IN BRIEF

NK CELLS

Bursting with zinc finger factor

Natural killer (NK) cells are innate lymphocytes that have features of adaptive immune cells, such as clonal proliferation and the generation of memory-like cells in response to infection. In C57BL/6 mice, recognition of the mouse cytomegalovirus (MCMV)-encoded glycoprotein m157 by the NK cell-activating receptor LY49H induces a proliferative 'burst' and an effector response that protects against infection. A new study shows that the zinc finger and BTB domain-containing transcription factor ZBTB32 is required for this protective response. Indeed. transfer of Zbtb32-/- LY49H+ NK cells to neonate mice (which lack mature B, T and NK cells) rescued one-third of mice from otherwise lethal infection with MCMV. Infection-induced ZBTB32 expression was not required for NK cell killing capacity, cytokine production or maturation but it was essential for NK cell clonal expansion. ZBTB32 expression is induced by pro-inflammatory cytokines and promotes NK cell proliferation by suppressing the anti-proliferative factor B lymphocyte-induced maturation protein 1 (BLIMP1).

ORIGINAL RESEARCH PAPER Beaulieu, A. M. et al. The transcription factor Zbtb32 controls the proliferative burst of virus-specific natural killer cells responding to infection. *Nature Immunol.* <u>http://dx.doi.org/10.1038/ni.2876</u> (2014)

HAEMATOPOIESIS

Stressed HSCs prefer to die

Haematopoietic stem cells (HSCs) have high levels of exposure to stress stimuli owing to their long lifespan and they are more likely to undergo apoptosis in response to cellular stress than their downstream progenitors. This could help to prevent the propagation of damaged HSCs and to maintain the integrity of the haematopoietic cell population. The accumulation of misfolded proteins in the endoplasmic reticulum as a result of cellular stress activates the unfolded protein response (UPR), which comprises PERK, IRE1 and ATF6 pathways. Expression of PERK pathway constituents was greater in HSCs than in downstream progenitors, which resulted in preferential triggering of an apoptotic response to chemically induced stress. Human HSCs genetically engineered to have a decreased UPR had increased engraftment capacity compared with control HSCs when transplanted into immunodeficient mice, which indicates the in vivo relevance of the propensity of HSCs to undergo apoptosis.

ORIGINAL RESEARCH PAPER van Galen, P. et al. The unfolded protein response governs integrity of the haematopoietic stem-cell pool during stress. Nature <u>http://dx.doi.</u> org/10.1038/nature13228 (2014)

MACROPHAGES

Tumour connection

Macrophages are important for host defence against pathogens but less is known about their function in chronic disorders such as cancer. This study shows that mammary tumour growth in mice induces the differentiation of tumour-associated macrophages — which are different to mammary tissue macrophages — from inflammatory monocytes. Gene expression profiling showed that this differentiation depends on recombination signal-binding protein for immunoglobulin κ J region (RBPJ), which is a transcriptional regulator of Notch signalling. Interestingly, mice that lack *Rbpj* have a reduced tumour burden, and the depletion of tumour-associated macrophages — but not of mammary tissue macrophages — restores tumour-infiltrating cytotoxic T cell responses and suppresses tumour growth.

ORIGINAL RESEARCH PAPER Franklin, R. A. et al. The cellular and molecular origin of tumor-associated macrophages. Science <u>http://dx.doi.org/10.1126/science.1252510</u> (2014)