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Altering the community of gut bacteria promotes health and increases lifespan

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Scientists at the Buck Institute for Research on Aging have promoted health and increased lifespan in *Drosophila* by altering the symbiotic, or commensal, relationship between bacteria and the absorptive cells lining the intestine. The research, appearing in the January 16, 2014 edition of *Cell*, provides a model for studying many of the dysfunctions that are characteristic of the aging gut and gives credence to the growing supposition that having the right balance of gut bacteria may be key to enjoying a long healthy life.

Even though recent research in humans has linked the composition of gut flora with diet and health in the elderly and the list of age-related diseases associated with changes in gut bacteria include cancer, diabetes, and inflammatory bowel disease, lead author and Buck faculty Heinrich Jasper, PhD, says there is no systematic understanding of how we go from having a young, healthy gut to one that is old and decrepit. "Our study explores age-related changes in the gut that include increased oxidative stress, inflammation, impaired efficiency of the immune response, and the over-proliferation of stem cells," said Jasper. "It puts these changes into a hierarchical, causal relationship and highlights the points where we can intervene to rescue the negative results of microbial imbalance."

Jasper says the bacterial load in fly intestines increases dramatically with age, resulting in an inflammatory condition. The imbalance is driven by chronic activation of the stress response gene FOXO (something that happens with age), which suppresses the activity of a class of molecules

(PGRP-SCs, homologues of PGLYRPs in humans) that regulate the immune response to bacteria. PGRP-SC suppression deregulates signaling molecules (Rel/NFkB) that are important to mount an effective immune response to gut bacteria. The resulting immune imbalance allows bacterial numbers to expand, triggering an inflammatory response that includes the production of free radicals. Free radicals, in turn, cause over-proliferation of stem cells in the gut, resulting in epithelial dysplasia, a pre-cancerous state.

Jasper said the most exciting result of their study occurred when his group increased the expression of PGRP-SC in epithelial cells of the gut, which restored the microbial balance and limited stem cell proliferation. This enhancement of PGRP-SC function, which could be mimicked by drugs, was sufficient to increase lifespan of flies. "If we can understand how aging affects our commensal population – first in the fly and then in humans - – our data suggest that we should be able to impact health span and life span quite strongly, because it is the management of the commensal population that is critical to the health of the organism."

More information: "PGRP-SC2 Promotes Gut Immune Homeostasis to Limit Commensal Dysbiosis and Extend Lifespan" ; publishing January 12, 2014 in *Cell*.

Provided by Buck Institute for Age Research