

INFLAMMATION

Live long and prosper with Siglecs

“ Siglec receptors may support longevity by protecting host tissues from oxidative stress ”

During inflammation, the generation of reactive oxygen and nitrogen species promotes immunity to infection; however, these toxic mediators damage host cells and have been proposed to contribute to the ageing process. Schwarz *et al.* now report that a subset of sialic acid-binding immunoglobulin-like lectin (Siglec) receptors is expanded in mammals with longer lifespans and may be important for protecting cells against oxidative stress.

Siglecs are predominantly expressed by cells of the immune system and can be divided into two main groups according to sequence homology and conservation. One group comprises the Siglecs that are

conserved across mammals, whereas the other (known as the CD33rSiglec family) consists of the Siglecs that vary greatly between different species in terms of gene number and sequence. As CD33rSiglecs have been shown to deliver inhibitory signals to immune cells, the authors questioned whether their anti-inflammatory activities may correlate with mammalian lifespans. Indeed, when they assessed 14 mammalian species, they found a strong positive correlation between the number of CD33rSiglec family genes and the maximum lifespan of a species.

To examine whether the CD33rSiglecs were contributing to longevity, the authors used

mice lacking Siglec-E. This receptor is expressed by neutrophils and tissue macrophages and is the predominant CD33rSiglec in mice. Compared with wild-type littermates, Siglec-E-deficient mice had markedly reduced survival over a period of 100 weeks and showed increased greying and thinning of the epidermis. They also showed poorer performance in tests designed to measure learning and spatial memory. The Siglec-E-deficient mice did not show any evidence of chronic systemic inflammation and had similar leukocyte counts to wild-type controls. However, Siglec-E-deficient mice showed sporadic development of inflammatory tissue foci in the liver, kidneys and lungs.

Closer study showed that activated neutrophils from Siglec-E-deficient mice generated higher levels of reactive oxygen species than wild-type neutrophils. In addition, the Siglec-E-deficient animals expressed lower levels of glutathione S-transferase 1, which protects cells against potentially damaging free radicals. Consistent with these changes, higher levels of DNA damage and a greater accumulation of oxidized amino acids were seen in the organs of older Siglec-E-deficient mice than in those from wild-type controls.

Further studies will be necessary to determine if the CD33rSiglec receptors found in other mammalian species function similarly to mouse Siglec-E, but the authors propose that Siglecs may support longevity by protecting host tissues from oxidative stress.

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ORIGINAL RESEARCH PAPER Schwarz, F. *et al.* Siglec receptors impact mammalian lifespan by modulating oxidative stress. *eLife* **4**, e06184 (2015)
FURTHER READING Macauley, M. S., Crocker, P. R. & Paulson, J. C. Siglec-mediated regulation of immune cell function in disease. *Nature Rev. Immunol.* **14**, 653–666 (2014)