Jia, K. H. Jockel, A. Jonsson, J. B. Jowett, T. Kadowaki, H. M. Kang, S. Kanoni, W. H. Kao, S. Kathiresan, N. Kato, P. Katulanda, K. M. Keinanen-Kiukaanniemi, A. M. Kelly, H. Khan, K. T. Khaw, C. C. Khor, H. L. Kim, S. Kim, Y. J. Kim, L. Kinnunen, N. Klopp, A. Kong, E. Korpi-Hyovalti, S. Kowlessur, P. Kraft, J. Kravic, M. M. Kristensen, S. Krithika, A. Kumar, J. Kumate, J. Kuusisto, S. H. Kwak, M. Laakso, V. Lagou, T. A. Lakka, C. Langenberg, C. Langford, R. Lawrence, K. Leander, J. M. Lee, N. R. Lee, M. Li, X. Li, Y. Li, J. Liang, S. Liju, W. Y. Lim, L. Lind, C. M. Lindgren, E. Lindholm, C. T. Liu, J. J. Liu, S. Lobbens, J. Long, R. J. Loos, W. Lu, J. Luan, V. Lyssenko, R. C. Ma, S. Maeda, R. Magi, S. Mannisto, D. R. Matthews, J. B. Meigs, O. Melander, A. Metspalu, J. Meyer, G. Mirza, E. Mihailov, S. Moebus, V. Mohan, K. L. Mohlke, A. D. Morris, T. W. Muhleisen, M. Muller-Nurasyid, B. Musk, J. Nakamura, E. Nakashima, P. Navarro, P. K. Ng, A. C. Nica, P. M. Nilsson, I. Njolstad, M. M. Nothen, K. Ohnaka, T. H. Ong, K. R. Owen, C. N. Palmer, J. S. Pankow, K. S. Park, M. Parkin, S. Pechlivanis, N. L. Pedersen, L. Peltonen, J. R. Perry, A. Peters, J. M. Pinidiyapathirage, C. G. Platou, S. Potter, J. F. Price, L. Qi, V. Radha, L. Rallidis, A. Rasheed, W. Rathman, R. Rauramaa, S. Raychaudhuri, N. W. Rayner, S. D. Rees, E. Rehnberg, S. Ripatti, N. Robertson, M. Roden, E. J. Rossin, I. Rudan, D. Rybin, T. E. Saaristo, V. Salomaa, J. Saltevo, M. Samuel, D. K. Sanghera, J. Saramies, J. Scott, L. J. Scott, R. A. Scott, A. V. Segre, J. Sehmi, B. Sennblad, N. Shah, S. Shah, A. S. Shera, X. O. Shu, A. R. Shuldiner, G. Sigurdsson, E. Sijbrands, A. Silveira, X. Sim, S. Sivapalaratnam, K. S. Small, W. Y. So, A. Stancakova, K. Stefansson, G. Steinbach, V. Steinthorsdottir, K. Stirrups, R. J. Strawbridge, H. M. Stringham, Q. Sun, C. Suo, A. C. Syvanen, R. Takayanagi, F. Takeuchi, W. T. Tay, T. M. Teslovich, B. Thorand, G. Thorleifsson, U. Thorsteinsdottir, E. Tikkanen, J. Trakalo, E. Tremoli, M. D. Trip, F. J. Tsai, T. Tuomi, J. Tuomilehto, A. G. Uitterlinden, A. Valladares-Salgado, S. Vedantam, F. Veglia, B. F. Voight, C. Wang, N. J. Wareham, R. Wennauer, A. R. Wickremasinghe, T. Wilsgaard, J. F. Wilson, S. Wiltshire, W. Winckler, T. Y. Wong, A. R. Wood, J. Y. Wu, Y. Wu, K. Yamamoto, T. Yamauchi, M. Yang, L. Yengo, M. Yokota, R. Young, D. Zabaneh, F. Zhang, R. Zhang, W. Zheng, P. Z. Zimmet, D. Altshuler, D. W. Bowden, Y. S. Cho, N. J. Cox, M. Cruz, C. L. Hanis, J. Kooner, J. Y. Lee, M. Seielstad, Y. Y. Teo, M. Boehnke, E. J. Parra, J. C. Chambers, E. S. Tai, M. I. McCarthy and A. P. Morris: Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet*, 46(3), 234-44 (2014)

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