Advances in Medical Sciences 61 (2016) 244–248

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Review Article

Recent advancements in diagnostic tools in mitochondrial energy metabolism diseases

Naazneen Khan *

Centre for Human Metabonomics, North-West University, Potchefstroom, South Africa

ARTICLE INFO

Article history:
Received 29 June 2015
Accepted 5 February 2016
Available online 17 February 2016

Keywords:
Mitochondria
Pathology
Monogenic
Aging
Therapy

ABSTRACT

The involvement of mitochondrial energy metabolism in human disease ranges from rare monogenic disease to common diseases and aging with a genetic and/or lifestyle/environmental cause. This wide ranging involvement is due to the central role played by mitochondrion in cellular metabolism, its role in cellular perception of threats and its role in effecting responses to these threats. Investigating mitochondrial function/dysfunction or mitochondria-associated cell-biological responses have thus become a common finding where the pathogenic processes are investigated. Although, such investigations are warranted, it is not always clear if mitochondria can indeed be associated with cause or merely playing a responsive role in disease pathology. As this key question is also essential to disease progression and therapy, it should be recognized in investigative design. We herewith, present an overview of the current approaches and technologies used and the practicalities around these technologies.

© 2016 Medical University of Bialystok. Published by Elsevier Sp. z o.o. All rights reserved.

Contents

1. Introduction . . . 244
2. Review . . . 245
   2.1. Overview of mitochondrion genomic architecture . . . 245
   2.2. Molecular genetics approaches and diagnostic tools . . . 245
   2.3. Diagnostic tools for genetic investigations . . . 245
   2.4. Classical approaches to modern approaches . . . 246
   2.5. Involvement of Genome Wide Association Studies (GWAS) . . . 247
   2.6. Role of metabolomics in mitochondrial disease . . . 247
3. Conclusion and future outlook . . . 247
   Acknowledgements . . . 247
   References . . . 247

1. Introduction

The first report linking a deficiency (or "loose coupling") of the mitochondrial oxidative phosphorylation system (OXPHOS) to a human disease phenotype was by Luft [1]. This introduced mitochondrial medicine and the concept of mitochondrial disorders/disease as an inborn disorder of energy metabolism [2]. Since then, the classical view of mitochondrial disease is a rare monogenic nuclear (nDNA) or mitochondrial DNA (mtDNA) encoded deficiency of the OXPHOS system, which has led to the identification of more than 241 genes involved in mitochondrial disease [3] and regarded amongst the most frequently inherited metabolic disorders in newborns with any mode of inheritance possible [4]. This may not be surprising considering that, of the ~1000 proteins making up the mitochondrion (Mitocarta), the OXPHOS system consists of 89 subunits, of which 13 structural subunits are encoded by mtDNA (in addition to 22 tRNA and two

* Correspondence to: Centre for Human Metabonomics, North-West University, Potchefstroom 2531, South Africa. Tel.: +27 018 299 4074.
E-mail address: naaz.27khan@gmail.com

http://dx.doi.org/10.1016/j.advms.2016.02.002
1896-1126/© 2016 Medical University of Bialystok. Published by Elsevier Sp. z o.o. All rights reserved.

rRNA's) and 76 are nuclear encoded [5,6]. In addition to these, a great number of proteins are involved in import, assembly and regulation of the OXPHOS system and its products. A further notable aspect of a deficiency of the OXPHOS system is varied and unpredictable biochemical consequences, which include alteration of respiration, coupling, ATP production, Reactive oxygen species (ROS) production and the structural and functional cellular effects that may result [7]. ROS production from mitochondria have been implicated in various forms of cell signaling processes including activation of eNOS [8], NF-κB [9], ERK, AKT, P38MAPK [10] and modulation of intracellular calcium [11]. Mitochondrial derived ROS serves as both; signaling agent as well as a major source of oxidative stress. Under mitochondrial stress, the Ca^{+2} level as well as ROS production increases, initiating apoptosis and necrosis. These factors, which are all key metabolites to cellular health sensing, contribute to the hallmark of mitochondrial disease, which is its clinical and biochemical heterogeneity and the wide-ranging approaches currently implemented or under consideration to treat disorders of energy metabolism [12]. It also created the awareness over time that the etiology of mitochondrial disease may not only be relevant to rare disease phenotypes, but also to other common diseases. As recently reviewed by Naviaux [13], cellular perception of threats (chemical, physical, microbial) are expressed in conserved but diverse metabolic signals in which mitochondria and mitochondrial-nuclear communication plays a central role. Consequently, with the elucidation of the molecular and cell biological fundamentals of human diseases, it is now clear that pathways directly or indirectly linked to mitochondrial energy metabolism is dysfunctional or deregulated in numerous rare and more common disease phenotypes. These include rare disease phenotypes such as Alpers disease, described already in 1931 [14], but only ~70 years later recognized as a mitochondrial disease resulting from *POLG* mutations [15]. The metabolic dysregulation of energy metabolism in cancerous cells described originally by Warburg in the late 1950s and 60s also helped to recognizing mitochondrial energy involvement in common disease phenotypes. Over recent times this involvement has been illustrated for several death-causing non-communicable and infectious diseases such as neurodegenerative diseases [16], cardiovascular diseases [17], type 2 diabetes mellitus [18], autoimmune disorders [19], cancers [20] and AIDS [21]. Moreover, a principle hypothesis for the aging process involves reduced mitochondrial function [22]. Not to be disregarded are the effects of modern environmental and other lifestyle factors (toxins, pollutants, diet, medication, etc.) which can impact directly or indirectly on mitochondrial function [23]. Much of these discoveries have come through the recent development of scientific methods and technologies directed at holistic and multidisciplinary investigations. With mitochondrial metabolism often playing a central role in disease pathology with various mitochondrial pathways involved and with varied cellular outcomes, such investigations are frequently warranted. We herewith present an overview of the current technologies used where mitochondrial function/dysfunction are investigated and the practicalities around these technologies.

2. Review

2.1. Overview of mitochondrion genomic architecture

Mitochondria are assumed to be originated from α-proteobacteria and found nearly in all eucaryotic organisms. Each mitochondrion contains circular double stranded DNA which is approximately 16.6 Kb in length and encodes for 37 genes that includes 22 tRNA, two ribosomal RNA genes used for RNA translation and thirteen structural subunits of oxidative phosphorylation (OXPHOS) of complex I (7 subunits), III (1 subunit), IV (3 subunit), and V (2 subunit) [5]. Inherited exclusively through the maternal line, the mtDNA has much higher rate of mutation as compared to nDNA [24]. It is believed that the absence of protective histones and its proximity toward OXPHOS system that produces ROS are major factors that contributed to mtDNA vulnerability. Although, the rate of mutation for nDNA was estimated to be 2.5×10^{-8} per base per generation, mtDNA mutation rate estimated to be 3×10^{-6}–2.7×10^{-5} per base per generation [25]. The high rate of mutation of mtDNA is not only responsible for the generation of deleterious mtDNA variants but also resulted in the accumulation of commonly occurring variants of mtDNA in various human populations that is why mtDNA is always a fascinating subject for evolutionary geneticist and population geneticist. Not only this, its property of having high number of copies in cells makes it a suitable target for forensic analysis. Interestingly, the presence of multiple copies of mtDNA per cell leaves upon the possibility that either all MtDNA in cells are not identical a termed known as heteroplasmy or the possibility of having identical mtDNA in all cells termed as homoplasmy [24]. Moreover, mtDNA in mammals are strictly maternally inherited with all homoplasmic DNA mutations transmitted to offspring [26], whereas, the transmission of heteroplasmic mtDNA mutations is complicated by both a selection process and a genetic bottleneck present during development of the female germline.

2.2. Molecular genetics approaches and diagnostic tools

Energy metabolism disorders are heterogeneous group of disorders that includes mitochondrial diseases caused by mtDNA and nDNA mutations. Since, these diseases are mainly diagnosed based on biochemical or molecular evaluation, both require extensive laboratory testing to determine whether the patient is affected with mitochondrial disease or not. Interestingly, molecular genetic testing is more important to solidify the diagnosis and have more inter-laboratory reproducibility [27] but also harbor disadvantage in presenting false positive result due to the presence of low heteroplasmy in peripheral blood samples. With the advancement in technologies, various molecular methodologies are used by different laboratories to overcome these diagnostic challenges.

2.3. Diagnostic tools for genetic investigations

In the past, diagnoses of mitochondrial diseases were carried out on the basis of family history, clinical, histological and biochemical studies. In addition to these studies, more testing tools had been utilized with the aim of better understanding of mitochondrial functionality such as screening of mutations in mtDNA/nDNA over the last several years. These techniques provided additional information on mitochondrial diseases that had not been detectable using traditional approaches. The major obstacle in the genetic investigation was to determine the mutations present in mitochondrial gene. Initially, the methods for screening of known or unknown mutations were indirect i.e. mutation was confirmed visualizing on gel. These can be easily done by the restriction fragment length polymorphisms (RFLP) [28], single strand conformation polymorphism (SCCP), temporal temperature gradient gel electrophoresis (TTGE), temperature gradient gel electrophoresis (TGGE) and denaturant gradient gel electrophoresis (DGGE). RFLP was considered as the first choice for genotyping. In this method, the PCR amplicons were generated to flank a polymorphic RE site and subjected to digestion and the site digested was determined using agarose gel electrophoresis and visualized under ultra violet (UV) radiation. The second method was SCCP that employs amplifying DNA fragments of 200–350 bp

Download English Version:

https://daneshyari.com/en/article/2031824

Download Persian Version:

https://daneshyari.com/article/2031824

Daneshyari.com