More anti-inflammatory genes mean longer lifespans for mammals

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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.

"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.

Provided by University of California - San Diego