Hairy guide to maintaining T_{RM} cells

Mammalian skin has long-term resident populations of memory T cells (T_{RM} cells). In *Nature Medicine*, Nagao and colleagues demonstrate that hair follicles are directly responsible for the maintenance of T_{RM} cells in the skin. Certain keratinocytes that line the hair follicles of both humans and mice express interleukin 7 (IL-7) and IL-15. Production of IL-15 by hair follicles is required specifically for the maintenance of $CD8^+$ T_{RM} cells but is dispensable for $CD4^+$ T_{RM} cells. However, follicular expression of IL-7 is necessary for the presence of both $CD4^+$ T_{RM} cells and $CD8^+$ T_{RM} cells in the skin. The absence of either of these cytokines impairs contact hypersensitivity or, for IL-7, impairs the accumulation of skin T cells in a model of cutaneous T cell lymphoma. These findings indicate that particular populations of follicle keratinocyte have an essential role in controlling the homeostasis of T_{RM} cells. ***ZF***

***Nat. Med.* (19 October 2015) doi:10.1038/nm.3962**

Nerve sentries

IL-17 protects host tissues against fungal and bacterial pathogens. In *Immunity*, Kashem *et al.* report that nociceptor-positive nerve cells in the skin can sense infection by the fungal pathogen *Candida albicans* and activate innate immune responses. After infection, these activated neurons release the calcitonin-like neuropeptide CGRP, which acts on $CD11b^+CD301b^+$ dermal dendritic cells and prompts their release of IL-23. In turn, IL-23 acts on innate skin-resident γδ T cells to elicit their production of IL-17. Loss of any of these cell subsets or antagonizing CGRP action compromises the ability of hosts to control infection with *C. albicans*. Thus, sensory neurons in the skin are able to sense infection by fungal pathogens and initiate protective responses by communicating such threats to cells of the innate immune system. *LAD*

Immunity **43**, 515–526 (2015)

Epigenetic silencing in tumors

Epigenetic changes such as histone modifications and DNA methylation are important tumorigenic mechanisms. In *Nature*, Zou and colleagues show that trimethylation of histone H3K27 mediated by the histone methyltransferase EZH2 and DNA methylation dependent on the enzyme DNMT1 repress induction of the chemokines CXCL9 and CXCL10 in tumor cells and subsequently interfere with the trafficking of effector T cells to the tumor. In a mouse model of ovarian cancer, combined treatment with inhibitors of EZH2 and DNMT1 slows tumor progression and increases the infiltration of effector T cells into the tumor and tumor expression of CXCL9 and CXCL10, which improves the efficacy of blockade of the costimulatory molecule PD-1 or adoptive T cell therapy. Blockade of the chemokine receptor CXCR3 abrogates the beneficial effect of EZH2 and DNMT1 inhibition on tumor progression. Trimethylation of H3K27 and DNA methylation repress tumor-cell chemokine expression independently. In patients, expression of EZH2 and DNMT1 in ovarian tumors is inversely correlated with the number of tumor-infiltrating $CD8^+$ T cells and patient survival. ***IV***

***Nature* (26 October 2015) doi:10.1038/nature15520**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Salted inflammation

Dietary factors such as a high salt content can exert a potentially important influence on autoimmune disease. Two related papers by Hafler and Müller and colleagues in the *Journal of Clinical Investigation* demonstrate that elevated concentrations of NaCl can directly alter the function of both adaptive immunity and innate immunity. High concentrations of NaCl both *in vitro* and *in vivo* impair the function and generation of alternatively activated (M2) macrophages and the function of regulatory T cells (T_{reg} cells). This perturbation seems to be unrelated to cell death or simple alterations in hypertonicity and instead requires activity of the kinase SGK1 in T_{reg} cells and of SGK1 and the osmotically regulated transcription factor NFAT5 in M2 cells. However, high concentrations of NaCl do not result in increased polarization to inflammatory M1 cells. These papers demonstrate how dietary increases in NaCl can impair the suppressive activity of T_{reg} cells and M2 cells and perturb their wound-healing function and together contribute to autoinflammatory disease. *ZF*

J. Clin. Invest. (20 October 2015) doi:10.1172/JCI81151 & doi:10.1172/JCI80919

Viral anti-STING factors

Cytosolic sensors can trigger type I interferon responses after the detection of duplex DNA viruses and subsequent activation of the cyclic GMP-AMP synthase (cGAS)–adaptor STING pathways, but several tumor viruses can evade this pathway. In *Science*, Lau *et al.* identify two viral proteins, adenovirus E1A and human papillomavirus E7, that inhibit the activation of STING. Transduction of transformed cells with either E1A or E7 is sufficient to blunt type I interferon production; however, knockdown of either viral protein in established transformed cell lines 'rescues' this response. Both E1A and E7 have a peptide motif consisting of Leu-X-Cys-X-Glu (where 'X' is any amino acid) that is required for the inhibition of STING. Whether this interaction is direct or requires other factors remains uncertain. What is clear, however, is that DNA viruses have evolved strategies to combat antiviral responses elictied by the STING pathway. ***LAD***

***Science* (24 September 2015) doi:10.1126/science.aab3291**

MALT1 regulates LUBAC

The CARD11-BCL1-MALT1 complex activates the transcription factor NF-κB downstream of antigen receptor signaling in B cells. In *Nature Communications*, Overall and colleagues use a highly sensitive proteomics approach (TAILS) in B cells from a patient with homozygous mutation of the gene encoding the paracaspase MALT1 to identify the ubiquitin ligase HOIL1, a component of the linear ubiquitin chain–assembly complex (LUBAC), as a substrate of MALT1 in human lymphocytes. MALT1 cleaves HOIL1, but not other LUBAC subunits, which leads to disengagement of HOIL1 from LUBAC, disassembly of LUBAC, less linear ubiquitination of target proteins, such as RIP1 and NEMO, and less activation of NF-κB. The initial triggering of NF-κB signaling downstream the antigen receptor in B cells and T cells is independent of MALT1's paracaspase activity, which suggest that the scaffolding role of MALT1 is more important at early stages, while cleavage of HOIL1 decreases NF-κB activation at later time points. These studies also show that HOIL1 is a target of MALT1 in mouse lymphocytes as well. *IV*

Nat. Comm. (3 November 2015) doi:101038/ncomms9777

© 2015 Nature America, Inc. All rights reserved.