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INFLAMMATION

Inflammasome-related ageing

> the expression level of inflammasome-related genes correlates with health and longevity

The chronic state of low-grade inflammation observed in many elderly individuals (sometimes referred to as 'inflammaging') is associated with increased risk of various diseases, including cardiovascular disease. It is not clear what causes the inflammatory response in these individuals, but Furman *et al.* now report in *Nature Medicine* that nucleotide metabolites in older individuals can activate the NLRC4 inflammasome.

Using gene-expression data from the Stanford–Ellison longitudinal cohort, the expression levels of 41 modules of co-expressed genes were shown to be correlated with age. The authors identified two modules from this set that are involved in cytokine production (modules 62 and 78), both of which contain inflammasome-related genes (*NLRC5* and *IL1B* in module 62; *NLRC4* in module 78). There was a significant age-dependent increase in expression of both modules when comparing young adults (aged 20–30 years) with older adults (aged 60 to ≥89 years).

Older adults were sorted according to the magnitude and chronicity of expression levels of modules 62 and 78 to yield two extreme phenotypes that the authors designate inflammasome module high (IMH) and inflammasome module low (IML) groups. Levels of 17 cytokines, in particular interleukin-1β (IL-1β), were increased in the serum of IMH individuals compared with IML individuals. With respect to clinical history, there was a significant association between IMH status and hypertension; 75% of IMH subjects were hypertensive compared with 9% in the IML group and 52% among all individuals in the older cohort. The expression level of module 78 at the start of the study was higher in subjects over 85 years of age who died during the study period (2008 – 2016) than in those who survived. Thus, the expression level of inflammasome-related genes correlates with health and longevity during ageing.

To identify the mechanism of IL-1β production in IMH subjects, the authors analysed a large number of serum metabolites as potential inflammasome activators. There was a significant increase between IML and IMH groups in the expression of metabolites and genes of the purine and pyrimidine metabolic pathways, such as adenine and N4A (N^4-acetylcytidine), respectively. Adenine induced a significant dose-dependent increase in IL-1β production by primary monocytes *in vitro*, and N4A but not adenine induced NLRC4 expression. Therefore, the authors propose that components of IMH sera can both prime and activate the NLRC4 inflammasome. Treating a monocyte cell line with both adenine and N4A induced a significant increase in IL-1β and IL-18 production in a caspase-1- and NLRC4-dependent manner. These metabolites were also shown to activate primary human platelets and neutrophils.

When N4A and adenine were injected daily into mice, they produced a borderline significant increase in blood pressure as early as 8 days after the first injection; this response could be increased by the addition of angiotensin II as a known pre-hypertensive stimulus. Further analysis of intracellular signalling proteins in immune cell subsets showed a higher level of immune activation in mice treated with adenine, N4A and angiotensin II compared with angiotensin II alone.

In summary, the data show that changes to nucleotide metabolism in older individuals, which might occur downstream of oxidative stress, can lead to activation of the NLRC4 inflammasome. Interestingly, caffeine was shown to impair priming of NLRC4 *in vitro*. In keeping with this, the IML group reported higher caffeine intake and had significantly increased levels of caffeine metabolites compared with the IMH group, which suggests that moderate coffee consumption might reduce inflammaging.

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ORIGINAL ARTICLE Furman, D. *et al.* Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. *Nat. Med.* http://dx.doi.org/10.1038/nm.4267 (2017)

FURTHER READING Brodin, P. & Davis, M. M. Human immune system variation. *Nat. Rev. Immunol.* **17**, 21–29 (2017)