Inflammatory Memory in Chronic Skin Disease

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Inflammation is a hallmark of remitting-relapsing dermatological diseases. Although a large emphasis has been placed on adaptive immune cells as mediators of relapse, evidence in epithelial and innate immune biology suggests that disease memory is widespread. In this study, we bring to the fore the concept of inflammatory memory or nonspecific training of long-lived cells in the skin, highlighting the epigenetic and other mechanisms that propagate memory at the cellular level. We place these findings in the context of psoriasis, a prototypic flaring disease known to have localized memory, and underscore the importance of targeting memory to limit disease flares.

Keywords: Epigenetics, Inflammatory memory, Psoriasis

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INTRODUCTION

The skin, our body's largest and outward-facing organ, serves as a physical barrier against terrestrial threats. In addition, an immunological arsenal of innate and adaptive immune cells actively patrols the skin to reinforce the physical barrier (Kobayashi et al, 2019). As such, injurious, infectious, noxious, and other external dangers that disrupt this barrier elicit potent inflammatory reactions. Owing to its large immunological footprint, the skin is also a predominant site of inflammatory and autoimmune diseases such as psoriasis (PsO), atopic dermatitis, cutaneous lupus, hidradenitis suppurativa, and alopecia areata (Guenin-Mace et al, 2023). These chronic conditions are rooted in aberrant immune activation and tissue damage and dysfunction. Although the etiology and pathology of these different conditions vary drastically, they share a pattern of a remitting-relapsing disease course. Molecular and immune profiling studies have revealed causal inflammatory factors in disease pathogenesis (Brunner et al, 2018; Ghoreschi et al, 2021). These foundational discoveries have led to the development of frontline precision biologic therapies targeting type-17 cytokines IL-17 and IL-23, type-2 cytokine IL-4, and general inflammatory cytokine TNFα, which drive histological and clinical resolution (Ghoreschi et al, 2021; Griffiths et al, 2021; Paller et al, 2022). Yet, long-term cures for chronic inflammatory skin diseases remain elusive. The highly regional recurrence of flares has spurred the hypothesis that relapse and chronicity are mediated by a locally encoded disease memory (Cheuk et al, 2014; Suárez-Fariñas et al, 2011). Focusing on PsO, a prototypic chronic immune-mediated skin disease, we discuss the present understanding of immune memory that may underlie long-term disease pathogenesis (Lowes et al, 2007). This emerging paradigm memory extends beyond adaptive immunity and underscores a functional alteration in the responsiveness of both innate immune and nonimmune cells between primary and secondary challenge. In so doing, we propose that targeting tissue memory is a potential path from repressive therapies to long-term cures.

PsO: A PROTOTYPIC INFLAMMATORY SKIN DISEASE WITH REMITTING-RELAPSING PATHOLOGY

Among the most common inflammatory skin conditions, PsO is driven by immune hyperactivation and epidermal pathology that result in the formation of scaly, red lesions or plaques. PsO can occur anywhere on the body but frequently presents on the scalp, trunk, elbows, or knees (Castillo et al, 2023). Genome Wide Association Studies have identified key loci associated with the disorder located in immune-related loci such as the major histocompatibility complex as well as epidermal-specific factors such as *Tp63* (Yin et al, 2015). Beyond genetics, the molecular pathogenesis of PsO has been traced to hyperactivated type-17 cells and the cytokine IL-17 that signals into epithelia, neurons, and other cell types resulting in pathological dysregulation. Indeed, the success of secukinumab, an IL-17A inhibitor, in clinical trials underscores the key role of type-17 cells in disease pathogenesis (Furue et al, 2020; Langley et al, 2014). However, even patients on frontline biologic therapies relapse after discontinuation of treatment (Figure 1) (Huang and Tsai, 2019; Warren et al, 2021). Thus, PsO is a recurring inflammatory condition, with location-specific persistence that can reactivate to cause flares. In the following sections, we discuss both canonical immune memory in adaptive and innate immune cells as well as emerging findings of memory in nonimmune cells and bone marrow–dwelling immune progenitors.

ADAPTIVE IMMUNE MEMORY

Memory and specificity have long-been hallmarks of the adaptive immune system. Clonal populations of B and T cells

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Abbreviations: AP-1, activator protein-1; HFSC, hair follicle stem cell; ILC, innate lymphoid cell; IMQ, imiquimod; IPL, immune gene-priming long noncoding RNA; lncRNA, long noncoding RNA; LPS, lipopolysaccharide; PsO, psoriasis; PTM, post-translational modification; STAT, signal transducer and activator of transcription; TF, transcription factor; Th17, T helper 17; Treg, regulatory T cell; Trm, tissue-resident memory

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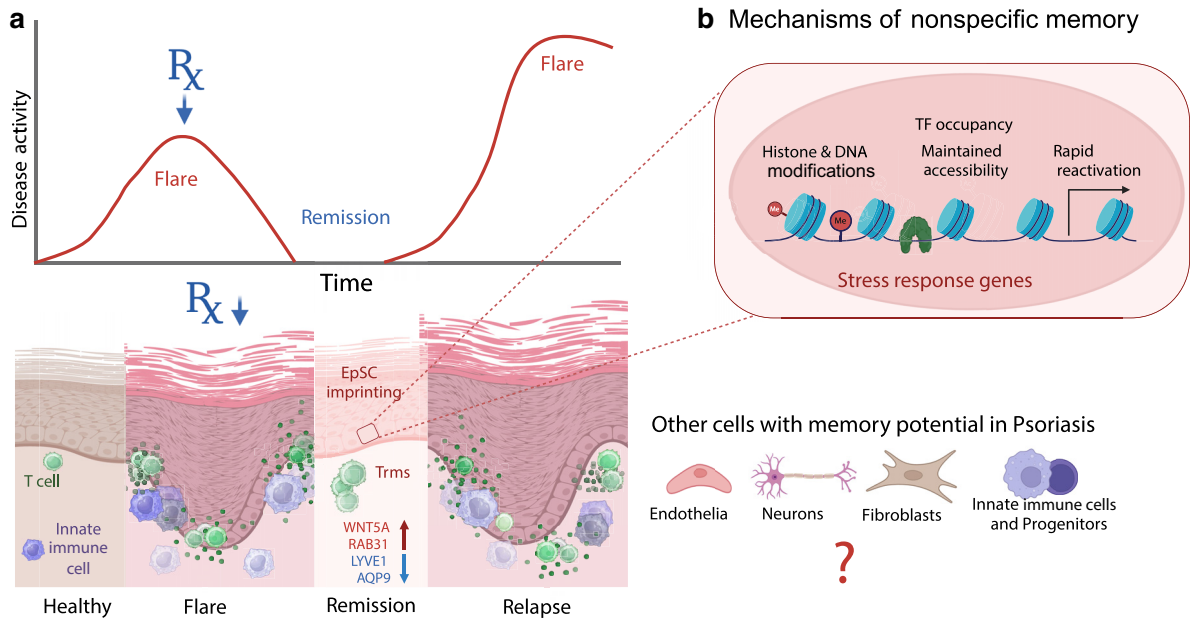

Figure 1. Cellular and molecular memory of skin inflammation. **(a)** Depiction of psoriatic disease activity over time: transitioning between healthy, inflamed, remission, and relapsed skin. Increase of type-17 immunity and presence of innate and adaptive immune cells are apparent in inflamed skin. With treatment (denoted as Rx), the skin enters remission. Postlesional skin maintains higher proportion of Trm cells and changes expression of certain genes (marked in red and blue). **(b)** Depiction of molecular mechanisms that have been shown to mediate inflammatory memory in EpSC and in the innate immune system. Depicted at the location of a stress response gene, histone and DNA methylation, changes in chromatin accessibility, and persistent TF occupancy maintain inflammation-primed cells in a poised state. Below are other nonimmune cell types involved in cutaneous inflammatory disorders that have memory potential in psoriasis. EpSC, epithelial stem cell; TF, transcription factor; Trm, tissue-resident memory.

activate and expand in response to cognate antigens and go on to form long-term memory. A role for cognate T-cell sensing of antigens is underscored by a 10-fold increase in susceptibility to PsO in patients with HLA-Cw6 (Gudjónsson et al, 2002). Yet, the precise contribution and clonality of T cells in PsO are not fully understood. Instead, the field has functionally phenotyped T-cell subsets in the skin and circulation during and after disease.

Focusing on T-cell memory, we now appreciate that there are many different locations for memory cells to patrol, including in systemic circulation through blood and lymph. A detailed discussion of T-cell memory subsets is well-beyond the scope of this review and can be found in the study by Sun et al (2023). Pertinently, tissue-resident memory (Trm) cells are nonrecirculating cells that persist in epithelial barriers such as the skin and have been observed in postlesional or resolved psoriatic skin (Figure 1) (Gaide et al, 2015; Gebhardt et al, 2009; Jiang et al, 2012). Residing at the frontlines, Trm cells rapidly reactivate at the pathogen encounter site and provide site-specific protection but are also heavily implicated in inflammatory and autoimmune diseases (Clark, 2015). The earliest evidence of Trm cell involvement in PsO came from a demonstration that nonlesional skin from human patients with PsO could produce psoriatic lesions when grafted onto immunodeficient mice (Boyman et al, 2004). Conversely, patients who were treated with anti–E-selectin antibody to limit infiltration of T cells from blood to the skin had no improvements in disease severity (Bhushan et al, 2002).

A landmark study from the Krueger laboratory evaluated resolved lesions from patients after anti-TNFα (etanercept) therapy in an effort to uncover lingering memory after inflammation in the skin. Transcriptomic analysis of whole skin revealed sustained expression of type-17 cytokines *IL17*, *IL22*, *IL12p35*, and *IFNG*, underscoring the persistence of T-cell memory in skin lesions (Suárez-Fariñas et al, 2011). In addition, genes from nonimmune cells—*LYVE1*, *AQP9*, *WNT5A*, and *RAB31*—were altered in postlesional skin. We will discuss these findings and their implications further in the inflammatory memory in nonimmune cells section below. A subsequent study demonstrated that resolved psoriatic lesions were enriched for both T helper (Th)17 and Tc17 ($CD8^+$ IL-$17A^+$ T cells) cells, effector subsets elicited by both commensal microbes and pathogenic infections (Cheuk et al, 2014; Hurabielle et al, 2020; Naik et al, 2015). In addition, an increased Th17/regulatory T cell (Treg) ratio has been shown to be linearly correlated with Psoriasis Area and Severity Index score because fewer T cells differentiate into memory regulatory cells in PsO (Priyadarssini et al, 2016). Nonregulatory memory T cells in postlesional skin are both capable of producing cytokines after ex vivo CD3 activation and enriched for specific T cell receptor clones (Gallais Sérézal et al, 2018; Matos et al, 2017). Importantly, stratification of the IL-17 tissue response after CD3-mediated T-cell activation predicted early relapse after UVB treatment (Gallais Sérézal et al, 2018). Although the enrichment of Th17 and Tc17 cells in postlesional skin makes a strong argument for their role in relapse, the mechanisms of their

site-specific localization remain unclear. Indeed, Th17 can recirculate in and out of skin, and yet they seem to linger in postlesional skin (Klicznik et al, 2019). It is thus tempting to speculate that the postlesional microenvironment specifically recruits and sustains effector T cells. Future studies examining the tissue-intrinsic mechanisms through which resolved lesions promote Trm cell persistence could inform novel points of intervention.

The role of T-cell memory in cutaneous inflammatory relapse is paramount, and much remains to be discovered. Understanding the interactions between T cells and other nearby cells, such as epithelia, endothelia, or fibroblasts, in the postinflammatory environment could uncover novel pathways of disease relapse and offer a target for erasure of cellular memory in the tissue. For instance, how the Trm cell niche changes with inflammation to promote the persistence of these inflammatory effectors remains entirely unknown.

Looking beyond resident memory cells, other lymphocytes can also be primed by inflammation. Type-3 innate lymphoid cells (ILCs), which produce type-17 cytokines, can also be entrained but in a nonspecific manner to promote long-term intestinal defense (Serafini et al, 2022). The role of ILCs and γδT cells in promoting murine models of PsO is widely accepted and attributed to an enrichment of these cells in mouse skin, compared with those in humans (Pantelyushin et al, 2012). Yet, how innate-like lymphocytes, including ILCs, γδ T cells, mucosal-associated invariant T cells, and others, contribute to human PsO pathogenesis and relapse is not understood. Just as effector T cells have heightened activity during inflammation, so do Tregs exhibit enhanced suppressive function to limit exuberant responses. However, in contrast with effectors, Tregs do not maintain a memory of their suppressive function and return to baseline (Van Der Veeken et al, 2016). Although a loss of tolerance in particular Tregs has been proposed as a key feature of disease onset, the role of Tregs and their inability to encode memory in disease relapse remain opaque. Understanding not just the dynamics of Trm cells but also of Tregs over the course of remission and relapse will provide critical insights into this open question.

INNATE IMMUNE MEMORY

Although cognate memory is a hallmark of the adaptive immune system, we now appreciate that cellular memory is also encoded within the innate immune system. Nonadaptive memory was first unveiled by studying tobacco plants, organisms without an immune system (Conrath, 2006). This memory is nonspecific, and in the innate system, vaccination to a particular antigen protects against heterologous infections, highlighting the adaptability of the innate immune system. In 2007, the Medzhitov group first pinpointed a mechanistic basis of this memory in macrophages that were tolerized by lipopolysaccharide (LPS) stimulation (Foster et al, 2007). This pioneering study demonstrated that LPS signaling resulted in long-lasting epigenetic modifications at inflammatory genes, restraining responses of tolerized macrophages to secondary LPS stimulus. Shortly thereafter, a similar innate-like memory was uncovered in natural killer cells, ILCs with cytotoxic ability, which conferred protection from repeated infections with cytomegalovirus infection (Sun et al, 2009). Similarly, RAG1-deficient mice that lack adaptive immunity exhibited heighted protection to repeated fungal challenges (Quintin et al, 2012). Protection from rechallenge was traced to epigenetic changes in monocyte populations, which led to an increase in inflammatory gene production with repeated triggers.

More recent work has highlighted that long-term memory (months to years) in the innate immune system is conferred by epigenetic training of precursor populations. Hematopoietic stem cells and myeloid precursors give rise to inflammatory progeny that better controls infection (Kaufmann et al, 2018). Indeed, such training of progenitors is critical for vaccine immunity but can also confer long-term changes in immune function. For instance, training of hematopoietic progenitors after SARS-CoV-2 may underlie facets of long-COVID–associated immune dysfunction (Cheong et al, 2023). Such long-term alternations in hematopoietic progenitors in the bone marrow have a profound implication for chronic diseases across the body. Myocardial infarction increases the rate of tumor growth through innate immune programming in a mouse model of breast cancer that is epigenetically imprinted in the bone marrow (Koelwyn et al, 2020). Furthermore, training of innate immunity in the bone marrow was shown to be maladaptive by continuously producing myeloid cells with increased inflammatory preparedness, underlying inflammatory comorbidities (Li et al, 2022). Yet, the present understanding of how innate immune memory, whether in skin-resident innate immune cells or their bone marrow–dwelling progenitors, contributes to recurrent disease or development of systemic comorbidities in PsO remains an open question.

INFLAMMATORY MEMORY IN NONIMMUNE SKIN CELLS

The study of how inflammatory onslaughts imprint our immune system has been the focus and basis of understanding immunological memory. Cells outside the immune system act as immune and damage sensors and play key roles in tissue remodeling, disease, and repair. Indeed, experimental data from the past 7 years have revealed that cells outside the immune system, not from hematopoietic origins, are also capable of remembering inflammatory stress. Perhaps the most widely studied cell type in this context is the epithelial stem cell, which sustains the epidermis throughout our lifetime.

The skin epithelia and their stem cell predecessors play an active role in inflammatory processes, acting as microbial and damage sensors, immune recruiters, and wound healers (Naik et al, 2018). Given their well-appreciated role as liaisons of immunity, we and others sought to examine epithelial stem cells as possible reservoirs of inflammatory memory (Naik and Fuchs, 2022). The first report of memory in epithelial stem cells came from an acute mouse model of psoriatic-like inflammation where mice were treated with imiquimod (IMQ), a toll-like receptor 7 agonist. Thirty or even 180 days after resolution of inflammation, mice that had previously been exposed to IMQ displayed a dramatic increase in wound-healing capacity compared with their naïve counterparts (Naik et al, 2017). This memory was rooted in persistent changes to chromatin accessibility at key stress response genes, allowing for their rapid reactivation upon a

heterologous secondary stimulus, in this case, a wound (Figure 1b). Epigenetic regulation of inflammatory memory in nonimmune cells enables rapid nonspecific reactivation of stress response genes, a stark contrast to the DNA-encoded specificity of the adaptive immune system. Yet, how these regions precisely maintained accessibility in postinflamed stem cells remained an open question. In a follow-up study, Larsen et al (2021) demonstrated that certain activator protein-1 (AP-1) transcription factor (TFs) units, JUN and FOS, maintain residence to index these regions and are rapidly recruited during a secondary response for reactivation. In addition to inflammatory stimuli, epithelial stem cells also are able to remember their origins. For instance, stem cells from the hair follicle could migrate to the epidermis to heal wounds but, when transplanted, were able to generate hair follicles once again (Gonzales et al, 2021). Not only can stem cells remember their developmental origins and inflammatory experiences but also can harness these memories to exert influence over their neighbors. The Donati group uncovered that the wound-healing effect on hair follicle stem cells (HFSCs) is not limited to the stem cells that began the wound-healing process but extends out to distal hair follicles (Levra Levron et al, 2023). Despite not being in the wound bed itself, HFSCs that are located a few millimeters away harbor key regions of chromatin accessible for weeks after wounding, thus altered by neighboring inflammation.

Although these adaptive facets of memory highlight the benefits of inflammatory priming, a dark side lurks in the context of cancer. In the pancreas, mice that had endured acute inflammation were more readily able to heal after damage but had heightened tumor progression months after inflammation (Del Poggetto et al, 2021). This propensity for tumorigenesis was pancreatic acinar epithelial cell intrinsic and, similar to inflammatory training of the skin epithelia, was traced to lasting accessibility, transcriptional changes, and histone methylation in previously inflamed acinar cells (Alonso-Curbelo et al, 2021). Work in organoid models of intestinal stem cells showed increased stemness and tumorigenicity after a high-fat diet or treatment with IL-22 (Beyaz et al, 2016; Lindemans et al, 2015; Pascual et al, 2021). Similarly, dietary palmitic acid was shown to induce prometastatic features in Schwann cells in the microenvironment of squamous cell carcinoma cells (Pascual et al, 2021).

Imprinting of epithelia by inflammation can also have profound consequences for crosstalk with the immune system and development of inflammation. Inflammation-entrained epithelia are functionally distinct from their naïve counterparts, responding differently to stressors and engaging in unique crosstalk with immunity. For example, after infection of pregnant dams, the intestinal epithelia of offspring were entrained by IL-6 to maintain heightened reactivity (Lim et al, 2021). The intestines of imprinted mice had higher frequencies of inflammatory type-17 immune cells. Strikingly, this in utero conditioning lasted well into adulthood, mediating enhanced pathogen response but predisposing mice to heightened inflammation. How epithelial imprinting in the skin leads to changes in the cutaneous type-17 milieu remains a key question, particularly in the context of PsO where IL-17A–producing Trm cells are known to linger in postlesional skin (Gaide et al, 2015; Gebhardt et al, 2009; Jiang et al, 2012).

In addition to epithelial cells, other cells, including endothelia and fibroblasts, are long-lived tissue components and are known to have the potential to encode memory. Fascinating work comparing the regenerative antler skin of reindeer with scar-forming hide skin used a combination of single-cell RNA and assay for transposase-accessible chromatin with sequencing to profile the differences in fibroblasts between these 2 locations (Sinha et al, 2022). Their work uncovered an epigenetic priming in regenerative fibroblasts that limits inflammatory responses and enables full regeneration rather than scarring. Fibroblasts' involvement in various cutaneous disorders such as scleroderma, spatially defined role in vitiligo, and subtype-specific capacity for LPS tolerization underscore their omnipresence and heterogeneity (Gilbane et al, 2013; Klein et al, 2017; Xu et al, 2022). Whether or not fibroblasts have capacity for nonspecific inflammatory memory has yet to be discovered, but their cross-tissue presence, involvement in both epithelial and fibrotic diseases, and homeostatic function make them a compelling cell type to study memory and how it may alter disease.

These early examples of nonimmune memory are illustrative of the profound and widespread impact of inflammation on our tissues. Yet, the skin comprises 56 different cell types and is innervated by somatosensory neurons that reside in the dorsal root ganglion and are known to contribute to PsO pathology (Yin et al, 2022). How these different cell types are influenced by inflammation to promote relapse, either directly or by engaging immunity, is an area begging to be explored.

MECHANISMS OF MEMORY

We now appreciate that in contrast to adaptive immune memory, which is specific and encoded through genomic rearrangement of the T cell receptors and B-cell receptors, nonspecific inflammatory memory is rooted in epigenetic mechanisms. How memory is encoded and recalled is an active area of investigation, and unlocking these mechanisms could be the key to reversing the long-term effects of inflammation (D'Urso and Brickner, 2014). The findings related to epithelial cells are summarized in Figure 1b.

The Medzhitov group first identified that chromatin remodeling underpinned LPS tolerance in macrophages (Foster et al, 2007). Using chromatin immunoprecipitation, the authors observed altered histone modifications in genes whose expression was dampened by LPS (tolerized) and enhanced recruitment of RNA polymerase II to genes that were not tolerized by LPS. Years later, work began to elucidate more mechanisms of inflammatory memory and trained immunity. The Netea group demonstrated that monocytes reprogrammed after *Candida albicans* infection incurred changes in histone K3K4 methylation that correlated with the functional transcriptional changes observed (Quintin et al, 2012). Outside of the innate immune system, it was shown that in the mouse mammary gland, previously pregnant mice had altered genome-wide DNA methylation patterns compared with nulliparous mice (Dos Santos et al, 2015). In addition, in a model of fibroblast inflammatory memory after

type-I IFN stimulation, memory genes had an increase in RNA polymerase II recruitment and H3.3 and H3K36me3 chromatin marks (Kamada et al, 2018). This mechanism appeared to be conserved in macrophages stimulated with IFNγ.

Although altered chromatin accessibility, DNA methylation, and histone post-translational modifications (PTMs) predominated the mechanistic studies (Figure 1b), long noncoding RNAs (lncRNAs) were shown to be crucial to the inflammatory memory in human macrophages and endothelial cells (Fanucchi et al, 2019). Using chromatin conformation capture techniques, the authors found that H3K4me3 TNFα-primed genes are brought closer to lncRNA, the group called immune gene-priming lncRNAs (IPLs). Interactions between the IPLs and promoters of target genes, particularly chemokines, within topologically associated domains induced rapid reactivation upon challenge. Importantly, these IPLs appeared to be unique to human cells, underscoring a species-specific variation in how memory may be encoded.

TFs are sequence-specific DNA-binding factors that regulate stimulus-specific gene expression, thus connecting environmental signals to chromatin state. A number of different stimulus-specific TFs are known to induce chromatin remodeling; however, the role of TFs in indexing memory domains was described in skin epithelia (Larsen et al, 2021). Whereas the primary inflammation engaged the TFs signal transducer and activator of transcription (STAT) 3 and AP-1, presumably establishing memory along with all the other inflammation-induced changes, during resolution, JUN, ATF3, and p63 remained bound to certain regions. These bookmarked regions recruited the AP-1 subunit FOS upon secondary challenge to mediate a heightened response. Adding another layer of complexity, modifications of TFs are also associated with the formation of memory. For example, STAT1 phosphorylation at serine 727 is maintained in IFN-primed cells, indicating that PTMs of nonhistone proteins may also underlie heritable changes to cellular function (Tehrani et al, 2023).

Despite these advances, many questions remain. What is the distribution of memory across a complex tissue? Which set of genes do cells choose to remember and how? How long does memory last, particularly in human skin? Given the remitting-relapsing nature of PsO and other chronic inflammatory diseases, it is imperative to address these elusive questions.

CONCLUSIONS AND FUTURE PERSPECTIVE

Remitting-relapsing inflammatory skin disorders are widely present and have varied causes for recurrence. Groundbreaking work has demonstrated the key role of adaptive immunity in disease relapse, namely the increase in type-17–producing T cells in postpsoriatic lesional skin. Work in other fields has demonstrated the innate immune system's capacity for memory, mediated by epigenetic mechanisms, findings that were then translated to the epithelia of mouse skin. Despite these inroads, much remains unknown about inflammatory memory in cutaneous disorders. We have yet to understand each cell type's capacity for memory and whether the effects differ if the diseases are immune-mediated, epidermal-or dermal-specific, or a byproduct of a systemic disease. Furthermore, we have little to no understanding of how different epigenetic changes are enacted in various disorders and how consistent they may be. For example, what forms of memory are encoded in different inflammatory disease, such as atopic dermatitis versus PsO. Other fascinating areas that require consideration are host genetics, nutrition, disease severity, and chronicity. Indeed, many inflammatory skin disorders have systemic comorbidities that could be rooted in interorgan communication and encoding of inflammatory memory through the production of systemic mediators or recirculation of cells. Work in the pancreas and gut epithelia highlights the cross-tissue implications of studying inflammatory memory. Thus, using the skin as an exemplar for inflammatory conditions that afflict other organs may reveal both fundamental disease mechanisms and durable treatment for a wide spectrum of immune-mediated indications.

Uncovering the relationship between clinical manifestations of disease and epigenetic mechanisms of memory may enable tailored therapeutic approaches in patients. Currently, erasure of the memory phenotype in humans is not possible, hence patients' tendency to relapse after discontinuation of treatment. Targeting the post-treatment state, when symptoms have resolved, to reverse the effects of inflammation presents a formidable challenge and transformative opportunity. As the field of inflammatory memory blossoms, the next decade is sure to bring transformative advances that aim to modulate memory and rejuvenate skin health.

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CONFLICT OF INTEREST

SN is on the SAB of Seed and receives funding from Takeda Pharmaceuticals for an unrelated study. The remaining author states no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: SN, JD; Visualization: SN, JD; Writing — Original Draft Preparation: SN, JD; Writing — Review & Editing: SN, JD

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

The authors declare no use of artificial intelligence/large language model in the preparation of this article.

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