Advances in Biotechnology

Chapter 2

Mitochondrial Diabetes – An overview

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1. Introduction

The most urgent problem in the field of diabetology, and one of the most important challenges for the XXI century medicine, is to find cure for type 2 diabetes mellitus (T2D). It is estimated that the number of people with diabetes worldwide exceeds 200 million and most of them are T2D patients. In the industrialized world the prevalence of this disease has reached an epidemic proportion and is still growing [1]. The adoption of a sedentary lifestyle, the consumption of non-traditional foods, and a genetic predisposition to the disease are thought to be the major underlying causes of the epidemic. In addition to the worrisome increase in the prevalence of diabetes mellitus (DM), the society at large will be further burdened with problems associated with various macro and microvascular complications of T2D. A major part of this burden (75%) will be borne by developing countries and India will be having the dubious honor of being host to the maximum number of diabetics and it is already called the diabetes capital of the world. Compounding factors like high prevalence of tuberculosis, unfavorable pattern of central obesity and inadequate health facilities add to the difficult survival of diabetics in India [2].

For many decades T2D (non insulin- dependent diabetes), has been regarded a less dangerous type of disease by both the patients and their doctors. But recent estimation revealed T2D as a leading cause of premature death, mainly due to cardiovascular causes and due to occurrence of complications that can lead to blindness, amputations, and renal insufficiency. The life expectancy of millions of patients is shortened due to the diagnosis of T2D [3]. The disease imposes huge economic burden on patients, their families, local communities, health care systems, and societies [4]. Hence T2D was considered as a major medical burden on

society.

Type 2 diabetes is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [5]. Interaction of genetic and environmental factors plays a major role in disease incidence. The looming epidemic of T2D is expected to trigger a steep rise in the complications such as ischemic heart disease, stroke, neuropathy, retinopathy and nephropathy. Moreover, there is growing evidence that genetic background also influences the complications of T2D [6-9]. Hence developing better treatments and novel prevention strategies for T2D is a matter of great urgency to provide patients and their families with prognostic advice. To accomplish this goal, it is necessary to understand the pathogenesis of T2D and its complications.

2. Understanding the Genetics of Type 2 Diabetes

Over the last three decades enormous efforts have been undertaken to understand the genetic basis of T2D and defects of beta cell function were recognized increasingly in patients with diabetes [10]. Several genes, such as the insulin gene [11], the insulin receptor gene [12], and the glucokinase gene [13] have been reported to be responsible for the subsets of the disease. These genes encode factors necessary for the metabolic processes from the insulin synthesis and secretion in pancreatic beta cells to the insulin action on various target cells. Apart from these genes, a pivotal role of mitochondria in the pathogenesis of T2D is underlined by the finding that mitochondrial DNA (mtDNA) mutations in humans, as well as deletion of mitochondrial genes in pancreatic beta cell animal models, reduces oxidative phosphorylation (OXPHOS) capacity and causes diabetes [14,15]. Data reported by different investigators suggest that beta cells normally contain a filamentous network of mitochondria, but when mitochondria become chronically fused or fragmented, glucose stimulated insulin secretion (GSIS) is impaired [16-18]. Abnormal mitochondrial morphology and function was observed in pancreatic beta cells from the postmortem studies of T2D patients [19].

The mitochondrial genome of mammalian cells encodes 13 polypeptides, 2 rRNAs and 2 tRNAS. The mitochondrially synthesized polypeptides are constituents of four enzyme complexes involved in OXPHOS and ATP production. Mitochondrial OXPHOS and ATP production in pancreatic beta cells are generally accepted to play a significant role in insulin secretion in response to glucose and other nutrients [20]. This clearly suggests the possible role of mitochondrial defect in GSIS of pancreatic beta cells.

Till now, a number of mtDNA defects have been implicated in the development of diabetes in various populations [21-24]. Most of the studies revealed one or more number of base substitutions in the $tRNA^{Leu}$ gene as the possible causative factor for T2D. As far as the T2D is concerned, genes encoding the mitochondrial respiratory chain play a crucial role in the production of ATP which subsequently releases the secreted insulin once it reaches the

threshold level inside the pancreatic beta cells. But sufficient data is not available to confirm the significant role of the mitochondrial defects in the development of T2D. Even though the history of mitochondria dates back to millions of years, the mitochondrial genetics is just 150 years old as the role of mitochondria in human diseases was realized only in 1962 after the description of a young woman with non-thyroidal hyper metabolism [25]. The genetics of mitochondrial diseases came to the limelight only in 1988 after the reports of a point mutation in Leber hereditary optic neuropathy (LHON) and large-scale deletions in mitochondrial myopathies [26].

Hence molecular basis of the mitochondrial diabetes needs extensive investigation to identify the location/region responsible for disease development. Mitochondrial DNA biology is also found to be complex in nature, however all the pathogenic mutations can occur at almost any site throughout the mitochondrial genome; hence comprehensive screening requires analysis of the entire mtDNA molecule. Also, nonfunctional homoplasmic variants are common and must be distinguished from functional heteroplasmic defects. Finally, mutations may be missed because of variable tissue expression. This is because the level of the mutated mtDNA in relation to the wild-type mtDNA (% heteroplasmy) varies between tissues, being high in post mitotic tissues, such as skeletal muscle and brain, and low in rapidly dividing tissues, such as blood leukocytes [27]. Hence post mitotic tissue will be the suitable sample for detecting mtDNA mutations than leukocyte DNA, where the occurrence of novel mtDNA mutations level will be very low and go undetected. As a consequence, lead to an underestimation of the true prevalence of mtDNA defects in conditions such as diabetes. But most of the studies concentrated mutations in the blood DNA since it is difficult to get post mitotic tissues. Also the reports on the association of mt DNA defects for the mitochondrial associated diseases through the sequencing of complete mitochondrial genome is less when compared to nuclear genome [23, 28-31].

3. Mitochondrial DNA Mutations and Diseases

The mitochondrial genome has a very high mutation rate, 10- to 17-fold higher than that observed in nuclear DNA. Although mtDNA repair systems do exist [32], they are not sufficient to counteract the oxidative damage sustained by the mitochondrial genome due to its proximity to the respiratory chain complexes in the inner membrane and the ROS they generate. Protective histones are also lacking, thus leading mtDNA more susceptible to mutations.

Number of pathological mtDNA mutations has been known for over a decade, yet their mechanistic is not well understood. The first pathogenic mtDNA mutations were identified in 1988 [26,33]. Since then, over 250 pathogenic mtDNA mutations (point mutations and rearrangements) have been characterized [34], shown to cause a wide variety of diseases with

a heterogeneity of phenotypes and a variable age of onset [35- 42]. The pathogenic mutations has been classified into three broad categories based on its position at mitochondrial region which include (i) point mutations affecting protein-coding genes (oxidative phosphorylation); (ii) point mutations affecting the protein synthetic apparatus; and (iii) large deletions [43].

3.1 Clinical Features of Human mtDNA Disease

A striking feature of mtDNA diseases is their clinical heterogeneity and the presence of heteroplasmy. The fraction of mutant mtDNA may vary from less than 1 % to more than 95 % in affected tissues of patients with mitochondrial disease. In addition, the amount of heteroplasmy varies from tissue to tissue and even between cells within a tissue [44], and, in some cases, heteroplasmy can change also with time [45]. The most functionally drastic mutations are always found in heteroplasmic state, since homoplasmy entails lethality. On the contrary, at modest levels of heteroplasmy even drastic mutations can have a subtle phenotypic effect. Conversely, functionally mild mutations that can segregate to homoplasmy in the germ line without compromising early development might have a profound effect in some specific tissues [43]. Nevertheless, for some mitochondrial diseases the phenotype is independent of mutant mtDNA abundance, suggesting the involvement of other factors. The threshold effect, the age and the environment can also influence the pathogenesis of mitochondrial disorders. In addition, the modulating effect of other mitochondrial and/or nuclear genes could also contribute to the diversity of clinical phenotypes [46]. Because the vast majority of the mitochondrial proteins are nucleus-encoded and correct structure and function of the respiratory chain requires many steps which are under control. Hereditary defects in the complex machinery of transport of nDNA-encoded proteins from the cytoplasm into mitochondria, can cause mitochondrial diseases, although only relatively few such disorders have been documented.

Despite the clinical importance of mitochondrial diseases and the fact that the sequence, the genes and the presumed function of mitochondrial chromosome have been completely described for decades, the molecular mechanisms leading from genotype to clinical phenotype remain unsolved. The pathophysiology of mitochondrial diseases is also not well known. While disruption of OXPHOS is central to mitochondrial diseases, many other factors such as calcium dyshomeostasis, increased oxidative stress, and defective turnover of mitochondrial proteins may also contribute.

3.2. Mitochondrial DNA Genotype-Clinical Phenotype Correlation

It seems to make sense that different mtDNA mutations can cause similar clinical manifestations since they cause disease through defective OXPHOS function. In contrast the same mtDNA mutations was found to cause different disease severity, totally different diseases or even does not cause diseases at al. For example, patients with *Kearns–Sayre syndrome (KSS)*, *Chronic progressive external ophthalmoplegia (CPEO) or Pearson syndrome (PS)*

can all carry the same species of large-scale mtDNA deletions. A3243G mutation, the most common mutation associated with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and also found in patients with DM, diabetes with deafness, maternal inherited CPEO and mitochondrial myopathy. Conversely other mutations in tRNA genes or protein coding genes are also implicated in MELAS [47].

The diversity of clinical phenotypes mtDNA can be partly ascribed to the difference between level of heteroplasmy in each patient, between each tissue in same patient or even between the each cell in same tissue. The interactions between the differences in the level of heteroplasmy and tissue or mutation specific threshold can give rise to varied clinical phenotype seen in patients. Several lines of evidence suggest that mtDNA backgrounds, nuclear gene backgrounds as well as environmental factors could be the factors modifying the effect pathogenic mtDNA mutations [48].

3.3. Treatment Strategy

At initial stage, T2D is usually treated with a single oral agent. Consistent with the progressive nature of the disease, patients often eventually treated with one or more additional oral agents and in many cases insulin [49,50]. Choice of specific agents is based on individual patient circumstances, including the need for weight loss and control of fasting versus postprandial glucose, the presence of dyslipidemia and HT, and the risk for and potential consequences of hypoglycemia [51]. Type 2 diabetes patients with severely uncontrolled and symptomatic hyperglycemia are best treated, at least initially, with a combination of insulin therapy and lifestyle intervention, often with metformin.

3.3.1. Antihyperglycemic Treatment Strategies

Lifestyle measures, medical nutrition therapy and appropriately prescribed physical activity were recommended for almost all patients with T2D, as well as weight loss for those who are overweight or obese. Unfortunately, many patients were failed to achieve glycemic goals with lifestyle measures alone and required the addition of pharmacotherapy [52]. Extensive development of new therapies during the past 15 years has resulted in more than 11 classes of approved antihyperglycemic medications with diverse mechanisms of action and varied effects on Hb_{A1c}, body weight, lipids, and other factors [53, 54]. These includes Sulfonylurea, Biguanides, Alpha-glucosidase inhibitors, Thiazolidinediones (TZD), Meglitinide, Dipeptidyl peptidase (DPP)-4 inhibitor, Bile acid sequestrant, Sulfonylurea and biguanide, Biguanide and glitazone, Sulfonylurea and glitazone, Biguanide and DPP-4 inhibitor.

3.3.2. Incretin-Based Therapies

Incretin-based therapies are currently part of the antihyperglycemic armamentarium

for the patients with T2D [53, 55]. These include GLP-1 receptor agonist exenatide and the DPP-4 inhibitors sitagliptin and axagliptin. The most recent update of the consensus algorithm statement of a joint ADA/EASD writing group included GLP-1 receptor agonists (but not DPP-4 inhibitors) in tier 2 of preferred agents, especially for patients who have concerns related to weight and hypoglycemia [51]. They noted that DPP-4 inhibitors may be appropriate choices in selected patients.

3.3.3 Antioxidant Therapy

Apart from these antihyperglycemic agents, additionally T2D patients have to be prescribed with antioxidants to limit mitochondrial radical production during hyperglycemia and to counteract their damaging effects. This may be useful complements to normalize blood glucose, as well as protecting peripheral tissues from hyperglycemia-induced oxidative damage. Antioxidants may have the additional benefit of improving GSIS, both by preventing the damage to β-cells and possibly by blocking the proposed ROS activation of UCP2 in β -cells. The advantage of natural antioxidants is their safety and that large oral doses are well tolerated [56]. To date, mitochondria-targeted versions of Coenzyme Q and vitamin E have been made and can be administered safely to mice [57].

Coenzyme Q_{10} administration to GK rats showed no success in preventing mitochondrial dysfunction [58]. The ineffectiveness of currently existing antioxidants in ameliorating oxidative-stress-mediated diseases points to the need in developing mitochondria-targeted antioxidants. Triphenyl phosphonium-based, amino-acid and peptide-based antioxidants have been shown to protect mitochondria against oxidative insult, which indicates mitochondrially targeted antioxidants are future promises for disease treatment.

3.2. Therapies in Development

Incretin-based therapies are currently in development which includes a novel once-weekly formulation of exenatide; taspoglutide, another once-weekly glucagon-like peptide (GLP) -1 receptor agonist; and liraglutide, a GLP-1 receptor agonist that is administered once daily (59). Liraglutide is currently being evaluated in clinical trials as a once-daily subcutaneous injection. Liraglutide has been reported to reduce Hb_{A1c} by 1.1 % at 26 weeks and up to 1.14 % at 52 weeks and result in weight loss (up to 2.8 kg at 26 weeks and up to 2.5 kg at 52 weeks) in patients with T2D who are treatment- naive or taking other antidiabetes agents, including metformin, sulfonylurea, and TZD (60-62). Evaluation of the once-weekly formulation of exenatide showed reductions in Hb_{A1c} of 1.9 % at 30 weeks and 2.0 % at 52 weeks with a weight loss of 3.7 kg at 30 weeks and 4.1 kg over 52 weeks of treatment [63,64].

4. Summary

Mitochondria play a primary role in the etiology of genetic forms of "mitochondrial" diabetes. Mitochondrial ATP plays a crucial role in the regulation of insulin release from the pancreatic β-cells. When the production ROS exceeds the threshold level, the capacity of β-islets in secreting insulin deteriorates gradually particularly in type 2 diabetes. This in turn leads to the patient to develop multiple complications such as coronary artery disease, neuropathy, retinopathy, nephropathy etc. Currently available treatment such as *Glimepiride, glimepiride-pioglitazone, glimeperide-rosiglitazone, gliclazide. glipizide glipizide-metformin, glyburide, glyburide-metformin etc* does control the level of glucose in the blood, however, there is no treatment which address both mitochondrial function and ROS production. Hence, new treatment strategies regulating mitochondrial biogenesis, ROS and respiration would help the diabetes patients in future.

5. References

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