Healing with hyaluronan

Specialized T cells in the skin lay a sugary foundation for macrophage migration into wounds, according to a study on page 1269. Jameson and colleagues show that the absence of dendritic epidermal γδ T cells (DETCs) removes the impetus for skin cells to secrete hyaluronan, an extracellular glycan that is required for macrophage entry into wounds. Without macrophages, wounds can't heal.

Wound healing is initiated when DETCs recognize an unknown antigen on damaged skin cells. Neutrophils and, later, macrophages migrate to the wound site; both cell types are needed for complete healing. This group had previously shown that wound repair breaks down in the absence of DETCs due to a lack of keratinocyte growth factors FGF-7 and FGF-10, which are produced by DETCs in wounds and stimulate keratinocyte regeneration.

Jameson et al. noted that nonhealing wounds in DETC-deficient mice were less inflamed than normal wounds. They now show that, though neutrophils arrived at the wound on schedule, macrophages showed up late. The macrophage tardiness could be traced back to the lack of FGF-7. In normal wounds, FGF-7 was found to trigger the production of hyaluronan by neighboring keratinocytes and hyaluronan was needed to recruit macrophages. If hyaluronan (or FGF-7) was added back to the wounds, the macrophages returned and healing was restored.

Impaired wound healing is prevalent in patients with diabetes and rheumatoid arthritis. The authors hope to investigate whether impaired DETC function may be to blame in these human diseases. JEM

Polymerase pinch hitters

On page 1191, Delbos and colleagues provide the first proof that the error-prone polymerase η (polη) is responsible for mutations at A-T base pairs during somatic hypermutation (SHM) of immunoglobulin (Ig) genes in mice. But when polη is removed from mice, another sloppy enzyme, not previously thought to contribute to SHM, can fill in as a pinch hitter.

SHM generates high affinity antibodies in response to antigenic challenge; it does so by introducing point mutations into the antigen-binding regions of B cell antibody genes. Mutations at C-G base pairs during SHM are the work of the enzyme AID (activation-induced cytidine deaminase), which turns cytosine into uracil. A-T mutations have been harder to explain. Error-prone polymerases are thought to be the culprits behind A-T mutation, but specific roles for these enzymes have been difficult to assign, as mice lacking individual polymerases have thus far shown no defects in SHM.

Polη has been the primary suspect charged with mutating A-T base pairs, as the pattern of errors made by polη in vitro is reminiscent of that seen in mutated Ig loci. In addition, humans lacking polη have fewer A-T mutations in their Ig genes than normal. Delbos et al. now solidify the evidence by showing that elimination of polη in mice decreases Ig gene mutations at A-T base pairs.

The few A-T mutations that occurred in the absence of polη—to the authors’ surprise—bore the signature of another polymerase, polk, which does not normally meddle in SHM. The authors suggest that the mismatch repair protein complex MSH2–MSH6, recently shown to recruit polη to AID–induced U-G mismatches, may in polη’s absence instead bind polk. The polk would then cause mutations at nearby A-T sites. JEM