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Fish as Model for Aging Research

Researchers at the Fritz Lipmann Institute in Jena are establishing Nothobranchius furzeri as a new model organism for studying aging processes

Nematodes, yeasts, and fruit flies belong to the most important model organisms used to research biological aging processes. They yield information about which physiological processes and molecular biological conditions accelerate or delay aging processes. These model systems for aging research are now seeing competition from a smart newcomer in the scientific field: the killifish Nothobranchius furzeri. This African fish has been popular for decades with aquarists and is known for its short life span. In three months, it completes the life cycle of birth, reproduction, and death. “We suspect that there is a genetic program behind this which regulates the life cycle and thus predetermines the aging process,” said Dr. Alessandro Cellerino of the Leibniz Institute for Age Research, Fritz Lipmann Institute (FLI) in Jena.

In Mozambique 2004, the research group leader was successful in tracking down a longer-lived killifish variant and breeding them. The fish of this variant do not age as rapidly as their shorter-lived relatives from the Gona Re Zhou National Park in Zimbabwe. Breeding these fish under lab conditions is demanding, but worth the effort. When comparing tissue samples, it can be observed that the age-related degeneration processes in the brain and liver do indeed occur more quickly in the shorter-lived variant than in the longer-living killifish. “Ability in terms of swimming also decreases more rapidly in the short-lived species,” pointed out the scientist.

Describing the differences regarding phenotype was the first step; now the objective is to understand the genetic control of these aging processes. Which molecular-genetic factors are responsible for the differences in life span? Are there genes for aging which determine the maximum life span of these organisms? Through experiments with cross breeding the short-lived and longer-lived variants, the genes that are responsible for these differences are to be mapped.

In the era of genome research, future projects will rely on detailed knowledge of the fish genome. Through the sequence analyses done in cooperation with Prof. Dr. Manfred Schartl of the University in Würzburg, the FLI lab led by Dr. Matthias Platzer has now laid the foundation for the characterization of the killifish genome. It was soon noticed that its genome is relatively large in comparison with the other model fish used in research (e.g. sticklebacks and zebra fish) and is approximately two-thirds of the size of the human genome. As in humans, a large proportion of the genetic sequences in the killifish repeat themselves frequently. “These repetitive sequences are common primarily in the sections of the chromosomes important for cell division, the centromeres,” explained Dr. Kathrin Reichwald, a scientist on Platzer’s team. The similarity to the human genome is especially gratifying since the fish model system, as the shortest-lived vertebrate, will hopefully yield information that could also be applied to humans. The repetitive sequences are, however, identical between the longer-lived and shorter-lived variants of the fish species. “We are still very eager to see the further results of the current cross breeding experiments which will hopefully be a big step forward for us,” commented Platzer.

Telomere research is a very promising area in the field of aging research for explaining the finiteness of life span.

Telomeres consist of repetitive DNA sequences at the ends of chromosomes and shorten with each cell division. When the telomeres have shortened to a certain length, then the cells stop dividing. FLI researchers in the lab led by Prof. Dr. Christoph Englert have now investigated whether telomere shortening plays a role in both Nothobranchius variants. They have compared the telomere lengths in the muscle and skin tissues of young and old fish of both variants. “Surprisingly, the effects of telomere shortening were present in the older tissue of the longer-lived variant, but not in the short-lived variant,” noted the scientists with wonder. “The shortening of the telomeres is in this case not the cause of the accelerated aging,” concluded the scientist Dr. Nils Hartmann. “We surmise that the telomeres in the short-lived variant are maintained in length, but lose their functionality,” said Englert. This is currently being investigated in further research.

Another finding no less astonishing for the researchers is the fact that caloric restriction has a different effect on the two types of fish. From experiments involving yeast, nematodes, and the fruit fly, it is known that a nutrient-reduced diet has the effect of prolonging life. “In terms of the short-lived killifish, the restriction of food clearly prolongs life. However, with the longer-lived variant it has an ambivalent effect. The longer-lived fish initially have a higher mortality rate under the diet. But those that survive go on to live that much longer,” was how Alessandro Cellerino described the observed effect. “We have now determined that the mortality triggered by the diet concerning the long-lived Nothobranchium is not age-related, but rather caused by stress reactions in the brain,” explained Cellerino. Those that survive the hunger are better protected against stress. “Hormesis” is the name scientist use for this increased resistance.

The FLI researchers are in the process of establishing the killifish as a very promising animal model in biological aging research. “The connection of phenotype, molecular biology, and genomics is important to us,” said Christoph Englert. In the meantime, multiple publications have arisen from this project. “With the attractive African killifish, a vertebrate, we are much closer to the human in terms of evolution than with yeast, fruit flies, or nematodes. We are assuming that the research results regarding Nothobranchius will allow themselves to be applied to humans in a better manner and that they will give aging research significant impetus,” FLI group leader Cellerino, Platzer, and Englert agree.

In 2006, federal funding in the amount of 620,000 Euros from the “Pakt for Research and Innovation” was granted to Platzer and Englert for the work being done at the Fritz Lipmann Institute in Jena to establish the killifish Nothobranchius furzeri as an innovative model for aging research. In response to Cellerino’s application, the German Research Foundation DFG has also made project funding in the amount of 220,000 Euros available.

Publications:

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