Nature Reviews Immunology | AOP, published online 19 October 2012; doi:10.1038/nri3331

T CELLS

When I get older, losing my miR…

As we age, our immune system becomes less efficient at protecting us from infection. Declining thymic function has been proposed to be a contributing factor, but several studies suggest that the overall diversity of the peripheral T cell receptor (TCR) repertoire does not significantly differ between the young and the old. Li *et al.* now offer an alternative explanation — they report that naive T cells from elderly individuals have increased TCR activation thresholds owing to an age-associated loss of expression of microRNA-181a (miR-181a).

In preliminary experiments, the authors found that purified naive CD4$^+$ T cells from older adults (aged 70–85 years) were less sensitive to TCR stimulation compared with naive CD4$^+$ T cells from young adults (aged 20–35 years). Naive CD4$^+$ T cells from older adults required higher antigen doses or higher affinity antigens in order to become activated, suggesting that TCR activation thresholds in these cells increase with age. When exploring the signalling events that may account for this, the authors found that TCR-dependent activation of ζ-chain associated protein kinase 70 kDa (ZAP70) and phospholipase C-γ1 (PLCγ1) was comparable in T cells from younger and older adults. However, naive CD4$^+$ T cells from elderly individuals showed defective activation of the extracellular signal-regulated kinase (ERK) signalling pathway following TCR stimulation, with further experiments indicating that this defect occurs downstream of RAS and RAF activation.

> “inhibition of DUSP6 could be a useful strategy for improving the efficacy of vaccines for the elderly”

As dual specificity protein phosphatase 6 (DUSP6) is known to attenuate TCR signalling by regulating ERK, the authors examined whether DUSP6 expression is also altered in T cells from older individuals. They found that levels of DUSP6 protein increased with age in naive CD4$^+$ T cells but were not affected in an age-dependent manner in memory T cells. Interestingly, however, similar levels of DUSP6 transcripts were found in naive CD4$^+$ T cells regardless of the age of the donor. This prompted the authors to measure the levels of miR-181a, which is known to regulate the expression of several phosphatases, including DUSP6. Notably, naive CD4$^+$ T cells from young adults had threefold higher levels of miR-181a compared with naive CD4$^+$ T cells from older individuals. Furthermore, the authors found that overexpression or silencing of miR-181a in CD4$^+$ T cells led to a respective decrease or increase in levels of DUSP6. Taken together, these data suggest that the loss of miR-181a expression that occurs in naive T cells during ageing leads to a corresponding increase in DUSP6 levels, thereby raising TCR activation thresholds in these cells.

Importantly, the authors were able to show that blocking DUSP6 expression in CD4$^+$ T cells from elderly individuals increased their responsiveness to TCR stimulation. They suggest that inhibition of DUSP6 could be a useful strategy for improving the efficacy of vaccines for the elderly.

Yvonne Bordon

GETTY

ORIGINAL RESEARCH PAPER Li, G. *et al.* Decline in miR-181a expression with age impairs T cell receptor sensitivity by increasing DUSP6 activity. *Nature Med.* **18**, 1518–1524 (2012)
FURTHER READING Rappuoli, R. *et al.* Vaccines for the twenty-first century society. *Nature Rev. Immunol.* **11**, 865–872 (2011)