Writing...
FACTS, OPINIONS & IDEAS

Mitochondrial disease – insight from a cell biologist!

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As an undergraduate student, I encountered an unexpected love; a love for cell biology and a compartment found within the confines of each of our cells, the mitochondrion. For cell biologists like myself, the term 'mitochondria' can evoke a feeling of enquiry and a reminder of the joy we experienced when learning about these marvellous cellular compartments. But for many, their first encounter with the term 'mitochondria' comes with a feeling of confusion and despair, often associated with their diagnosis, or that of a loved one with a mitochondrial disease. During this special week, Mitochondrial Disease Awareness Week, I am honoured to be able to provide a glimpse into the world of mitochondrial biology and the reality that is faced by those families affected by a mitochondria disease.

What are mitochondria?

In biology, the smallest unit and building block of all living things, is referred to as the cell. It is the quest of all cell biologists to understand the inner workings of these fundamental units and the components within them that allow organisms to thrive. In our cells, tiny compartments known as organelles carry out specific functions essential to support cell health and growth. One such organelle, the mitochondrion is also referred to as the powerhouse or energy factory of the cell. It might be obvious from these designations that the mitochondrion is the site for energy production.

Here, components of the food we eat are converted to energy. The magic that happens in our mitochondria sustains most life as we know it. If something goes wrong in the powerplant and our ability to generate energy is impacted, the implications on cell health and ultimately human health can be severe.

Mitochondrial disease – what is it and what are the symptoms?

Mitochondrial diseases are chronic (long-term), genetic, usually inherited disorders. They can be broadly described as energy generation disorders.[1] When the normal function of mitochondria in the cell is disrupted, and this results in less energy being produced and can result in organ dysfunction. This impacts different cells in our body in often devastating ways, and energy-demanding organs like the brain, the heart and muscles feel the consequences of sick mitochondria to a great extent.

Mitochondrial disease is complex, and a feature of this complexity is genetic heterogeneity. Unlike a condition like cystic fibrosis which is associated with mutations in one specific gene (*CTFR*)[2], mitochondrial diseases stem from mutations in many genes. Current estimates suggest that mitochondrial disease can be caused by changes (mutation) in over 350 different genes, and these can affect any or all organ systems.[3,4] In Australia, mitochondrial diseases affect at least one child born each week.[5] These diseases can be present at birth, but can also manifest at any age. They devastate families and sadly take the life of too many.

The severity of mitochondrial disease symptoms is different from person to person. Common symptoms include but are not limited to; impaired physical or cognitive development, cardiomyopathy (disease of heart muscle), myopathy (disease that affects muscle), diabetes, deafness, blindness, strokes and dementia. Patients can alternate between periods of clinical stability and episodic decline, often triggered by acute infection or other stress.[1] Symptoms can

be absent in parents, but they might have silent genetic defects that can cause disease in their children. In many, the symptoms are complex and span multiple organs, resulting in advanced disease. Many combinations of symptoms are also possible, even in people that possess the same genetic defect. This makes diagnosis of mitochondrial diseases very challenging from a clinical perspective.

Genetics of mitochondrial disease

Nearly every cell in our body contains DNA (deoxyribonucleic acid), the hereditary material in most organisms. DNA consists of four different molecules that act as 'letters' to form a code that is used by the cell to build new cells and repair itself. Interspersed among long sequences of DNA are our genes, the functional units of heredity. The Human Genome Project estimated that humans have approximately 20,000 genes.[6] Our genetic information, or genome, is stored in a cellular compartment known as the nucleus, where it is referred to as nuclear DNA. But, did you know that we have a second genome? Yes, a tiny amount of DNA is also located within our mitochondria (called mitochondrial DNA, or mtDNA). The mtDNA is another special feature of the mitochondrion and instead of being linear like the chromosomes in the nucleus, this genome is circular. Furthermore, while nuclear DNA is inherited from both parents, the mtDNA is inherited exclusively from the mother. Though small in size, the mitochondrial genome is responsible for ensuring that the powerhouses of our cells function properly.

Mitochondrial diseases can arise from changes or mutations in both the mitochondrial and nuclear genomes. Mitochondrial diseases caused by genetic changes in the mtDNA are transmitted by maternal inheritance, while mitochondrial diseases caused by genetic changes in nuclear genes can follow different modes of transmission, including but not limited to autosomal dominant and autosomal recessive inheritance (defined below). Current estimates suggest at least 350 genes are linked to distinct mitochondrial

disease.[4] New presentations of disease appear regularly, hence there is the potential for hundreds more mitochondrial diseases to be identified in the future.

Here is a snapshot of some of the modes of inheritance observed in mitochondrial disease:

- Autosomal recessive inheritance: child receives one mutated copy of a gene from each parent. There is a 25% chance that each child in the family will inherit a mitochondrial disease.
- Autosomal dominant inheritance: child receives one mutated copy of a gene from either parent. There is a 50% chance that each child in the family will inherit a mitochondrial disease.
- Mitochondrial inheritance: Mitochondrial disorders caused by mutations in the mitochondrial DNA are exclusively inherited from the mother. If this is the way a mitochondrial disease was inherited, there is a 100% chance that each child in the family will inherit a mitochondrial disease.
- De novo inheritance: Introduction of a mutation within a gene randomly and that is not inherited from a parent.

Mitochondrial disease diagnosis

In addition to the genetic heterogeneity introduced above, the symptoms of mitochondrial disease are also highly heterogeneous, further complicating diagnosis. Indeed, to prove the existence of mitochondrial disease in a newly presenting patient can be a long and painstaking process for families. Recently, I had the pleasure of interviewing two parents of children with mitochondrial disease. Their description of those initial events surrounding diagnosis, the uncertainty of this time, and being transferred from one specialist to another, all the while watching their child deteriorate, was challenging to hear, even for me as a researcher within the field. The wickedness of these disorders and the challenges they present

to families cannot be emphasised enough. For many the journey might begin with a family doctor or with a paediatrician shortly after the birth of a child. For others it may be an unexpected episode, such as a seizure, that brings them to the emergency room. Basic investigations can include blood and urine tests that can be done straight away. More specialised investigations will require transfer to a mitochondrial specialist or other specialists depending on the pathologies presented; for example, a neurologist or a metabolic geneticist. This journey can take months or even years.

When all evidence is pointing to a rare genetic disorder such as a mitochondrial disease, vital information and a final prognosis can be obtained with genetic testing. Thankfully these tests are becoming more accessible due to reductions in price over time. A genetic test can look at the patients mtDNA, which has 37 genes or all the genes in the nuclear genome. Genetic testing examines our genes, specifically a unique letter sequence of A, G, C and T that makes up each gene. Genetic testing will identify changes in this sequence that can be the basis for the pathologies observed in the patient. Often DNA from unaffected parents is included and this can provide detailed information on the inheritance pattern of the specific gene change and explain how the condition might have been inherited within a family. Whole genome sequencing can read all 3 billion letters of the human genome in an effort to pinpoint the changes that have resulted in disease. The rapid advancement of such DNA sequencing technologies over the last decade has facilitated novel gene identification in mitochondrial disease research, but most importantly precise diagnosis for families that can then facilitate medical management of symptoms or other treatment options.

Examples of mitochondrial disease

Leber's hereditary optic neuropathy (LHON) is the most common inherited mitochondrial disorder and results in vision loss.[7] LHON is

often characterised by bilateral, subacute loss of central vision during young adult life. Symptoms often begin with one eye, followed by visual failure in the other eye within weeks or months. LHON is caused by mutations in the mtDNA and it is therefore strictly transmitted by maternal inheritance. A significant percentage of people with a mutation that causes LHON do not develop any features of the disorder. For unknown reasons, males are affected much more often than females. LHON mainly affects central vision, which is crucial for tasks such as reading and driving. The mechanism underscoring the disease is believed to be death of cells in the optic nerve that relay visual information from the eye to the brain.[7]

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) affects many of the body's systems, particularly the brain and nervous system (encephalo-) and muscles (myopathy). The disease is also characterised by lactic acidosis (build-up of lactate in the body) and stroke-like episodes. MELAS symptoms can appear in childhood and can include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures.[8] MELAS is caused by mutations in the mtDNA and is maternally inherited. Most individuals with MELAS can experience stroke-like episodes beginning before age 40. Repeated stroke-like episodes can progressively damage the brain, leading to vision loss, problems with movement, and a loss of intellectual function (dementia).[8]

Leigh syndrome is a neurometabolic disorder that is clinically heterogeneous, with significant variation between patients with respect to age of onset, age of death and presentation of symptoms. Generally, disease onset occurs by two years of age and is characterised by progressive loss of mental and movement abilities and can result in death during childhood. Signs of Leigh syndrome in infants can include vomiting, diarrhoea, and difficulty swallowing, which disrupts eating and leads to failure to thrive. As

the disease progresses, the muscular system through the body is debilitated. Some individuals with Leigh syndrome do not develop symptoms until adulthood or have symptoms that worsen over time. Leigh syndrome can manifest from genetic changes in either the mtDNA (maternal inheritance) or nuclear DNA. To date, pathogenic mutations in an astounding >75 genes have been identified in affected patients.[9] In approximately 20% of patients with Leigh syndrome the mode of inheritance is maternal, stemming from mutations in the mtDNA.

Treatment options

Sadly, there is no effective treatments or cures for mitochondrial disease. Current options include management of mitochondrial disease symptoms with supportive therapy, which can include nutritional management, exercise and/or vitamin or amino acid supplements. Patients can be given a 'mitochondrial cocktail', which consists of a variety of vitamins and cofactor supplements, that are supposed to help boost mitochondrial function and health and in turn support the energy demands of the patient. There is no 'standard' cocktail and the constituents of the cocktail can be tailored to the individual. But without detailed molecular understanding of what is going on inside the mitochondria in the case of disease, targeting the sick mitochondria can be very challenging. This is where biologists like myself have a big role to play. We can use molecular techniques to ask the following – Why are the mitochondria sick when gene X is mutated? We can do this for all 350 genes linked to mitochondrial disease. This personalised approach to mitochondrial disease can provide a roadmap for helping develop targeted therapies for specific mitochondrial diseases.

Gene therapy also presents an exciting prospect for the treatment of mitochondrial disease.[10] Gene therapy manipulates the genes inside your body's cells in an effort to treat or stop disease. Gene therapy is being explored in the treatment of LHON and phase 3

clinical trials are showing promise.[11] A further development and hope for families in the mitochondrial disease community stems from a technology referred to as mitochondrial donation. The technology encompasses an assisted reproductive technology, which can help women carrying pathogenic mtDNA mutations from transmitting their mtDNA and ultimately mitochondrial disease to their biological children. In this approach a reproductive clinic will take an embryo that contains the nuclear DNA from a man and a woman (the prospective parents) and combine it with the mitochondria from an egg donated by another woman (the mitochondrial donor). Since the mtDNA only contains 37 genes (out of a possible 20,000 genes required to make a human) the child will not have any of the physical traits of the mitochondrial donor. In this way the risk of the biological mother transmitting her mitochondrial DNA and mitochondrial disease to the child is minimised. In March 2022, the Australian Parliament passed the Mitochondrial Donation Law Reform (Maeve's Law) Bill, which will allow the use of mitochondrial donation to prevent transmission of severe mitochondrial disease. The law introduces mitochondrial donation through a staged approach under strict regulatory conditions. The Mitochondrial Donation Law Reform (Maeve's Law) Act 2022 takes effect on 2 October 2022.

Mitochondrial disease – a final word

My job as a researcher has given me the privilege of meeting and engaging with members of the mitochondrial disease community. Like many diseases, mitochondrial disease goes beyond the person and has severe impacts on the carers and family of the individual. Mitochondrial disease is unpredictable, with good days and bad days for patients. There are numerous organisations around the world that provide support to patients and families and provide support for research into mitochondrial disease. Here in Australia, we have the Mito Foundation (https://www.mito.org.au). I encourage you to visit their website and the numerous fundraising

opportunities undertaken by the Mito Foundation. For example, you might be courageous enough to join us on the next Bloody Long Walk, a 35-km walk held in all major cities around Australia, to raise awareness and crucial funds for mitochondrial disease.

As we come together on this mitochondrial disease awareness week let us acknowledge the thousands of families that face the reality of living with mitochondrial disease. As a researcher you are always at the forefront of our minds as we plan and develop our research questions and programs. I am always inspired and motivated by the resilience and bravery shown by members of the amazing Mito Community.

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