Possessed! The powerful aliens that lurk within you

- 22 September 2014 by Garry Hamilton

The micromanagers (Image: Brett Ryder)

Once they were free-living bacteria, then they hijacked complex cells, now it turns out they have a hand in everything from memory and ageing to obesity

YOU'VE got aliens inside you. It sounds crazy, and for nearly a century science steadfastly refused to believe it. Mitochondria, tiny bodies that swarm inside almost every one of our cells and supply them with power, are actually descendants of a separate life form: a free-living bacterium probably not unlike many of the little terrors that surround us today.

Although the idea of this merger is now widely accepted, it continues to be seen through biased eyes. The hapless mitochondrial ancestor was enslaved, so the story goes, its once proud genome reduced to a few genes and its job limited to the provision of energy.
Autonomy? Long gone. It's as if we were trying to pretend this side of our family tree never existed.

But these residents are becoming increasingly difficult to ignore. Far from being passive power plants, it seems mitochondria influence some of the most important aspects of human life – from memory and ageing to combating stress and disease. They even have influence over the DNA in your cell nuclei, and change and evolve during your lifetime, giving you an unexpected source of adaptability to cope with a world in flux. Given what we are now finding out about the extent of mitochondrial activities, you might be forgiven for feeling a bit possessed.

Found in almost every cell of every multi-celled life form on the planet, mitochondria are lozenge-shaped organelles no more than 1 micrometre in diameter. We inherit ours from our mothers in the cytoplasm of the egg from which we develop. The number in a given cell varies widely depending on the organism, tissue type and physiological conditions, with some cells having just one and others up to several thousand.

That we have underestimated their autonomy is not really surprising. The mitochondrial genome is puny: in humans, it is just 16,569 base pairs long, compared with 3 billion in the DNA in our cell nuclei. When mitochondria were sequenced in 1981, researchers found only 37 genes. Thirteen of these encode proteins involved in their most essential function: operating the molecular assembly line in which oxygen and nutrients are used to make ATP, a vital compound used all over the body to store energy and subsequently release it. The rest of the genes code for proteins involved in making other proteins. However, mitochondria require hundreds more proteins to function, and these are produced by the cell nucleus and then imported via the cell's cytoplasm.

"Everybody acknowledges that mitochondria are important, but if you ask why, they say they generate energy and receive signals from the cell," says Changhan Lee at the University of Southern California, Los Angeles. "It's like an 'end-function organelle' – a slave organelle that just sits there."

Dynamic dynamos

Not so, as we are beginning to discover. Mitochondria change shape. They migrate around the cell. Under certain conditions they fuse into web-like networks, swapping their contents before dispersing once again as rod-shaped granules. They multiply when greater production of energy is needed, and trigger their own self-destruction when damaged.

This is no idle dynamism, either. In the brains of mice, for example, the migration of mitochondria within individual neurons towards the junctions between them, the synapses, boosts the transmission of electrical impulses. In forgetful monkeys, the synapses of neurons involved in working memory have fewer mitochondria and a greater proportion of irregular-shaped mitochondria compared with monkeys with sharper mental skills.
We still don't understand what's going on here, but that mitochondria can influence memory is just the latest in a string of functions now attributed to them. The first inkling that mitochondria are not merely one-trick, energy-making ponies dates to the mid-1990s, when researchers discovered that, by releasing proteins mostly used in their ATP-making machinery, they have a hand in whether cells live or die – and a fundamental role in ageing (see "Engines of youth?"). Since then, mitochondria have been found to produce hemes, molecules that among other things are used by haemoglobin to transport oxygen. They are also involved in regulating cell division. And, like canny commodity traders, they control the availability of calcium, which is required in a wide variety of processes, from bone growth to the activation of neurons. In fact, delve deeper into the various tissues of the body, and you see mitochondria performing specialised functions almost everywhere, from synthesising steroids in the gonads to detoxifying ammonia in the liver.

But perhaps the most intriguing of these newfound mitochondrial functions involves a molecule called humanin. Originally identified in human brain cells more than a decade ago, this small peptide helps protect against Alzheimer's disease by preventing beta amyloid proteins from destroying neurons. Injections of humanin also improve the health of diabetic rats and mice by increasing sensitivity to insulin, so improving sugar tolerance. In mice prone to atherosclerosis, meanwhile, humanin reduces the arterial plaques that in humans are the number one cause of heart disease.

Humanin is secreted by cells, is present in the blood, and binds to cell membranes, all of which suggests it belongs to a particular class of biomolecule. "Essentially you could call it a hormone," says Pinchas Cohen at the University of Southern California. The main human genome is littered with humanin-like sequences, but it turns out that humanin has an amino-acid sequence that is an exact match for a stretch of DNA nestled within one of the genes of the mitochondrial genome. Cohen says his lab has recently conducted work that supports suspicions that humanin is in fact a product of the mitochondrial genome, and that the blurrily similar sequences in our main genomes are the result of the many times in evolutionary history that mitochondrial DNA has insinuated itself into the nucleus.

Genes within genes

This might be just the first glimpse into an entirely new class of biological signals. "We've now identified several other new peptides within the mitochondrial DNA," says Cohen. "They're of mitochondrial origin and they have distinct and unique biological activity." Although yet to be published, the results make sense given the mitochondrion's origins: bacteria are famous for getting the most out of small genomes, and one effective strategy is nestling genes within genes. Now that researchers are giving the mitochondrial genome a closer look, there is evidence that we may have as many as 500 of these Russian-doll genes hidden away in our mitochondrial DNA.
Adding further to this unfolding picture, last year Wei Yan at the University of Nevada in Reno and his team reported that mitochondrial DNA also generates thousands of distinct small non-coding RNAs. These molecules are able to influence how the nuclear genetic code is expressed through processes such as methylation, which alters gene activity, thus modifying which proteins are produced.

So the picture of the enslaved organelle seems to be precisely the wrong way around – in many ways, these bacterial "slaves" are in fact masters of our fates. "These findings really create a new paradigm," says Cohen. "It suggests the mitochondrion is an important organelle in terms of initiating biological signals." He is not alone in his interpretation. "It gives the mitochondrial genome a completely different level of power," says Jonci Wolff, a molecular biologist at Monash University in Melbourne, Australia.

Wolff and others are convinced that mitochondrial DNA is deeply wired into the basic functioning of cells, and probably has been from the start – whenever that was. The realisation that all eukaryotes – life forms consisting of cells with a DNA-based nucleus – have or once had mitochondria suggests the original incorporation of the bacterium that made the mitochondria happened much earlier than was thought, at least before the evolution of the nucleus some 2 billion years ago. One theory is that only by acquiring mitochondria was an originally very simple host able to overcome the energetic constraints that limit genome expansion in single-celled life forms. It was this vital merger that opened the door to genome complexity, which in turn made possible the evolution of multicellular life. If so, it suggests that the mitochondrion isn't an evolutionary bystander, but a bona fide second genome – and even a second source of genetic adaptability.

That would be a mind-bender. Like their bacterial ancestors, mitochondria lack the sophisticated DNA-maintenance tools that help limit change in the nuclear genome. As a result, mitochondrial DNA picks up mutations at a much faster rate. With each mitochondrion possessing hundreds of copies of the same genome, and hundreds of mitochondria per cell, our bodies are a constantly changing stew of mitochondrial DNA variation. What's more, a remarkable discovery made last year reveals that, contrary to what has long been assumed, we are born with multiple mitochondrial DNA variations, which originate in the egg at the time of fertilisation. And, some researchers wonder, if mitochondrial DNA really does have such wide-ranging effects, might useful mitochondrial adaptation occur over much shorter timescales than standard genetic adaptation? Supporting evidence for this idea comes from recent studies in Tibet, where analysis of mitochondria from people living at different altitudes has revealed striking correlations between certain mitochondrial DNA mutations and elevation. Given how long these communities have been living at altitude, this hints at the possibility of mitochondrial adaptation to low-oxygen conditions having occurred in time frames as brief as centuries.

Another hint comes from research done by Bill Ballard at the University of New South Wales in Sydney, Australia, which suggests that fruit flies are able to survive in different parts of the
world partly as a consequence of mutations in their mitochondrial DNA that arose in response to different diets. By raising colonies of flies that share the same nuclear genome but different mitochondrial DNA sequences, Ballard has found that specific mitochondrial genomes inevitably rise to dominance within a population. Which one comes to the fore over the generations depends on what the flies have eaten. Ballard suspects that the different mitochondrial genomes can help flies thrive in different environments through the role they play in orchestrating fundamental cellular processes, such as those controlling the rate at which an individual develops.

Rapidly adapted

In humans, it might be that our mitochondria evolve beneficial adaptations not just across generations, but within our own lifetimes. Scott Williams at Vanderbilt University in Nashville, Tennessee, and his colleagues analysed mitochondrial DNA sequences from 10 different tissue types in four human volunteers. Each tissue type tended to have its own distinct pattern of mitochondrial mutations, however, these patterns were remarkably similar from one individual to the next. The team speculates that specific mitochondrial DNA mutations may proliferate partly in response to the varying needs of cells in different parts of the body. In other words, our mitochondria evolve as we develop, becoming adapted to the cellular environment in which they find themselves.

Given the role of mitochondrial activity in common human ailments such as diabetes, obesity, atherosclerosis and Alzheimer's disease – and even just the general effects of ageing – recognising the true nature of our chimeric identity might offer a possible route to treating such conditions. But there is also a potentially worrying aspect to all this. Mitochondria have been in the news lately with debates over whether the UK should permit the creation of so-called three-parent babies – where an embryo is made using the nuclear DNA from the mother and father transferred into a donor egg with its nucleus removed. This would allow a woman whose mitochondrial DNA is faulty to avoid passing on a serious illness to her child. Most debate around the issue has worked on the assumption that mitochondria are simply cellular powerhouses. However, given their new-found influence over our bodies the implications of this technology may be far more radical than we have assumed.

Whether generating excitement or concern, the revisionist view of mitochondria is tempered by the reality that researchers must now dig in and discover how it all works. At the very least, it's time we invited our long-neglected interloper back to the table.

*This article appeared in print under the headline "The micromanagers"*