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Microbiology

Gut microbes as a novel anti-aging intervention?

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Ours is a world dominated by microbes. Diverse microbial communities colonize just about any available space, even deep within our bodies' cavities. Remarkably, every human being carries as many bacteria as human cells, leading us to question the very meaning of what constitutes a human. These private individual communities of microbes, or 'microbiota', encompass bacteria, but also other microorganisms such as fungi, viruses, protists, and Archaea. Within our body, the large intestine is the area most densely populated by microbes. Our microscopic companions are not just opportunistic passengers, but they provide us with essential nutrients, shape our immune system and even influence our behavior.

In the past few years, the role of the gut microbiota in human health and disease has become better understood. While the intestinal microbiota composition is rather stable during adulthood, distinct changes occur during aging. In the intestine itself, the composition of bacterial communities decreases from very diverse in young-adults to more homogeneous as people get older. However, little is known about whether 'our' microbes play any causal role during the normal aging process. Even though work by the Russian zoologist Ilya Metchnikoff about a century ago suggested an important connection between gut microbes and lifespan, surprisingly little research has been done on this topic since.

Studying how microbiota composition changes over a lifetime is quite challenging in humans given the relatively long life expectancy of our species. Asking this question in mice would require experiments to last several years to provide an answer – mice in the laboratory live 2.5-3 years. This is the reason why we adopted the naturally short-lived African turquoise killifish to study whether gut microbes influence the aging process. Turquoise killifish have fascinating, unique features. They are the shortest-lived vertebrates kept in captivity, with an average lifespan of only 4 months. In this short time, they complete sexual maturation and show several age-related changes. Like elderly humans, their skin becomes less pigmented, their brains undergo neurodegeneration and they develop cancer.

Harnessing the short lifespan of this species, we asked whether gut microbes could causally affect aging and life span in this species. We first characterized the bacterial composition of young and old killifish and found that killifish guts harbor a complex microbiota that is comparable to mammals in terms of abundance and composition. Similar to humans, upon aging individual killifish host fewer – and potentially pathogenic – microbial species.

We asked whether microbes associated with young killifish were overall beneficial to the host. To test this, we performed an experiment to 'reset' the killifish gut microbial community towards a youthful state. Middle-aged killifish – at an age comparable to a 50-year-old human – were treated with antibiotics to eliminate most of their own resident bacteria. We then reintroduced the 'young' bacteria by adding whole intestinal contents from young fish to the water. Compared to control groups of fish that either did not receive a transfer or received bacteria from cohorts of the same-age, fish treated with young-associated bacteria lived over 30% longer, proving that young-associated bacteria can actively influence individual

lifespan. We additionally tested whether gut bacteria derived from young donors could also affect fish motility, which normally declines with age. Indeed, youthful gut microbes induced an improvement in motility until late age. This was quite striking as it proved for the first time that young-associated bacteria can modulate host physiology towards a healthier and youthful state.

We discovered that individual fish, that had received a microbiota transfer from young donors, could host the transferred bacterial community even during aging. Therefore, the bacterial transfer was effective as the donors' bacteria could become established in the recipients' guts. Additionally, this result suggested that specific bacteria were likely mediating these significant pro-longevity effects. Further analyses enabled us to identify a set of key bacterial genera importantly associated with a youthful state, i.e. present both in young individuals, as well as in long-lived subjects. The persistence of a youthful microbial composition during host aging was associated with molecular signatures of enhanced response against bacterial infection, mobilization of immune cells and modifications in key components of the gut extracellular matrix.

Based on these findings, we can conclude that commensal bacteria do contribute to host aging – at least in killifish. One acute transfer of young microbiota not only led to a substantially longer life but furthermore to an overall healthier condition at old age. As microbiota transfer is already adopted in clinical applications for specific diseases, these findings could help extend microbial interventions towards future therapeutic applications targeting a broader spectrum of age-related disorders.