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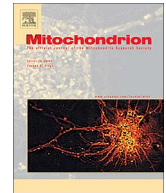

Review

Metabolomics of mitochondrial disease

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ABSTRACT

Mitochondrial disease (MD) diagnostics and disease progression investigations have traditionally relied very little on metabolic data, due to a lack of biomarker sensitivity and specificity. The recent drive to find novel, low intervention biomarkers and new therapeutic approaches have revived an interest in what metabolic data can offer, as presented in this timely review. We review how metabolomics has been applied to MD and provide an extensive overview of the reported metabolic perturbations and common mechanistic features that may provide a basis for future research. We conclude by highlighting the substantial potential of metabolomics for future diagnostics and mitochondrial medicine.

1. Introduction

Mitochondrial disease, when defined as disorders resulting from deficiencies in the mitochondrial oxidative phosphorylation (OXPHOS) system, has a current minimum prevalence of one in every 5000 live births and is therefore considered one of the most common inborn errors of metabolism (Gorman et al., 2015; Schaefer et al., 2004). Although diagnostic methods for mitochondrial disease are available, several studies have highlighted limitations in the diagnostic approach, including overlapping phenotypes, patient selection, disease monitoring and response to treatment, to name but a few (DiMauro and Schon, 2003; Reinecke et al., 2012; Schaefer et al., 2004; Smuts et al., 2013). Metabolomics is one of the more recent additions to the "-omics" family and can be defined as the detection, quantification and identification of all small-molecule metabolites present in a biological sample (Dunn et al., 2005). Since the metabolome is at the end-point of all cellular activity, implementation of metabolomics in a study holds the potential to overcome some of the limitations currently observed in the study of mitochondrial disease. With these limitations in mind, various studies have used a metabolomics approach to study mitochondrial disease and, with significant progress made in recent years, a review of these contributions and the potential they reveal is long overdue. Here we review metabolomics as a relatively novel approach to the field of mitochondrial disease research and diagnostics, with a focus on the instrumental platforms, practicalities and future prospects.

2. Mitochondrial disease as an inherited metabolic disease

Since the first inborn error of metabolism (IEM) was identified by Archibald E. Garrod in 1904, diagnosing IEMs has evolved extensively and to date more than 500 IEMs, affecting various metabolic pathways, can be diagnosed using an array of analytical techniques (Kamboj, 2008; Martins, 1999). Diagnosing most IEMs involves targeted analyses, which measures a specific metabolite(s). Altered concentrations of a specific metabolite(s) usually results from a specific enzyme defect. An example is the case of isovaleric acidemia, in which isovaleric acid coenzyme A (CoA) dehydrogenase is defective, resulting in the accumulation of isovalerylglycine in urine. Another example is propionic acidemia, where propionyl-CoA carboxylase is defective, resulting in the accumulation of propionic acid. Thus, for many IEMs, altered levels of one (or a few) specific metabolite(s) are analyzed in a biological sample and used to diagnose the disease. In contrast, a defect of the OXPHOS system results in insufficient ATP production due to the inhibited flow of electrons through the respiratory chain, resulting in a NAD^+/NADH redox imbalance, oxidative stress and a reduction of the mitochondrial membrane potential. Compared to an IEM where fewer metabolites are usually affected, the redox imbalance ultimately results in a plethora of possible cellular responses, generally affecting a large number of metabolites (Brière et al., 2004; Naviaux, 2014; Reinecke et al., 2009; Smeitink et al., 2006).

For mitochondrial disease, the current gold standard for diagnosis is measuring the activity of the respiratory chain enzymes in tissue biopsies plus complex V and functional tests if fresh samples are available, in combination with other assessments. These assessments includes brain imaging, genetic testing for specific mutations, histochemical investigations as well as exercise stress tests to determine the arteriovenous oxygen difference (a-vO2 difference) (Haas et al., 2008; Menezes et al., 2014; Taivassalo et al., 2012). Over the past 15 years,

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various scoring systems for mitochondrial disease have been developed (for both pediatric and adult patients) to assist physicians in screening patients for the disease (Bernier et al., 2002; Koene et al., 2016; Parikh et al., 2015; Phoenix et al., 2006; Schaefer et al., 2004; Wolf and Smeitink, 2002). However, the use of metabolite data is very limited in these scoring systems and includes only a few selected metabolites (lactate, pyruvate, alanine, tricarboxylic acid cycle intermediates, ethylmalonic acid, 3-methylglutaconic acid, dicarbonic acids, acylcarnitines) (Parikh et al., 2015; Phoenix et al., 2006; Rasanu et al., 2011; Schaefer et al., 2004; Wolf and Smeitink, 2002). Few studies have used semi-targeted or untargeted metabolomics to study mitochondrial disease, despite the potential of the technology to find metabolites/biomarkers not previously associated with the disease. Such an approach might be useful in understanding and diagnosing the disease, as well as screening and monitoring of patients.

3. Metabolomics: general applications and platforms

Metabolomics was first defined in 1998 (by Oliver et al., 1998) and has since become a popular investigative tool for research on biological systems and complex disease models, using a wide range of biofluids, tissues and cell cultures (Dunn et al., 2011; Nikolic et al., 2014). Metabolomics usually follow one of three approaches: a *targeted* approach where a group of small metabolites are quantified and identified, a *semi-targeted* approach that focuses on a specific class of metabolite (for example amino acids, organic acids or acylcarnitines), or an *untargeted* approach, which is the unbiased detection and quantification of all the metabolites in a sample using a single- or multiple-platform approach (Álvarez-Sánchez et al., 2010; Dunn et al., 2011; Dunn et al., 2013; Monteiro et al., 2013).

Analytical techniques used in metabolomics studies usually include a technique to separate the metabolites in the biological matrix [gas chromatography (GC), liquid chromatography (LC) or capillary electrophoresis (CE)] coupled with a detection system [mass spectrometry (MS) or nuclear magnetic resonances (NMR)]. To increase the sensitivity of the analytical technique, numerous different combinations of these components are available (Bouatra et al., 2013). It is also important to realize that the specific metabolites detected by metabolomics studies depends on various factors, for example more polar compounds are usually investigated with an LC-system, whereas a GC-system is the preferred technique for more non-polar metabolites. While NMR is not as sensitive as mass spectrometry, it is a useful technique when sample volumes are limited as it is a non-destructive technique. Another factor to take in consideration is the stability of a compound as some metabolites are unstable and therefore more difficult to detect - some of these metabolites might require a derivatization step to increase stability. Data pre-processing and clean-up can also influence the metabolites reported by a study. During the clean-up process, metabolites may be removed from the data matrix for numerous reasons (like a high coefficient of variance in the quality control samples etc.), thus a specific metabolite may not be in the data set to be considered for statistical analyses and is thus not reported on by the study. Another factor to take in account is the availability of spectral libraries for data interpretation. LC-MS and NMR has a limited number of databases available compared to GC–MS, which has a wide range of public as well as commercial spectral libraries available (Monteiro et al., 2013). To summarize, each analytical platform has both advantages and disadvantages that should be taken into account before deciding on an appropriate technique (Fang and Gonzalez, 2014). The use of different combinations of platforms is encouraged to analyze a larger portion of the metabolome, since the different analytical methods usually complement each other (Bouatra et al., 2013).

4. The application of metabolomics in mitochondrial disease research

4.1. Models

The use of metabolomics in the field of mitochondrial disease research has been very limited, compared to its use to study other human diseases, such as diabetes and cardiovascular disease. This is probably a result of the relatively small number of well-defined (phenotype–genotype) samples available in mitochondrial disease patient cohorts and the heterogeneous nature of the disease. To address this challenge, numerous models have been developed to study the disease.

One such animal model uses the nematode *Caenorhabditis elegans* (*C. elegans*). This model is favored because the *C. elegans* respiratory chain (RC) subunits are morphologically very similar to the human RC. Using these nematodes, various knockout models have been generated to mimic different mitochondrial diseases, including a complex I knockout (CI KO) model [gas-1(fc21), a complex II knockout (CII KO) model [mev-1 (kn1), a complex III knockout (CIII KO) model [isp-1(qm150), a tricarboxylic acid (TCA) cycle knockout model (idh-1(ok2832) and coenzyme Q biosynthesis knockout model [clk-1(qm30) (Butler et al., 2013; Falk et al., 2008; Morgan et al., 2015; Vergano et al., 2014). In addition to the nematode, another animal model frequently used in metabolomics studies is a mouse model such as the *Ndufs4* knockout mouse model. Due to the size of complex I, various mutations have been associated with the complex, including a mutation in the *Ndufs4* gene, which is involved in the assembly and stability of complex I. Another mouse model used is a deletor mouse model, which contains a 13 amino acid duplication situated in the mitochondrial helicase Twinkle. This deletor model is used to study adult-onset mitochondrial myopathy also known as progressive external ophthalmoplegia (PEO). Animal models such as these are currently favored in metabolomics studies to investigate the altered metabolism in mitochondrial disease, due in part to the more homogenous nature of experimental animals, compared to the more heterogeneous nature of human samples (Ahola-Erkkila et al., 2010; Leong et al., 2012; Nikkanen et al., 2016; Tyynismaa et al., 2010). Additionally, due to its controlled environment, animal models are also useful in therapeutic studies, as it is much easier to investigate the effect of potential treatment (Leong et al., 2015).

Although not as commonly used as animal models, a few studies have used cell cultures for the investigation of mitochondrial disease (Bao et al., 2016; Kami et al., 2012; Shaham et al., 2008; Shaham et al., 2010; Sim et al., 2002; Vo et al., 2007). Cell cultures are particular useful study models, as the metabolite profiling of the extracellular medium provides rich information on the uptake, metabolism and secretion of metabolites. Cell cultures used for the metabolomics investigation of mitochondrial disease includes fibroblasts to investigate Leigh's disease, human embryonic kidney cells to investigate how mitochondrial dysfunction alters the one-carbon metabolism pathways, cybrid cells from 143B osteosarcoma cells to investigate the m.A3243G MELAS mutation and muscle cells to investigate induced complex I and complex III defects with rotenone and antimycin A, respectively.

The application of metabolomics in human biofluids is a major objective of current research in the field as it holds potential to clarify the complex biochemistry and the involved diagnostics. A reason for this is that metabolites are the end products of cellular processes and the variability in their concentrations could be due to changes in biological systems, which could, in turn, be linked to phenotype. Human biofluids that have been used in metabolomics studies investigating mitochondrial disease include plasma, blood and urine. Urine samples have become a favored sample choice for investigating mitochondrial disease, as it is easy to obtain and requires minimal sample preparation (Esteitie et al., 2005; Reinecke et al., 2012; Smuts et al., 2013; Venter

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