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# Locked and Loaded: Inflammation Training Prepares Skin Epithelial Stem Cells for Trauma

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### Locked and loaded: inflammation training prepares skin epithelial stem cells for trauma

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#### **Abstract**

Memory of a trauma and how to cope with it is useful for acting rapidly in the event of a second traumatic incident. Recently, Naik et al. reported in Nature that skin epithelial stem cells have this ability by maintaining long-term chromatin features acquired during the first assault.

#### **Short Preview**

Learning from past experiences is a winning strategy for evolution, not only at the level of the whole organism, but also at the cellular level. It is anticipated that each living cell, from bacteria and yeast to mammalian and plant cells, needs to be prepared to address environmental stresses of all origins. In vertebrates, the idea of cellular memory has been associated with adaptive immune cells. Thanks to their ability to respond more rapidly to a second assault by the same pathogen, vaccination strategies have been successful in preventing potentially lethal diseases, including some cancer types. Recently, innate immune cells, such as macrophages, have also been shown to remember previous assaults through epigenetic reprogramming, termed trained immunity or innate immune memory (Netea et al., 2016).

Naik and collaborators have now demonstrated the ability of skin epithelial stem cells (EpSCs) to similarly acquire long-term memory of an injury consisting of maintaining modified locus specific DNA accessibility (Naik et al., 2017).

Epithelial cells are a barrier that separate an external space with the rest of a tissue or organ; for skin, their role is particularly important since they are the first line of defence to protect the organism from environmental and microbiota assaults.

To study the enduring consequences of an inflammatory event, Naik and colleagues chemically induced acute inflammation in skin, followed by a wound as a second assault 30 days later. This time in between assaults is enough to restore the low proliferation and apoptosis rates of EpSCs, characteristic of homeostatic conditions. Comparing the healing ability of the inflammation-experienced (IE) versus –unexperienced (IU) skin, they clearly showed that IE skin was able to heal faster a wound (up to 180 days later), independently of the source of the first inflammatory stimulus and of the presence/absence of immune cells such as T cells and macrophages (Figure 1A).

Genome wide chromatin accessibility assays (ATAC-Seq) showed that during the first inflammatory event, EpSCs acquire changes in their chromatin accessibility status. While most of the genomic loci return to their original state, around 2000 genomic loci maintain an open chromatin conformation for 30 days and some of them remain open for at least 180 days. Most of these persistent chromatin changes were not accompanied by sustained transcription of their associated genes, which can be promptly transcriptionally up-regulated, but only after a second

assault (trainable genes in Figure 1B). The molecular investigation of the events revealed that the acquired faster-healing ability relies on inflammasome signalling and in particular on Aim2, which is a gene strongly upregulated during both the initial inflammatory event and the following wound (Figure 1B). The accelerated healing is also dependent on the activation of Aim2 downstream targets, Casp1 and II1b.

Altogether, the data collected by Naik et colleagues support the idea of an EpSC long-term epigenetic memory characterised by chromatin accessibility changes acquired during an inflammatory event. These changes represent a resource for a locus-specific faster transcriptional (re-)activation of the associated genes during a secondary assault.

Re-epithelialization during wound healing is achieved through a coordination of multiple cellular behaviours. A region at the wound edge, characterised mainly by migrating epithelial cells, is surrounded by an area where epithelial cells proliferate at a high rate (Aragona et al., 2017). In between, a coexistence of cell proliferation and migration leads to local expansion and promotes the extension of the epithelial sheets (Park et al., 2017). IE skin displays accelerated reepithelialization during subsequent wound healing without affecting proliferation, but through promoting migration. IE skin also displays epidermal thickening, possibly due to enhanced survival or delayed terminal differentiation, suggesting that inflammatory memory might confer higher plasticity to EpSCs to improve their adaptability.

The inflammatory memory is advantageous in the case of a secondary assault. However, if a subsequent assault does not occur for a long time, maintaining the memory could be a waste of energy and the memory could be discarded. This logic could explain why the inflammation-associated accessible genomic loci persist long term but decrease over time. This reduction might be due to the loss of most of the IE EpSCs through differentiation or negative selection with respect to other IU EpSCs. In this case, just a small fraction of EpSCs would persist in the skin, turning into "memory" cells, similarly to what happens for immune memory cells (Figure 1C). Since in skin, there are multiple lineages maintained by their specific EpSCs, and since some lineages have shown unexpected plasticity (Donati et al., 2017), there is also the possibility that predetermined features make an epithelial lineage more prone or refractory to long-term memory.

Following the parallelism with immune memory, are the mechanisms at the basis of the memory shared between immune and epithelial cells (Figure 1C)? For instance, chromatin memory could be mediated by latent enhancers as was recently demonstrated in macrophages (Ostuni et al., 2013), or by a mitochondrial-based selection of cells towards the memory fate as was determined for T cells (van der Windt et al., 2012). This last possibility suggests a very intriguing crosstalk between metabolism and chromatin. Finally, the contribution of the microenvironment to cellular memory, as seen with the tissue resident macrophages (Gosselin et al., 2014) deserves further investigation. It is plausible that there may be an existence of a feedback loop between chromatin and the cellular niche. The extracellular matrix might indeed provide long-term storage of the secretome released at the time of the first inflammatory event. Thanks to new technologies, all these very fascinating hypotheses might be interrogated by integrating bulk/single cell genomics and transcriptomics with lineage tracing experiments combined with high-throughput functional screening (Rathert et al., 2015; Walko et al., 2017).

This pioneer paper from the Fuchs laboratory might suggest that EpSCs in other organs could be able to remember previous traumas. If so, deregulation of memory in EpSCs might not only have an impact on chronic inflammatory skin diseases (i.e. psoriasis and atopic dermatitis), but also on cancer and on other diseases characterised by intermittent or chronic inflammation in different epithelia (i.e. inflammatory bowel disease and asthma).

The identification of an inflammatory memory in EpSCs allows us to envision the future clinical possibility of implementing a sort of "vaccination strategy" to boost the resiliency of our non-immune cells towards different damages through "training sessions." The clinical potential of this discovery could thus be manifested through the stimulation of "cell resiliency" to prevent the onset of pathological conditions.

### **Figure Legend:**

Inflammatory memory of skin epithelial stem cells. A. Skin subjected to inflammatory stimuli (chemical agents, microbiota, or mechanical abrasion) reacts faster to a secondary assault. This acquired ability is independent of some immune cells. B. Enduring consequences of an inflammatory event on chromatin rewiring and gene expression in EpSCs on trainable genes and Aim2 loci. The newly acquired open chromatin loci allow a prompt transcriptional re-activation in the event of a second assault. C. Hypothetic mechanisms of long term EpSC memory acquisition, maintenance, re-activation, loss, and crosstalk between chromatin, metabolism and the cellular niche.

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