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COMPLEX TIME

AGING, ADAPTATION & THE ARROW OF TIME

Aging in Single-celled Organisms: From Bacteria to the Whole Tree of Life

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Post-meeting Reflection by Presenters

Jacopo Grilli (ICTP)

Talks:

- **Matteo Osella:** Interesting idea of connecting laws of physiology (Hwa) with aging/senescence. Not trivial how to do that for single cells.
- **Lin Chao:** Aging and asymmetry in E. coli. Advantage of asymmetry is portfolio diversification. Somewhat optimal level of asymmetry emerges.
- **Uli Steiner:** Fitness as combination of fecundity and mortality. Death in the mother machine (surprisingly high): mother (early daughter) has an increased mortality rate with age, while her latest daughter has an approximately constant mortality rate. Idea: late daughter inherits the damage, while the mother was starting with minimal damage. No correlation between mother and late daughter lifespan.
- **Sri Iyer-Biswas:** Cool data on C crescents and collapses. Interesting observation of memory of past conditions lasting for long time.
- Owen Jones. Senescence across the tree of life. Measure shape and pace (timescale)

Ideas:

- What is aging? Requires asymmetry in division and the ability to label individual with a "time stamp". In E. coli age of the pole, in mycobacteria cell wall. Senescence is the loss of function associated to aging. The question then is what is function. We have a bias for growth rate.
- It is very unclear to my whether asymmetry is adaptive or not. It is also unclear how to prove it.
- The other axis is memory. Memory (information) about the environment. Unclear how that is related with aging.

Matteo Osella (Univ. Turin)

- General disagreement on the definitions of aging and senescence. It does not seem a purely semantic problem, but reveals the lack of universally accepted essential conditions to define the aging process.
  - Example: Role of asymmetry (necessary condition or not) in the cellular division process for the emergence of aging.
- Discussion on the more appropriate measure of time to observe aging of living things.... The intrinsic timescale of different organisms (for example doubling time in fast-growing conditions) and the timescale fixed by the environment (e.g. feast and famine cycles) should be taken into account.
  - [interesting parallel with the approximately constant lifespan of mammals if measured in heart beats shown by G.West]

- In several different systems the hazard rate (for cell division or for death) shows an exponential increase followed by a plateau (e.g. in mortality rate in E.coli shown by Uli and from Lindner group) . Different theoretical models can reproduce such a trend. Is there a way to do model selection?
- Need for measurements of metabolic rate in bacteria in order to build a complete phenomenological theory of resource partitioning and its relations with growth and mass. An extension of existing theories built on data based on balanced exponential growth probably need to include survival and the cost of maintenance...

Srividya Iyer-Biswas (Purdue Univ./SFI)

- This was an exciting meeting with a lot of animated discussions leading to interesting confluences and diverges of opinions.
- Basic questions that came up again and again: What is aging? Given how contextual it is, what is a good operational definition? How to design and refine specific experiments that get to the interplay between asymmetry generation, aging, memory formation, rejuvenation, information processing, statistical learning, energetics, individual specific histories, intrinsic stochasticity in organismal growth, resilience to different perturbations, homeostasis, adaptation, evolvability, plasticity and tradeoffs therein.
- I especially enjoyed discussions about new technologies and tools that can be co-opted and added as modules to ongoing experiments to get at some of these exciting questions.

Martin Picard (Columbia University)

- Experimental models to study cellular aging vary dramatically.
- We clearly need a consensus definition of aging, or more specific concepts. Is aging the loss of specific functions, the loss in the ability to divide, "senescence" (which itself does not have a consensus definition), the movement towards mortality, or the accumulation of "information" over time? Can there be a single definition of aging across the tree of life - from single cells to complex multicellular organisms like mammals?
- If the definition is a functional one - aging is the loss in the ability to perform X function, then aging needs to be contextualized. Organisms at different scales (prokaryotes vs birds vs humans) have dramatically different "purpose" in the living world, and they carry out very different functions. Is there one type of aging that unites them all? Or qualitatively different forms of aging, or aging processes?
- An interdependent challenge with the previous one is the issue of measurement. What are good measures of aging - again it depends on how it is defined.
- If aging is defined as *something* that tells us how close to death an organism is to end of life (i.e,, mortality) or to loss of function, then it implies that aging biomarkers need to be developed prospectively. In other words, the aging marker need to predict some future behavior. One example is the DNA methylation or epigenetic clocks.

Uli Steiner (University of Southern Denmark)

- The discrepancies what aging entails seems to be related to the difference of fields and questions tackled. To me as an evolutionary biologist aging is simply the process of senescence, where senescence is the deterioration of function, or more precisely the change of function with age. This change does not need to be a directional decline. Function should be somewhat related to fitness, which explains that survival and reproduction are first targets to quantify aging, though all functional traits could be and should be considered for understanding senescence. However, if fitness is the parameter that integrates the processes, it is evident that a cell within a multi-cellular organism has a different definition of fitness than a whole organism in itself, be it unicellular or multi-cellular.
- The generalities as described by Chris are highly interesting and inspirational. I gained much inspiration on how senescence is unified across cells of different level of biological organization, but where, how, and why these universal patterns fall apart is something I would love to deepen discussing.
- The differences in heterogeneity and homeostasis among cells that has been shown by Sri, where I was really puzzled how similar cells are and how such similarity could be maintained, and Bree's system where the heterogeneity is large, though spatially still well structured.
- What are the most prominent markers that we should focus on? How can we measure these?

Sabrina Spencer (CU Boulder)

- What is holding back the field of aging? First is a definition of aging, which we have generally agreed represents deterioration of function. Second then, is how to measure deterioration of function. We lack good markers for most relevant items at the single-cell level: 1. Cumulative DNA damage, 2. Telomere length, 3. Oxygen consumption rate, 4. Presence of original or newly replicated DNA strand. 5. epigenetic clock measured by DNA methylation.
- Of course, there are single-cell DNA damage markers, but as far as I know, they only mark current existing mismatches, damaged bases, single-strand or double-strand breaks etc., but not cumulative damage. The need for a cumulative/historical marker speaks to the idea Sri proposed that aging requires a cellular memory - something needs to be accumulated as cells age, otherwise cells would not know or have an age. While a snapshot of telomere length does contain a historical record, telomere length and oxygen consumption rate are easily measured on a population level, but not in single cells. The single-cell aspect is important because while telomere length decreases with increasing passage number, Martin Picard showed that telomere length does not correlate with when a population hits its Hayflick limit. This may well be because what cells care about is the shortest telomere in a cell, not the population telomere length. Tracking the immortal strand is technically difficult. For the epigenetic clock measured by DNA methylation, the conceptual link with deterioration of function is unclear.
- Then there's the ability to return to homeostasis as a general definition of aging, but how to measure that is unclear.
- The one thing that can currently be measured in single cells both in a snapshot and over time is protein aggregation. Lin Chao measures this with IBPA-GFP. Maybe measuring protein aggregates is our best bet since that is measurable and since it has been shown to cause dysfunction, particularly in neurons.

Meeting statements:

1. Aging is the cost organisms pay to have offspring that are free of damage.
2. Aging is a spandrel
3. Aging is a consequence of the chemical reactions, energy flux, 2nd law, etc. needed for life.
4. Asymmetry is inevitable.
5. The parent cell will be defined here as the cell that accepts the majority of the damage.
6. Which damaged components matter the most is unclear (e.g. old pole protein, mitochondria, immortal strand)
7. Therefore, there will be no universal marker for aging (more granular: damage) and what we need instead is various functional definitions that are context dependent (when can we project this onto fitness of vice versa)?
8. The major issue is that we don’t have the right data or know what to measure? i.e. We don’t know the currency of aging.

Lin Chao (UC San Diego)

- What is aging? Classical definition from Medawar aging is passage of time and aging is the deterioration of function with time. Aging and senescence is nowadays used to mean equivalently the deterioration with time. We will used aging and senescence in this more contemporary context, and refer to the passage of time specifically as chronological aging. However, because in some organisms the deterioration can be reversed, we will describe those instances as reversed or positive senescence or aging (discuss?).
- Following Medawar, we also can distinguish aging that results from wear and tear from interactions with the environment much as an automobile parked by the ocean will rust and fragment. However, because the hallmark that distinguishes physical objects such as a car and a biological organism is the latter's ability to change through evolution by natural selection, aging can be accelerate in living systems beyond physical wear and tear. The acceleration results from the production of asymmetrical daughters by dividing mother cells. While the asymmetry can result from a combination of factors, some beneficial and others deleterious, a possible cause may be damaged cellular molecules and organelles. The daughter that receives more damage ages and the other rejuvenates. The aging daughter can be viewed as the continuation of the mother, the daughter receiving less can be regarded as the new juvenile offspring. This concept can be extended to metazoans and the asymmetry

Bree Aldridge (Tufts Univ.)

- I was stuck by the constant "laws" across species that are scale free. I am interested in how this may extend to single-cells in a populations and whether the scaling laws can be expanded from multicellular to intracellular organisms.
- Aging (and the fitness objective) needs to be continuously defined and multiple forms of aging coexist in the same population.
- Asymmetry is a mechanism to encode aging. Is the functional consequences of aging an evolutionary driver of asymmetry?
- How do we experimentally measure aging and the effect of aging in single-cells? We are missing key experimental approaches.

Owen Jones (University of Southern Denmark)

- This has been an inspiring meeting. Fantastic to hear diverse ways of studying and thinking about aging/senescence, and how we can measure and follow fates of cells in lab context.
- Nomenclature differences among fields can cause some confusion. e.g. aging vs. senescence. In my subfield - senescence can be positive (deterioration with age), negligible (stasis with age) or negative (improvement with age). The term "aging" is therefore just the passage of time. (Based on work of Medawar, and more recently Vaupel and colleagues).
- One major goal should be to be able to generalise understanding of aging/senescence across organisms as diverse as *E. coli*, TB, mice, humans, plants and even colonial organisms. We will undoubtedly need to scale data for different taxa (or different environmental conditions within species) to make them comparable. In this context I was especially inspired by Chris Kempes' work and Geoffery West's talk showing striking invariants across really diverse species. How will these scaling rules be across groups e.g. single celled - metazoans - colonial.

Other questions that emerged:

- Is resilience to perturbation (homeostasis) a useful marker of senescence?
- Asymmetry in cell division - isn't asymmetry inevitable?
- Is complexity of the organism (e.g. differentiated tissues/cell types) important to aging trajectory? e.g. does it make homeostasis harder?
- Is senescence a spandrel? Can it be adaptive?