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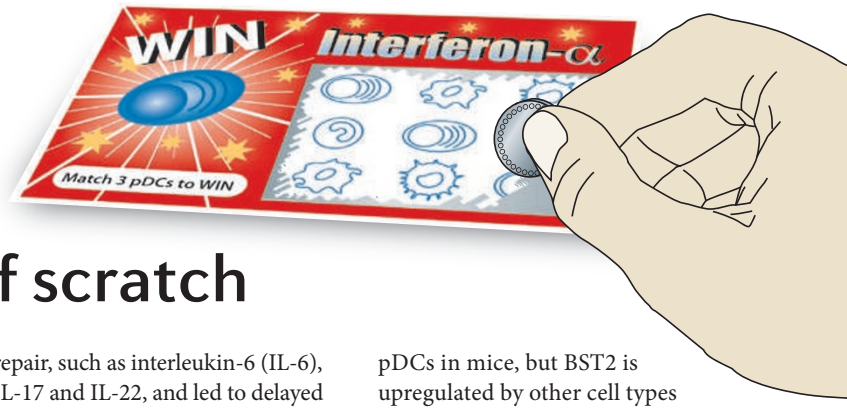

DENDRITIC CELLS

pDCs play off scratch

Plasmacytoid dendritic cells (pDCs) express Toll-like receptor 7 (TLR7) and TLR9 and produce large amounts of type I interferons (IFNs) in response to viral nucleic acids. However, the contribution of this rare circulating cell population to host immunity remains unclear. Two recent studies in the *Journal of Experimental Medicine* now show that, although they are absent from normal skin, pDCs are rapidly recruited to sites of cutaneous inflammation. Here, they serve as an early source of type I IFNs and contribute to wound healing in normal mice, but can promote an autoimmune skin reaction in lupus-prone animals.

Using a mechanical tape-stripping model to induce acute skin inflammation in mice, Gregorio *et al.* found that pDCs infiltrated and transiently accumulated in the injured skin around 24 hours after injury. Infiltration of pDCs to injured skin was associated with the production of type I IFNs, and antibody-mediated depletion of pDCs abrogated the IFN response, suggesting that pDCs were the chief source of the IFNs. Mice that were treated with IRS954 (a selective inhibitor of TLR7 and TLR9) prior to tape stripping failed to upregulate type I IFNs, indicating that activation of pDCs through these TLRs is necessary for IFN production. The sterile nature of the model suggested that pDCs were activated by host-derived nucleic acids, possibly those released by damaged keratinocytes.

Depletion of pDCs or blockade of IFN-mediated signalling prior to tape stripping decreased the production of cytokines that are involved in wound repair, such as interleukin-6 (IL-6), IL-17 and IL-22, and led to delayed regrowth of the epidermis. In healthy human volunteers, mechanical or chemical-induced skin injury also led to pDC recruitment and upregulation of type I IFNs early in the immune response, suggesting that the transient recruitment of IFN-producing pDCs may contribute to wound healing in humans as well as in mice.

Similarly, Guiducci *et al.* found that tape stripping led to early recruitment of IFNα-producing pDCs to the skin, and that treating mice with IRS954 reduced the expression of IFNs and other inflammatory cytokines in injured skin. In addition, these authors found that in a lupus-prone mouse strain, tape stripping led to the development of chronic skin lesions resembling those seen in patients with cutaneous lupus. Treating lupus-prone mice with IRS954 or depleting pDCs before tape stripping prevented the development of these skin lesions, suggesting that pDCs and signalling through TLR7 and TLR9 are necessary for this pathological response. Furthermore, IRS954 promoted healing in lupus-prone mice with already established skin lesions, indicating that continued signalling through TLR7 and TLR9 was necessary for the chronic inflammatory response; however, the exact role of pDCs was not identified.

The ability to explore the functions of pDCs in chronic skin lesions may have been hampered by a lack of suitable reagents to deplete pDCs. Antibodies against bone marrow stromal antigen 2 (BST2) are commonly used to deplete pDCs in mice, but BST2 is upregulated by other cell types during inflammation. A new transgenic mouse, in which pDCs can be conditionally depleted, has been described in a recent *Immunity* article and could clarify this matter. Using this mouse to explore pDC functions during viral infection, Swiecki *et al.* found that pDCs are only essential for type I IFN production during the early stages of infection with murine cytomegalovirus or vesicular stomatitis virus; however, this early pDC response can, depending on the viral load, be crucial for containing these viruses.

Together, these studies suggest that the physiological role of pDCs is to serve as an early, transient source of type I IFNs following activation by foreign or endogenous damage-associated nucleic acids. As such, pDCs seem to be important for containing early viral infections and promoting tissue repair following acute injury. However, in genetically susceptible individuals, pDCs may become chronically activated and contribute to the breakdown of tolerance and the development of autoimmunity in the skin.

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ORIGINAL RESEARCH PAPERS Gregorio, J. *et al.* Plasmacytoid dendritic cells sense skin injury and promote wound healing through type I interferons. *J. Exp. Med.* 29 Nov 2010 (doi:10.1084/jem.20101102) | Guiducci, C. *et al.* Autoimmune skin inflammation is dependent on plasmacytoid dendritic cell activation by nucleic acids via TLR7 and TLR9. *J. Exp. Med.* 29 Nov 2010 (doi:10.1084/jem.20101048) | Swiecki, M. *et al.* Plasmacytoid dendritic cell ablation impacts early interferon responses and antiviral NK and $CD8^+$ T cell accrual. *Immunity.* 2 Dec 2010 (doi:10.1016/j.immuni.2010.11.020)