Aging in fast motion: Short-lived fish offer new insights into the aging immune system

Aging causes the immune system to become less effective, increasing susceptibility to infections and age-related diseases. Researchers at the Leibniz Institute on Aging (FLI) in Jena have now created a comprehensive molecular and cellular map of immune aging in a vertebrate using the short-lived turquoise killifish (*Nothobranchius furzeri*). Using a multi-omics approach, they identified key features of immune aging, including chronic inflammation, DNA damage in progenitor cells, and remodeling of the hematopoietic organ. The study shows that important aspects of immune aging are evolutionarily conserved. This makes the killifish particularly well suited for studying the mechanisms of immune aging and for testing potential interventions.

Jena/Cologne. Our immune system protects the body from infections and harmful changes throughout our lives. However, it loses its effectiveness with age, resulting in an increased risk of disease. But what happens when the immune system ages—and can this process possibly be stopped?

In a study now published in *Nature Aging* (Cover article), researchers at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) have taken an important step towards answering these questions. They used the extremely short lifespan of the turquoise killifish (*Nothobranchius furzeri*) and identified key characteristics of immune aging within a few weeks. This makes this model particularly well suited for rapid mechanistic discoveries and testing potential interventions.

The study combines various analytical methods, such as cytometry, single-cell transcriptomics, proteomics, AI-supported image classification, in situ imaging, histology, and functional immunoassays. With the new established open multi-omics resource KIAMO, it thus provides a comprehensive overview of immune aging in a short-lived vertebrate. The work began at the Max Planck Institute for Biology of Ageing (MPI-AGE) in Cologne and was alter continued at the FLI in Jena.

The researchers show that key features of immune aging are present in killifish and are strikingly similar to those seen in mammals and humans. The study provides unique insights into the mechanisms of so-called “immune aging”. Since killifish only live for a few months, aging processes can be observed in fast motion within a few weeks—a major advantage for experimental research.

“The killifish system once again surprises us as it reveals that key aspects of immune aging—both at molecular and cellular level—are deeply conserved evolutionary,” says Prof. Dario Riccardo Valenzano, pioneer of killifish research and Scientific Director at the FLI. “Our findings prove that killifish could be an optimally suited model to test interventions that by targeting immune aging improve systemic aging.”

Inflammatory processes increase with age

One of the central findings of the study is the presence of a pronounced systemic inflammatory signature in older fish, often referred to as “inflammaging.” Blood analyses revealed increased

levels of acute-phase proteins as well as markers of metabolic imbalance. Similar inflammatory signatures are well known in aging mammals and humans and are associated with a wide range of age-related diseases.

Changes in the immune cell factory

Age-related changes were particularly evident in the kidney marrow, main hematopoietic organ in fish and the functional counterpart of mammalian bone marrow. With increasing age, the researchers observed structural remodeling, fibrosis, tissue alterations, and shifts in immune-cell populations.

At the same time, the data indicates an expansion of progenitor and stem-like immune cells. However, these cells accumulate DNA double-strand damage and show reduced markers of active DNA repair. Importantly, this accumulation of DNA damage cannot be explained by replication alone, suggesting a state consistent with cellular senescence and impaired differentiation capacity.

“I have always been fascinated by the idea that biological processes, including aging, follow principles that can be understood and eventually translated into interventions. Rather than accepting decline as inevitable, the Killifish model gives us a way to dissect aging mechanisms in a compressed time frame, while recapitulating key aspects of immune aging seen in mammals”, explains Gabriele Morabito, PhD student and first author of the study.

Impaired immune response in old age

Functional experiments confirmed these observations. Immune cells isolated from older killifish responded significantly less strongly to bacterial stimulation than cells from young animals.

In cell-culture experiments, pre-treatment with a senolytic partially restored youthful immune responses *in vitro*, indicating that senescent cells may contribute to the functional decline of the aging immune system.

This suggests that senescent cells actively contribute to the age-related impairment of the immune response. The killifish therefore represents a promising model to test interventions targeting immune aging.

New open resource for research community

Alongside the study, the researchers established a publicly accessible multi-omics platform called KIAMO (Killifish Immune Aging Multi-Omics). The platform provides the international research community with extensive molecular datasets, including single-cell gene-expression profiles, proteomics data, and imaging resources.

A model organism for studying immune aging

Although the study provides detailed insights into immune aging in the hematopoietic system, important questions remain. It is still unclear how strongly these changes influence aging processes in other organs.

However, the killifish offers a unique opportunity to experimentally investigate these relationships, according to Prof. Valenzano. With its short lifespan, conserved immune biology, and the newly established KIAMO resource, the turquoise killifish provides a powerful experimental platform to study immune aging in vertebrates and to accelerate the development of strategies aimed at improving health during aging.

Publication

Spontaneous aging-associated inflammation and genome instability in the immune system of turquoise killifish. Morabito G, Dönertas HM, Sperti L, Seidel J, Poursadegh Zonouzi A, Poeschla M, Valenzano DR. Nat Aging. 2026, 6(3):665-681. DOI: 10.1038/s43587-026-01086-2.

https://www.nature.com/articles/s43587-026-01086-2

Data platform KIAMO (Killifish Immune Aging Multi-Omics):

https://genome.leibniz-fli.de/shiny/kiamo/

Picture

The turquoise killifish provides a powerful experimental platform to study immune aging in vertebrates and to accelerate the development of strategies aimed at improving health during aging. (Image: FLI / Nadine Grimm)

Contact

Dr. Kerstin Wagner
Press & Public Relations
Phone: 03641-656378, Email: presse@leibniz-fli.de

Background

The Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena is a federal and state government-funded research institute and member of the Leibniz Association (Leibniz-Gemeinschaft). FLI conducts internationally recognized, high-impact research on the biology of aging at the molecular, cellular, and systems levels. Scientists from around 40 countries investigate the mechanisms of aging to uncover its root causes and pave the way for strategies that promote healthy aging. Further information: www.leibniz-fli.de.

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