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REVIEWS: CURRENT TOPICS

The role of mitochondrial DNA in the development of type 2 diabetes caused by fetal malnutrition☆

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Abstract

Epidemiological studies have revealed strong and reproducible links between indices of poor fetal growth and susceptibility to the development of glucose intolerance and insulin resistance syndrome in adult life. To explain these associations, the thrifty phenotype hypothesis has been proposed. Mitochondrial DNA abnormalities have been known to cause insulin deficiency, insulin resistance and diabetes mellitus. In this review, we propose that mitochondrial dysfunction is a link between malnutrition during early life and disease in adult life. The potential mechanism for mitochondrial dysfunction will be focused on availability of the taurine and nucleotides, and imprinting on the genes.

Keywords: Mitochondrial DNA; Type 2 diabetes; Fetal malnutrition; Thrifty phenotype

1. Introduction: metabolic syndrome and the thrifty phenotype hypothesis

Metabolic syndrome, a clustering of cardiovascular risk factors such as diabetes, hypertension, dyslipidemia and obesity, is now recognized as a major health problem in westernized countries [1]. Insulin resistance has been recognized as the fundamental metabolic defect of this syndrome [2], although the underlying causes of insulin resistance itself remain largely unknown. A number of epidemiological studies have revealed links between various indices of reduced intrauterine and early postnatal growth, and susceptibility to insulin resistance syndrome in adult life [3–7]. On the basis of these observations, Hales and Barker [8] suggested the "thrifty phenotype" hypothesis: poor nutritional condition in early life programs a phenotype in later life, in a way that is beneficial to survival under poor nutritional conditions but detrimental when nutrition is abundant. Programming, an event operating at a critical or sensitive period, results in a long-term change in the structure or function of the organism that predisposes to disease in adult life. Programming is a well-established biological phenomenon, and fetal nutrition has been proposed as one of the central programming stimulus [9]. This idea can be compared with the thrifty genotype hypothesis proposed by Neel [10], which was proposed to explain the very high prevalence of obesity and diabetes in some American Indians such as the Pimas. This hypothesis suggested that native Indians might have accumulated genetic changes (thrifty genotypes) that are beneficial for survival under famine conditions, but are detrimental when society becomes affluent. The thrifty genotype/phenotype hypotheses are illustrated in Fig. 1.

In this review, we would like to discuss the thrifty phenotype hypothesis based on the mitochondrial genome [11]. Mitochondria are the intracellular organelles that generate energy for cellular processes, by producing ATP through oxidative phosphorylation. Mitochondria have their own DNA (mtDNA) and an independent replication system. Human mtDNA is a double-stranded, circular molecule, 16,569 bases in length, that encodes 13 protein subunits of respiratory chain complexes and its own structural rRNAs and tRNAs. mtDNA is inherited maternally and mutations

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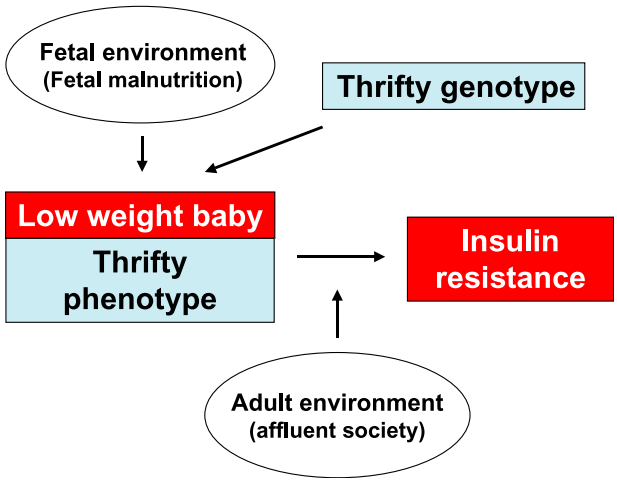

Fig. 1. Diagram of the thrifty genotype/phenotype hypotheses.

in mtDNA thus accumulate sequentially through maternal lineages. There are cumulating evidences showing mitochondrial dysfunction is a central pathophysiological abnormality in type 2 diabetes mellitus and insulin resistance. We hypothesize that poor nutrition during early life leads to mitochondrial changes that contribute to the development of type 2 diabetes and insulin resistance in adult life.

2. Mitochondrial abnormalities in diabetes and insulin resistance

Approximately 0.5–1.5% of all diabetic patients exhibit pathogenic mtDNA defects such as duplications [12], point mutations [13] and large-scale deletions [14]. Most of the known mtDNA mutations cause diabetes by affecting insulin secretion from pancreatic beta cells [15]. Gerbitz et al. [16] have well illustrated the mitochondrial metabolisms in the process of glucose-induced insulin secretion in beta cells. Glucose enters the cells through a specific transporter and stimulates binding of glucokinase to the mitochondrial pore protein, porin. This is followed by phosphorylation of glucose, activation of glycolysis and stimulation of mitochondrial oxidative phosphorylation, resulting in an increase of intracellular ATP. This leads to the closure of the ATP-sensitive K^+-channel, the opening of the Ca^{2+}-channel and the increased intracellular Ca^{2+}, which eventually triggers insulin secretion. It is thus likely that pancreatic beta cells with abnormal mitochondria would show a poor insulin secretory response to glucose stimulation. The mtDNA A3243G mutations in cybrid cell lines (i.e., cells repopulated with donor-derived mutant mitochondria) lead to a reduction in oxygen consumption and oxidative phosphorylation [17]. In addition, pancreatic beta cell lines in which the mtDNA content was significantly reduced by treatment with ethidium bromide showed a loss of glucose-induced insulin secretion [18,19]. Taken together, these data support the concept that mitochondrial function could play an important role in regulating insulin secretion in beta cells.

In addition to reducing insulin secretion, mitochondrial abnormalities can also cause insulin resistance. Poulton et al. [20] reported that a polymorphism in the first hypervariable region of the mtDNA control region (16,189 T > C) is associated with insulin resistance in the English population. The finding was confirmed in other populations, including Koreans [21–25].

Quantitative changes in mtDNA are also implicated in type 2 diabetes and insulin resistance. Antonetti et al. [26] reported that mtDNA copy number was lower in the muscles of diabetic subjects, but they concluded that this depletion was the result of diabetes, as this decrement was observed in both type 1 and 2 diabetes. However, we found that the decreased mtDNA density in peripheral blood preceded the development of type 2 diabetes [27], suggesting that mitochondrial abnormalities could be the cause of type 2 diabetes. Furthermore, inverse correlations were observed between mtDNA content and components of the metabolic syndrome such as blood pressure, fasting glucose level and waist-to-hip circumference ratio [27]. These data strongly suggested that quantitative abnormality of mtDNA might be associated with insulin resistance. This is further supported by the recent findings that mtDNA density was also associated with insulin sensitivity in the offspring of type 2 diabetic patients [28].

Park et al. [29] investigated the effects of mtDNA depletion on glucose metabolism in mtDNA-depleted (ρ0) human hepatoma SK-Hep1 cells. When the cells were treated with sublethal doses of ethidium bromide, they lost mtDNA, and phenotypes occurring in these ρ0 cells are due to loss of mtDNA. ρ0 cells failed to hyperpolarize their mitochondrial membrane potential in response to glucose stimulation. In addition, intracellular ATP content, glucose-stimulated ATP production, glucose uptake, steady-state mRNA and protein levels of the glucose transporters, and cellular activities of the glucose-metabolizing enzymes including hexokinase were decreased.

Petersen et al. [30,31] further explored the implications of deranged mitochondrial function in insulin resistance. They reported that elderly people were insulin resistant compared with young controls matched for lean body mass and fat mass, and this resistance was attributable to reduced insulin-stimulated muscle glucose metabolism. These changes were associated with increased fat accumulation in muscle and with a 40% reduction in mitochondrial oxidative and phosphorylation activity. This group extended the study to the insulin-resistant diabetic offspring, and found that they have an 80% increase in intramyocellular lipid content and a 30% reduction in mitochondrial phosphorylation activity compared with insulin-sensitive, age-, height-, weight-matched control subjects [31]. It was suggested that an increase in the intracellular concentration of fatty acid metabolites may

activate a serine/threonine kinase cascade leading to defects in insulin signaling in muscle and liver, and resulting in insulin resistance [32].

In aggregate, mitochondrial dysfunction or mitochondrial DNA abnormalities lead to decrease in mitochondrial oxidative phosphorylation and increased intracellular lipid content that consequently disturbs insulin signaling and results in insulin resistance.

The mechanisms for mitochondrial dysfunction or decreased mtDNA content in type 2 diabetes mellitus or insulin resistance are unclear. Recently, it was shown that both nuclear respiratory factor-1 (NRF-1), the transcriptional factor that regulates the expression of proteins in oxidative metabolism, and peroxisomal proliferator-activated receptor γ coactivator 1 (PGC1), coactivator of NRF-1 and peroxisomal proliferator activator receptor (PPAR)-dependent transcription, were decreased in muscle of type 2 diabetic subjects and nondiabetic subjects with family history of diabetes [33]. It is therefore conceivable that impaired mitochondrial function may result from decreased expression of critical nuclear-encoded mitochondrial genes related to alterations in PGC1-mediated coactivation of PPAR- and NRF-dependent transcription [33]. Mitochondrial transcription factor A (Tfam), one of the major regulatory factors for mitochondrial transcription and replication, is regulated by NRF-1. The mechanism of insulin resistance by decreased mitochondrial function could be a result of decreased PGC1, and consequently, mitochondrial transcription and translation (Fig. 2). However, it is as yet unclear why expression of these genes should decrease in subjects with type 2 diabetes and in their offspring.

3. Animal studies on fetal malnutrition and diabetes

3.1. Calorie and protein malnutrition lead to poor islet development

Maternal nutrition may affect fetal growth and development directly through the availability of nutrients for the fetus and permanently alter glucose/insulin metabolism [34,35]. Reduction of caloric intake by 50% from the 15th day of gestation until delivery resulted in the growth retardation of the rat pups, lower numbers of islets, lower beta cell mass and lower total pancreatic insulin content [36]. Extended maternal undernutrition until the end of lactation brought a more profound reduction of beta cell mass. Subsequent renutrition of these offspring after weaning was insufficient to fully restore beta cell mass by 3 months of age [37], and apoptosis of beta cells; a process that participates in the remodeling of the endocrine pancreas is threefold higher in these pups [38]. At 3 months of age, a decreased insulin response was observed in response to glucose challenge, but the glycemic reactions remained normal, suggesting increased insulin sensitivity in the young adult period. However, by 12 months of age, they developed profound insulinopenia and marked glucose intolerance [38].

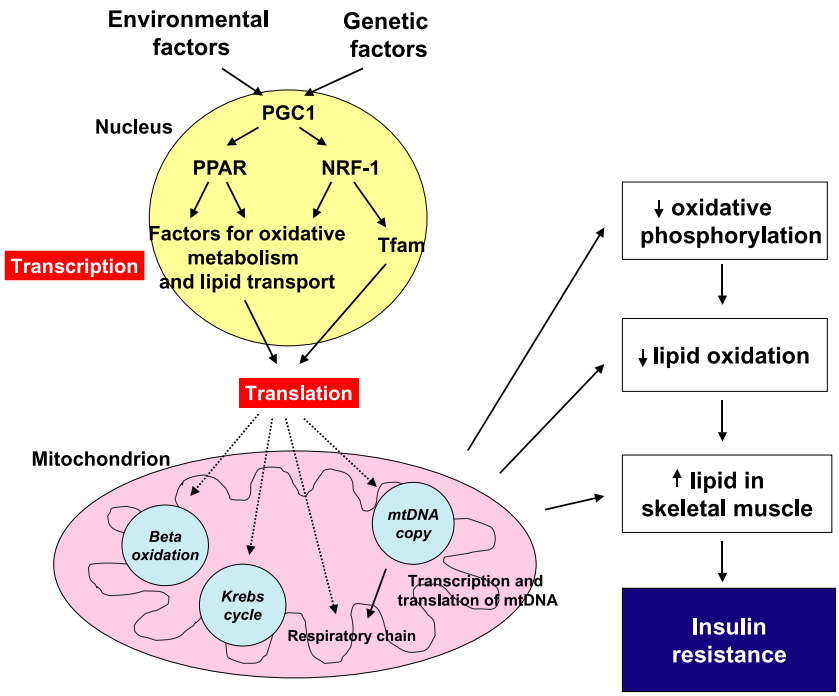

Fig. 2. Proposed mechanism of insulin resistance by decreased mitochondrial transcription: scheme modified according to reference [35,36]. PPAR, peroxisomal proliferator activator receptor; PGC1, PPARγ coactivator 1; Tfam, mitochondrial transcription factor A; NRF-1, nuclear respiratory factor-1.

Another animal model in which intrauterine growth retardation (IUGR) and/or postnatal growth retardation is produced is that in which pregnant and lactating rats are fed isocaloric diet with reduced protein content (8% instead of 20% protein) [39]. In the offspring of mothers fed on a low-protein diet, islet cell proliferation and size were reduced [39,40], and beta cell death by apoptosis was enhanced [41]. These islets were also less vascular [39], and their insulin secretion was reduced [42]. A low-protein diet administered only during gestation did not permanently affect the body weight of the offspring, since low-protein pups recovered body weight immediately after birth [42]. In contrast, when the low-protein diet was maintained during lactation, pups exhibited a lower growth rate, and the insulin secretion in response to glucose challenge was significantly reduced [35].

Proteome analysis of the fetal pancreas to examine the intrauterine programming of beta cell gene expression showed that the expressions of 70 proteins were changed by fetal protein malnutrition [43]. They include the proteins related to mitochondrial energy transfer, glucose metabolism, RNA and DNA metabolism, protein synthesis and metabolism, the cell cycle and differentiation, cellular structure and cellular defense.

Taken these data together, fetal malnutrition leads to decreased beta cell mass and reduced glucose-induced insulin secretion with changes in beta cell gene expression including mitochondrial genes.

3.2. Insulin resistance in malnutrition models

Several metabolic abnormalities that lead to insulin resistance in protein malnourishment models also have been suggested. The muscle and liver organ weights were reduced in these models [34], and the activities and gene expression of insulin-sensitive hepatic enzymes were changed. In addition, glucokinase activity was reduced and phosphoenolpyruvate carboxykinase activity was increased, resulting in increased hepatic glucose production [44,45]. The ability of insulin to inhibit glucagon-stimulated glucose output from the perfused liver was lost and indeed reversed [46]. Recently, it was reported that insulin-stimulated phosphatidylinositol-3 kinase activity was impaired in adipocytes from 15-month-old fetal malnourished rats [47]. The glucose tolerance of the offspring of low-protein-fed dams was markedly age dependent. The younger of such offspring had improved glucose tolerance at 12 weeks of age when compared with controls [35]. This can be explained by adaptation of the peripheral tissue through increased whole-body insulin sensitivity [48–50]. Nevertheless, these animals showed a greater age-dependent loss of glucose tolerance, and at the age of 15 months, their glucose tolerance was worse than that of the controls [35].

Ogata et al. [51,52] have developed a rat model using uteroplacental insufficiency as a cause of IUGR by inducing ischemia to the fetus by partially ligating the placental blood supply. This model exhibits marked insulin resistance early in life, characterized by blunted whole-body glucose disposal in response to insulin [53] and impaired insulin suppression of hepatic glucose output [54]. Mitochondria in skeletal muscle from IUGR rats exhibited significantly decreased rates of stage 3 oxygen consumption with pyruvate, glutamate, alpha-ketoglutarate and succinate. This leads to a chronic reduction in the supply of ATP available from oxidative phosphorylation in mitochondria. These data suggested that impaired ATP synthesis in muscle compromises energy-dependent glucose transport, and glycogen synthesis in turn contributes to the insulin resistance and hyperglycemia of type 2 diabetes [55].

To summarize these data, fetal malnutrition leads to insulin resistance characterized by decreased insulin-stimulated glucose utilization and impaired insulin suppression of hepatic glucose production that was accompanied by impaired insulin signaling or impaired ATP synthesis from mitochondria.

3.3. Mitochondrial changes as a link between poor nutrition in early life and altered glucose/insulin metabolism in later life

As stated above, dysfunction of the mitochondria and reduced mtDNA level are associated with insulin resistance in addition to impaired insulin secretion. Moreover, mtDNA is transmitted exclusively from the mother and easily influenced by environment because of its location outside the nucleus. Therefore, we hypothesized that changes in the mitochondria may link poor nutrition in early life with altered glucose/insulin metabolism in later life. There are several evidences supporting this hypothesis. It was shown that 50% food restriction for 3 days reduces the mitochondrial substrate oxidation activity in the liver [56]. In humans, peripheral blood mtDNA levels of mothers correlate with the birth weight ($r=.63$, $P<.01$) and mtDNA levels of cord blood ($r=.55$, $P<.01$, Fig. 3) [57]. In the offspring of dams fed a low-protein diet during gestation and lactation, the mtDNA content of the liver and skeletal muscle was reduced and did not recover until 20 weeks of age, despite restoration of nutrition after weaning [58]. The reduced mtDNA content was accompanied by a decrease in mtDNA-encoded gene expression [58]. These rats also have decreased mtDNA levels in the pancreas at 25 weeks of age, accompanied by decreased pancreatic beta cell mass and reduced insulin secretory responses to glucose load [59]. These findings indicate that poor nutrition in early life causes long-lasting changes in the mitochondria, which may contribute to the development of type 2 diabetes in later life.

4. Mechanisms of mtDNA depletion by protein malnutrition in early life

The control of mitochondrial biogenesis is extremely complex, involving the coordinated expression of hundreds of genes. The detailed process of mtDNA replication is well reviewed by Clayton [60] and Lecrenier and Foury [61]. The

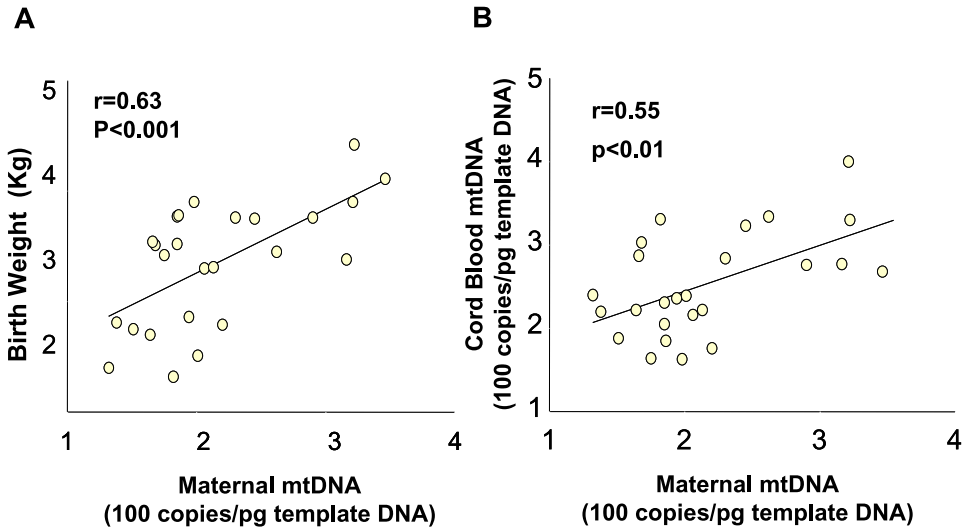

Fig. 3. Relationship between mtDNA content of maternal peripheral blood and birth weight (A) and cord blood mtDNA content (B) in 27 pairs of singleton pregnancy.

nuclear respiratory factors NRF-1 and NRF-2 are transcriptional regulators for the genes of subunits of the oxidative phosphorylation system, as well as for many genes involved in mtDNA replication such as the Tfam gene [62].

The mechanisms by which malnutrition in early life induces mtDNA reduction that lasts until the adult period without recovery despite restoration of nutrition have not been identified yet. Here we provide several hypotheses to explain the mechanism.

4.1. Altered stability of tRNA of mtDNA by reduced taurine availability

In an isocaloric, low-protein, fetal-malnutrition model, while basal blood sugar and plasma insulin were not modified, the amino acid profile was disturbed in the maternal and fetal plasma as well as in the amniotic fluid [63]. The levels of essential, branched and sulfur-containing amino acids were reduced. The most affected amino acid in maternal and fetal plasma, amniotic fluid and fetal islets is taurine. Taurine is an amino acid that does not participate in protein synthesis but has a function in cholesterol excretion, as a neurotransmitter, and as a potent antioxidant (for review, see Ref. [64]). Taurine is not considered an essential amino acid for humans as it can be synthesized from cysteine in the liver [65]. However, the plasma concentration of taurine in the fetus is 1.5-fold that of maternal blood, and this level is mostly dependent on transport from the maternal blood through the placenta because the bioregulatory systems for taurine in the fetus are not fully developed [66]. Reduced activity of placental taurine transporters results in low fetal taurine levels and IUGR fetuses [67]. Bertin et al. [68] reported that a lowered fetal plasma taurine level from a low-protein diet was the main predictor of the fetal plasma insulin level.

A recent report provides the evidence that taurine could critically affect mitochondrial function. Suzuki et al. [69] found two novel taurine-containing modified uridines, 5-taurinomethyluridine and 5-taurinomethyl-2-thiouridine, in mitochondrial DNA, and showed that taurine was a constituent of mitochondrial tRNAs. Modification of the taurine-containing uridines was lacking in mutant mitochondrial tRNAs for Leu (UUR) and Lys in pathogenic cells of the mitochondrial encephalomyopathies, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode (MELAS) and myoclonus epilepsy associated with ragged red fibers (MERRF), respectively (Fig. 4). This abnormality causes defective translation owing to weak codon–anticodon interactions, which might significantly contribute to the defective mitochondrial function in mitochondrial diseases.

Based on this, we can suppose that low taurine in the fetus may induce a deficiency of modification of nucleosides that leads to defective translation activity and mitochondrial dysfunction that may result in both impaired insulin secretion and insulin resistance.

4.2. Depletion of the nucleotide pool by lowered availability of nucleotides

Perturbations of dNTP pools such as decreased level of one of the four dNTPs or an imbalance among them can cause serious diseases [70]. The mitochondrial dNTP pool is separated from the cytosolic pool because the mitochondrial inner membrane is impermeable to charged molecules. The pool is maintained either by import of cytosolic dNTPs through dedicated transporters or by salvaging deoxynucleosides within the mitochondria: apparently, enzymes of the de novo dNTP synthesis pathways are not present in the mitochondria. These transporters can meet mitochondrial dNTP needs if cytosolic synthesis is operative. However, in quiescent cells, cytosolic dNTP synthesis is limited, whereas mtDNA is continuously replicating, rendering mitochondrial synthesis vital for the maintenance of the mitochondrial

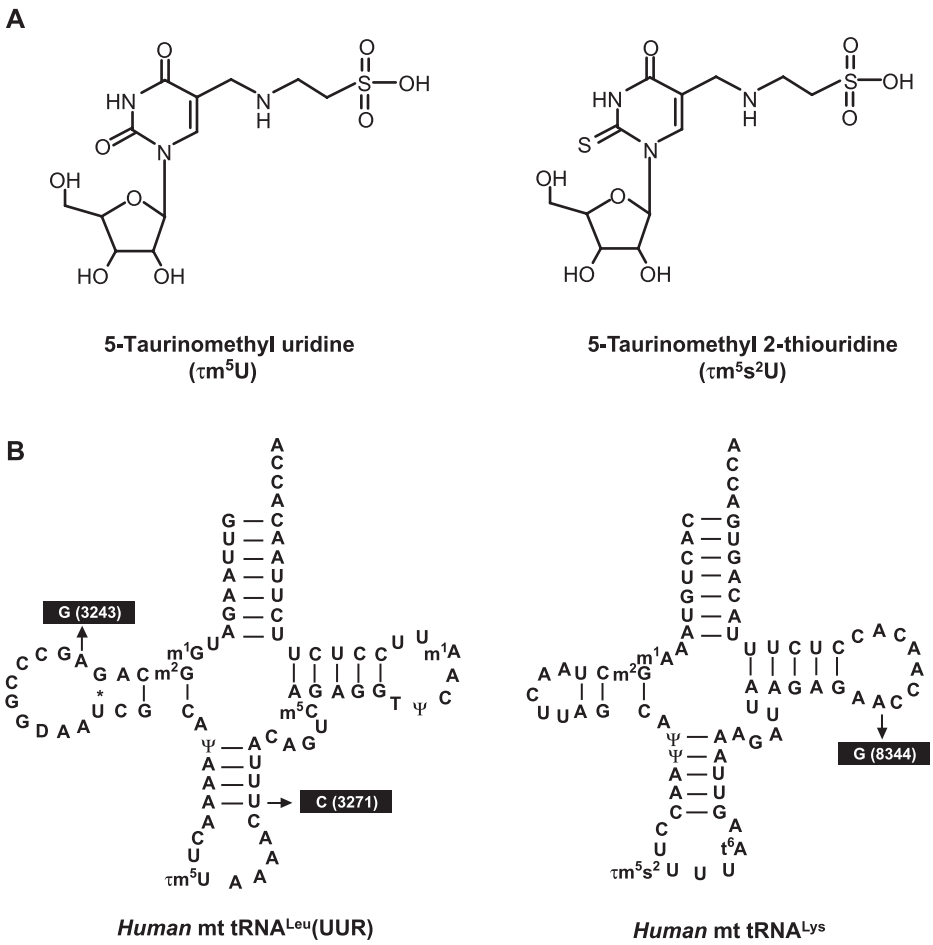

Fig. 4. (A) Chemical structures of τm5U and τm5s2U. (B) Structures of human mt $tRNA^{Leu}$(UUR) and mt $tRNA^{Lys}$ with modified nucleotides. The pathogenic point mutations of MELAS (3243 and 3271) and MERRF (8344) are indicated. Figures are reprinted from Ref. [76] with permission.

genome [71]. Thus, an enzyme deficiency in the mitochondrial dNTP salvage pathway could cause mitochondrial depletion syndrome [72–74].

Because the purine and pyrimidine bases of nucleotides are assembled from a variety of amino acids, the mitochondrial nucleotide pool will be reduced in the malnourished state, and in the situation of amino acid deficiency, this will ultimately lead to mitochondrial depletion. In the proteome analysis of the fetal protein-malnourished pancreas, nucleoside diphosphate kinase A and adenylate kinase enzyme 4, both involved in maintaining intracellular concentrations of dinucleotide-triphosphate, were down-regulated, indicating decreased production of nucleosides [43].

4.3. Genomic imprinting

The long-term programming effect of early malnutrition can be explained by an epigenetic mechanism, as inheritance of the thrifty phenotype shows characteristics of genetic imprinting. Genomic imprinting is an epigenetic phenomenon in which only a single allele of a gene is expressed in a parent-of-origin-dependent manner (for review, see Ref. [75]). In mammals, the imprinted genes are particularly implicated in the regulation of fetal growth and development, cancer and aging. In early primordial germ cells, an erasing of the preexisting imprint signal, inherited from previous generation, occurs [76]. This is followed by establishment of a specific differential allelic imprint that can be transmitted to the next generation [77]. Finally, this imprint is maintained through mitosis [78]. The DNA modification for imprinting includes DNA methylation, histone modifications and differences in chromatin structure. The mice with deficient DNA-methyltransferase-1 die at early postimplantation, and in that, some imprints are lost, indicating a crucial role for DNA methylation in determining the imprinted status of genes [79].

Transient nutritional stimuli at critical ontogenic stages can yield lasting influences on the expression of genes by interacting epigenetic mechanisms [80]. If certain genomic regions such as imprinted domains are especially labile to such influences, early nutritional influence on these genomic components could have a long-lasting impact on phenotype. Indeed, nutrition can affect imprinted growth factors such as IGF-2 and insulin in animal experiments [81]. Several studies revealed that early nutritional changes, by changing the culture media used during in vitro manipulations of early mouse embryos, alter allelic meth-

ylation and expression of imprinted genes [82,83], and lower birth weight [83]. Waterland and Garza reported that two of 10 differentially expressed genes in the islets of undernourished rats during the suckling period were imprinted genes [84].

Relatively, little is known about the mechanisms of how nutrition affects imprinting; however, in terms of DNA methylation, there is some evidence supporting the link between nutrition and epigenetic modification. Mammalian one-carbon metabolism, which ultimately synthesizes *S*-adenosylmethionine providing the methyl group for all biological methylation reactions, is highly dependent on dietary methyl donors and cofactors [85]. Dietary methionine and choline are the major source of one-carbon units, and folic acid, vitamin B12 and pyridoxal phosphate are critical cofactors in methyl metabolism. The availability of dietary methyl donors and cofactors during critical ontogenic periods therefore might influence DNA methylation patterns [86]. For example, the coat-color distribution of A^{vy}/a offspring was shifted when their mothers' diets were supplemented with methyl donors and cofactors [87]. The coat-color shift in the offspring caused by methyl donor supplementation of the dam was revealed to be caused by altered methylation status of the agouti promoter in the offspring [88], suggesting the epigenetic effects of dietary nutrition.

Regarding the epigenetic modification of mtDNA biogenesis, Tfam is a good candidate gene that may be imprinted because the human Tfam promoter has 67 potential CpG methylation loci. A recent report by Choi et al. [89] showed that in vitro methylation of the NRF-1 binding region strongly inhibited the transcriptional activity of the Tfam promoter in a transient transfection system. This strongly suggests that the methylation of the Tfam promoter might be a route for silencing, resulting in decreased mitochondrial biogenesis. However, whether the methylation status of Tfam is altered by early malnutrition, or whether this is associated with reduced mtDNA content, remains to be investigated.

4.4. Oxidative stress

Protein malnutrition is associated with depressed antioxidant defense systems and increased oxidative stress [90]. Proteome analysis of fetal protein-malnourished pancreas revealed that antioxidant protein 2, which protects the pancreas against oxidative injury [91] by reducing hydrogen peroxide (H_2O_2), was down-regulated [43]. Because the cumulative data suggest a role of oxidative stress in mtDNA damage [92], we can speculate that oxidative stress might be involved in malnutrition-associated mitochondrial changes. Indeed, exogenous H_2O_2 decreased Tfam promoter-driven transactivation [93]. Increased oxidative stress reduces the effective NO level because the superoxide anion ($O_2^{\cdot-}$) binds NO to produce peroxynitrate. Since NO stimulates mitochondrial biogenesis via a soluble guanylate-cyclase-dependent signaling pathway that activates PGC1-α, a master regulator of mitochondrial content [94], oxidative stress could decrease the content of mtDNA through reduced

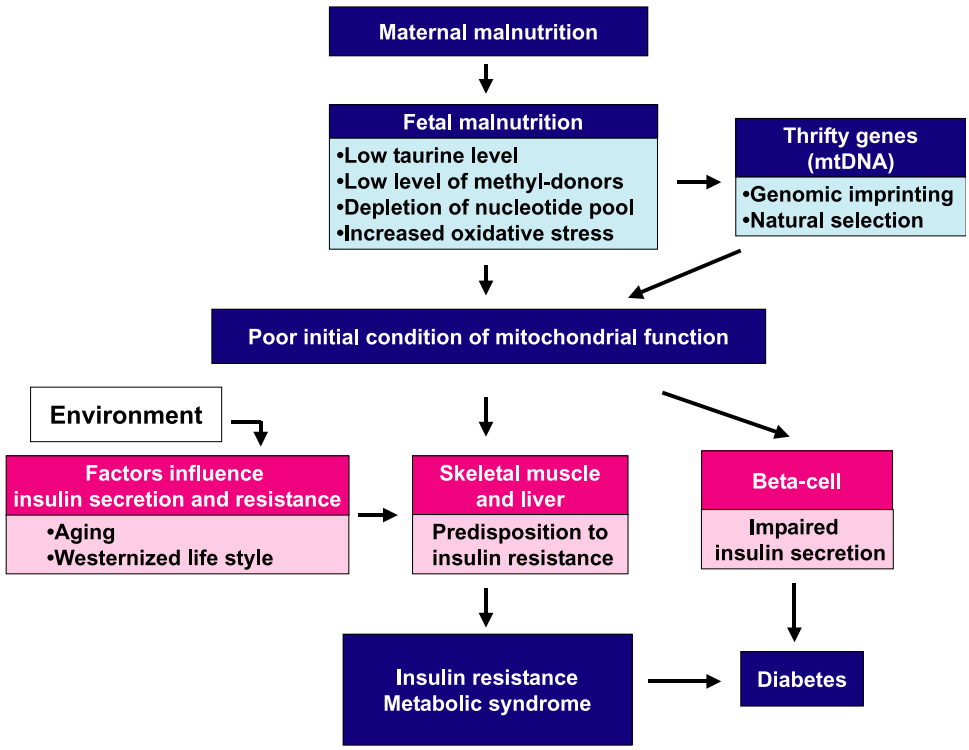

Fig. 5. General outline of the mitochondrial hypothesis.

replication due to decreased NO, and through DNA damage by peroxynitrate.

5. Conclusion

A growing body of epidemiological evidences suggests that fetal malnutrition is linked to the risk of developing both type 2 diabetes and insulin resistance syndrome. In the light of advances made in the last few years, including development of the thrifty animal model, the thrifty phenotype hypothesis as a possible explanation for these links has been clarified, but its essence remains unclear. Furthermore, the vast amount of work in mitochondrial research and in the area of the pathophysiology of type 2 diabetes supports the hypothesis that mitochondrial dysfunction may be a link between malnutrition in early life and type 2 diabetes and insulin resistance in adult life. In this review, we suggest several mechanisms including genomic imprinting that change mtDNA content according to the nutritional status of fetal or early development (Fig. 5). However, exact molecular mechanism of fetal programming is still not clear. To identify genes whose expression is persistently altered by early malnutrition, epigenetic approaches as well as genomic approach would be necessary to measure gene-specific changes in DNA methylation, especially at the genes that control mitochondrial replication. Although there have been a large number studies of mtDNA replication and its control, further studies should be performed to understand the detailed mechanisms of mitochondrial biogenesis and the implications for malnutrition-induced insulin resistance syndrome.

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