

Mitochondrial Disease: General Background and Overview of NIH Efforts

Overview of Mitochondrial Disease

Mitochondria are structures (organelles) located within every human cell except red blood cells. The mitochondria are a cell's "power plant" – they convert oxygen and calories into the energy needed to power cellular activity and thereby sustain human life.

Mitochondrial disease generally refers to a group of disorders that are attributable to malfunctioning mitochondria -- mitochondria that are unable to efficiently or effectively generate energy. This results in a lack of cellular energy to perform various functions and in the accumulation of byproducts that impair or destroy the cell itself. Because mitochondrial dysfunction can occur in the cells of numerous organs and body systems, dozens of different conditions have been identified as mitochondrial diseases. Currently there are more than 40 identified mitochondrial diseases. While many body systems and functions can be implicated in mitochondrial disease, some of the most profound effects are seen in the brain and the muscles because they are heavy users of energy. Other commonly affected organs include the heart, liver, nervous system, eyes, ears, and kidneys.

Generally mitochondrial diseases cause progressive deterioration and weakness. The prognosis for patients with mitochondrial diseases varies greatly, depending largely on the type of disease and the degree of involvement of various organs. Half of those affected by mitochondrial disease are children who show symptoms before age five and approximately 80% of whom will die before the age of 20. In addition, mitochondrial dysfunction is associated with numerous other diseases and conditions, and more and more questions are being raised about the role of mitochondrial function in a range of illness, including numerous diseases associated with aging (such as Alzheimer's, diabetes, cardiovascular disease, cancer, stroke and Parkinson's syndrome) and neurological conditions such as autism spectrum disorder and cerebral palsy.

Mitochondrial dysfunction is most commonly the result of genetic mutation. Mitochondria are interesting structures in that they have their own DNA that is maternally inherited and independent of the DNA found in the nucleus of the cell. In any given mitochondrial disease, the causative mutation might be in the cell nucleus or in the mitochondrial DNA, and it might be either inherited or a spontaneous mutation. [Modern genomics has improved the ability to identify genetic markers for certain mitochondrial disease.] Some mitochondrial dysfunction is also attributable to environmental factors that may interfere with the mitochondria and result in symptoms.

[Researchers generally describe mitochondrial disease as either primary or secondary. In primary mitochondrial disease, a mutation in the mitochondria causes the organelle to malfunction and produce symptoms. In secondary mitochondrial disease, the organelle possesses a genetic alteration but the alteration does not produce any symptoms of disease until an external environmental force, such as a drug administered for some other purpose, triggers mitochondrial dysfunction.]

Symptoms of mitochondrial disease may include muscle weakness and pain; exercise intolerance; heart failure or rhythm disturbances; dementia; movement disorders; stroke-like episodes; deafness; blindness; droopy eyelids; limited mobility of the eyes; gastro-intestinal disorders and swallowing difficulties; seizures; loss of motor control; poor growth; cardiac disease; liver disease; diabetes; respiratory complications, visual/hearing problems; lactic acidosis; developmental delays; and susceptibility to infection.

Mitochondrial diseases are a relatively newly-diagnosed group of diseases, first recognized in an adult in the late 1960s and then in pediatric cases in the late 1980s. Diagnosis is extremely difficult for a number of reasons -- including the wide range of specific diseases that can be the result of mitochondrial dysfunction in different organs or symptoms, the confusion of mitochondrial diseases with other disorders or conditions, the lack of widespread provider awareness regarding mitochondrial disease, and the lack of screening procedures or diagnostic biomarkers that are both sensitive and specific. Diagnosis can be an extremely lengthy and difficult process that begins with a general clinical evaluation, followed by metabolic screening, medical imaging and ultimately genetic testing and invasive biochemical and histological analysis. While the identification of some known mitochondrial mutations assists in diagnosis, in many cases the underlying genetic mutation can elude detection.

Given the difficulty of accurate diagnosis, it is generally acknowledged that the true incidence of mitochondrial disease is probably under-estimated. Nonetheless, researchers estimate that one in 4,000 children will develop a mitochondrial disease by age 10, and that 1,000 to 4,000 children are born with some type of mitochondrial disease each year. [All of the more than 40 identified mitochondrial diseases continue to be classified as orphan diseases].

There is no cure for mitochondrial diseases. Neither is there a specific treatment for any of the diseases. Rather, treatment is individualized by patient, and is aimed at reducing symptoms or at delaying or preventing the progression of the disease. Certain vitamin and enzyme therapies, along with occupational and physical therapy may help some patients to realize some improvement in fatigue and energy levels. In the future, a cure may involve mitochondrial "transplant" or therapy to correct underlying defects.

Mitochondrial Research: General Considerations

Mitochondrial disease is a challenging and somewhat unique area of scientific endeavor in a number of respects:

- Mitochondrial dysfunction does not involve a particular organ or system of the human body. Rather, mitochondria are organelles found by the hundreds or thousands within every cell in the human body (other than red blood cells) and serving to provide energy to those cells. Mitochondrial dysfunction can occur within the cells of any of a number of organs and body systems and can therefore be implicated in a myriad of disorders and conditions. For this reason, improvements in the basic science of understanding mitochondrial dysfunction has potential application to numerous areas of biomedical research involving numerous NIH institutes and centers. Simply put, the science of mitochondrial dysfunction is in the truest sense a fundamental area of "cross-cutting" research. It is also an area of research that has been identified as one that could benefit from a comprehensive "systems biology" approach.
- Mitochondrial dysfunction is also unique and complex with respect to its genetics. All human cells have nuclear DNA that guide their composition and replication and that can be prone to mutations or variations that may be implicated in certain diseases. But the mitochondria organelle within a cell has its own unique and independent DNA, and mutations or variations within this mitochondrial DNA must be understood distinct from changes in nuclear DNA. Mitochondrial DNA is less complex than nuclear DNA and not inherited under the classic Mendelian pattern (a combination of the DNA of both parents). Rather Mitochondrial DNA is entirely passed from mother to child. Because it is less complex than nuclear DNA, this mitochondrial DNA is also subject to greater potential for significant mutation and alteration. Further, mutations in mitochondrial DNA may replicate in a heterogeneous manner such that not all the hundreds of mitochondria in a particular cell contain the mutation. Thus the level of mitochondrial mutation within an organ or body system could range anywhere from zero to 100%. Finally, in any given expression, mitochondrial dysfunction may be the result of genetic alteration in nuclear DNA, alteration in the mitochondrial DNA or an interaction between the two.
- Some aspects of mitochondrial disease and dysfunction that garner significant attention, include –
 - *Neurological Disorders.* The neurological system, and the brain in particular, is an intense consumer of energy. As a result, mitochondrial dysfunction in the neurological systems can have the most profound impact, including severe neurological disorders. There is growing interest in the relationship between mitochondrial dysfunction and several major neurological diseases with which it is associated – including autism spectrum disorders, Parkinson's disease and ALS.

- *Children.* Primary mitochondrial dysfunction expresses itself early in life, with dramatic and tragic impacts on small children. Half of those affected by mitochondrial disease are children who exhibit symptoms before age five, and approximately 80% of them will die before the age of 20.
- *Cardiovascular Disease.* Like the brain, the cardiovascular system is a major user of energy and there is strong and growing interest in understanding the role of mitochondrial dysfunction in heart failure and other cardiovascular diseases.
- *Aging.* Mitochondrial dysfunction is associated with numerous aging related diseases, such as Alzheimer's, Parkinson's, stroke and cancer. [Indeed, some hypothesize that mitochondrial function is at the heart of the aging process itself.]

National Institutes of Health (NIH) Support for Mitochondrial Disease Research

NIH has taken an increased interest in mitochondrial disease and dysfunction and sponsored a number of activities in recent years aimed at advancing this science. Some noteworthy examples include:

- ***Transformative Research Grants on Functional Variations in Mitochondria.*** In September of 2009, NIH announced its intent to invest \$250 million over five years in an effort to support exceptionally innovative, high risk, original and/or unconventional research projects that have the potential to profoundly impact a broad area of biomedical research. This so-called "Transformative Research" (T-RO1) program was undertaken by the Office of Portfolio Analysis and Strategic Initiatives under the Office of the Director as part of the NIH Roadmap for Medical Research initiative. Functional Variations in Mitochondria was one of six areas of highlighted need that was identified through an NIH strategic planning process and eligible for funding under the T-RO1 Program. Significant mitochondrial disease-related challenges to be addressed under the T-RO1 program include defining variability in human mitochondrial structure and function within and between cells and tissues in health and disease; developing tools and technologies to identify, study and manipulate human mitochondrial function; and elucidating the complexity of human mitochondrial function. A Funding Opportunity Announcement (FOA) providing an initial \$25 million in research grants in the six identified areas was released.
- ***The NHLBI Working Group Meeting on Modeling Mitochondrial Dysfunction in Cardiovascular Disease.*** In July of 2007, the NHLBI convened this working group meeting to better explore the role of mitochondria in cardiovascular disease and computational tools to study mitochondria. Certain areas of research and opportunity were identified, including the need to use a systems biology approach toward understanding mitochondrial function; the need for

cross-disciplinary collaboration on mitochondrial disease research projects; the need for new models and tool to facilitate research; and the need to develop tools to measure mitochondrial function in humans (as opposed to computational and animal modeling). NIH also held a meeting in Fall, 2008 on *Mitochondrial Biology in Cardiovascular Health and Diseases*. Currently, the NHLBI currently is accepting grant applications to investigate the role of cardiomyocyte mitochondria in heart disease. The NHLBI intends to award up to \$16 million over the next four years to fund up to six grants under this research initiative.

- ***NINDS/NIMH/CDC/FDA Workshop on Mitochondrial Encephalopathies and their Potential Relationship to Autism.*** This workshop was convened in Indianapolis in June of 2008 to, in part, examine a number of recent reports describing evidence of mitochondrial disease in children with autism or autism spectrum disorders. The workshop reviewed evidence on the clinical parallels between mitochondrial disease and autism spectrum disorder and focused on how to develop a program of research into the potential relationship between mitochondrial dysfunction and ASD.
- ***NICHD and the National Children's Study.*** NICHD has supported research on mitochondrial dysfunction related to pediatric disease and cerebral palsy. The National Children's Study (NCS), an ambitious long-term longitudinal study of a large cohort of women and children from pre-birth to adulthood, has established a number of hypotheses that will be applied during the course of the NCS. NCS research plans currently envision isolating mitochondrial DNA from whole blood of NCS participants that will be obtained several times during development. This should permit an improve understanding of the maternal lineage of mitochondrial DNA and its mutation.

The foregoing examples are far from exhaustive of the role that NIH has to play in mitochondrial disease research. Numerous NIH institutes – including NIA, NIEHS (which sponsors the Mitochondrial DNA Replication Group), NIDDK, NCI (which is currently accepting grant applications to investigate mitochondria in cancer epidemiology, detection, diagnosis and prognosis) and other institutes are active in mitochondrial disease research. NIH-wide, there are at least 23 separate clinical trials that are investigating mitochondria in some manner.