Dancing Between Purity and Pollution

Readers Summary

1. What defines human aging?
2. Are free radical always bad?
3. How does mitochondria effect life and death?
4. How do mitochondria interact with apoptosis, autophagy, and telomeres?
5. Why do Okinawans really live long?

Mitochondria can allow life or kill us. Mitochondrial DNA has only 37 genes. From those 37 genes comes just 13 proteins. Those 13 proteins code for the electron chain transport complexes. The remainder of the genes code for tRNA. Mitochondria also cant grow outside the cell. They require the 30,000 genes in the nucleus to make up another 1500 proteins for them to function. Mitochondrial DNA and nuclear DNA have to have precise lock and key fit to generate energy production. If not, the cell eliminates itself by apoptosis (levee 19) fast. If It works well, this combination is naturally selected for future cell division to generate energy. Aging is quantified by how "leaky" our mitochondria are to free radicals at complex ones in electron chain transport. Their own DNA is adjacent to the first complex in electron chain transport. So the more leakage, the more damage is done to its DNA and energy production will fall. Moreover, that is the signal to make more mitochondria or undergo cell suicide! This first complex (NADH) is by far the most leaky to free radicals of all the complexes. This paradox of fate caused evolution to select for 10-20 copies of mitochondrial DNA in each cell to sustain energy production of an organ in question. So mitochondria can breathe life into us and end it based upon how many good mitochondria we have in

a tissue.

So as we age, our mitochondria generate many mutations due to the free radical damage at complex one. This especially occurs in active tissues like the heart or brain. These ironically undermine the metabolic function of the organ in question by depleting energy sources. The only way to overcome this is to recreate new mitochondria by biogenesis. In essence, we need to create new power plants constantly. We face a problem when we run out of perfectly functioning mitochondria and have to begin to clone genetically damaged ones because the well is dry. When this happens, the cells in question have to commit suicide called apoptosis. So as a tissue ages, the cumulative mitochondrial damage is removed by apoptosis and we never see evidence of this genetic damage in older organs like the brain or heart when we look for it. The remaining good cells in the heart are saved by autophagy. Autophagy is self repair of the remaining good cells as we age. The cells removed by apoptosis are turned to scar. This is precisely how the human heart ages. We see it get larger with scar and have smaller numbers of cardiomyocytes that get recycled because there are no other stem cells left to replace the old heart muscle cells. With those losses we also lose function as well. These losses are very tolerable in younger tissues because there are so many copies of mitochondrial DNA to choose from. But as one ages, the cells get closer to their ends of replication. We call that end their apoptotic threshold or Hayflick limit. This occurs when the cells telomeres are too short for cell division. The Hayflick limit is the amount of times a cell can divide before it has to die by apoptosis. This number is determined by the length of our telomeres. Telomeres can be thought of like the ends of a shoelace. They are an extra piece of DNA that is sacrificed in every cell division. As a cell divides the telomeres get shorter and we age in corresponding fashion. Once the telomere is short, the cell no longer can divide and enters a phase called senescence. Senescence correlates with aging.

This mechanism exists to prevent genomic instability and the development of cancer. If a cell divides with a short telomere the chance of developing cancer rises exponentially. Therefore, "mitochondrial leakiness" is the key determining factor in aging. The more leakiness that occurs at the first complex causes the generation of more free radicals which damages subsequent copies of our mitochondria DNA to generate cellular energy.

When I was in medical school, we were taught to believe that free radicals were bad for cells. This was a tenet of the mitochondrial theory of aging. It appears that is more dogma that is now updated by biology's truths. It now appears that biology uses this free radical generation to eliminate bad mitochondria and stimulate the genesis of new good mitochondria to make energy for cells. This is a great thing for a cell's longevity. So antioxidants won't prolong your life, in fact, they could shorten it because it interferes with the sensitivity of mitochondrial signaling.

Animals that leak free radicals faster tend to have shorter lifespans. Rodents are a good example. Birds and humans, however, do not leak as fast as rodents and therefore they have longer lifespans. The key point here is that to age well and live longer. the strategy should be to restrict free radical leakiness of our respiratory chains. In 1998, Tanaka reported in The Lancet on the super-centenarians of Okinawa. He found that a lot of them had a single base change in subunit one of the respiratory chain where most leakiness occurs in humans. That one base change was responsible for their longevity. This was irrespective of their diets and life style. Many other authors have tried to link the Okinawans longevity to their lifestyle but it now appears that this blue zone occurs because that one base change makes their mitochondria less leaky at complex one. This allows for less mitochondrial damage and less need for new mitochondria to be made over time to support the organ in question. In effect,

aging slows down for that tissue. The key it appears to a longer healthier life is having more mitochondria to generate energy and not use up the mitochondria they were born with.

We have already said that leakiness of free radicals causes us to amplify more mitochondria, so it also stands that to live longer requires us to have a more sensitive detection system to pick up that leakiness signal. Many diet gurus tout us taking antioxidants in large doses for health. We now can see this advice runs completely counter to how mitochondria really work. The intracellular environment requires less antioxidants to make sure the signal is heard and mitochondria can be made when the tissue requires it. So taking a ton of antioxidants every day may not be the correct thing to do. This may explain why the studies on exogenous antioxidant use has been so disappointing to so many.

So to live optimally, we see that it is tied to our mitochondria. When they ultimately fail, we die. The strategies we have to optimize ourselves are to decrease the leakiness to free radical at complex one to protect our mitochondrial DNA from damage. Or we can uncouple our electron chains, to decrease leakiness by using uncoupling proteins as we saw in the leptin blogs. There is another method that birds and bats use. They over produce their capacity of mitochondria. If you have more, you can afford to lose more. Birds and bats have more mitochondria because they require more energy for flight. That naturally selected trait has given them their longevity compared to their metabolic rate.

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