

## QUICK SUMMARY

# Mitochondrial Disease and Toxins

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Detailed slides accompanying this presentation can be found at:

<http://www.mitoaction.org/mitochondrial-disease-and-toxins>.

### **Mitochondrial disease**

The major focus of research and literature has been the study of mitochondrial and nuclear DNA mutations causing a genetically caused mitochondrial disease. This discussion, however, will focus on the non-genetic, or somatogenic, causes of mitochondrial disorders and dysfunction. The symptoms very closely resemble a genetically inherited mitochondrial disease, but the causative agent is acquired by exposure to drugs, environmental, or occupational chemicals.

All of the cell's energy, namely ATP, is generated within the five complexes or clusters of up to 42 proteins of the electron transport chain (slide 4). Each of the 5 complexes require proteins for normal function and where those complexes are encoded -- either in the nDNA or the mtDNA. Most proteins are encoded in the nuclear DNA, meaning that if a mutation is acquired in the nuclear DNA that stops the production of the protein, the entire electron transport chain's ability to produce energy becomes dysfunctional.

**Somatogenic Etiology of Mitochondrial Disorder - "Mitochondrial Toxicity"** describes the etiology of mitochondrial disorders acquired from pharmaceutical, environmental, and/or occupational exposure that damage the cell's ability to produce energy (slide 5-7).

### **Chemical Targeting to Mitochondria**

Positively charged chemicals are drawn from the cell contents into and accumulate preferentially in the mitochondria, running the risk of causing dysfunction in energy production.

### **Substrate Delivery and Mitochondrial Toxicity** (slide 13-16)

If the substrates needed for the electron transport chain are not available, the cell will "starve," ultimately inhibiting the production of ATP (INDIRECT INHIBITORS!). Basically— if all the components needed to make energy are not available, the whole "factory" will be shut down or at least production lines will be slow ... components range from enzymes, co-factors, etc. ... and each step of the production of those components can be inhibited by the chemical, drug, and/or environmental factors Dr. Wallace addresses.

### **Molecular Targets for Mitochondrial Toxicity**

- Gene Translation - translating the genetic code to a message ( messenger RNA)

- Protein Translocation and Assembly - movement of proteins within the cell for assembly within the complexes. This process uncovers several potential targets for chemically induced mitochondrial disease due to mutations in the genetic code in the nucleus, cytosolic ribosomes (protein synthesis within the cytoplasm), and/or precursor protein processing. Any chemical that changes the charge of the proteins outside the cell, thus depolarizing membrane potential, will inhibit those proteins from entering the cell as the ion gradient will no longer exist. Drugs that inhibit protease enzymes interfere with the snipping of the precursor from the protein, rendering that compound non functional in the electron transport chain. Most of the 84 proteins needed to produce energy must go through this process through TOM and TIM and are subject to ill effects of toxins along this pathway.
- Mitochondrial DNA Replication and Translation - Topoisomerase enzymes helps to untwist the mtDNA so it can be read, and Polymerase helps assemble individual nucleic acids into a chain. These enzymes are a target for toxicity and damage.
  - Nucleus Reverse Transcriptase Inhibitors (NRTIs) - drugs designed to inhibit the replication of viral DNA (such as HIV). Human host cells have over five DNA polymerase enzymes, but these drugs target just one of these enzymes, namely DNA Polymerase Gamma. Mitochondria, unfortunately, only have one DNA Polymerase that happens to be the DNA Polymerase Gamma. Using these drugs to treat viruses carries the unwanted side effect of inhibiting the replication of the mitochondrial genome.
- Protein Synthesis - At the ribosome, the RNA's message is translated into a specific protein and is another target for toxicity. Bacteria carry the same single mitochondrial ribosome (because mtDNA was derived from bacteria). Antibiotics aimed at that specific ribosome can also damage mitochondria via protein synthesis inhibition.

Additional chemicals or environmental mitochondrial toxicities are known to interfere with mitochondrial function, but the mechanism is not yet fully understood:

- Cigarette smoke
- Air pollution and particulates
- Poly aromatic hydrocarbons (PAHs)
- Herbicides 2, 4-dichlorophenoxyacetic acid, dinoseb
- mtDNA geneotoxins, mutagens
- and others

### **“Hazard” vs “Risk!”**

Bear in mind, reports of demonstrated mitochondrial toxicity represent a “hazard” that may or may not be a “real” risk under normal or intended exposure conditions! Over-interpretation of data will overestimate real risk for the patient. Just because a chemical has the capacity, or even potential, to interfere with mitochondrial function, does not mean that adverse outcomes will invariably occur. The degree of exposure is critical to real risk.

The threshold for concern when using a medication known to be potentially toxic to the mitochondria yet has some benefit for the patient warrants a discussion with the medical physician or team.