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Inflammatory memory and tissue adaptation in sickness and in health

Shruti Naik[1,2,3,4,✉], **Elaine Fuchs**[5,✉]

[1]Department of Pathology, New York University Langone Health, New York, NY, USA.

[2]Department of Medicine, New York University Langone Health, New York, NY, USA.

[3]Ronald O. Perelman Department of Dermatology, New York University Langone Health, New York, NY, USA.

[4]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA.

[5]Howard Hughes Medical Institute, Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development, The Rockefeller University, New York, NY, USA.

Abstract

Our body has a remarkable ability to remember its past encounters with allergens, pathogens, wounds and irritants, and to react more quickly to the next experience. This accentuated sensitivity also helps us to cope with new threats. Despite maintaining a state of readiness and broadened resistance to subsequent pathogens, memories can also be maladaptive, leading to chronic inflammatory disorders and cancers. With the ever-increasing emergence of new pathogens, allergens and pollutants in our world, the urgency to unravel the molecular underpinnings of these phenomena has risen to new heights. Here we reflect on how the field of inflammatory memory has evolved, since 2007, when researchers realized that non-specific memory is contained in the nucleus and propagated at the epigenetic level. We review the flurry of recent discoveries revealing that memory is not just a privilege of the immune system but also extends to epithelia of the skin, lung, intestine and pancreas, and to neurons. Although still unfolding, epigenetic memories of inflammation have now been linked to possible brain disorders such as Alzheimer disease, and to an elevated risk of cancer. In this Review, we consider the consequences—good and bad—of these epigenetic memories and their implications for human health and disease.

Adaptation is a fundamental organismal property that maximizes fitness to environmental pressures. For nearly a century, biologists, clinicians and epidemiologists have observed adaptive responses. Tobacco plants, for instance, developed systematic resistance following localized infections[1]. Bacillus Calmette–Guérin (BCG) vaccination afforded infants broad protection against tuberculosis, neonatal sepsis and viral infections[2]. Bacterial pyrogens exposure protected animals from febrile responses upon subsequent higher-dose challenge[3,4]. Children born during the 1944–1945 Dutch famine had increased life-long risk

✉**Correspondence and requests for materials** should be addressed to Shruti Naik or Elaine Fuchs, Shruti.Naik@nyulangone.org; fuchslb@rockefeller.edu.

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of weight gain, type 2 diabetes and mortality[5]. Despite decades of fascination to biologists and importance to clinicians, these events have so far lacked a molecular understanding.

As knowledge of the immune system unfolded, a cellular basis for resistance to re-infection began to emerge. The concept of 'memory', or the ability to mount more effective anti-pathogen responses upon re-infection, became a hallmark of adaptive immunity[6]. Upon infection, antigen-presenting dendritic cells select for and activate T lymphocytes with receptors that specifically recognize pathogen moieties. The humoral response is simultaneously induced by selection and maturation of antibody-producing B cells. Following clonal expansion, effector T cells are recruited to the site of infection, and plasma B cells secrete pathogen-specific antibodies to opsonize the invader and mark it for clearance. Following pathogen elimination, a small subset of potent and antigen-specific lymphocytes are maintained as an arsenal of immune 'memory' that swiftly expands and attacks the pathogen on the next encounter. These facets of adaptive memory responses have been leveraged for vaccine development with resounding success, most recently against the novel SARS-CoV-2 virus[7–10]. However, this view of immunological memory as the ability to respond in an antigen-specific manner does not explain broader non-specific responses, such as those observed in plants that survive one pathogen and acquire resistance to pathogens that they have never encountered before.

Such non-specific augmentations of host inflammatory and microbial defence responses have pointed to the view that other cellular players are involved that can respond to a diverse array of pathogens or irritants with heightened sensitivity following recovery from an initial unrelated inflammatory stimulus. Indeed, such features of inflammatory memory persist even in the absence of B lymphocytes and T lymphocytes[11].

The identification of lasting molecular and functional changes in macrophages and natural killer cells following exposure of their Toll-like receptors to microbial peptides widened the lens of immunological memory to encompass innate immune cells[12,13], which, unlike adaptive immunity, can be initiated in a non-pathogen-specific manner. Shortly after these early mechanistic insights, Netea and colleagues coined the term 'trained immunity' to describe inflammatory memory in innate immune cells[14]. Expanding the memory paradigm to cells outside the immune system, we discovered that epithelial stem and progenitor cells of the skin remember their inflammatory encounters with enduring and profound consequences for tissue fitness and function[11]. Similar reports of memory in other tissue stem cells and/or progenitors have followed[15–19], cementing the notion that long-lived tissue cells are essential proprietors of inflammatory memory.

Here we review the seminal studies that have illuminated tissue adaptation to inflammation, with a particular focus on immunological training of tissue progenitor cells. We delve into the recently unearthed cellular and molecular mechanisms that govern inflammatory memory in immune and non-immune cells (Table 1). We discuss how memory can be bestowed in the womb, enabling the developing fetus to inherit heightened protection from the exposure of the mother to a pathogen. Although such adaptations are rooted in beneficial outcomes, they can also be co-opted in inflammatory diseases and cancers (Fig. 1). We also discuss recent findings that have shown that progenitors can accumulate memories

of different kinds of experiences, with both beneficial and detrimental consequences. Finally, we discuss the open questions in the field and our perspective on therapeutically manipulating memory to boost tissue health and mitigate disease.

Innate tolerance and trained immunity

Inflammatory adaptations in innate immune cells can either augment secondary responses (immune priming or trained immunity) or dampen them (tolerance) to ensure host fitness[4,20]. A landmark study by Medzhitov and colleagues explored the molecular basis of these phenomena by examining macrophage responses to bacterial lipopolysaccharide (LPS)[12]. Interestingly, pro-inflammatory genes, for example, *Il6*, displayed a 'tolerizing' behaviour, losing active chromatin marks at their promoters and displaying dampened transcription following a second LPS exposure. By contrast, antimicrobial genes displayed a 'priming' behaviour, with heightened expression upon LPS restimulation. This augmented transcriptional response was attributed to a more rapid recruitment of RNA polymerase II to primed gene promoters.

The gene priming response uncovered by Foster et al. was later termed 'trained immunity', and has now been studied extensively in the context of pathogen challenge and/or inoculation with pathogen-associated molecular patterns, such as LPS and β-glucan[21,22]. However, in vitro-generated macrophages and circulating blood monocytes only survive for a few days. Thus, works examining memory in such short-lived cells did not explain clinical and epidemiological observations that innate training could sometimes last months and even years[5,23].

The longer lifetimes of tissue-resident macrophages over circulating monocytes provided the avenue needed for researchers to show the lasting effects of priming. Chen et al. found that the effects of a worm infection persisted for 45 days in resident lung macrophages and were even retained upon macrophage transfer to naive mice[22]. Similarly, Yao et al. found that memories induced by adenovirus infection lasted for about 1 month in tissue-resident alveolar macrophages[24]. Other tissue-resident immune cells (for example, innate lymphoid cells) can also be trained to more robustly proliferate and produce inflammatory cytokines during a pathogen re-challenge that occurs months later[25] (Fig. 1). Overall, these studies pointed to the view that longer-lived cells may be essential proprietors of prolonged inflammatory memory.

Haematopoietic stem cells and their multipotent progenitors in the bone marrow give rise to myeloid and lymphocyte lineages throughout our lifetimes. Indeed, the mystery of how innate training outlasts the short lifespans of macrophages and monocytes was solved by examining their long-lived predecessors. A series of elegant studies reported that BCG vaccination or β-glucan conditions bone marrow-dwelling haematopoietic progenitors, skewing their fate towards myeloid lineages with heightened antimicrobial activity[17,26,27] (Fig. 1). Remarkably, BCG protection was even conferred to unvaccinated mice receiving bone marrow-derived macrophages from BCG-conditioned mice, underscoring the ability of long-lived progenitors to pass on their inflammatory training to their progeny[17].

Calorie-laden western diets also elicit potent inflammatory responses. This becomes exacerbated when a high-fat diet is administered to mice lacking the low-density lipoprotein receptor (*Ldlr*) gene, a well-known atherosclerosis susceptibility locus. Correspondingly, these mice display reprogramming of granulocyte–monocyte progenitor cells via sensing of oxidized LDL by the NLRP3 inflammasome, a key trigger linking diet-induced inflammation to innate immune priming[16]. Even after returning to standard chow, mice previously fed a western diet retained higher numbers of circulating monocytes and granulocytes with enhanced responses to secondary stimuli such as LPS.

The question of how long inflammatory memory and pathogen protection can be maintained remains. Given their ability to convey information across generations, our germ cells are perhaps the longest lived cells in the body. Transgenerational epigenetic inheritance and pathogen avoidance behaviour is well documented in *Caenorhabditis elegans*, but then again, the lifespan of these worms is only 20–30 days[28,29]. Although paternal transference of trained immunity was recently reported in mice infected with one of a number of different pathogens, a follow-up investigation did not observe the transfer of innate memory across generations, for reasons still unclear[30,31]. Although such Lamarckian inheritance of immune priming remains hotly debated, the above studies suggest that the persistence of inflammatory training in the haematopoietic lineage may be critically dependent on the lifespan of the cell within which memory is encoded[30,31].

Memory beyond immunity

As the immune system is virtually ubiquitous to every tissue, communications between immune and tissue cells are particularly evident in barrier organs, which routinely encounter infectious and inflammatory assaults[32]. These interactions are often mediated by cytokine signals produced by activated immune cells[33]. In addition to sensing of the local cytokine milieu, non-immune cells also have the ability to sense and respond directly to microbial stimuli. Together, these concepts prompted the field to investigate the possibility that trained immunity, that is, the epigenetic memories that cells retain from their inflammatory experiences, may not be restricted to haematopoietic cells.

Venturing into this arena, we learned that when the skin is transiently exposed to imiquimod, an acute inflammatory stimulus that activates a type 17 immune response resembling psoriasis, their subsequent ability to heal wounds heightened[11]. As re-epithelialization during wound repair depends on epidermal stem cells, we consequently investigated and found that they can develop epigenetic memories of their inflammatory experiences. They do so by retaining chromatin accessibility at a cohort of inflammation-induced genomic loci, long after the inflammation had subsided, and transcription had largely returned to baseline. These accessible ‘memory domains’ are recalled upon a secondary assault, when their associated genes were rapidly re-activated.

Recently, it has been discovered that in addition to stimulus-elicited stress responses, for example, T helper 17 cell-induced inflammation, epithelial stem cells also have the capacity to remember their previous microenvironmental experiences, cellular identities and functions[34]. Stem cells that are responsible for generating hair, for instance, can move out

from their niche in the hair follicle and repair the compromised epidermal barrier while also remembering their origin, remarkably retaining the capacity to make hair even after acquiring their new epidermal identity.

The emerging roles for immune–tissue stem cell interactions heightened the interest that lasting memory in non-immune cell progenitors may also underlie inflammatory adaptations in other tissues. Indeed, the concept of inflammatory memory has recently been extended to the nasal, intestinal and pancreatic epithelia[15,18,35,36]. Memory-like states have also been described following muscle injury[37]. Transient inflammatory exposure protected pancreatic acinar cells from subsequent damage and limited the release of caustic pancreatic enzymes into the parenchyma[35]. Thus, in addition to barrier tissues, the epithelial boundaries of our internal secretory organs are also bolstered by inflammatory education, which is leveraged to contain tissue damage.

In the past 2 years, the importance of inflammatory memory in epithelial tissues has reached new heights. In a remarkable study, Belkaid and colleagues discovered that during pregnancy, exposure to discrete infection elevates circulating levels of IL-6, triggering inflammatory memory within IL-6R-expressing fetal intestinal epithelial cells[18]. Although exposure to circulating maternal IL-6 was transient, the ensuing inflammation-induced epigenetic rewiring of fetal intestinal epithelium persisted to adulthood. As a result, inflammation-primed offspring exhibited enhanced protection against *Salmonella* infection.

The means by which inflammatory memory can be passed on to offspring provide insight into observations made on the Dutch famine of 1944, when children born during but not post-famine showed predisposition to metabolic diseases[5]. Thus, a picture is emerging in which a cell must directly experience injurious, inflammatory mediators or microbial stimuli to be entrained, and if that cell is a progenitor, it is able to pass on its education to its progeny. These stimuli may be experienced at the site of damage or via systemic dissemination of mediators.

A major question still unanswered is just how long inflammatory memory in non-immune cells can last. Studies on laboratory mice have suggested that epigenetic memories can last for months. But, it is important to note that laboratory mice are reared in relatively sterile conditions and largely shielded from the myriad of environmental stressors that might otherwise augment or attenuate a memory of exposure to a pathogen, wound or other inflammatory stimulus over time. In the future, studying durability and reversibility of inflammatory memory in human tissues or wild mice may provide physiological insights into these parameters.

Mechanisms of memory

Since the inception of inflammatory priming or trained immunity as a concept, its roots have been entrenched in epigenetic mechanisms encoded at the level of chromatin[12] (Table 1). Following an initial inflammatory or microbial trigger, cells modify histones and chromatin accessibility to activate transcription of inflammatory, antimicrobial and stress-associated genes. Although most of these genes return to their baseline epigenetic state shortly after

withdrawal of the stimulus, a cohort is slow to resolve H3K4me1 marks at enhancers and/or H3K4me3 marks at proximal promoters[21,38]. The chromatin also remains accessible at these associated gene loci, thereby permitting the rapid recruitment of RNA polymerase II and transcriptional activation upon a secondary trigger[11,12] (Fig. 2). How a cell decides which of the myriad genes activated during inflammation will be flagged and maintained in primed state, whether histone modifications are sufficient to maintain memory domains in an open configuration in the absence of inflammation, and what explains the broadened array of distinct secondary stimuli (micro-organisms, metabolites and injury) that is able to trigger this memory are questions that remain. Whereas the underlying principles guiding these decision-making processes have long been elusive, recent studies have begun to shed light on the answers to these questions.

In probing the nuclear machinery responsible for enhancing the H3K4me3 modifications at trained immune genes, Mhlanga and colleagues uncovered UMLILO, a long non-coding RNA[39] that, similar to the other immune genes in the locus, is upregulated upon exposure of monocytes to β-glucan. Upon gene activation, as topologically associated chromatin domains form, the immune gene promoters are brought into close proximity with UMLILO, which then directs the histone modifiers WDR5 and MLL5 to these genes, enhancing their H3K4me3 marks and heightening their sensitivity to subsequent inflammatory encounters (Fig. 2).

Histone modifications, such as H3K4me1 and H3K4me3, are generally viewed as reflections of an already open chromatin state. By contrast, there are multiple examples of transcription factors that can bind to these histone-modifying enzymes, as well as transcription factors that can act as pioneer factors to bind to nucleosomes and directly open chromatin[40,41]. In probing how chromatin accessibility is established at inflammation-trained loci, researchers have been particularly attracted to inflammation-sensing transcription factors that are activated upon exposure to cytokine or microbial stimuli. For instance, members of the STAT family are rapidly induced by JAK–STAT signalling downstream of various cytokines; NF-κB is released from its inhibitor upon TNF or Toll-like receptor signalling; and C/EBPβ levels can be elevated through one of several inflammation-associated pathways[11,38,42]. In the first such study of its kind, Sun and colleagues showed that natural killer cells activate STAT1 and STAT4 downstream of IFNα and IL-12, respectively, and that STATs are essential for the initial response that leads to the establishment of inflammatory epigenetic memory[38]. Similarly, a type 17 response in the skin leads to activation of STAT3, and this too is essential to establish epigenetic memory in epidermal stem cells[43]. Although STATs have not been implicated in β-glucan stimulation of inflammatory memory, a study on haematopoietic progenitors showed that C/EBPβ might have an analogous function in that it participates in establishing epigenetic memory in these cells[42].

Recently, Larsen et al. discovered that establishing memory requires not only a stimulus-specific factor, for example, STATs, to specify the inflammatory genes to be activated and open their memory domains de novo but also the general stress-responsive transcription factor FOS and one of its heterodimeric partners of the AP-1 family, such as JUN, to subsequently gain access, remodel the chromatin and activate transcription[43]. Once the chromatin has been opened, inflammation-independent, pre-existing transcription factors

gain access and can bind to and be retained at memory loci. Along with associated histone modifications, these pre-existing transcription factors preserve accessibility long after the inflammation and stress-responsive transcription factors are no longer present. Although keeping memory domains open is not sufficient to drive sustained transcription at most memory-associated genes, the pioneer-like factors, for example, STATs, are no longer required for FOS to gain access and reactivate transcription of memory-associated genes. In this way, memory recall can be triggered by a diverse array of general cellular stresses, most, if not all, of which trigger FOS (Fig. 2).

By harnessing an in-depth analysis of existing databases on inflammatory responses and memories across a diverse array of human and mouse cells, FOS-associated AP-1 factors surface as a likely universal component essential for memory establishment and recall[43]. Overall, these recent findings have provided a molecular explanation for why tissues and animals that survive an initial infection are often sensitized to respond more quickly and to a broader array of secondary stimuli in the next assault.

Despite these crucial inroads, many questions regarding the mechanisms of inflammatory memory remain such as how inflammatory memory is retained through cell division and differentiation and then passed on from one cell to its daughters, whether there is heterogeneity in how cells within the same or different lineages encode memory, and whether we can artificially activate memory loci to harness de facto immunity. Decoding these cell biological facets of memory may allow for the development of precise strategies to manipulate host responses to infection and injury.

Memory and maladaptation

Although playing a paramount role for host survival in the short term, many factors mediating host protection and tissue repair can in the long term, if unchecked, drive inflammatory pathologies and cancer. This Jekyll and Hyde aspect of biology is also evident when modulating inflammatory set points in cells with trained immunity. Chronic epithelial inflammatory disorders with remitting–relapsing pathologies often reoccur in the same tissue area. Psoriasis, for example, is an inflammatory skin disease that commonly manifests in flaring erythematous plaques that result from epithelial hyperproliferation[44]. Remarkably, during remission or following successful therapeutic intervention, plaques subside and the skin can look phenotypically normal. Despite achieving macroscopic resolution, transcriptional profiling of resolved skin has revealed the persistence of disease-related genes that distinguish it from healthy uninvolved skin[45]. Although epigenetic elements of trained immunity have yet to be determined in human psoriasis, psoriasis-like inflammation in mice does prime epidermal stem cells for subsequent triggers[11,43].

Similar sensitization and recurrent pathology are implicated in allergic diseases and inflammatory bowel disease[15]. Indeed, although maternal inflammatory training of intestinal stem cells protected offspring from infection, it also worsened pathology in a model of colitis[18]. The pathology of inflammatory bowel disease is driven by repeated cycles of colonic epithelial injury and repair and, ultimately, result in catastrophic breakdown of gastrointestinal function[46]. Modelling cyclical epithelial damage in vitro has been

shown to result in progressive accumulation of stem cell dysfunction, epigenetic marks at inflammatory genes and augmented expression of inflammatory mediators, culminating in regenerative failure[47]. Decline in regenerative prowess has also been observed in axolotls following repeated limb amputations[48]. The stark dichotomy between acute damage that can reinforce the repair machinery, and repetitive damage that promotes a chronic inflammatory state that hinders healing, underscores the drawbacks of using epigenetic training as an aid for tissue fitness.

Overall, too much of a good thing may in fact be harmful. It is thus tempting to speculate that the cumulative effects of inflammatory tissue damage over our lifetimes are a key driver of cellular and organismal ageing. Indeed, inflammatory factors have been linked to telomere shortening and aged tissue stem cells often accumulate epigenetic marks at inflammatory loci[49,50]. Epigenetic memories may also underlie the deleterious consequences of COVID-19 such as long COVID. Recently, it was shown that haematopoietic progenitors from patients with COVID-19 retain epigenomic alterations that are conveyed, through differentiation, to innate immune cell progenies. These changes in circulating haematopoietic progenitors vary with disease severity and can persist for months to 1 year, findings that could have profound implications for millions of survivors who have overcome the virus but are now vulnerable to secondary conditions[51]. In line with a role for haematopoiesis driving systemic maladaptive responses, a recent study has uncovered that IL-1-trained haematopoietic stem and progenitor cells in periodontal disease potentiated arthritis via hyperinflammation[52].

The link between wounding and cancer has also been long appreciated, and cancer is often referred to as a wound that never heals[53,54]. Three decades ago, chickens infected with Rous sarcoma virus were shown to exhibit normal pathology, but following injury, developed tumours along the wound site[55]. Similarly, mutant mice that heal wounds faster have also been shown to display increased sensitization to oncogenic stimuli[56,57]. More recently, it has been shown that aberrations in epithelial–immune cell crosstalk are at the roots of at least some of these connections. Thus, when the pancreas experiences simultaneous injury and KRAS oncogenic assaults, a cancer-associated epigenetic state emerges within several days that involves an acinar-to-neoplasia ‘chromatin switch’ driven by an alarmin, IL-33, produced by the pancreatic epithelial cells[58].

Narrowing in on the role of inflammatory memory and cancer susceptibility, it has been recently discovered that during a heart attack, bone marrow-dwelling monocytes are tolerized by systemic inflammatory signals, resulting in an increased susceptibility to breast cancer in mice and in humans[59]. Intriguingly, the entrained monocytes displayed immunosuppressive activity at the tumour site, allowing cancerous cells to flourish even in the presence of an immune system. Another study found that inflammatory training of tumour-generating cells themselves can also confer enhanced cancer susceptibility. Although acute pancreatitis mitigates subsequent tissue damage, it also potently predisposes acinar cells to malignant transformation upon an oncogenic assault[35,60]. Conversely, β-glucan training of monocytes boosts antitumour immune responses to pancreatic cancer, suggesting that cell compartment-specific checks and balances are in place to preserve heightened responsiveness and limit adverse consequences of inflammatory memory[61]. Finally, similar

to links between western diet and inflammatory memory in haematopoietic progenitors[16], dietary palmitic acid, but not healthier olive oil, has been found to promote pro-metastatic epigenetic memory in oral carcinomas and melanomas[62].

Conclusions and open questions

In the past 5 years, we have come to appreciate that long-lived cells within tissues remember their experiences and can harness them in manners that are either beneficial (anti-pathogen and pro-repair) or detrimental (inflammatory disease and cancer) to the host (Fig. 1). Thus, the ability to tune tissue responses via their long-lived cells could be a promising means of boasting health and mitigating disease. Manipulating cellular memories, however, requires detailed context-specific maps of memory in different human cell types and following various stimuli, akin to the Human Cell Atlas[63].

Tissues are composites of epithelial, mesenchymal, endothelial, neuronal, immune, microbial and other cells that collectively experience health and disease. Although memory has been examined in individual cell types, largely focused on long-lived immune and epithelial cells, the relative contribution and cooperation of inflammatory training of different cellular compartments within a given tissue is unclear. In addition, it is interesting to consider that dysbiosis of the maternal gut microbiome along with an altered inflammatory milieu that results from infection, altered diet or stress during pregnancy may trigger epigenetic memory within the growing fetus[18], and also systemically signals to affect brain development and neuronal behaviour in the offspring[64–66]. Like many tissue stem cells, the longevity of neurons makes these cells ideal for storing epigenetic memories long term, potentially in partnership with microglia—the resident macrophage of the brain that is shown to respond to signals from the gut microbiota[67]. Indeed, a recent study found that neurons in the insular cortex can remember intestinal inflammation and, when selectively reactivated, are sufficient to drive inflammation[68]. In the future, it will be interesting to follow advances in this arena, particularly with mounting evidence linking Alzheimer disease to inflammation and microglial dysfunction[69].

Many studies on laboratory mice have used tissue injury models as a proxy for interrogating inflammatory memory, linking anti-pathogen and inflammatory responses to reparative programs. However, tissue injury and subsequent repair are complex processes, in which damaged-induced responses that evoke tissue memory may underlie broad physiological adaptations. Exploiting this complexity, it has recently been discovered that following a skin wound, entrained epithelial stem cells accumulate and retain distinct epigenetic memories of their diverse experiences, which collectively improve upon their functionality and resilience (cell-fate plasticity, wound repair and protection against infections)[34].

Throughout our lifetimes, our bodies are exposed to a plethora of different inflammatory and injurious triggers. Central to this issue will be our understanding of epigenetic memories in the context of human physiology and their longevity within different cellular players. In this regard, it will be important to see whether other cell types besides epithelial stem cells store memories of their distinct experiences and if so, whether they too can selectively engage memories to suit new challenges. The issue is a critical one; although cumulative

memories have attractive implications for enhancing tissue fitness, diverse and cumulative memories are also likely to contribute to maladaptive consequences such as chronic inflammatory diseases and cancer. In the future, understanding how distinct memories are compartmentalized and selectively recalled might provide valuable inroads for developing therapeutic strategies to harness the good memories and erase the bad ones.

In closing, despite the explosion of research in this field, there is still much to be learned about the epigenetic memories that long-lived cells of our tissues acquire when they encounter stress. Given the dramatic changes in our exposome that result from shifts in climate, such as pollution, and new pathogens, such as allergens, decoding the details of environmental imprinting provide insights into the evolutionary trade-offs between heightened tissue fitness and susceptibility to chronic disease.

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Competing interests

S.N. is on the scientific advisory board of Seed Inc., is a consultant for BiomX and receives research funding from Takeda Pharmaceuticals. E.F. has recently served on the scientific advisory boards of L'Oreal and Arsenal Biosciences, and owns stock options for Arsenal Biosciences.

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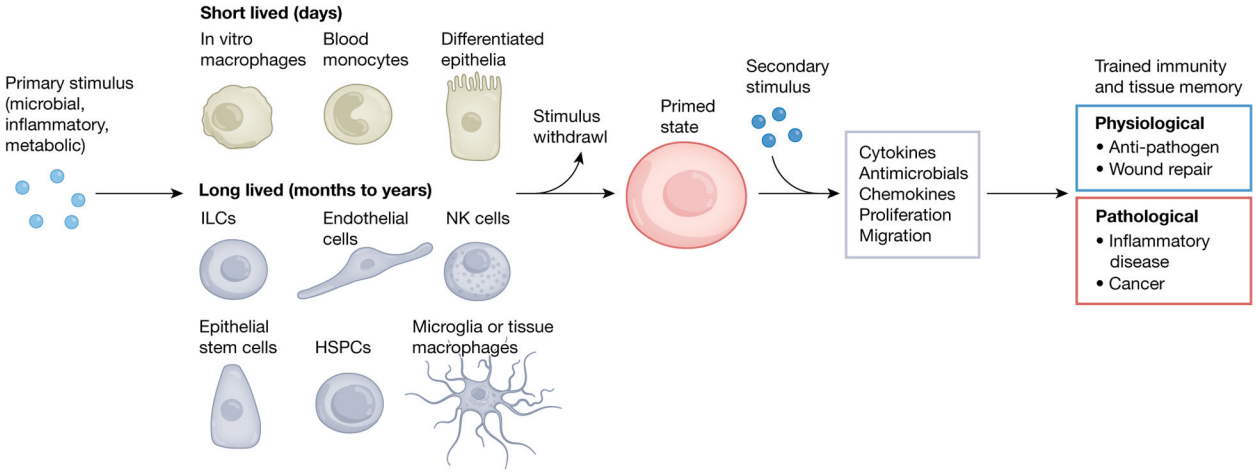

Fig. 1 |. Overview of inflammatory and tissue memory.

Short-lived and long-lived cells in our tissues sense and response to inflammatory, metabolic and microbial stimuli and maintain a state of alertness even after withdrawal of the initial stimuli. Primed cells are able to respond more rapidly to secondary triggers, which provide anti-pathogen and pro-repair functions. When unchecked, these same primed cells can fuel inflammatory pathologies and give rise to cancers. HSPC, haematopoietic stem and progenitor cell; ILC, innate lymphoid cell; NK, natural killer.

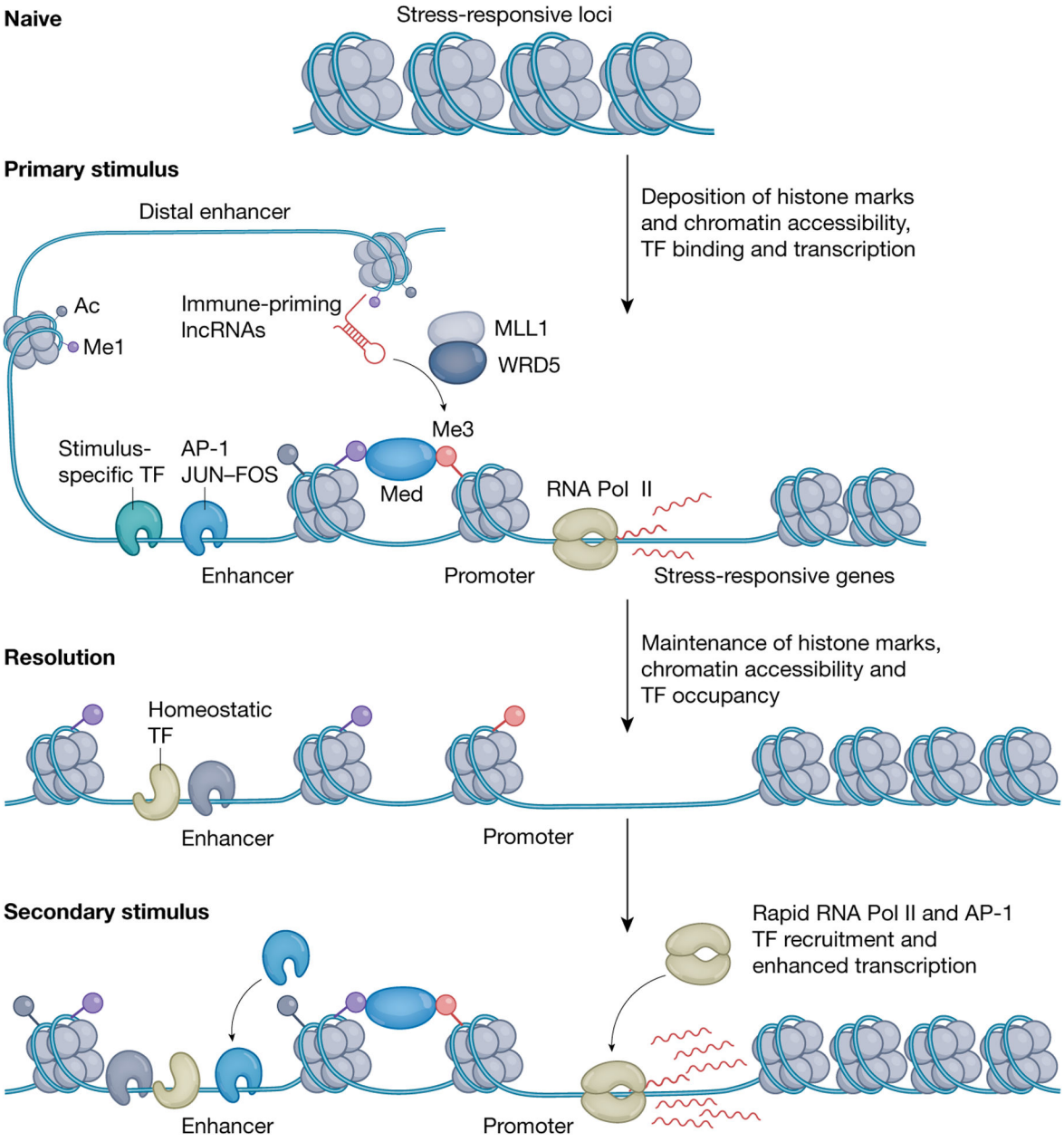

Fig. 2 |. Mechanisms of memory.

Following a primary stimulus, a subset of stress-responsive loci—'memory domains'—located within distal (enhancer) regions of key inflammatory memory genes, are opened. Accessibility is made possible through stimuli-specific transcription factors (TFs) that have the ability to recognize and bind to their motifs in otherwise closed chromatin. Once the memory domain is accessible, the broad stress-responsive TF FOS, which heterodimerizes with other AP-1 family members (for example, JUN), gains access along with several homeostatic TFs that also have binding motifs within these domains. During this inflammatory phase, certain immune-priming, long non-coding RNAs (lncRNAs) are transcribed, binding to the Mediator complex (Med), which topologically brings together the stimuli-activated enhancers with their gene promoters to initiate RNA polymerase II (Pol

II)-mediated transcription. Both TFs and lncRNAs can bind to and recruit histone modifiers, in particular, H3K4me1 at enhancers and H3K4me3 at promoters. Once inflammation and stress have subsided, while stimuli-specific TFs, FOS and lncRNA expression wanes, homeostatic TFs and these histone modifications keep memory-associated genes primed, but largely transcriptionally inert. In this open memory state, the TF FOS, activated by a diverse array of stresses, can then operate independently of chromatin-opening ‘pioneer-like factors’ to rapidly recall memory-associated transcription at memory-associated genes. Ac, acetylation; Me, methylation.

Table 1 |

How long memories last

Cell type	Refs.	Species	Model	Stimuli	Duration tested	Proposed cellular mechanisms
Immune cells						
Bone marrow-derived macrophages	12	Mouse	In vitro	Toll-like receptor ligands, metabolites and cytokines	Days	Altered histone acetylation and accessibility; rapid recruitment of RNA polymerase II; or loss of chromatin accessibility (tolerance)
Tissue-resident macrophages and microglia	19,22,24	Mouse	In vivo	Bacterial and worm infection, LPS and cytokines	Weeks to months	Retention of H3K4me1 and H3K4me3 marks; or loss of chromatin accessibility (tolerance)
Monocytes	21,23,39,59	Mouse and human	In vivo and ex vivo	*Candida albicans* infection, LPS, β-glucan and myocardial infarction	Days to week	Enhanced differentiation to macrophages; retention of H3K4me1 marks at distal regulatory regions; loss of NF-κB-associated genes and heightened inflammasome activity; immune gene priming long non-coding RNA-mediated H3K4me3 epigenetic priming
Haematopoietic progenitors	17,27,52	Mouse and human	In vivo and ex vivo	Western diet, LPS, β-glucan, COVID-19, experimental periodontitis and cytokines	Weeks to 1 year	Enhanced differentiation/myelopoiesis; C/EBP-dependent chromatin accessibility; retention of histone marks at promoters (H3K4me3) and enhancers (H3K4me1)
Natural killer cells	13,38	Mouse	In vivo	Murine cytomegalovirus	Days to months	Self-renewing memory populations; pSTAT4-mediated chromatin remodelling at distal enhancers
Innate lymphoid cells	25	Mouse	In vivo	*Citrobacter rodentium* infection	Days to month	Metabolic rewiring and enhanced oxidative phosphorylation
Non-immune cells						
Skin epithelial stem cells	11,34,43	Mouse	In vivo	Imiquimod, TPA, *C. albicans* infection and wound	6 months or more	pSTAT3 and FOS–JUN co-establish chromatin accessibility at memory domains, allowing stem cell transcription factors and histone modifiers to maintain the open state long after inflammation has subsided. In memory recall, pSTAT3 is dispensable, as its primary function is to select target genes and open the chromatin at memory sites. FOS is still required for memory recall and transcriptional activation. FOS readily gains access to these open memory domains, explaining why a diverse array of secondary stresses can trigger epigenetic memory
Intestinal epithelial cells	18	Mouse	In vivo	Maternal *Yersinia pseudotuberculosis* infection	6 weeks or more	IL-6–pSTAT3-mediated epigenetic reprogramming; altered tissue type 17 responses independent of microbiota
Nasal epithelial stem cells	15	Human	Ex vivo	Allergic inflammation	Days (following culture)	Altered chromatin accessibility
Muscle stem cells	37	Mouse	In vivo	Muscle injury	Concomitant effect on distal stem cells	mTOR activation and enhanced responsiveness to injury
Endothelial cells	39	Human	In vitro	TNF	Days	Altered chromatin topology; immune gene priming long non-coding RNA-mediated H3K4me3 epigenetic priming
Pancreatic epithelia	35,58,60	Mouse	In vivo	Caerulein	28 days	IL-6–pSTAT3-mediated epigenetic reprogramming

Cell type	Refs.	Species	Model	Stimuli	Duration tested	Proposed cellular mechanisms
Schwann cells	62	Mouse	In vivo	Palmitic acid	14 days	Retention of H3K4me3 marks
Spermatozoa	30	Mouse	In vivo	Paternal *C. albicans*	Intergenerational (F1)	DNA methylation in immune gene loci

Current literature on trained immunity and epigenetic memories of inflammation, including studies on both immune and non-immune cell types. For each cell type, the collective literature has been compiled and the references provided. TPA, tetradecanoylphorbol acetate.