FROM SMALL THINGS

Once the preserve of cell biology textbooks at medical school, mitochondria are now finding their way into all sorts of clinical practice, as **Toby Reynolds** explains

STEVE G. SCHNEIDER/SPR

Mitochondria: not just the cell's power house

What links Parkinson's disease, exercise intolerance, diabetes, and organ failure in sepsis? Anything common to such a disparate group would need to be quite fundamental, and there aren't many things more elementary than generating the energy needed to stay alive. This is the job of the mitochondrion—the dynamo of the cell—and recent research indicates that it contributes to a wide range of diseases.

Mitochondria are thought to have started off as free living prokaryotes that were engulfed by the ancestors of modern nucleated cells millions of years ago. One of the features hinting at their previous lives is that they have retained some of their own DNA.

Although the role of these tiny intracellular organelles is vital, their relevance to clinical practice has often seemed obscure. Cell biologists worked out how mitochondria make energy four decades ago. Since then medical students have had to trace out how, after a glucose molecule is broken down, electrons from its oxidised metabolites move along a series of mitochondrial membrane bound proteins, building up an electrochemical energy gradient that can be harnessed to make adenosine triphosphate (ATP), the main energy source for cellular reactions. But they have usually struggled to relate this to anything encountered on the wards.

Some clinicians may have encountered one or two of a handful of disorders attributed to mutations in mitochondrial DNA such as the maternally inherited Leber's hereditary optic neuropathy, which results in degeneration of the optic nerve. But diseases related to such mutations were regarded as rare, affecting perhaps one or two per million in the population, and the province of a few specialists.

Rising from obscurity

This view has now changed, says Doug Turnbull of Newcastle University's mitochondrial research group. Because almost all tissue types rely on mitochondria to generate energy, genetic disorders causing mitochondrial dysfunction can manifest themselves at any age and in any organ system, often in several. Cells in muscle, the liver, the retina, and the central nervous system all perform highly energy intensive tasks, making these tissues particularly susceptible.

Reviewing epidemiological data, Professor Turnbull and colleagues suggest the minimum prevalence for single gene mitochondrial disorders is likely to be 1 in 5000, placing this among the most common types of human inherited disease.¹ "Primary mitochondrial disease is seen to be much more common than previously thought," he said. "These were rarities that used to be seen by very specialist neurologists, yet

the incidence of these abnormalities in the population is much greater than we had previously considered."

Leber's hereditary optic neuropathy is the most common single gene mitochondrial disease, and the mutations most frequently associated with it are found in 2% of those registered blind in Australia.² Researchers have identified more than 100 mutations in mitochondrial DNA that cause disease, and over 130 mutations in nuclear DNA have also been associated with disorders of mitochondrial dysfunction.³

In recognition of the importance of mitochondrial disease, the NHS this year designated three centres in London, Newcastle, and Oxford as referral points for diagnosis and management of these disorders. Since mitochondria and their internal DNA are inherited along the maternal line, and relevant nuclear genes can also be passed on, the centres also provide genetic counselling.

"In terms of clinical practice, our current understanding might make people think more about mitochondrial disease as the cause of the symptoms, and if that turns out to be correct, then they might look at other complications of mitochondrial disease," Professor Turnbull said. "If you look at somebody who has paralysis of the eye muscles, which is quite a common presentation in patients with mitochondrial disease, if they have mitochondrial disease then they might be at increased risk, say, of developing

diabetes or cardiomyopathy, and therefore you would try to screen for things which are potentially treatable.”

Role in major disease

In addition to monogenic disorders, scientists are also discovering that mitochondria have a secondary role in many more diseases. One of the most common, and potentially most important, presentations of mitochondrial dysfunction is diabetes, which is after all a disorder of altered fatty acid and carbohydrate metabolism. How mitochondria contribute to the disease is not entirely clear, but some mutations in mitochondrial DNA are associated with type 2 diabetes, as are some changes in genes regulating mitochondrial biogenesis—the process of organelle growth, maintenance, and replication.

“In many major diseases people are now looking at mitochondria,” said Mervyn Singer, professor of intensive care medicine at University College London. Sepsis is one such area. “You get an excessive amount of inflammation in sepsis, but how do the released cytokines and mediators actually cause the organs to fail? And if the organs fail, how do they then recover? There is minimal cell death, so one way to view organ failure is as a protective mechanism akin to hibernation,” Professor Singer said.

Many changes that occur in acute critical illness switch off mitochondria, such as the release of inflammatory mediators like nitric oxide. “You have many factors conspiring at the same time to inhibit the activity of mitochondria, damage them, or reduce turnover of new mitochondrial protein,” he added. “It all implicates a mitochondrial pathology as being core to the process of organ failure. If the patient gets better, then, if this hypothesis is correct, the mitochondria must start functioning to provide the necessary energy for normal metabolic processes.”

He points out that antibiotics are among the most potent inhibitors of mitochondrial biogenesis. Perhaps this is hardly surprising considering the organelle’s prokaryotic origins, but he adds that perhaps this means the way infections are treated may also be delaying recovery. “From a sepsis point of view we have made relatively minimal inroads into treating patients with new drugs in the last 20 years.

“We are sorely in need of completely new therapeutic paradigms. What excites me is

that if we can target either factors causing damage to mitochondria, or perhaps encourage their earlier activation or regeneration, the affected organs may start functioning sooner. This would undoubtedly save lives, improve morbidity, and shorten stay, all crucial goals worth aiming for.”

Mitochondria have also turned out to be central to the process of programmed cell death. Failure of this process is important in cancer, and researchers are looking at ways that mitochondrial dysfunction may be involved in tumour development. And because mitochondria generate energy, it is unsurprising that mutations in their DNA have a role in exercise intolerance. Changes in genes coding for membrane bound proteins that transport electrons in the mitochondrion have been associated with extreme and premature muscle fatigue.

Another factor that has turned researchers’ heads towards mitochondria is the realisation that molecular damage from reactive oxygen radicals is important in the pathogenesis of a huge range of disorders. With their chain of oxidation reactions, mitochondria are the main source of oxygen radicals in the cell. Damage to mitochondria from oxygen radical production may hold the key to a whole group of neurodegenerative diseases, such as Parkinson’s disease, says Auckland based neurologist Barry Snow.

“Until recently we really had a great deal of difficulty understanding the pathogenesis of these diseases,” he said. “We still don’t

know what causes them, but there is a strong feeling that there must be a common process in these diseases. There is

a common pattern—they are more common in older people, have a gradual progression, a lack of overt inflammation—and gradual mitochondrial failure actually fits all those criteria very nicely.”

Dr Snow is running a phase II clinical trial of an antioxidant drug that is designed to accumulate in mitochondria and protect them from damage from oxygen radicals. There is some evidence that antioxidants are depleted in mitochondria in neurodegenerative diseases, and one small trial found that an untargeted antioxidant, coenzyme Q10, helped slow the progression of Parkinson’s disease.⁴

The interior of a mitochondrion has a strong negative charge, however, making it difficult for antioxidants to enter. The drug in the trial, called MitoQ, combines the antioxidant activity of coenzyme Q10 with

a positively charged domain to help it get into the mitochondrion. Dr Snow’s trial has recruited 128 patients who have recently had Parkinson’s disease diagnosed but who are not yet receiving drug treatment for symptoms. He is following them for a year to see whether the disease progresses more slowly in those taking MitoQ. “It is hard to prove, but all the circumstantial evidence points towards oxidative damage in mitochondria being involved in Parkinson’s disease. And in the early onset familial forms of Parkinson’s, which are very rare but point to aspects of the mechanism, a lot of those mutations turn out to be in mitochondrial proteins,” said Michael Murphy, leader of the mitochondrial dysfunction group at the Medical Research Council Dunn Human Nutrition Unit at Cambridge University, who was involved in designing MitoQ.

“If it works then it would be the first time anyone has successfully targeted mitochondrial oxidative damage in a disease. That would be quite an interesting breakthrough,” said Dr Murphy. “Oxidative damage seems to be involved in a wide range of diseases, so if it worked in one the same approach might work in heart damage or liver damage or whatever. Even in things like sepsis we might expect it to work.”

Successful treatments targeting mitochondria are still some way away, and Professor Turnbull emphasises that the main clinical application of the growing appreciation of their importance in disease is a higher profile for mitochondrial disorders. “It is really about awareness of these diseases, and being aware that there are other potential complications or potentially important genetic implications of establishing a diagnosis,” he said. “The research directing understanding about the mitochondria and about the patients is leading directly to ideas about ways in which we might target treatment for patients with mitochondrial problems. We are much more hopeful about things than we were before, but we still have a very long way to go.”

Competing interests: None declared.

- 1 Schaefer AM, Taylor RW, Turnbull DM, Chinnery PF. The epidemiology of mitochondrial disorders—past, present and future. *Biochim Biophys Acta* 2004;1659:115–20.
- 2 McFarland R, Taylor RW, Turnbull DM. Mitochondrial disease—its impact, etiology, and pathology. *Curr Top Dev Biol* 2007;77:113–55.
- 3 Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005;6:389–402.
- 4 Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 2002;59:1541–50.

Toby Reynolds medical student and former Reuters journalist, St George’s, University of London, London SW17 0RE Toby.reynolds@gmail.com