More Anti-inflammatory Genes Mean Longer Lifespans for Mammals

Mammal species with higher copy numbers of siglec receptor genes have longer maximum lifespans

April 07, 2015 | Heather Buschman, PhD

We age in part thanks to "friendly fire" from the immune system — inflammation and chemically active molecules called reactive oxygen species that help fight infection, but also wreak molecular havoc over time, contributing to frailty, disability and disease. The CD33rSiglec family of proteins are known to help protect our cells from becoming inflammatory collateral damage, prompting researchers at the University of California, San Diego School of Medicine to ask whether CD33rSiglecs might help mammals live longer, too.

In a study published April 7 by *eLife*, the team reports a correlation between *CD33rSIGLEC* gene copy number and maximum lifespan across 14 mammalian species. In addition, they found that mice lacking one *CD33rSIGLEC* gene copy don't live as long as normal mice, have higher levels of reactive oxygen species and experience more molecular damage.

Mammal species with more copies of *CD33rSIGLEC* genes tend to live longer.

"Though not quite definitive, this finding is provocative. As far as we know, it's the first time lifespan has been correlated with simple gene copy number," said Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine and member of the UC San Diego Moores Cancer Center. "Since people also vary in number of *CD33rSIGLEC* gene copies, it will be interesting to

see if these genes influence variations in human lifespan as they do in mice."

Varki led the study, along with Pascal Gagneux, PhD, associate professor of pathology.

The *CD33rSIGLEC* genes encode siglec receptors that bind sialic acids — sugar molecules found on many cells. These siglec receptors stick out like antennae on the outer surface of immune cells, probing the surface of other "self" cells in the body. When sialic acids bind siglec receptors, they transmit the message to the inside of the cell. This signal relay puts a brake on immune cell activation. In this way, the CD33rSiglec receptors help dampen chronic inflammation and reactive oxygen species in the body.

Different mammal species carry different numbers of the *CD33rSIGLEC* genes in their genomes. In this study, Varki, Gagneux and colleagues surveyed 14 different mammalian genomes, including those of elephants, dogs, monkeys and humans, and found that *CD33rSIGLEC* gene number correlates with maximum lifespan. In other words, species with more copies tend to live longer, even when the researchers controlled for other factors, such as body mass, adjacent genes and shared evolutionary history.

To dig deeper, Varki, Gagneux and team turned to a mouse model. They discovered that mice that were missing one *CD33rSIGLEC* gene and experienced inflammation early in life showed signs of accelerated aging (gray hair, disorientation, thin skin), had higher levels of reactive oxygen species and did not live as long as normal mice.

"The higher *CD33rSIGLEC* gene number can be thought of as an improved maintenance system that co-evolved in mammals to buffer against the effects of many infectious episodes fought off by the immune system of long-lived mammals," said Gagneux.

Study co-authors include Flavio Schwarz, Oliver M. T. Pearce, Xiaoxia Wang, Annie N. Samraj, Heinz Läubli, Javier O. Garcia, Andrea Garcia-Bingman, Patrick Secrest, Casey E. Romanoski, Charles Heyser, Christopher K. Glass, and Nissi Varki, UC San Diego; Hongqiao Lin, Xiaoming Fu and Stanley L. Hazen, Cleveland Clinic Lerner Research Institute.

This research was funded, in part, by the National Institutes of Health (grants P01HL107150, P01HL076491 and RO11065732), Ellison Foundation, Mathers Foundation of New York, Novartis Foundation for medical-biological research, Cancer Research Institute and AB SCIEX.

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