Power, Sex, Suicide

Mitochondria and the Meaning of Life

Introduction. Mitochondria: Clandestine Rulers of the World

Nick Lane
Biochemist and writer

About

Dr Nick Lane is a British biochemist and writer. He was awarded the first Provost's Venture Research Prize in the Department of Genetics, Evolution and Environment at **University College London**, where he is now a Reader in Evolutionary Biochemistry. Dr Lane's research deals with evolutionary biochemistry and bioenergetics, focusing on the origin of life and the evolution of complex cells. Dr Lane was a founding member of the UCL Consortium for Mitochondrial Research, and is leading the UCL Research Frontiers Origins of Life programme. He was awarded the 2011 BMC Research Award for Genetics, Genomics, Bioinformatics and Evolution, and the 2015 Biochemical Society Award for his sustained and diverse contribution to the molecular life sciences and the public understanding of science.

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Introduction. Mitochondria: Clandestine Rulers of the World

Mitochondria are a badly kept secret. Many people have heard of them for one reason or another. In newspapers and some textbooks, they are summarily described as the ‘powerhouses’ of life – tiny power generators inside living cells that produce virtually all the energy we need to live. There are usually hundreds or thousands of them in a single cell, where they use oxygen to burn up food. They are so small that one billion of them would fit comfortably in a grain of sand. The evolution of mitochondria fitted life with a turbo-charged engine, revved up and ready for use at any time. All animals, the most slothful included, contain at least some mitochondria. Even sessile plants and algae use them to augment the quiet hum of solar energy in photosynthesis.

Some people are more familiar with the expression ‘Mitochondrial Eve’ – she was supposedly the most recent ancestor common to all the peoples living today, if we trace our genetic inheritance back up the maternal line, from child to mother, to maternal grandmother, and so on, back into the deep mists of time. Mitochondrial Eve, the mother of all mothers, is thought to have lived in Africa, perhaps 170,000 years ago, and is also known as ‘African Eve’. We can trace our genetic ancestry in this way because all mitochondria have retained a small quota of their own genes, which are usually passed on to the next generation only in the egg cell, not in the sperm. This means that mitochondrial genes act like a female surname, which enables us to trace our ancestry down the female line in the same way that some families try to trace their descent down the male line from William the Conqueror, or Noah, or Mohammed. Recently, some of these tenets have been challenged, but by and large the theory stands. Of course, the technique not only gives an idea of our ancestry, but it also helps clarify who were not our ancestors. According to mitochondrial gene analysis, Neanderthal man didn’t interbreed with modern Homo sapiens, but were driven to extinction at the margins of Europe.

Mitochondria have also made the headlines for their use in forensics, to establish the true identity of people or corpses, including several celebrated cases. Again, the technique draws on their small quota of genes. The identity of the last Russian Tzar, Nicholas II, was verified by comparing his mitochondrial genes with those of relatives. A 17-year-old girl rescued from a river in Berlin at the end of the First World War claimed to be the Tzar's lost daughter Anastasia, and was committed to a mental institution. After 70 years of dispute, her claim was finally disproved by mitochondrial analysis following her death in 1984. More recently, the unrecognisable remains of many victims of the World Trade Center carnage were identified by means of their mitochondrial genes. Distinguishing the 'real' Saddam Hussain from one of his many doubles was also achieved by the same technique. The reason that the mitochondrial genes are so useful relates to their abundance. Every mitochondrion contains 5 to 10 copies of its genes. Because there are usually hundreds of mitochondria in every cell, there are many thousands of copies of the same genes in each cell, whereas there are only two copies of the genes in the nucleus (the control centre of the cell). Accordingly, it is rare not to be able to extract any mitochondrial genes at all. Once extracted, the fact that all of us share the same mitochondrial genes with our mothers and maternal relatives means that it is usually possible to confirm or disprove postulated relationships.

Then there is the 'mitochondrial theory of ageing', which contends that ageing and many of the diseases that go with it are caused by reactive molecules called free radicals leaking from mitochondria during normal cellular respiration. The mitochondria are not completely 'spark-proof'. As they burn up food using oxygen, the free-radical sparks escape to damage adjacent structures, including the mitochondrial genes themselves, and more distant genes in the cell nucleus. The genes in our cells are attacked by free radicals as often as 10,000 to 100,000 times a day, practically an abuse every second. Much of the damage is put right without more ado, but occasional attacks cause irreversible mutations – enduring alterations in gene sequence – and these can build up over a lifetime. The more seriously compromised cells die, and the steady wastage underpins both ageing and degenerative diseases. Many cruel inherited conditions, too, are linked with mutations caused by free radicals attacking mitochondrial genes. These

diseases often have bizarre inheritance patterns, and fluctuate in severity from generation to generation, but in general they all progress inexorably with age. Mitochondrial diseases typically affect metabolically active tissues such as the muscle and brain, producing seizures, some movement disorders, blindness, deafness and muscular degeneration.

Mitochondria are familiar to others as a controversial fertility treatment, in which the mitochondria are taken from an egg cell (oocyte) of a healthy female donor, and transferred into the egg cell of an infertile woman – a technique known as 'ooplasmic transfer'. When it first hit the news, one British newspaper ran the story under the colourful heading 'Babies born with two mothers and one father'. This characteristically vivid product of the press is not totally wrong – while all the genes in the nucleus came from the 'real' mother, some of the mitochondrial genes came from the 'donor' mother, so the babies did indeed receive some genes from two different mothers. Despite the birth of more than 30 apparently healthy babies by this technique, both ethical and practical concerns later had it outlawed in Britain and the US.

Mitochondria even made it into a Star Wars movie, to the anger of some aficionados, as a spuriously scientific explanation of the famous force that may be with you. This was conceived as spiritual, if not religious, in the first films, but was explained as a product of 'midichlorians' in a later film. Midichlorians, said a helpful Jedi Knight, are "microscopic life forms that reside in all living cells. We are symbionts with them, living together for mutual advantage. Without midichlorians, life could not exist and we would have no knowledge of the force." The resemblance to mitochondria in both name and deed was unmistakeable, and intentional. Mitochondria, too, have a bacterial ancestry and live within our cells as symbionts (organisms that share a mutually beneficial association with other organisms). Like midichlorians, mitochondria have many mysterious properties, and can even form into branching networks, communicating among themselves. Lynn Margulis made this once-controversial thesis famous in the 1970s, and the bacterial ancestry of mitochondria is today accepted as fact by biologists.

All these aspects of mitochondria are familiar to many people through newspapers and popular culture. Other sides of mitochondria have become well known among scientists over the last decade or two, but are perhaps more esoteric for the wider public. One of the most important is apoptosis, or programmed cell death, in which individual cells commit suicide for the greater good – the body as a whole. From around the mid 1990s, researchers discovered that apoptosis is not governed by the genes in the nucleus, as had previously been assumed, but by the mitochondria. The implications are important in medical research, for the failure to commit apoptosis when called upon to do so is a root cause of cancer. Rather than targeting the genes in the nucleus, many researchers are now attempting to manipulate the mitochondria in some way. But the implications run deeper. In cancer, individual cells bid for freedom, casting off the shackles of responsibility to the organism as a whole. In terms of their early evolution, such shackles must have been hard to impose: why would potentially free-living cells accept a death penalty for the privilege of living in a larger community of cells, when they still retained the alternative of going off and living alone? Without programmed cell death, the bonds that bind cells in complex multicellular organisms might never have evolved. And because programmed cell death depends on mitochondria, it may be that multicellular organisms could not exist without mitochondria. Lest this sound fanciful, it is certainly true that all multicellular plants and animals do contain mitochondria.

Another field in which mitochondria figure very prominently today is the origin of the eukaryotic cell – those complex cells that have a nucleus, from which all plants, animals, algae and fungi are constructed. The word eukaryotic derives from the Greek for ‘true nucleus’, which refers to the seat of the genes in the cell. But the name is frankly deficient. In fact eukaryotic cells contain many other bits and pieces besides the nucleus, including, notably, the mitochondria. How these first complex cells evolved is a hot topic. Received wisdom says that they evolved step by step until one day a primitive eukaryotic cell engulfed a bacterium, which, after generations of being enslaved, finally became totally dependent and evolved into the mitochondria. The theory predicted that some of the obscure single-celled eukaryotes that don’t possess mitochondria would turn out to be the ancestors of us all – they are relics from the days before the

mitochondria had been ‘captured’ and put to use. But now, after a decade of careful genetic analysis, it looks as if all known eukaryotic cells either have or once had (and then lost) mitochondria. The implication is that the origin of complex cells is inseparable from the origin of the mitochondria: the two events were one and the same. If this is true, then not only did the evolution of multicellular organisms require mitochondria, but so too did the origin of their component eukaryotic cells. And if that’s true, then life on earth would not have evolved beyond bacteria had it not been for the mitochondria.

Another more secretive aspect of mitochondria relates to the differences between the two sexes, indeed the requirement for two sexes at all. Sex is a well-known conundrum: reproduction by way of sex requires two parents to produce a single child, whereas clonal or parthenogenic reproduction requires just a mother; the father figure is not only redundant but a waste of space and resources. Worse, having two sexes means that we must seek our mate from just half the population, at least if we see sex as a means of procreation. Whether for procreation or not, it would be better if everybody was the same sex, or if there were an almost infinite number of sexes: two is the worst of all possible worlds. One answer to the riddle, put forward in the late 1970s and now broadly accepted by scientists, if relatively little known among the wider public, relates to the mitochondria. We need to have two sexes because one sex must specialise to pass on mitochondria in the egg cell, while the other must specialise not to pass on its mitochondria in the sperm. We’ll see why in Chapter 6.

All these avenues of research place mitochondria back in a position they haven’t enjoyed since their heyday in the 1950s, when it was first established that mitochondria are the seat of power in cells, generating almost all our energy. The top journal Science acknowledged as much in 1999, when it devoted its cover and a sizeable section of the journal to mitochondria under the heading ‘Mitochondria Make A Comeback’. There had been two principal reasons for the neglect. One was that bioenergetics – the study of energy production in the mitochondria – was considered to be a difficult and obscure field, nicely summed up in the reassuring phrase once whispered around lecture theatres “Don’t worry, nobody understands the mitochondriacs”. The second reason related to

the ascendancy of molecular genetics in the second half of the 20th century. As one noted mitochondriac, Immo Schaeffler, noted: “Molecular biologists may have ignored mitochondria because they did not immediately recognize the far-reaching implications and applications of the discovery of the mitochondrial genes. It took time to accumulate a database of sufficient scope and content to address many challenging questions related to anthropology, biogenesis, disease, evolution, and more.”

said that mitochondria are a badly kept secret. Despite their newfound celebrity, they remain an enigma. Many deep evolutionary questions are barely even posed, let alone discussed regularly in the journals; and the different fields that have grown up around mitochondria tend to be pragmatically isolated in their own expertise. For example, the mechanism by which mitochondria generate energy, by pumping protons across a membrane (chemiosmosis) is found in all forms of life, including the most primitive bacteria. It’s a bizarre way of going about things. In the words of one commentator “Not since Darwin has biology come up with an idea as counterintuitive as those of, say, Einstein, Heisenberg or Schrödinger”. This idea, however, turned out to be true, and won Peter Mitchell a Nobel Prize in 1978. Yet the question is rarely posed: Why did such a peculiar means of generating energy become so central to so many different forms of life? The answer, we shall see, throws light on the origin of life itself.

Another fascinating question, rarely addressed, is the continued existence of mitochondrial genes. Learned articles trace our ancestry back to Mitochondrial Eve, and even use mitochondrial genes to piece together the relationships between different species, but seldom ask why they exist at all. They are just assumed to be a relic of bacterial ancestry. Perhaps. The trouble is that the mitochondrial genes can easily be transferred en bloc to the nucleus. Different species have transferred different genes to the nucleus, but all species with mitochondria have also retained exactly the same core contingent of mitochondrial genes. What’s so special about these genes? The best answer, we’ll see, helps explain why bacteria never attained the complexity of the eukaryotes. It explains why life will probably get stuck in a bacterial rut elsewhere in the universe: why we might not be alone, but will almost certainly be lonely.

There are many other such questions, posed by perceptive thinkers in the specialist literature, but rarely troubling a wider audience. On the face of it, these questions seem almost laughably erudite – surely they would hardly exercise even the most pointy-headed boffins. Yet when posed together as a group, the answers impart a seamless account of the whole trajectory of evolution, from the origin of life itself, through the genesis of complex cells and multicellular organisms, to the attainment of larger size, sexes, warm-bloodedness, and into the decline of old age and death. The sweeping picture that emerges gives striking new insights into why we are here at all, whether we are alone in the universe, why we have our sense of individuality, why we should make love, where we trace our ancestral roots, why we must age and die – in short, into the meaning of life. The eloquent historian Felipe Fernández-Armesto wrote: “Stories help explain themselves; if you know how something happened, you begin to see why it happened.” So too, the ‘how’ and the ‘why’ are intimately embraced when we reconstruct the story of life.

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www.nick-lane.net