Senescent Cells and the Diseases of Aging

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The question

Very early in my practice I started to wonder why it is that some people developed osteoarthritis while others did not. I wondered why joints not known to be all that subject to wear and tear such as the pinkie fingers would develop arthritis, where much harder working joints nearby would not. I had no clue, and no particular help in finding an answer. All I could find were articles on treatment of arthritis with various supplements. In practice I found that most of these supplements were of very limited usefulness.

A few years ago, I found an article on PubMed that seemed to provide a tentative answer. In this article the authors described a study they did where they did biopsies of the cartilage cells and the bone beneath the cartilage cells of arthritic joint tissue. What they found was fascinating.

Energy Metabolism

Energy metabolism in the body in normal, healthy tissue usually takes place by way of a process called oxidative phosphorylation. With this process, a single molecule of sugar or the breakdown product of fat digestion is turned into to 38 units of ATP, the energy currency of the body. All of this activity takes place in the mitochondria of the cell.

ATP is used to drive all kinds of reactions, helping the body to synthesize need molecules, detoxify dangerous substances, power the brain and heart, to name just a few of the thousands of uses the body has for ATP.

There is an evolutionarily older form of energy metabolism called aerobic glycolysis. This type of metabolism is much less efficient, producing only 2 units of ATP for the same molecule of sugar or fat. Typically, the body will use oxidative phosphorylation whenever possible because it is so much more efficient.

It turns out that when the biopsies were done of the cartilage and bone in an arthritic joint, the cells were using aerobic glycolysis to make energy. This is a huge problem when this becomes the main way of making energy in a given tissue. A very large part of the energy made by the normal route of oxidative phosphorylation is used to protect the cell from oxidative stress. Most especially, this protection is for the mitochondria, the part of the cell that houses the chemical factory that makes the ATP by oxidative phosphorylation. What happens is that for some reason, the cells stop making energy with oxidative phosphorylation which results in further damage to the cells.

Why might this be happening?

The question I had at the time I read this paper was why this would happen in the first place. What happens to the mitochondria so that they stop functioning. At first, I wondered if it was a problem with circulation, with having enough oxygen to fuel the mitochondria. When the study was done, the researchers looked at the oxygen level in

the blood leaving the arthritic tissue and found that it had plenty of oxygen. I was left with a vague idea that for some reason, the mitochondria stopped working. I had no clear idea why.

A clue and a possible general principle

Jason Fung, MD who writes about the effects of fasting made an observation that has been in the back of my mind since I read it a few years ago. He said that in several of his patients with osteoarthritis, their arthritic nodules decreased in size when the patient did some fasting. I finally put two and two together and did a search on the web for senescent cells and osteoarthritis. Senescent cells are those that are tagged for removal because they are not functioning properly for a whole variety of reasons.

It turns out that there are senescent cells everywhere in osteoarthritic joints. I wondered if they were found in osteoporosis, and again, a search showed their presence in osteoporotic bone. Being on a bit of a roll, I did a search for Alzheimer's, and sure enough, senescent cells were abundant. I even looked at peripheral neuropathy, and there were hints that this may be an issue there as well. Just recently, I read about macular degeneration. In the information I read, it turns out that the venous blood leaving the eye was full of oxygen- the same hallmark found in osteoarthritis. So perhaps senescent cells are involved in macular degeneration. With further searching, I found a paper describing senescent cells in the macula of the eye in patients with macular degeneration.

Why the accumulation of senescent cells?

If all of these degenerative diseases are marked by a decrease in mitochondrial function, then what might be done to clear out the defective (senescent) cells? This is important for several reasons. It appears that senescent cells don't just sit there passively. They actively do harm to their neighbors. The process then spreads to their neighbors, harming them as well, thus creating a nasty chain reaction.

Autophagy is the process that the body uses to clear out old or defective cells. The cells are tagged, signaling that they are slated for recycling. When these cells are removed, the contents of the cell are recycled for repair and maintenance in the body. Autophagy is triggered when we haven't had food in a while. When we haven't eaten, the body will look to stored energy for fuel. When readily available food starts to run out, autophagy really kicks into gear, breaking down senescent cells, using the breakdown products for repair and maintenance as well as for energy.

If autophagy is triggered by fasting, what happens if we eat all day and end with a midnight snack? We never trigger the low level of autophagy induced by the overnight fast. The senescent cells accumulate. Our ancestors had fairly regular periods of food insecurity. Fasting was sometimes involuntary. Fasting for religious reasons has largely fallen by the wayside, so that avenue has closed as well. Food insecurity where the food is of poor quality often results in a diet very high in refined carbohydrates and high in fructose in the form of high fructose corn syrup. These foods are cheaper in the short run at great cost to our health in the long run. These foods are especially good at

blocking autophagy because insulin levels tend to run very high, and high insulin stops autophagy. This is likely to allow senescent cells to accumulate.

The body is intelligent. I suspect that it will “save” senescent cells for use when we have run out of food. The cells are tagged but not necessarily removed until there is a need for raw material for tissue repair and maintenance. This works well if there are regular periods of low food intake, but not so well when there is relative overabundance of food. In this situation these senescent cells accumulate to a much larger extent than is probably healthy.

On an interesting sidenote, the so-called “Blue Zones”- those parts of the world where healthspan and lifespan are extended, a common feature is that the diets are commonly somewhat protein and calorie deficient. This may well mean that the body is constantly tapping the cells marked for autophagy for removal to keep up with repair and maintenance in a mildly deficient diet.

What to do?

On a day-to-day level, the simplest thing to do is to practice what is called “time restricted eating.” Here you simply keep your food intake to a relatively shorter period for the day. A typical time period would be to eat during an eleven-to-twelve-hour window. This will help keep your body on track to do autophagy, albeit on a somewhat more limited basis.

To fully activate autophagy, we will likely need to mimic what our ancestors had to deal with. Periodic food insecurity was the norm back beyond a hundred years ago. It would be relatively rare for there to be complete famine, but probably pretty common to have periods of time when food was a bit more scarce.

Valter Longo, Ph.D. detailed what he termed a “**fasting mimicking diet**” where periodically you would eat a higher fat, low protein and low carbohydrate diet for five days. He found through multiple studies that autophagy is activated by doing this, with very positive benefits on the health. He recommends doing a cycle like this once a month for three to four months, followed by doing it quarterly.

Longo’s two books, The Longevity Diet and Fasting Cancer detail his research. Multiple positive benefits were found in many different disease states. My only caveat with Longo’s work is that he is a proponent of a low protein, near vegan/ pescatarian diet, citing research on what have been termed “Blue Zones”. Blue zones are parts of the world where people are eating this way live longer. For a variety of reasons, I am not a fan of such a low protein, low calorie way of eating.

Fasting Mimicking Diet

Please see my separate paper on various ways of constructing a fasting mimicking diet. Longo has a company that provides food for a 5-day FMD. He recommends this to make it easy for people to do the diet. I have not tried his food package. From what I understand, he donates all profits from this product to charity or research.