MIAMI BIO/TECHNOLOGY WINTER SYMPOSIUM

MITOCHONDRIAL DEFECTS AND DISEASE

MIAMI BEACH, Fla.—What is the most wide-spread genetic disease? It may be aging. Researchers at Emory School of Medicine (Atlanta, GA) have shown that mitochondrial respiratory complexes fade with age in all populations, controls as well as patients.

At the 1991 Miami Bio/Technology Winter Symposium, held here in late January, Emory investigator Douglas Wallace called the finding, "an exciting result for those of us who have been trying to show that mitochondrial disease exists. This shows that mitochondrial disease is the most common disease in the world because everybody has it."

It has been a long road to the idea that genetic defects in the mitochondria could have health effects, a road made rockier by the peculiarities of mitochondrial organization and inheritance.

At first blush, the mitochondrial geneticist's job might look easy. Mitochondria, of course, are inherited somatically—they are inherited only from the mother in sexual recombination. So, to the mitochondrial geneticist, the genetic universe is like a vast X chromosome.

This is a mixed blessing. Each cell contains thousands of mitochondrial DNA (mtDNA) molecules, which replicate and segregate independently during cell division. Thus, statistical flukes of organism development (replicative segregation, for short) can see mutated mtDNA accumulating in some tissues and, at the same time, disappearing from others.

The effects can be subtle, too. Damage to mtDNA affects a mix of proteins in the oxidative phosphorylation pathway—which is, of course, the body's principal source of energy. Accumulating mtDNA mutations mean proportional decreases in the cell's overall energy level. To the observer, mtDNA defects affect the cell like an electrical dimmer switch. On-lookers accustomed to the more dramatic on-or-off switches of nuclear DNA can find the effects hard to see.

Moreover, different tissues have different energy requirements. Some can tolerate a high burden of nonfunctioning mitochondria. Others shut down early (a phenomenon called threshold expression).

Thus, researchers trying to track down the effects of mitochondrial mutation must peer through the triple haze of maternal inheritance, replicative segregation, and threshold expression—so that a single genetic condition may wear myriad clinical faces.

So far, says Wallace, three neuromuscular diseases can be traced to flawed mtDNA: Leber's hereditary optic neuropathy, myoclonic epilepsy and ragged red-fiber disease (Merrf), and ocular neuropathy.

Leber's neuropathy is a late-onset, bilateral blindness, in which the patient's central vision goes first. The researchers traced the cause to a missense Arg-to-His mutation in a single locus of the 16,569 base pair NADH dehydrogenase gene.

Merrf is caused by a single nucelotide substitution in a transfer RNA for lysine (an A-to-G change at position 8,344). The disease itself varies in severity, but can manifest itself as uncontrolled jerking repeated every one to three minutes. Wallace and his co-workers found the defect by examining patients' changes in their anaerobic thresholds—an index of the muscle's oxidative work capacity. And, indeed, the researchers found that there were strong correlations with accumulated mtDNA defects. That sparked the hunt for the specific gene defect.

Aging complicates the Merrf picture. The respiratory threshold declines with age in Merrf patients...and in controls.

Ocular myopathies and Merrf both respond to metabolic therapy: coenzyme Q, an anti-oxidant and electron carrier, scavenges the oxygen free-radical products of the flawed respiratory pathways, preventing damage to the mitochondrial membranes.

A patient with Merrf treated over five months with 300 mg/day of coenzyme Q showed improvements in a host of distressing symptoms: myoclonic epilepsy, lactic acidosis, and respiratory failure.

An ocular myopathy patient exposed for thirty days to the same regimen supplemented with 6 g/day of succinate, showed a marked reduction in respiratory failure.

—Jennifer Van Brunt