# Inhibiting age-related inflammation maintains healthy gut microbiota and extends lifespan

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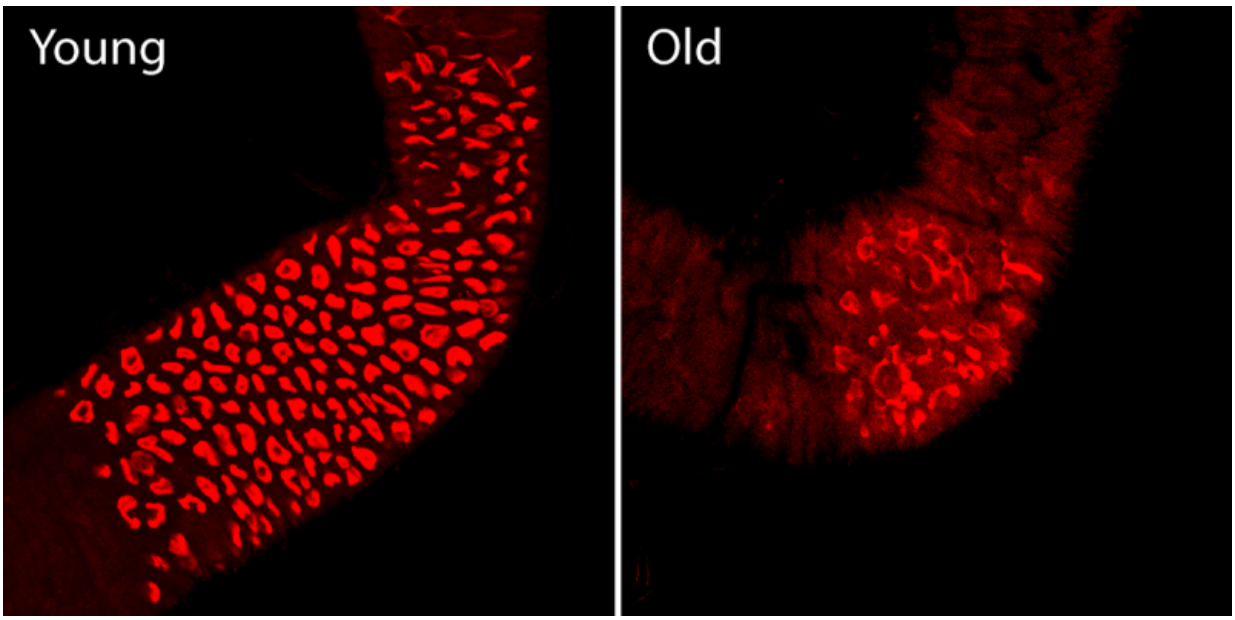


Age-related gastric decline in *Drosophila* is indicated by acid-producing copper cells (red, anti-Cut). Credit: Hongjie Li, Buck Institute for Research on Aging

Aging is associated with a wide range of tissue dysfunctions. Among these are metaplasias - conditions in which one kind of tissue is replaced by another type, causing misregulation of regional tissue functions. Metaplasias in the gastrointestinal (GI) tract are common maladies that have been associated with cancers and other diseases. Research at the

Buck Institute uses the fruit fly *Drosophila* to study the origin of metaplasias and to identify ways to reverse or delay them.

Publishing in *Cell Host & Microbe*, the Jasper lab now shows that age -related inflammation drives metaplasia in the fly equivalent of the stomach. This gastric metaplasia causes changes in the regional distribution of the commensal microbiota, the total species of gut bacteria, resulting in age-related intestinal pathologies and a shorter lifespan. Strikingly, the research shows the effects are reversible. Using genetic tools to reduce inflammatory signaling in the gastric region of the gut, researchers prevented metaplasia, maintained a healthy commensal population, and extended lifespan in the flies by up to 18%.

Senior scientist and Buck faculty Heinrich Jasper, PhD, said the findings have implications for human disease, adding that metaplasia is the first step in the development of Barrett's Esophagus, whereby cells in the esophagus take on the characteristics of the stomach, and that some forms of colon cancer begin with metaplasia. "We don't really understand the cellular processes underlying these diseases yet," said Jasper. "What this study shows is that chronic age-related inflammation may drive a natural predisposition to metaplasia. In the fly, this metaplasia causes an imbalance or dysbiosis of the microbiota, resulting in pathologies that include stem cell deregulation along the gastrointestinal tract."

Researchers found that the age-related metaplasia is initiated by chronic activation of a well-characterized inflammatory response JAK/Stat signaling pathway. Activation of this pathway is implicated in age-related inflammation, and its chronic activation disrupted normal cellular composition and activity of the stomach-like copper cell region in the middle midgut of the fly. When JAK/Stat signaling was inhibited in this region specifically, the flies lived longer. "Interestingly, these flies also lived longer when we cultured them in a germ-free condition," said

Hongjie Li, a graduate student in the Jasper lab. "This indicates that activity in the gastric region contributes to gut homeostasis in addition to its role in controlling gut microbiota."

In addition to identifying the metaplasia, researchers characterized the changes in the fly microbiota that followed the loss of acid-producing copper cells in gastric region. Interestingly, they found that the copper cell region seems to serve as a "sieve" to control the regional distribution of commensal bacteria. They also found that the age-related metaplasia resulted in changes in this distribution and in the overall composition of the commensal microbiota. Jasper said these findings offer another potential path for future treatments. "Perhaps it will be possible to prevent or delay these age-related changes in the gut by altering the composition of the microbiota," he said, adding a cautionary note that it is far too early to recommend the use of probiotics to assuage the impact of aging on the human gastrointestinal tract. "We still don't know which bacteria are beneficial and there is currently no way of guaranteeing that specific bacteria survive the digestive process and get to the place in the intestine where they would be needed."

Now that Jasper's team has been able to identify the different age-related changes in the microbiota throughout the intestinal tract of the fly he says the next step of the research will involve testing various bacterial interventions to see how they impact gut health and the longevity of the animals. "Doing this type of research in humans would require biopsies and no one would recommend that," he said. "It would be possible to do the research in mice, but that would be costly and time-consuming. Doing this type of site-specific inquiry can be accomplished quite easily in the fly gut highlighting the value of basic research."

**More information:** Preventing age-related decline of gut compartmentalization limits microbiota dysbiosis and extends lifespan, DOI: 10.1016.j.chom.2016.01.008

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