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FORUM Inflammation

Memory beyond immunity

Epithelial stem cells maintain the skin's epidermis and promote wound healing in response to injury. Scientists from two fields discuss implications of the discovery that these stem cells harbour a memory of previous injuries, which enables skin to respond rapidly to subsequent assaults.

THE PAPER IN BRIEF

- Activated epithelial stem cells (EpSCs) give rise to skin-cell lineages that can replace damaged cells and heal wounds.
- In a paper online in *Nature*, Naik *et al.*[1] report that mouse EpSCs that have been exposed to inflammation caused by damage retain a memory of the event in the form of changes to their chromatin — the material in which DNA is packaged with proteins in cells.
- Chromatin changes make key stress-response genes such as *Aim2* accessible to transcription factors. This enables their rapid expression, and thus accelerated wound healing, if injury occurs again (Fig. 1).
- This is the first identification of inflammatory memory in a non-immune cell.

Stem cells remember to heal

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The ability of stem cells to promote healing decreases with age. But, it now emerges, their previous experience also matters. Naik and colleagues provide compelling evidence that the healing potential of skin is enhanced by previous exposure to chemical, mechanical or microbial stimuli even in the absence of key cell types of the immune system. Thus, remembering inflammation is not a job that is restricted to immune cells — it is also undertaken by adult stem cells for the sake of tissue fitness. The results provide a glimpse into a previously unknown aspect of stem-cell biology.

Naik *et al.* found that many regions of chromatin in EpSCs became more open (and so more permissive to transcription of the genes packaged within them) during inflammation. Some of these changes persisted long after inflammation subsided. Whether persistent regions of open chromatin truly act as 'memory carriers' that causally confer a healing advantage remains to be proved. But in support of this idea, the researchers demonstrated that genes associated with these open chromatin domains, such as *Aim2*, were among the earliest to be activated in response to a subsequent injury. A fundamental issue yet to be investigated is how inflammation-induced chromatin changes are initiated and maintained at a mechanistic level.

Do all inflammation-sensitized EpSCs carry the same chromatin changes? Naik *et al.* found that the magnitude of inflammation-induced open chromatin across EpSC populations diminished over time after the first inflammatory event. Perhaps some EpSCs undergo differentiation to become mature skin cells, and so are no longer present in the authors' analyses. Alternatively, this finding could indicate that only a subset of inflammation-experienced EpSCs retain regions of open chromatin.

If a memory EpSC subset does exist, what mechanism enables it to selectively preserve open chromatin? Chromatin is disassembled and reassembled during DNA replication and cell division, which poses a challenge to the retention of associated landmarks[2]. A low rate of cell division might therefore enable certain cells to better maintain a chromatin memory. Skin has several types of EpSC that are involved in wound repair[3] and have variable proliferation rates[4]. The authors studied EpSCs in the epidermis and the upper portion of hair follicles; in the future, cell-lineage-tracing experiments could be used to examine the specific contribution of the various skin EpSC subsets to the newly formed epidermis during post-inflammation wound healing.

Naik and colleagues' work raises both basic and clinical questions. Is inflammatory memory a general feature of all adult-tissue stem cells? This is of particular interest in tissues such as the intestine, which, similarly to skin, acts as a gateway between the body and environment, and is therefore prone to external assaults. What are the long-term health ramifications of EpSC memory? Wound healing is a complex and highly regulated process; if memory-accelerated healing does not involve careful coordination between EpSCs and surrounding skin and immune-cell types, aberrant scarring may ensue.

Chronic inflammation is associated with an enhanced risk of cancer[5]. It is possible that the lingering memory of acute inflammation would lead to super-reactive EpSCs and enhanced production of inflammatory molecules called cytokines, mimicking chronic inflammation. If so, EpSC memory could be prone to becoming maladaptive, predisposing to skin cancer. EpSC memory might also contribute to relapses in inflammatory skin diseases such as psoriasis. Finally, precocious EpSC activity might eventually lead to stem-cell exhaustion and premature ageing. Investigation of these fascinating avenues of research is sure to alter our understanding of EpSC biology even further.

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Inflammatory horizons expand

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Two types of immune memory are acquired when a host encounters a pathogen — life-long memory, conferred by the adaptive immune system, and the short-term memory of the innate immune system. The first involves the proliferation and differentiation of rare immune-system cells (T and B lymphocytes) specific for the pathogen, enabling a rapid protective response to subsequent encounters. The second involves temporary changes in the chromatin of immune-system cells called macrophages, altering the accessibility of their transcriptional machinery such that a particular gene-expression pattern is induced following repeated pathogen stimulation during the same or subsequent infection events[6].

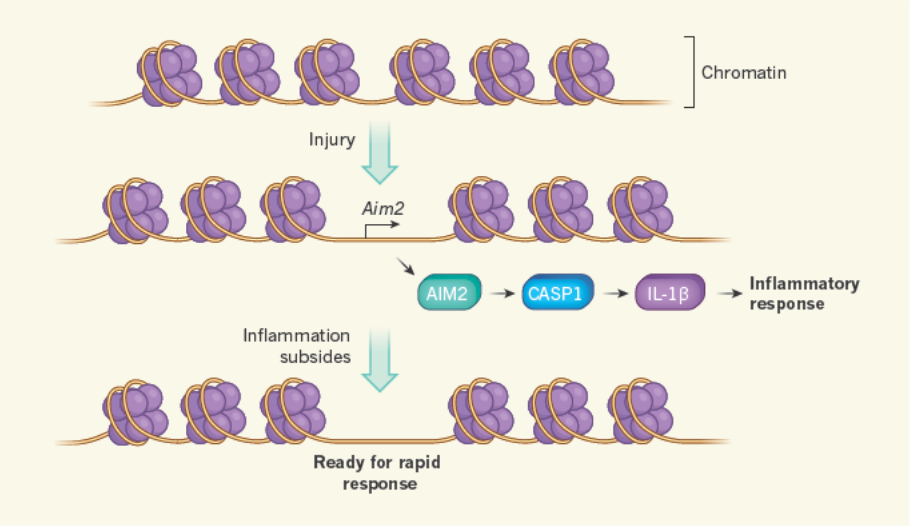

Figure 1 | Rapid-response stem cells. DNA is packaged around proteins to form a complex called chromatin. In regions where DNA is tightly packaged, gene expression is often repressed. Naik *et al.*[1] demonstrate that specific chromatin regions in epithelial stem cells in mouse skin become open when the skin's epidermal layer is injured. This leads to the rapid activation of the stress-response gene *Aim2*, which encodes a protein that activates the downstream proteins caspase-1 (CASP1) and interleukin-1β (IL-1β), triggering an inflammatory response. The authors find that some chromatin regions remain persistently open after inflammation subsides, enabling an accelerated healing response to subsequent skin injuries.

Naik *et al.* add to this list EpSC memory, which, by virtue of a fixed geographical distribution of EpSCs, has a spatial component. In doing so, they broaden the concept of inflammatory memory.

The molecular basis of the EpSC memory uncovered by Naik and colleagues involves dynamic changes in chromatin accessibility that enable cells to respond more rapidly and strongly to subsequent inflammatory challenges than to the primary inflammation. Surprisingly, this memory depends not only on the AIM2 protein, but also on the cytokine interleukin-1β (IL-1β). AIM2 is a component of a protein complex called the inflammasome, which controls the processing and secretion of IL-1β by the protein caspase-1. The inflammatory response triggered by IL-1β secretion promotes wound repair.

AIM2 is activated by the presence of bacterial or viral DNA in the cell cytoplasm, and can also be activated when double-stranded breaks in host DNA are detected in the nucleus[7]. It would be interesting to investigate whether the role of AIM2 in EpSC memory is related to its DNA-sensing function, and if so, to determine the source of the DNA that activates it. This might reveal a previously undocumented role for DNA surveillance in tissue repair.

Superficially at least, EpSC memory seems to be similar to the short-term macrophage memory of the innate immune system — both are based on stable changes in chromatin that alter the accessibility of select groups of genes[8]. However, the possibility that different subsets of cells have different roles has not yet been explored in either case. Indeed, one could imagine that a primary challenge might selectively activate subsets of cells that have predetermined characteristics (such as a specific arrangement of chromatin). If this were the case, then innate immune memory and EpSC memory would use the same principle as adaptive immune memory, which is based on the selection of a subset of progenitor cells and their subsequent proliferation and differentiation.

Finally, Naik and colleagues' discovery raises questions about the relative roles of epithelial-intrinsic memory and immune memory in skin inflammation and repair[9]. Why is memory partitioned into epithelial and immune compartments? And how do the two types of memory interact to provide optimal protection from subsequent challenges? One possible scenario is that EpSCs, macrophages and lymphocytes are specialized to 'remember' different aspects of the environment, and that the different cell types exchange signals to orchestrate tissue-repair responses. Indeed, EpSC-derived cytokines that are produced following damage induce lymphocytes in the skin to secrete growth factors. These growth factors in turn affect the differentiation of EpSCs towards specific lineages[10]. The interplay between these two memory compartments is a fascinating area for future research. ■

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