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INFLAMMATION

# Inflammatory memory is skin deep


Immunological memory is a hallmark of adaptive immunity but an emerging concept is that innate immune cells also show memory-type behaviour. A new study by Naik, Larsen *et al.* now describes inflammatory memory in a non-immune cell population, specifically in epithelial stem cells (EpSCs) of the skin.

EpSCs reside in the basal layer of the skin epithelium and self-renew or undergo a terminal differentiation programme to maintain epithelial integrity. The authors used an imiquimod (IMQ)-induced model of skin inflammation to explore how EpSCs respond to inflammatory challenges. Topical application of IMQ induced hyperthickening and parakeratosis in the epidermis and this was accompanied by EpSC hyperproliferation and apoptosis, which peaked at day 6 and subsided by day 30. Lineage-tracing experiments showed that EpSCs persisted in the skin in equivalent numbers before, during and after the resolution of inflammation, whereas progenitors that had committed to terminal differentiation were shed. To test whether the inflammatory challenge had a lasting effect on EpSCs, the authors compared wound healing in naive mice and mice that had recovered from IMQ-induced inflammation. Notably, mice previously exposed to inflammation closed their wounds ~2.5 times faster than naive mice. Enhanced wound healing was also seen when mice were previously exposed to other inflammatory stimuli or infected with the fungal pathogen *Candida albicans*. Therefore, skin previously exposed to one inflammatory challenge responds faster to an unrelated secondary challenge.

Following wounding, re-epithelialization is mediated by EpSCs, but these cells also respond to soluble tissue factors and signals from immune cells. Mice treated with IMQ on one half of their dorsal skin and subsequently wounded on the other side showed comparable wound healing to untreated controls, which suggests that soluble factors do not accelerate wound healing in previously inflamed skin. Furthermore, mice depleted of skin-resident macrophages or lacking lymphocytes still showed faster wound closure in previously inflamed skin. Therefore, EpSCs themselves seem to retain a memory of previous inflammatory challenges. To test the mechanistic basis of this, the authors purified EpSCs from IMQ-treated skin at the peak and following resolution of inflammation and used ATAC-seq to identify accessible chromatin. These analyses suggested that EpSCs retain an epigenetic memory following IMQ exposure with increased accessibility in genes related to inflammation and hyperproliferation. Importantly, subsequent studies showed that 52% of the genes rapidly upregulated by post-inflamed EpSCs during wounding corresponded to ATAC-seq peaks that were acquired and sustained in EpSCs during the initial IMQ-induced skin inflammation.

Finally, the authors addressed how the epigenetic memory acquired in EpSCs during skin inflammation accelerates subsequent wound repair. Pathway analysis software indicated that the AIM2 inflammasome and its downstream components are upregulated in post-inflamed EpSCs, and transcription of *Aim2* was also increased in EpSCs during wounding. Notably, AIM2-deficient mice did not show accelerated wound repair in previously inflamed skin, whereas induced expression of *Aim2* in the skin epithelium improved wound repair in the absence of pre-challenge with IMQ. Further studies showed that the AIM2 inflammasome accelerates wound closure through caspase 1-mediated activation of IL-1β.

These data indicate that EpSCs retain an epigenetic memory of inflammatory challenges that enables them to respond more rapidly to a secondary tissue challenge. Although this may be beneficial to the host in accelerating wound repair, the authors caution that this inflammatory memory may contribute to epidermal cancers as well as to autoimmune diseases, such as psoriasis and atopic dermatitis.

*Yvonne Bordon*

> “inflammatory memory in a non-immune cell population”

**ORIGINAL ARTICLE** Naik, S. *et al.* Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. *Nature* http://dx.doi.org/10.1038/nature24271 (2017)