INNATE IMMUNITY

Skin fibroblasts shield mast cells

Extracellular ATP is released in response to cellular stress and serves as a 'danger' signal that can activate immune cells via P2 purinoceptors, such as $P2X_7$. Previous work has shown that mast cells from the skin and intestine have differential $P2X_7$ expression but it has been unclear why this is. Kurashima *et al.* now show that skin fibroblasts inhibit mast cell expression of $P2X_7$ by producing enzymes that degrade retinoic acid (RA), a vitamin A metabolite. This activity of fibroblasts promotes homeostasis in the skin by limiting mast cell activation.

The authors isolated mast cells from various tissues and, in keeping with previous findings, showed that intestinal mast cells express higher levels of $P2X_7$ compared with mast cells from other tissues. Mast cells from the lungs and peritoneum expressed intermediate levels of $P2X_7$, whereas skin mast cells showed very low levels of $P2X_7$ expression. Accordingly, although mast cells from other sites produced pro-inflammatory mediators following stimulation with ATP, skin mast cells did not respond. Experiments in which bone marrow-derived mast cells were transferred into the skin of mast cell-deficient mice indicated that local environmental factors suppress mast cell expression of $P2X_7$. Studies using germ-free mice or mice deficient in various immune cell populations suggested that this suppression of $P2X_7$ expression did not depend on the commensal microbiota or on local immune cells. Similarly, inhibition of $P2X_7$ expression did not require skin-associated immunomodulatory mediators such as interleukin-10, prostaglandin E2 and vitamin D3 metabolites. However, the co-culture of bone marrow-derived mast cells with skin fibroblasts (but not with intestinal fibroblasts) suppressed their expression of $P2X_7$. This suggests that skin fibroblasts limit the expression of $P2X_7$ by local mast cells.

> "skin fibroblasts limit the expression of $P2X_7$ by local mast cells"

To unravel the mechanisms involved, the authors carried out gene microarray analyses. They found that skin fibroblasts expressed higher levels of the RA-degrading enzymes *Cyp26a1* and *Cyp26b2* compared with intestinal fibroblasts, and that exposure of mast cells to RA promoted their upregulation of $P2X_7$. Furthermore, the treatment of skin fibroblasts with an inhibitor of CYP26B1 led to increased expression of $P2X_7$ by co-cultured mast cells. Disruption of retinoid signalling has previously been associated with skin inflammation, so the authors examined whether high doses of RA can disrupt skin homeostasis by upregulating $P2X_7$ on mast cells. Indeed, mice that were repeatedly administered high doses of RA developed dermatitis, and this skin inflammation was exacerbated if the mice were treated with a CYP26B1 inhibitor. Notably, the RA-induced dermatitis was associated with high concentrations of extracellular ATP in the skin and was ameliorated in mice deficient in $P2X_7$ or mast cells. The authors found that the skin microbiota also contributes to the development of RA-induced dermatitis; signals from local commensals seem to recruit and activate monocytes and macrophages, and increase their release of ATP and other $P2X_7$ ligands.

In summary, this study shows the importance of local fibroblasts in maintaining mast cell quiescence and homeostasis in the skin. Of note, previous studies have linked high levels of vitamin A intake with the exacerbation of skin inflammation in humans — these new data offer a possible mechanistic explanation.

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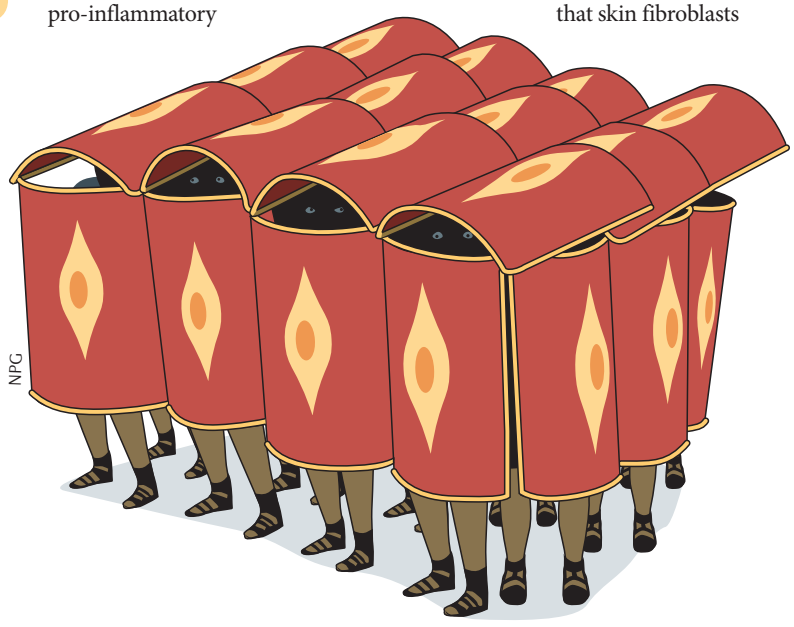

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ORIGINAL RESEARCH PAPER Kurashima, K. *et al.* The enzyme Cyp26b1 mediates inhibition of mast-cell activation by fibroblasts to maintain skin-barrier homeostasis. *Immunity* http://dx.doi.org/10.1016/j.immuni.2014.01.014 (2014)