An Overview: Power, Sex, Suicide: Mitochondria and the Meaning of Life
by Nick Lane

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Nick Lane is an honorary senior research fellow at University College London. The following is a very abbreviated and loose description of his presentation in the second volume of his two-volume work on the evolution of life and its implications for aging.

In the first volume, Lane argues that eukaryotic cells came about through the symbiotic merger of two prokaryotic cell lines (bacteria and archaea). Volume Two begins with a long discussion of the reasons why eukaryotic cells could never have evolved from earlier prokaryotic cell lines. Lane begins the argument with an exploration of respiration chains within cells that use oxygen to break down glucose into its constituent parts. One result is hydrogen, which is broken up into protons and electrons. The electrons pass down the respiratory chain moving between electron carriers. Each carrier undergoes a redox reaction, in which it first gains electrons (reduction) and then passes on electrons (oxidization). The result of the redox reactions is the release of energy, which is largely used to drive protons across the mitochondrial membrane where they are synthesized into ATP and stored for subsequent use to power cellular processes. At the end of the chain, the electrons encounter oxygen and protons and form water. Under certain conditions the flow of electrons can back up and escape from the respiratory chain, where they react with oxygen and form destructive free radicals. The critical piece of this process is proton pumping, in which protons are pushed across the mitochondrial membrane. A similar process occurs in prokaryotic cells, but the proton pumping is across the cell's membrane. Lane asserts that energy production by pumping protons across a membrane is fundamental to life on earth, very ancient and as fundamental as DNA.

He shows that the primary reason energy production through proton pumping is so critical is that the process places significant restrictions on prokaryotic cells because they employ their external membrane for proton pumping. The most important restriction is on their size. They can never evolve to the size of eukaryotic cells because with increases in size the surface area (membrane) to volume area (internal components) ratio falls geometrically as does the cell's respiratory efficiency. With this limitation on size, the complexity of a eukaryotic cell cannot be achieved and the basic building block needed for complex organisms comprised of many specialized cells is not possible. Thus, Lane argues that eukaryotic cells could not have evolved by natural selection but rather could only have come about by endosymbiosis and appears to have happened only once in the history of life on earth. The importance of the symbiotic bacterium that became mitochondria is now revealed as the key to the evolution of complex life forms. Because eukaryotic cells generate energy by proton pumping across the mitochondrial membrane, which is inside the cell, it has no energy limitation on it size or complexity because it can increase energy production by simply replicating additional mitochondria within the cell.

Another critical piece of the energy process has to do with the inability of bacteria to aggregate the core collection of genes needed to regulate energy production on a large scale. This inability, Lane explains, is due to evolutionary pressures that give an advantage to bacteria that keep their genome as small as possible. This same tendency has caused the bacterium that became mitochondria to also cast off genes, and many of them were relocated to the cell nucleus. Lane discusses some of the disadvantages to mitochondria retaining any genes but notes that all mitochondria have retained a small set of genes despite billions of years of evolution. The essential question is why have these mitochondrial genes been retained? The answer appears to be because they are necessary for efficient energy regulation requiring quick adaptation to changing demand. Each mitochondrion in a cell is regulated independently, which requires each mitochondrion to have a set of regulatory genes for this purpose. These mitochondrial genes, if housed in the cell nucleus, would, when expressed, broadcast their regulatory proteins and impact all mitochondria within the cell. They would thereby lose the great efficiency gained by individual, independent regulation of each mitochondrion according to its needs.

For brevity, I will omit Lane's discussion of the mitochondrial basis for the evolution of complex animal forms, the size limitations on animal life, the evolution of warm-blooded animals, the evolution of sex and specifically the evolution of two sexes. Which brings us to an important question, why do mitochondria ultimately kill us?

The answer to this question is complex in its details but relatively simple. Recall the earlier discussion of electron leakage from the respiratory chain and the resulting oxidative reactions that produce free radicals. This cascade of events is, unfortunately, channeled in such a way as to take place in the immediate vicinity of the mitochondrial DNA. Mutations in this DNA accumulate and reduce the efficiency of an affected mitochondrion. Interestingly, the free radical level for the mitochondrion is part of a feed-back mechanism (retrograde response), which when a critical level of free radical leakage is reached. triggers apoptosis. This eliminates the damaged mitochondrion from the cell. In the meantime the nucleus sends a signal for mitochondrial replication, which causes replacement mitochondria to be produced by the still functional mitochondria in the cell. This process maintains a good level of mitochondrial functioning in cells by getting rid of dysfunctional mitochondria and replacing them with functional mitochondria.

However, there are limits on this process. Mitochondria are not eliminated until their level of dysfunction and hence free radical leakage reaches a sufficient level to trigger their elimination. Thus, mildly dysfunctional mitochondria continue to be replicated. Since mitochondria are replicated by mitosis, there is no way to refresh their DNA. Over time, the overall efficiency of the mitochondria declines due to the cumulative effect of dysfunction below the threshold necessary to trigger apoptosis and the inability to generate new mitochondria with undamaged DNA. As the proportion of mildly dysfunctional mitochondria in a cell increases, the more oxidizing the cell's internal environment becomes.

What appear to be affected by this increasingly oxidative environment are the operative genes and especially the transcription factors, which are particularly sensitive to

the redox state. One result of this is that genes that protect the cell from stress are activated. These genes call on immune and inflammatory responses for help, which ultimately leads to chronic low-grade inflammation in cells. More and more cellular resources become devoted to maintenance rather than to energy production. leading to a slow decline in energy level and speed of recovery from injury and illness. Lane proposes that it is this process that leads to the degenerative diseases associated with aging, which in many ways define aging itself. Of critical importance are the effects on cells that can't replenish themselves through division of stem cells such as neurons and the cells comprising heart muscle. The tissue composed of these irreplaceable cells becomes populated with less and less functional cells that are eventually killed off by apoptosis, which places the remaining cells under greater and greater stress. As the stress on these cells builds, more are pushed to the point of apoptosis. This is a process that is exacerbated by both inherited genetic factors and environmental factors like smoking, obesity and infections. Understanding this process leads to the recognition that eliminating degenerative conditions such as cardiovascular disease, arthritis and cancer, to name a few, means attacking the underlying cause of aging. Thus, medical science should not be focused on these conditions as individual diseases but as varied outcomes of the same underlying process.

So what is to be done? One approach that would slow down the aging process is called uncoupling, which is the dissociation of electron flow from ATP production so that respiration dissipates as heat and thereby generates fewer free radicals and thus less leakage of free radicals. One common but mild respiratory decoupler is aspirin. There are no doubt many other possibilities both known and unknown. Exercise, while consuming more oxygen, speeds up the flow of electrons in the respiratory chain, which makes the process temporarily less reactive. These approaches, however, are unlikely to be the ultimate solution.

What Lane suggests is needed is spare capacity. What this would entail would be a larger population of mitochondria within cells. When the amount of work required of the mitochondria decreases because there are more mitochondria doing a given amount of work, the density of electrons in respiratory chains is diminished. The less tightly packed electrons are in the chain the less electron leakage there is and thus the fewer free radicals produced. The fewer free radicals produced the less damage there is to mitochondrial DNA. The less damage to mitochondrial DNA the less stressed the mitochondria and the longer they are able to direct most of their resources to energy production rather than maintenance. Lane suggests that one possible mechanism through which caloric restriction may work is by reducing the workload in respiratory chains.

In the end, Lane indicates that a radical solution to the problem of aging probably requires finding agents that will stimulate overproduction of mitochondria by a relatively small amount, say 10%, whenever a signal for apoptosis and replication is triggered by free radical levels. However, since creating spare capacity will reduce free radical production, another modification that will be needed is a more sensitive detection system to trigger the feedback loop between mitochondria and the nucleus.