Pancreatic cell size linked to mammalian lifespan, finds zoo animal analysis

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Siberian tiger (P. t. altaica), also known as the Amur tiger. Credit: Wikipedia.

More than two thousand years ago, Greek philosopher Aristotle observed that larger animals tend to live longer than smaller ones. On June 18 in the journal *Developmental Cell*, scientists report that it's cell size, not

body size, that intrinsically correlates with and perhaps affects lifespan. By examining the pancreases of 24 mammalian species—including shrews, humans, and tigers—researchers in Israel, Canada, and Germany found that animals with larger pancreatic cells tend to age faster, while smaller cells seem to go hand in hand with longer lifespans.

"That there was a correlation between two things that are so remote was shockingly beautiful and unexpected," says senior author Yuval Dor, who studies developmental biology at the Institute for Medical Research Israel-Canada and The Hebrew University-Hadassah Medical School in Jerusalem.

"This study has exposed a trend that seems to transcend all animal life," says co-author Ran Kafri, a computational biologist at the University of Toronto and the Hospital for Sick Children in Canada. "It demonstrates that there's a property that can be measured on a single cell that predicts the lifespan of a whole animal."

Scientists had thought that after birth, most mammals' organs, including the pancreas, grow by cell proliferation. However, Dor, Kafri, and colleagues made a serendipitous observation; they needed a higher magnification to look at pancreatic cells of new-born mice through a microscope than they did to look at those of adults, suggesting that each cell's volume was substantially increasing from infant to adult life.

Repeated measurements showed that the growth of individual exocrine pancreatic cells, known as acinar cells, is responsible for much of the overall organ growth after birth. "This was surprising because the assumption was that postnatally, the pancreas grows by increasing the number of cells just like most organs that we think about," says Dor.

But when the researchers looked at the same cell type in humans, they realized that cell replication, not individual cell expansion, was solely

responsible for our pancreatic growth. This got them curious, so they ventured to neighboring labs, the Jerusalem Biblical Zoo and the Kimron Veterinary Institute to examine pancreases from across the mammalian class, from Etruscan shrews (the smallest mammals in the world) to giraffes (the tallest).

Upon analyzing the data, the scientists found a strong negative correlation between the size of individual acinar cells and lifespan. Mammalian species that aged faster had larger acinar cells, while species that lived longer had smaller acinar cells.

To explain the correlation, the researchers are narrowing in on the underlying molecular mechanism, and their "prime suspect" is mTOR, a protein that has been highly conserved in evolution and is already known to exist at the junction between cell size and lifespan.

"The working hypothesis is that mTOR activity via enhanced cell size is giving you an advantage in early life possibly by allowing faster growth and a shorter time to sexual maturity and reproduction, but that it is also driving deterioration and aging later in life," Dor says. "This might explain why some mammal species would sacrifice longevity for the rapid early organ growth associated with cell growth instead of replication; you get the selective advantage in early life, and you pay the price later on.

"This gives a molecular face to an evolutionary theory of aging called 'antagonistic pleiotropy', suggesting that aging is the unintended consequence of mechanisms that are advantageous during reproduction age," he adds. "Obviously, more experiments are needed now to test this hypothesis."

More information: *Developmental Cell*, Anzi and Stolovich-Rain et al.: "Postnatal exocrine pancreas growth by cellular hypertrophy

correlates with a shorter lifespan in mammals"
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