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October 30th, 2017

Theorizing that Aging is an Emergent Property of Cellular Competition

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Why does aging exist? Why, when we look about the world, can we only find two defensible examples of an immortal species, the hydra and the jellyfish Turritopsis dohrnii? There are a few other species that might be immortal, but the evidence is fairly shaky in near all cases, meaning that it is more of a challenge than is usually the case to show aging, or the data is sparse. These species are probably only negligibly senescent, meaning that they tend to decline rapidly at the end of life and otherwise show few signs of aging up until that point. Lobsters fall into this category, for example. Given that there is exactly one species with good evidence of its immortality - no-one has yet run an equivalent to the rigorous testing of hydra mortality rates in Turritopsis dohrnii - and countless species that clearly age, what are the odds that any given species with poor data is actually immortal? Not so good, I think.

The authors of the paper noted below have an interesting view on why aging is an inevitable outcome of evolutionary processes. To their eyes the declines of aging are an emergent property of competition between classes of cell in multicellular organisms. You might contrast this with the view that aging is a race to the bottom that occurs because environments change, often radically in comparatively short periods of time, and species in which individuals age have a greater ability to adapt to that change than species in which individuals are immortal. Thus aging species out-compete the immortal species in every evolutionary niche over long periods of time. That model has the advantage of predicting that we might see a few immortal species at any given moment, but we should not expect them to last. So while the paper below is thought-provoking, the primary problem I see here is that there is no acknowledgement of the existence of hydra - something of a challenge to a model that presents aging as absolutely inevitable.

In fact, the authors come on very strong with this view of aging as inevitable and beyond our power to defeat in the publicity materials. I have to think that they are quoted out of context and the quotes then assembled by someone who doesn't understand the research, which entirely relates to the evolution of aging, not our ability to intervene in the aging process. How it is we find ourselves stuck in these corroding bodies is a somewhat separate topic from what we choose to do about it - meaning the identification of the best strategies for periodic repair of our failing biochemistry. So I'd say skip the publicity materials, which I think are trying, poorly, to express the idea that there is no way to prevent breakage from occurring in cellular biochemistry, and go straight to the paper. It isn't open access, but the usual way past those barriers works just fine.

It's mathematically impossible to beat aging, scientists say

> "Aging is mathematically inevitable - like, seriously inevitable. There's logically, theoretically, mathematically no way out. As you age, most of your cells are ratcheting down and losing function, and they stop growing, as well. But some of your cells are growing like crazy. What we show is that this forms a double bind - a catch-22. If you get rid of those poorly functioning, sluggish cells, then that allows cancer cells to proliferate, and if you get rid of, or slow down, those cancer cells, then that allows sluggish cells to accumulate. So you're stuck between allowing these sluggish cells to accumulate or allowing cancer cells to proliferate, and if you do one you can't do the other. You can't do them both at the same time."
>
> Although human mortality is an undisputed fact of life, the researchers' work presents a mathematical equation that expresses why aging is an "incontrovertible truth and an intrinsic property of being multicellular. People have looked at why aging happens, from the perspective of 'why hasn't natural selection stopped aging yet?' That's the question they ask, and implicitly in that is the idea that such a thing as non-aging is possible, so why haven't we evolved it? We're saying it's not just a question of evolution not doing it; it can't be done by natural selection or by anything else."
>
> "You might be able to slow down aging but you can't stop it. We have a mathematical demonstration of why it's impossible to fix both problems. You can fix one problem but you're stuck with the other one. Things will get worse over time, in one of these two ways or both: Either all of your cells will continue to get more sluggish, or you'll get cancer. And the basic reason is that things break. It doesn't matter how much you try and stop them from breaking, you can't."

Intercellular competition and the inevitability of multicellular aging

> Whereas mutation accumulation and antagonistic pleiotropy theory address the role of organismal selection in aging, we ask here whether aging is a fundamental and intrinsic feature of multicellular life. For an organism to avoid aging, it must overcome or mitigate the consequences of heritable changes in somatic cells, the vast majority of which are deleterious, and hence best thought of as "damage." Heritable cellular degradation is a product not just of somatic mutations but also of other changes, such as epigenetic drift and the accumulation of misfolded proteins. In unicellular organisms, competition between cells can weed out deleterious heritable changes, allowing a population to exist indefinitely despite individual degradation. Just as competition between individuals can eliminate deleterious alleles from a unicellular population, competition between cells within a multicellular organism can weed out malfunctioning, slower growing cells within an organism. Therefore, intercellular competition seems to hold the potential for immortality; by continually eliminating damaged cells, a multicellular organism might persist in perpetuity if only selection to do so were somehow strong enough.
>
> Aging in multicellular organisms occurs at both the cellular and intercellular levels. Multicellular organisms, by definition, require a high degree of intercellular cooperation to maintain homeostasis. Often, cellular traits required for producing a viable multicellular phenotype come at a steep cost to individual cells. Conversely, many mutant cells that do not invest in holistic organismal fitness have a selective advantage over cells that do. If intercellular competition occurs, such "cheater" or "defector" cells may proliferate and displace "cooperating" cells, with detrimental consequences for the multicellular organism. Cancer, a leading cause of death in humans at rates that increase with age, is one obvious manifestation of cheater proliferation.
>
> Thus, intercellular competition proves to be a double-edged sword; competition can remove damaged cells, but competition can also allow cheating cells to prosper. Here, we derive a general model of the effect of somatic evolution on aging and examine the behavior of a related model of discrete genotypes in simple numerical cases. Aging is characterized by the dual, but seemingly contradictory, features of loss of cellular vigor and uncontrolled cell growth, and we model the evolution of two corresponding cellular traits. First, we use the term "vigor" to reflect general cellular function or metabolic activity. Second, we use the term "cooperation" to represent investment in traits that are costly to the cell but beneficial for the organism as a whole; one manifestation of loss of cooperation is an increased propensity toward cancer. We show that intercellular competition produces a double bind resulting in inevitably declining organismal vitality with age in multicellular organisms.
>
> Given most organisms' capacity to grow and regenerate, aging does not seem, at first glance, inevitable. Consequently, many have argued that aging is an accident of imperfect selection, where selection fails to purge deleterious, age-related mutations from an otherwise potentially immortal genotype. We have shown that even if selection against aging could be made more powerful, aging would remain an inescapable facet of multicellular life. As our model addresses the role of somatic evolution in aging, it should be seen as complementary, rather than contradictory, to models of aging via evolution by natural selection of multicellular individuals. Our model points to intercellular competition as a key factor in navigating the double bind of cellular degradation and cancer. It suggests that research programs focusing on quantifying the degree of intercellular competition and making comparisons across taxa, among individuals in the same population, among tissues of the same individual, and across developmental time, may be key to understanding the evolution and progress of aging.

Comments

Actually if you click on the name of the author and then click on the paper you can read the whole paper. I think it's open access but under review or something similar. It even says the article is licensed under Creative Commons so it should be free.

Posted by: Anonymoose at October 30th, 2017 7:37 PM

Senolytics conbined with induced cellular turnover ought to fix the problem if these theory is correct, as well as if aging is due to nuclear DNA damage.

Posted by: Abelard Lindsey at October 30th, 2017 10:48 PM

https://www.inverse.com/article/37885-mathematically-impossible-beat-aging-lifespan

And here it is... the pop science article we were all expecting to end up with after this publication.

There is one thing more inescapable than aging - clickbait.

Posted by: Anonymoose at October 31st, 2017 3:48 AM

I don't think that in hydra and similar asexual organisms there is such a thing as somatic cells. Really all cells are both somatic and germinal.

Posted by: Antonio at October 31st, 2017 3:58 AM

Isn't this just rephrasing what everyone has known for decades? Obviously we need a way to counteract this decay. Evolution shows that you can easily extend lifespan to hundreds maybe thousands of years and to gain more we'll have to address entropic change that cannot be correct by within tissue competition (and therapies imposing selective pressures like senolytics and cell ablation).

But tissue engineering with functional selection solves this per definition. It's just a question when this becomes feasible (it's unlikely to be practically impossible, much less physically impossible).

Posted by: kismet at October 31st, 2017 5:39 AM

Another foolish way to say -- 'if we do nothing, we have nothing'! SENS is *all* about removing bad cells and engineering good cells. I believe we should not spend our time on such a work.

Posted by: Ariel at October 31st, 2017 7:59 AM

I mean such article -- of course.

Posted by: Ariel at October 31st, 2017 8:00 AM

I think this paper is actually an argument FOR SENS, or other rejuvenation therapies that require repeated interventions in order to reset the state of the organism to one of (non-cancerous) health.

All it is saying is that you cannot create an intrinsically immortal multicellular organism because of the trade off between senescence and cancer.

Posted by: Mark at October 31st, 2017 8:25 AM

@Mark

Agreed.

While mathematical biology may be a bit esoteric to many, the topics of cellular competition, fitness fingerprints, etc. are of intrinsic importance in both development and aging and should be fully understood, especially when it comes to interventions at the tissue level

I suggest everyone read up on the learnings of groups like Dr. Eduardo Moreno's on these themes

http://moreno-lab.org/

Posted by: Ira S. Pastor at October 31st, 2017 8:36 AM

Hi all,

Interesting, just my 2 cents, I think that the element that is lacking from this study is the lack of taking account consequentiality. It assumes that cancer is consequential and you are dead if you have it; because it will, at some point, have taken over you (metastasized etc).
But, what if it was inconsequential. It does not factor that in. Cancer can be(come) inconsequential. That's the main point of OncoSENS. And thus makes this study become mostly invalid. Studies that do not factor - Other factors - don't always make the best answers/results. This one is 'face value' - on Mathemathical temrs - only. if factoring just that. Yes we are screwed. But we will Circumvent that. Mathematics can be circumvented by other methods and factors; that this study does not factor in; and thus becomes invalid (valid mathematically, for everything else invalid..there is still hope). We must take this study with a grain of salt and say; ok, True. But, we will find a solution - and Will find it 100% or nearly sure of that (because SENS OncoSENS is going to do its best to keep this rogue cells inconsequential and remove them at the same time. I know it's much easier said than done..see others posts about telomerase"ALT p53 p16 p21 c-myc CDs highjacking some redox and impostering avoiding immune detection in cancers). Aging is not something uncurable, this article helps me understand even more even if it says the contrary.

PS: btwHappy Halloween (I am seeing a couple of dead cadavers roaming the streets, (kids dressed as zombies and would want halloween 365 days; immortality as zomby and junkfodd-candy fed and staying 11y-young forever (sadly it does not work, halloween = diabetes/atherosclerosis/death (if you want to become a (real) zombie cadaver, it's the perfect day - indulge)); that is why I also see vegetarian draculas who given up on pints of blood and carry a veggie-ready basket for halloween) (jk))). Gonna go watch 'Thriller' (MJ) now....

Posted by: CANanonymity at October 31st, 2017 6:17 PM

Good point CANanonymity. Also, cellular senescence is not a problem if you can periodically remove the accumulation. This then allows you to make the lifeform more robust against cancer - as you say, this exactly what SENS seeks to do by making the body LESS robust against senescence (no telomerase or ALT), but more resistant against cancer, and compensate for the senescence with engineered stem cell infusions (or perhaps a reoccurring exogenous telomere lengthening treatment).

I also think that long, long term we will be able to create a body that ages very incrementally. This paper only states homeostasis will be lost eventually, it says nothing about when that might be, it could be 1000s years.

Posted by: Mark at November 1st, 2017 5:03 AM

If this paper is true, then how does the germline maintain itself over millions of years? It seems to me that molecular biology should contain within itself the ability to maintain homeostasis of a life-form indefinitely.

Posted by: Abelard Lindsey at November 1st, 2017 10:38 AM

@ Abelard

Because it is only one type of cell (before differentiation)

Posted by: Mark at November 1st, 2017 11:39 AM

Additionally, it seems to me that homeostasis ought to be maintainable indefinitely by periodically purging the body of dysfunctional cells (senolytics) and then replenishing using some method of induced cell turnover.

Posted by: Abelard Lindsey at November 1st, 2017 2:07 PM

The more I think about this paper, the more it seems bogus to me. These researchers are simply rehashing the old aging/cancer trade off idea. this trade off is that aging somehow serves as an inhibition of cancer. The problem with this idea is that cancer actually correlates very strongly with aging. This would not be the case if the trade off between aging and cancer was real. Young people don't get cancer very often. That fact alone ought to tell you the trade off between cancer and aging idea is bogus.

Posted by: Abelard Lindsey at November 1st, 2017 2:29 PM

@Abelard Lindsay: it is the trade-off between (a) loss of regenerative capacity / cell activity / growth in response to rising levels of damage versus (b) cancer, rather than a trade-off between aging and cancer in general. If our systems didn't shut down slowly with age, we'd have shorter live spans due to cancer, or so goes the consensus view. Selection pressure for longer life spans, with the rise of intelligence, the Grandmother hypothesis, etc, has been satisfied by this particular collection of mechanisms in our case.

Posted by: Reason at November 1st, 2017 3:41 PM

Reason, yes, I get the concensus point and that is why I don't buy it. If the consensus view was true, one would expect the probability of cancer to either remain the same or decline with age. The fact is that it increases dramatically with age, which should tell you the youthful molecular biology has something that controls the emergence of cancer and that this mechanism declines due to the aging process, resulting in the increased incidence of cancer with age. The latter is observable reality. The theories that suggest that cancer is a mitochondrial disorder and/or an immune system disorder are consistent with this observable reality.

I believe the position of the authors that cancer is inherent to multicellular system is correct. However, youthful molecular biology has mechanisms that control and eliminate them. The loss of those systems, due to aging, is what allows cancer to become more and more of a problem as one gets older. At least this is my view of aging and cancer, which is, infact, consistent with observable reality.

Posted by: Abelard Lindsey at November 1st, 2017 6:03 PM

@ Abelard,

Wrt ablation, yes as already stated an exogenous process could restore homeostasis.

Wrt cancer, this paper is assuming that cancer is the end. Of course it is not; cancer arises in our bodies all the time, but it is eliminated or arrested before it can be recognized clinically. It could be argued that cancer arises more regularly in younger bodies, but is eliminated much more efficiently. But the argument of the paper is that eventually cancer would get even a perpetually young person, which is probably true.

Posted by: Mark at November 2nd, 2017 3:45 AM

Hydra is a primitive multi-cellar organism that has the unusual characteristic of being immortal. It has a form of the FOXO gene that maintains stem cells that form buds for new Hydras that breakoff vegetatively to multiply the species. Apparently the stem cells do not get old, they just keep growing and budding off like this, under the maintenance and protection of the FOXO gene. Apparently, more advanced forms of FOXO determine the lifespan of all higher organisms, by protecting and maintaining the stem cell pool, but with the problem that the stem cells accumulate mutations and eventually age and di.

Posted by: Biotechy at November 2nd, 2017 6:52 PM

As the authors cite our SciRep paper on aging, we feel obliged to share our perspective as well. Find it here, if interested: https://medium.com/hacking-aging/inevitable-aging-you-got-it-wrong-8b677d9b7d69

Posted by: Ksenia@Gero at November 8th, 2017 10:24 AM

Name: Email:

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