How systems biology can help solve the enigma of aging

The editors speak to computational systems biologist Jing-Dong Jackie Han about her pathway into aging research and the value of multi-disciplinary collaboration. Han discusses exciting questions and the latest evidence on rejuvenation and aging trajectories, and highlights the development of large-scale datasets in China to facilitate future discoveries.

Tell us about your earlier research experiences. What drew you to aging-related research in the first place?

I originally studied molecular pharmacology for my Ph.D. with Charles Rubin at Albert Einstein College of Medicine. I then conducted post-doctoral research at Harvard Medical School on computational systems biology with Marc Vidal and Fritz Roth, whose research does not focus on aging. But I became interested in aging when I was analyzing protein–protein interaction network topology, in general and in cancer. I was searching for a 'universal' biological process that will reveal the fundamentals of biological network design principles to study in my own lab. I came across the first brain aging microarray dataset generated by Bruce Yankner's lab and was immediately drawn to it. I thought that aging was this universal process that I was looking for, as it is universally present for all living things, and underlies almost all complex human diseases, including cancers. Starting from this brain aging dataset, we saw the aging protein–protein interaction network dynamically partition into two pairs of alternative and mutually inhibitory modules, which reach a balance between differentiation and proliferation or growth, and between reductive and oxidative metabolism, respectively (Xue et al. *Mol. Syst. Biol.* **4**, 147; 2007). I then gobbled down over a thousand papers on aging, first trying to making sense of our discovery, and that got me more and more fascinated by the enigma of aging.

As a researcher who investigates the molecular mechanisms of aging and aging-related disease, do you have a different or specific perspective on what 'aging' actually means?

I now view aging as a trajectory — diverging from the young resilient state and moving to an old state that is less resilient to stress and challenge. Aging-related diseases are alternative old states that are particularly sensitive to certain types of stress and challenge.

Credit: Bingchuan Wu

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Your lab has published on a wide range of topics, from the evolution of long non-coding RNAs that affect aging to facial image analysis of aging, as well as stem cell and developmental biology and the genetic bases of different kinds of disease in general — what inspires new approaches or projects in your lab, and do you have tips for successfully running a research group with very diverse projects?

As a computational systems biologist, you never know where your data will lead you. We try to do as much as we can to validate the results of analyses, either in our own lab or through collaborations. As our first aging network analysis revealed a loss of balance between differentiation versus proliferation, and growth dominates the aging process and shows a continuation from early development, I have always kept a view of aging from the perspective of development. Only later on, when I started working on stem cells and development, did I realize that there is a big field using stem cells to tackle aging processes, which is often called regeneration, or part of rejuvenation. I envision that our two ends of research will meet on this line in the near future.

People in my lab are from diverse backgrounds — from biology to mathematics, to computer sciences, to physics and chemistry. Some are more interested in development, some in epigenetics and single cells, some in AI and algorithms, and most in aging, the universal topic. We find that such a setting is particularly stimulating for new ideas and approaches; we all learn from each other and can easily form an integrative team, which is essential for a systems biology lab.

What are the big open questions about aging at the molecular and cellular levels that should be prioritized? What do you see as the major challenges in aging research, and what might the future hold?

Some of the big open questions from the systems biology perspective include, for example, whether aging in different tissues is synchronized, and whether any one tissue is most important for aging and rejuvenation. When Steve Horvath generated a pan-tissue methylation clock, he found that clocks in different tissues seemed to tick at different rates; and a study from Michael Snyder's group using multiomics signatures defined four ageotypes, and also found that these were not synchronized (S. Ahadi et al. *Nat. Med.* **26**, 83–90; 2020). Our study on facial aging rate and blood transcriptome aging rate also showed that only among fast- and slow-aging outliers was there significant consistency between the two aging rates, but not among the general population (X. Xia et al. *Nat. Metab.* **2**, 946–957; 2020). These studies suggest that different tissues are not aging at the same rate, and might not start at the same time, but most such studies have been cross-sectional analyses. Large-scale longitudinal analyses are needed to confirm this, and to verify the rate and temporal

order of tissue aging. The sequence of tissue aging may give us some clues about which is the first tissue to target to prevent or delay aging onset, or the last tissue to guard against the collapse of the whole system. However, the temporal order does not necessarily correspond to the importance of impact.

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Another question is, how do different tissues interact to drive aging and rejuvenation? The answers to this question are key to understanding the mechanisms at play. A recent study has shown that immune system aging alone can drive aging of solid organs and the whole system. Obviously, whether this is true for other tissues (and their associated microbiomes), and whether targeting the immune system alone can rejuvenate the whole system, awaits more extensive studies. Parabiosis studies have already shown that sharing the young blood system can rejuvenate many tissues and organs in old mice. However, the detailed tissue–tissue interactions have yet to be mapped and delineated.

There are also questions about heterogeneity in aging, as we know people age biologically at different rates. What are the major contributors to heterogeneity of aging across individuals? When do aging and aging heterogeneity start? When should rejuvenation begin or stop? Our recent study on the human facial aging clock and the blood transcriptome clock both showed a drastic increase in heterogeneity in aging rate at 40 years of age and a peak at around 50 (X. Xia et al. *Nat. Metab*. **2**, 946–957; 2020). Such heterogeneity can be attributed to different lifestyles of the individuals, which suggests that middle age is perhaps a stage for personalized aging intervention. More dimensionality and preferably longitudinal data are needed to confirm this. Although both aging rate and its heterogeneity become lower in old age, this could also mean that rejuvenation can work more uniformly among older individuals. Indeed, many aging interventions, such as rapamycin, as shown by Matt Kaeberlein's and Joan Mannick's groups, work effectively in old age. Identifying the windows for intervention and rejuvenation has yet to be done in a systematic manner, in particular in human populations.

Related to this is the question of how many aging trajectories exist. Can a new trajectory lead to rejuvenation or everlasting youth? Many studies on aging transcriptomes, including our own, have shown that aging trajectories are often a continuum of developmental trajectories, and that lifespan-extending interventions such as caloric restriction delay these trajectories. However, not many studies set out to address whether different trajectories exist across different individuals. As a salient exception, recently Nan Hao's group has shown beautifully, using live reporter systems to follow the replicative aging of each single yeast, two distinct trajectories — one characterized by mitochondrial decline, the other by ribosomal decline (Y. Li et al. *Science* **369**, 325–329; 2020). More interestingly, genetically boosting both mitochondria and ribosomes created a new aging trajectory with a much longer lifespan. Our own research, combining network dynamics simulation and transcriptome profiling in *Caenorhabditis elegans*, has also shown that mildly but synergistically boosting multiple nodes in the aging regulatory circuitry can keep the network more frequently in the young versus the old steady state when compared with a strong perturbation of any single node, which may be lethal to the organism (Hou et al. *Cell Metab*. **23**, 529–540; 2016). It would be interesting to see in theory and in practice whether such different perturbations can result in different aging trajectories. These studies evoked the intriguing possibility that systems or network approaches hold the key to more effective rejuvenation, consistent with the dramatic rejuvenation effects demonstrated for combined Yamanaka factor treatment by the groups of Juan Carlos Belmonte, Tom Rando, David Sinclair and others. I believe that in the future theorists and experimentalists will join forces to search for new trajectories — not only for longer lifespan, but also rejuvenation, or even a state of eternal youth.

I think the major challenges in aging research are, first, how to translate the results of animal research to humans (to intervention studies in human populations); and second, how to share and tap into the rich human phenome and medical records to predict aging trajectories and the effects of interventions for a particular individual — that is, to achieve personalized prediction and intervention.

What do you see as the potential benefits of more multi-disciplinary studies on aging and what is the best way to encourage and support these?

Aging has now been recognized as a true systems biomedicine problem, and now more and more grants are focused on multi-disciplinary studies of aging, which is a key factor in supporting this type of research. And there is genuine interest from the research community to engage in it. The rapidly aging global population is certainly a challenge for society, but it is also an unprecedented opportunity for aging research. All of a sudden, everyone is interested in aging, government and private funding are flourishing, so the challenge for us is how to deliver something useful for humans and translatable to large populations to address the pressures of aging populations. In fact, when deciding on the topic of our Center for Quantitative Biology's summer symposium, the faculty, including many physicists and mathematicians, unanimously voted for aging and rejuvenation.

However, there are also some practical challenges to overcome to truly embrace multi-disciplinary aging research. Although many journals are still hanging on to the classical 'cell to animal study' paradigm of research, many other journals, such as *Nature Aging*, are more open to multi-disciplinary studies. As an editor myself on many journals, I can understand how difficult it is to find the right editors and reviewers for such studies, but I envision that this will change as more researchers are educated and supported to be multi-disciplinary, like the students in our Academy for Advanced Interdisciplinary Studies in Peking University.

The pandemic has affected most research communities quite severely; how have researchers in China been coping or adapting to restrictions to mitigate the spread of SARS-CoV-2, and have many researchers pivoted to working on more pandemic-related projects?

Conducting our research has definitely been more difficult recently owing to the COVID-19 pandemic. During the lockdown, only those who had published on or have grants relating to SARS-CoV-2 were allowed to return to the lab. We were fortunate that we could do computational work remotely from home. Still, out of responsibility as biomedical researchers, we also worked on a few SARS-CoV-2 data analysis projects. China handled the epidemic swiftly and effectively, and got back to normal fairly quickly. Now we cherish such opportunities and work harder to make up for the time lost.

What is happening in China in the aging space right now? Are there any big projects underway, unique approaches, or challenges associated with China's demography and aging population?

In addition to the dedicated aging research programs at the National Science Foundation of China (NSFC) and the Ministry of Science and Technology (MOST), other programs, such as the MOST Development Program and the Human Phenome Project, have also started to fund aging research to generate big data on China's aging population. The Phenome Project aims to deeply and quantitatively phenotype, molecularly profile and genotype tens of thousands Chinese individuals across a large age range to understand the interplay between genetic and environmental factors that drives complex human phenotypes. The big challenges will be how to cross-examine these large multi-dimensional datasets and infer causal factors that can be translated into large-scale health interventions.

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