https://doi.org/10.1038/d41586-026-00639-0

News & views

Cancer

Remembrance of inflammations past

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Chronic inflammation increases the risk of colon cancer. This inflammation drives epigenetic changes in the nucleus of stem cells that promote tumour formation.

A condition involving chronic inflammation of the colon, called ulcerative colitis, is associated with an increased risk of developing colorectal cancer[1]. Moreover, this risk correlates with the cumulative effect of inflammatory episodes rather than the extent of active inflammation at the time of diagnosis[2]. Writing in *Nature*, Nagaraja *et al.*[3] reveal that chronic colonic inflammation results in changes (called epigenetic modifications) that poise stem cells to form tumours if cancer-promoting genetic alterations subsequently occur.

The hypothesis that chronic inflammation promotes cancer dates back to nineteenth-century observations by the physician Rudolf Virchow of immune cells infiltrating tumours, and has since been supported by a wealth of evidence[1,4,5]. Studies seeking to uncover the underlying mechanisms have focused mainly on cell-extrinsic factors in the tumour's environment, such as signs of remodelling of the tumour microenvironment or the presence of immune signalling molecules called cytokines[6]. However, it is also possible that inflammation induces long-lasting changes to the epigenome – chemical modifications to DNA and its associated proteins that influence which genes are active – of the same cell populations that ultimately give rise to the cancer. But what form would such epigenetic 'memories' of inflammation take, and does this causally contribute to the development of colorectal cancer? And, if so, how?

Clues come from studies of inflammatory memory, a concept originally identified in the innate branch of the immune system, and subsequently shown to extend to epithelial cells that form barriers and to stem cells[7–11]. Those investigations established that inflammatory experiences leave epigenetic traces through the remodelling of a DNA and protein complex called chromatin. This includes altering the accessibility of chromatin and modifications of DNA-binding proteins called histones. These traces persist long after the inflammation has ended[8–11]. Such epigenomic memories have consequences that range from heightened inflammatory reactivity to increased cancer risk[8,10,11].

Central protagonists in the process of epigenetic-memory formation are members of the AP-1 transcription factor family. These proteins include FOS and JUN. The AP-1 family has a key role in how cells inscribe inflammatory experiences in epigenomic changes[12–14]. During inflammation, AP-1 proteins bind to

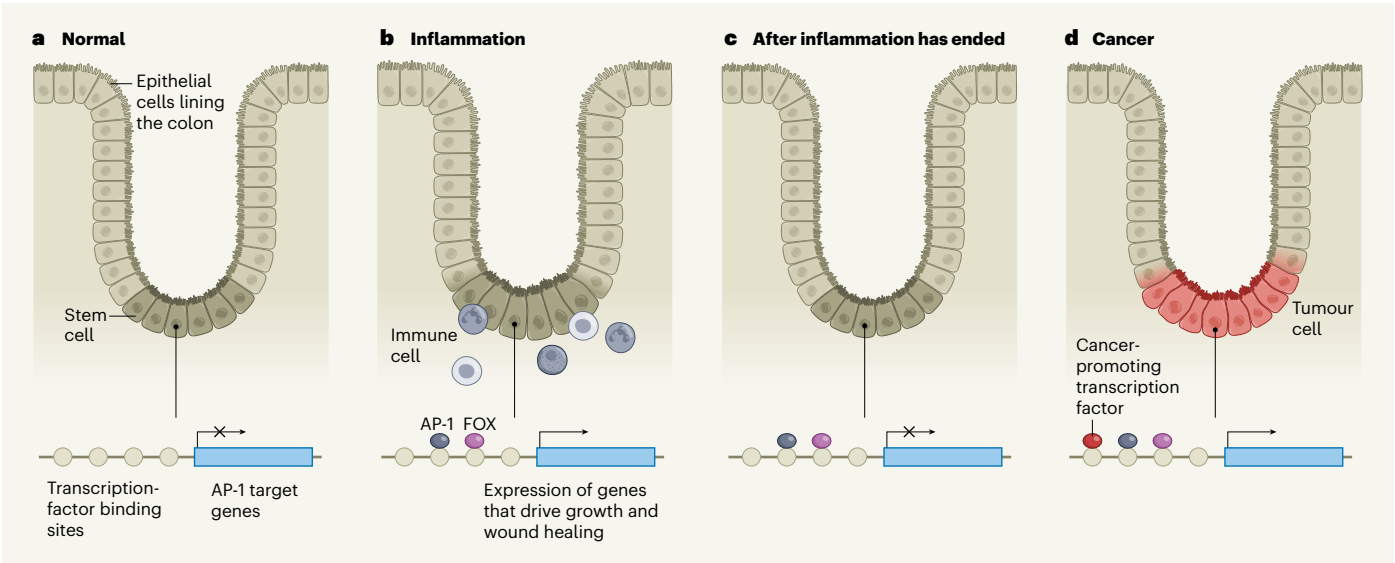

Figure 1 | How inflammation can promote cancer formation. Nagaraja *et al.*[3] present studies in mice revealing that colon inflammation, a condition called colitis, can poise stem cells to form tumours if tumour-promoting mutations occur. **a**, If the colon has not experienced inflammation, genes that can be activated by expression of the transcription factor family of AP-1 proteins are not expressed and transcription-factor binding sites near such genes are unoccupied. **b**, If colitis and inflammation occur, immune cells are present, and AP-1 proteins and another transcription factor from the FOX family bind to transcription-factor binding sites and genes are expressed that encode proteins that help to respond to inflammation. **c**, When the inflammation has ended, gene expression stops, but changes known as epigenetic modifications are retained in the region around the genes activated by AP-1 proteins in stem cells that poise the cells for further gene expression. **d**, If the stem cell subsequently acquires a mutation that drives expression of a cancer-promoting transcription factor, this can lead to gene expression that promotes tumour formation.

regions of DNA called enhancers that promote gene expression. These enhancers are associated with genes that encode proteins that act when cells undergo stress or need to initiate repair processes. AP-1 proteins help to recruit chromatin-remodelling machinery and aid the modification of histone proteins in ways that promote gene expression.

Crucially, AP-1 proteins remain bound to enhancers after the stimulus has ended, enabling faster gene reactivation on future injury[15,16]. Stem cells in the skin, for example, retain an epigenetic memory of previous inflammation, which accelerates wound healing if reinjury occurs[8]. AP-1 protein binding during inflammation is necessary, and sufficient, to establish chromatin states that can be inherited when cells divide[17]. There is also evidence that extends this principle beyond the context of inflammation: cells of a type of skin cancer called melanoma gain epigenetic memories of therapy exposure, which are present as AP-1-dependent chromatin memories[18]. AP-1 proteins are emerging as key architects of cellular biographies, which convert transient experiences, whether inflammation or drug treatment, into stable chromatin states that outlast the signal and shape the cell's future.

Nagaraja and colleagues used the colon as a model system (Fig. 1) to further extend and investigate the mechanisms that underlie AP-1-mediated epigenetic memories. By profiling both chromatin accessibility and gene expression at the level of single cells, the authors show that rounds of colonic injury and recovery leave mouse colonic stem cells with lasting epigenetic changes in the form of greater chromatin accessibility at AP-1 binding sites. These epigenetic memories persist for at least 100 days after recovery, and, remarkably, this persistence is independent of the expression of the AP-1 family member, Fos, which is originally required for their formation. This implies that once created, the memory is stable, and no longer requires the transcription factor that initiated the process.

Strikingly, these epigenetic memories are functionally consequential. In a mouse model of colon cancer, animals that had recovered from colitis developed larger tumours than did animals that had not had colitis, on loss of expression of the tumour-suppressor gene *Apc*. Tumours with the highest AP-1 activity co-opted extra cancer-promoting gene expression programs, suggesting that AP-1 memory does not merely lower the barrier to cancer development but also actively shapes tumour biology. Crucially, drug inhibition of AP-1 proteins during tumour initiation curtailed tumour growth in colitis-experienced tissue, establishing AP-1 as a driver, rather than a correlative bystander, of tumour growth that can be targeted with therapy.

That this memory is cell-autonomous was confirmed by *in vitro* experiments using tissue models called organoids. Stem cells derived from the tissue of mice with colitis maintained their altered chromatin state and proliferated more rapidly than did those from animals without colitis. In further support of autonomous heritability, the authors incorporated sequence 'barcodes' into the genome of cells to track cell lineages and showed that the state of chromatin associated with high levels of AP-1 is a heritable property of specific cell lineages (clones), and is propagated across cell divisions. This reveals a type of inheritance of epigenetic changes analogous to that demonstrated in the context of treatment resistance in melanoma[18]. Deep-learning-based modelling of chromatin-accessibility patterns revealed that AP-1 proteins partner with the FOX-family transcription factors FOXP1 and FOXA1 to stabilize memory-associated chromatin, with FOX recruitment depending on AP-1 proteins.

These findings invite a broader question: if AP-1-dependent chromatin remodelling occurs in response to certain cellular experiences in epithelial stem cells, how widely is this phenomenon found across tissues and cell types? Intriguingly, although AP-1 proteins have been investigated in neuronal long-term memory formation; their involvement has not been found consistently across studies[19]. This raises the possibility that related mechanisms underlie cellular memory across contexts as distinct as wound healing, cancer predisposition and cognition. If so, the ability to record[20], erase or rewrite epigenetic memories — whether in the colon, skin or brain — could be an exciting new therapeutic frontier.

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The authors declare no competing interests.