An Introduction to Evolutionary Biology

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Week 6 Lecture 32

Mechanistic Theories of Aging

Hi, so in our last discussion, we said that aging is one of the most well-studied phenomena in biology. And there are more than 300 theories of why aging occurs. We also said that it is not possible for us to look at all those theories, and we will look at just a few more prominent ones. So, if you look at the theories of aging, there are different classes of them, and there are two broad classes. the so-called mechanistic theories of aging and the so-called evolutionary theories of aging. So, in this discussion, we are going to look at the first category of theories: the so-called mechanistic theories of aging.

And as I said, we are only going to look at a few more prominent ones. One of the well-known mechanistic theories is the so-called rate of living hypothesis, which was proposed by Raymond Pearl in 1928. So, this is the same Raymond Pearl who developed the logistic model of population growth. So, he has made very significant contributions to the field of population dynamics as well.

But in this particular case, we are more interested in what he had to say about aging and why aging happens. So, what Raymond Pearl said was very simple. He said that, look, aging is primarily determined by the pace of living; in other words, the metabolic rate, right? And he said that species that have a higher metabolic rate age or die faster. So, think of it as, you know, candles; let us say all the candles have the same height. So they have the same amount of wax in them, but some of them are burning faster; therefore, They get over faster; some of them are burning at a slower rate, and therefore, they last longer.

So, it is pretty much exactly the same thing with organisms, those that are spending their energy at a higher rate. Therefore, having a higher metabolic rate, they are the ones who are expected to age or die faster. Now, how are you going to check this out? Fortunately, checking this out is very simple. There are all kinds of ways in which one can measure the metabolic rate of organisms. So, all you have to do is take a bunch of organisms and measure their metabolic rates measure their average lifespan and see if there is a correlation between that and not. And this is exactly what Austad and Fischer did in 1991. So, what they did was look at the amount of energy spent per gram of tissue per lifetime. And they did this for 164 mammalian species spread across 14 orders. And what they found was, or rather what they predicted was, that mammals which have a higher metabolic rate, They will have a lower lifespan, and vice versa; easy prediction.

But what they found was that bats, remember these are flying mammals, and therefore they have the highest metabolic rates. No surprise there, but they also tended to live three times longer than the other mammals. So, obviously, this is not in line with the prediction. Similarly, they saw that marsupials, such as kangaroos and other, you know, pouched animals, They have the lowest metabolic rates, yet they also have the lowest longevity. And neither of these two observations supports the rate of living theory.

Now, of course, one can say that you know this is just about mammals; maybe it is not true in mammals. Maybe it is true for other kinds of organisms. So, people then looked across, you know, the life table of different organisms, and what they roughly found looked like this. So, if you take birds and mammals, remember that birds are mostly flying and therefore have a much higher metabolic rate. And therefore, you expect them to have lower longevity, but in reality, it is the birds that have higher longevity compared to the mammals of corresponding sizes, it is not working out. Similarly, if you look at ectotherms, you will remember that there are two kinds of organisms. Ectotherms, which cannot maintain their own body temperature through endogenous mechanisms, and endotherms. For example, mammals and birds can maintain their body temperature through internal mechanisms. So, ectotherms in general have a lower metabolic rate; therefore, one would expect them to live longer.

If the rate of living theory were correct, in reality, ectotherms also have a lower longevity. Which basically means that this is not working out in the context of the rate of living theory. And then finally, in 2007, there was an analysis of mammals and birds again; this includes 467 species overall. They ended up rather conclusively showing that there was no correlation between basal metabolic rate and longevity. So, taken together, it is reasonably clear that the rate of living theory is not supported by any kind of observations.

So, what about other kinds of mechanistic theories? So, one other class of mechanistic theories is the so-called wear and tear hypothesis. And this basically says that aging is due to some kind of accumulation of damage to cells and tissues. So, this is coming directly from thinking of organisms as machines, like a car, for example. So, the whole idea is that if you use a machine for a long time, it is going to accumulate small tears. Small imperfections or small wears, and so on.

And over time, all these will accumulate and make the machine non-functional, like a broken-down car. And that is exactly what is happening to the organisms. Due to your knowledge of the functioning of organisms, there are all kinds of damage to cells and tissues. For example, you can have damages in terms of toxic metabolic byproducts, such as reactive oxygen species. So, this was a theory that was proposed in 1956 by a guy named Harman, or you can even have a variant in terms of DNA damage.

So, this was a theory that was propounded by a very famous physicist named Leo Szilard. So, this was a Hungarian physicist, and he is extremely famous because he made fundamental contributions to nuclear physics. More importantly, he was the person who drafted the letter that was then signed by Einstein. and sent to the American President Roosevelt, which finally led to the Manhattan Project, ultimately leading to the atomic bomb. So, basically, Leo Szilard was the person who was very directly responsible to reduce the longevity of many human beings on this planet is not his fault. I obviously do not want to blame him here. But he also ended up making very fundamental contributions in multiple other subjects, including biology. And this was one of his contributions to biology. He proposed the theory that there are cumulative damages to the DNA over time, which is why organisms age.

So, we are going to look at both of these theories in some amount of detail. So, let us first look at the free radical theory. What is it saying? So, it is saying that due to cellular respiration, There are these things known as reactive oxygen species, also abbreviated as ROS; you know, H2O2, for example. These are the molecules that damage all sorts of cellular components. Now, these are typically produced, as I said, in the mitochondria as a normal byproduct of cellular metabolism.

Now, the thing is that all cells have multiple ways of taking care of these molecules. Because if they cannot take care of these molecules, they are essentially going to die. So, for example, all cells have antioxidant compounds like vitamin C and vitamin E, molecules that directly quench these ROS. You also have enzymes like catalase and superoxide dismutase, which protect against these ROS. So, it has been shown that if you look at oxidative damage in various tissues, Then the extent of that damage increases as the age of the tissue increases.

So, this is one of the major reasons why people thought that this is what is leading to aging. Now, look at how things happen. What has been seen is that as the tissues age, there is more oxidative damage. The free radical theory is inverting this and stating that because there is more oxidative damage, there is aging. Now, the question is, does it work? Can we do this inversion, logical inversion? Now, in order to test this theory, if the aging is indeed due to reactive oxygen species, Remember, aging is the deterioration of function, right? So, if aging is indeed due to ROS, then that basically means that whatever antioxidant enzymes Antioxidant molecules like vitamin C and vitamin E are not sufficient, correct.

So, if that is the case, that means that if you increase the amount of these enzymes or If you increase the amounts of vitamin C and vitamin E, then that should reduce aging, increase lifespan, or maybe both, right? If the amount of the chemical is limiting, then you should increase the amount of the chemical to prevent aging. Alternatively, if you take the existing amount of these chemicals and somehow reduce it, Then the other prediction is that it itself should increase aging or lead to a reduction in lifespan. So, very often this aging and, you know, lifespan are kind of taken, you know, studied simultaneously and synonymously with each other. Now, how will you test this? Again, testing is relatively easy. So, for example, you know that lots of people find it very easy to include these kinds of antioxidants, like vitamin C and vitamin E, in their diet.

And this is something that has been done for a very long time; these experiments turn out that there is either weak. or zero evidence to indicate that dietary supplementation of antioxidant molecules influences the aging process. So, here is a review that you can look up if you are interested. Then, there were lots of experiments that were done using genetic manipulation. So, in one such experiment, what Remmen et al did was They looked at mice in which there is only one functional copy of the superoxide dismutase gene. Remember, superoxide dismutase plays a role in, you know, cutting down the ROS molecules and getting rid of them. So, if that is the case, then you expect such mice to show a greater amount of oxidative damage; it turns out they see that. But now, if you look at the aging in these animals or the lifespan of these animals, it turns out that Neither of them is significantly different from the controls, which basically means that the oxidative damage is happening. But the extra oxidative damage is not really leading to a change in lifespan or aging which basically says that these two are not causally related. Oxidative damage is not causally related to aging, and there are many more such studies. So, here is a quick, you know, small review; well, it is not a review; it is actually a chapter on aging. But it has a very nice section on the free radical theory, and it gives you more examples. Basically, what happens is that although it has become clear that ROS can play a role in aging-related pathologies, On the aging-related negative effects that we see, there is little reason to believe that it is causing aging to begin with.

In other words, that logical inversion we were talking about—that aging is because of ROS—has no evidence to support it. So suppose it is not ROS; we also had one more, which was DNA damage. So it has already been seen that if you look at older animals, then at least for some of the tissues that these animals possess, They seem to contain a greater amount of mutations and a greater amount of DNA lesions in them, with breaks occurring at a higher frequency. Now, this obviously means that DNA damage is something known to happen. But if that is the case, does that lead to aging? Can we connect that to aging, or can you say that it is a cause of aging? So it turns out that if you take mice that overexpress proteins related to DNA repair, Remember, the body has all kinds of repair mechanisms that take care of whatever mutations happen during DNA replication.

So if you overexpress proteins that lead to less DNA repair, you would expect that there is more repair happening; therefore, there is less aging. Yet such animals, such as mice, have the same lifespan; they do not have an increased lifespan, and their aging process is also similar. So, the pathologies also do not show up any differently, suggesting that there is probably no causal relationship. Now, this particular theory of DNA damage. It has not been conclusively proven or disproven that direct damage to DNA occurs, and the evidence is equivocal.

However, there is a class of DNA damages that you know about. So, one of the major kinds of DNA damage that can happen and has been implicated in the context of aging is The so-called telomere shortening. What is the telomere? So, telomeres are basically regions of repetitive nucleotide sequences. which are located at the ends of linear chromosomes in almost all eukaryotes. So, just to show you a picture so you can see the chromosomes over here, and Can you see these white dots at the ends of the chromosomes that have been pointed out by the two white arrows? These are the telomeres.

Now, what is the function of telomeres? So, it turns out that they actually prevent the

DNA repair systems from misinterpreting the ends of the DNA strands. So, what happens is, as I said, we have lots of repair mechanisms for mutations in our body. So, many of these repair mechanisms activate whenever they see a break in DNA. They assume that you know there is a break, and they end up repairing it. Now, if you come to the end of the DNA, obviously it is a break, right? So, the DNA repair mechanism might end up interpreting it as a break and might start trying to repair it, which is the problem.

So, the telomeres prevent that, and by preventing that, they act like protective caps. They safeguard the terminal regions of the chromosomal DNA from degradation. Because otherwise, these DNA repair mechanisms can actually end up, you know. Marking that particular DNA for destruction, the telomeres prevent it. Now it is known that at every replication, a small part of the telomere is lost; you cannot do anything about it.

Now, when the length of the telomere becomes too short, there are certain enzymes. Known as sensor kinase enzymes, they activate a particular protein called a transcription factor, p53. Now, when this particular protein gets activated, there are many other, you know, cascading reactions that happen. Other proteins get activated, and because of the whole thing, the cell can become non-dividing. Or it can even undergo programmed cell death, known as apoptosis.

Now you can imagine that this is one of the mechanisms by which the body actually fights cancer, right? Because cancer is what? Uncontrolled growth of cells. So, p53 is able to take certain cells and mark them for destruction, or, you know, arrest their growth. But the arrest of growth or, you know, the death of the cells is also something that is related to aging. So, the hypothesis here is that organisms age because, over time, their telomeres become too short, and When that happens, the chromosomes, and hence the cells, become too damaged to function normally. They basically become non-functional or dysfunctional, and at that point, the organism starts showing all kinds of symptoms of aging.

So, if that is the case, then what is my prediction? My prediction is that if I have longer telomeres, then it will take much longer to degrade that telomere to a level. at which p53 will start acting on it. Therefore, longer telomeres should imply greater longevity. So, is there a positive association between telomere length and longevity? So, it turns out that in a few cases it has indeed been seen. So, for example, here is a bird, the zebra finch, a very well-known bird, and it has been shown that the finches which have A longer telomere length at 25 days of age seems to correlate with a much greater lifespan, and it is a statistically significant relationship.

So, this suggests that there might be some truth to it, but is this something that has been replicated? Is this known in other systems? Have we seen it in multiple cases? And it turns out that this is where things become complicated. So, for example, there was a study of telomere length across 57 mammalian species, and what they found was this. So on the x-axis, you have the length of the telomere; on the y-axis, you have the maximum lifespan, and you expect a positive relationship. What you are seeing is a very clear negative relationship, right? Suggesting that the longer-lived mammals are the ones who actually have the shorter telomeres, it is just reversed, right? So then people sought to look at it in other kinds of organisms, and again the story became very, very complex. So, for example, if you look at multiple strains of this worm called Caenorhabditis elegans, Then you know it is a very famous model system and has been used extensively in the context of aging research.

In those, you actually do not find a relationship between telomere length and longevity across strains. In a few strains, you might end up finding it, but if you look at many strains, you are not going to find it. Similarly, if you look at the relationship between telomere length and longevity in humans, You are actually going to see that there is no such correlation, and this is very interesting. This is a study on mice, and what they did was take wild-derived strains, which are strains that had shorter telomeres. And yet, if you look at their longevity, it was not significantly different from laboratory strains, which had longer telomeres.

So, taken together, it is now more or less established that there is no relationship between aging and telomere shortening. I mean there are a few studies that do report some relationship, but there is no general relationship across the board. Now please appreciate one thing: I have already said that telomere shortening is one of the hallmarks of aging; that is correct. But what I am now saying is that telomere shortening is not a predictor of aging, or shorter telomeres do not mean. That you know aging is going to be accelerated; both statements are correct.

As an organism ages, its telomeres get shortened, but if you have short telomeres to begin with, that does not mean. That you are going to live less is the point that needs to be taken from here. So, we do not seem to have any good, consistent evidence for any candidate for the wear-and-tear theory, but there is a problem. What is the problem? The problem is that if you do not have proof of something, that is not proof that that thing does not exist, right? So, what happens if we have not— I mean, the wear and tear theory is correct? It is just that we have not hit upon the correct candidate, or alternatively, you know what happens. If there is a limit to which the errors can be corrected, and the organisms have already reached that limit.

I mean, if that is the case, then that might explain why, when we are supplementing the diets with antioxidants, or when we are Increasing the amounts of the enzymes, you know, superoxide dismutase or whatever, is why those things are failing to have an effect. So, if we take this, you know, possibility, then what is the prediction? The prediction is that all organisms have already reached the limits of their error correction. They have reached the limits of their lifespan, and if that is the case, there is no genetic variation left. Which means that if you try now to select for increased lifespan, then that selection should fail. In other words, what we are trying to say is that the mechanism is correct; it is just that the mechanism is, you know, Wear and tear mechanisms are the ones that are leading to aging, but they are operating at their limits, which is why ff you change the levels, there is no effect happening, and the corollary of that is therefore. It should not be possible to select for increased lifespan in any organism. So, this is something that, of course, can be very easily checked for, and it has been checked for in multiple organisms. A particularly good amount of work has been done on the common fruit fly Drosophila melanogaster.

So, this is work done by Luckinbill et al. in 1984. So, what they did was take two replicate populations of Drosophila melanogaster and maintain them in milk bottles. And every 48 hours, you know the milk bottles had Drosophila food; the flies were on the food, and, Every 48 hours, they would transfer the flies to a different bottle containing Drosophila food; fresh food, basically. And they kept on doing this every 48 hours, every few days, and every few generations. They would push back the day on which they were collecting the eggs for creating the next generation.

So, this is a discrete generation system. So, obviously, after a few days, they would collect eggs for the next generation. But the day on which they are doing that collection, they are pushing it back every few generations. Now, what is happening because of it? Remember, in a system like this, reproduction is conditional upon living to a later age. In other words, suppose you know, let us say, on day 20, they decide to collect the eggs to make the next generation. So, they are only taking eggs that are laid on day 20 or day 30, whatever.

So, obviously, only those flies that are surviving until day 30 will be able to lay eggs on day 30, right? So, that is what I mean by saying that reproduction is conditional upon living to a later age, right, and every few generations. They would push back the day on which they are collecting the eggs to 30, 35, 40, and so on. And they did this for a few generations, and every few generations they would also measure. What was the maximum lifespan of the flies, and what they found was very, you know, stark. So, when the whole experiment started, the mean longevity of the flies across the two replicates was somewhere around 25 days and within about 13 generations of selection, this had increased to close to about 40-50 days or so. So, roughly speaking, within a span of about 13 generations, they had doubled the mean lifespan, roughly double the mean lifespan. Now you can imagine that is a huge, huge change in a very, very short amount of time. Were they the only people to see such a result? Absolutely not.

There were many such experiments. One very famous experiment was conducted by Michael Rose and his colleagues, published in the year 1984. They ended up showing the same thing: that the longevity of the organisms can be increased via selection. So, this proved that the limit to lifespan has not really been reached in many organisms, and after the 80s, you know. These kinds of experiments have been repeated in a large number of organisms. A large number of organisms across taxa, and in many of those cases, they have been able to replicate this result.

So, it is a very strong result, which means that selection can increase the lifespan, and the limit has not yet been reached. And therefore, we can conclude that the variant theory definitely is not something that can be generalized. In most cases, it does not seem to hold. As I said, people at this stage can say, "Look, we do not know what really is happening, but maybe somewhere it is all in the genes." After all, everything that organisms do, we think, is because of their genes, and therefore it has to be in the genes.

And that is one reason you know those 3 lakh plus studies people have been searching madly for genes that will enhance longevity. And why they are doing so is because, as I said, you know, it is very much a commercial and a social angle to it. So, I cannot really blame them entirely, but when it comes to the science, you know, it is not entirely clear. Whether this is leading to something or not, one thing is clear: it is leading to a lot of discoveries.

So, thousands of genes have been implicated in aging. Implicated means that people have shown that if you knock them out or if you create a mutation. Then that can cause some changes in terms of the aging pattern. So, just to give you a comprehensive listing, I have given you this link, you know. As of December 2024, this is the last time they updated this particular database; there were 2,205 genes in this database. In some system or another, in some strain or another, these are the genes that have been shown to have an effect.

And yet there is no single gene or set of genes that is implicated in aging across all taxa.

However, given the commercial incentives, etc., the search is still on. So, this is where we will conclude our set of mechanistic theories of aging and our overview of them. And when we come back for our next discussion, We are going to talk about the second class of theories of aging, the so-called evolutionary theories of aging. See you then. Goodbye.