Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Inflammatory Memory in Epidermal Stem Cells - A New Strategy for Recurrent Inflammatory Skin Diseases

Qian Gao[1,2], Ping-Sheng Hao[1]

[1]Dermatology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [2]Department of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China

Correspondence: Ping-Sheng Hao, Email hpswl@126.com

Abstract: The ability of the skin to "remember" has been a potential mechanism for studying recurrent skin diseases. While it has been thought that the ability to retain past encounters is the prerogative of immune cells, it has recently been discovered that skin tissue stem cells can also take on this task. Epithelial stem cells undergoing inflammation retain their "memory" through epigenetic reprogramming and exhibit rapid epithelialization and epidermal proliferation upon secondary stimulation. This is a non-specific memory modality independent of conventional immune memory, in which histone modifications (acetylation and methylation) and specific transcription factors (AP-1 and STAT3) are involved in the establishment of inflammatory memories, and AIM2/Caspase-1/IL-1β mainly performs the rapid effects of memory. This finding is intriguing for addressing recurrent inflammatory skin diseases, which may explain the fixed-site recurrence of inflammatory skin diseases and develop new therapeutic strategies in the future. However, more research is still needed to decipher the mysteries of memory.

Keywords: inflammatory memory, recurrent inflammatory skin diseases, epigenetics, skin tissue stem cells

Introduction

The skin has the ability to remember past injuries. However, "memory" is two sides of the same coin; it plays a protective role against trauma and infection, but it can also be the cause of recurrence of inflammatory skin diseases. For example, psoriasis and fixed drug rashes, which often recur in the same tissue area.[1,2] Understanding and recognizing "memory" has always been the focus of the treatment of inflammatory skin disease flares. Previous studies have focused on immune cells such as Tissue-Resident T Cells (TRM), Langerhans Cells, and Regulatory T Cells. Some studies have demonstrated that the phenomenon of "immune memory" in immune cells is an important factor in the recurrence of psoriasis, vitiligo, pemphigus, and atopic dermatitis (AD).[3–6] However, the immune memory does not fully explain the complex mechanism of skin "memory". It has been shown that the expression of epidermal structural genes is upregulated in the "residual gene profile" of healed psoriasis skin tissues.[7,8] These studies show that the role of skin tissue cells in "memory" cannot be ignored. In 2017 Naik et al proposed in Nature that epithelial stem cells (EpSCs) "remember" primary inflammatory stimuli by maintaining a chromosomal landscape induced during inflammation, and that subsequent stimuli exhibit rapid epithelialization and epidermal proliferation, and they termed this phenomenon "inflammatory memory".[9] This finding shifts the perspective of skin "memory" from immune cells to epithelial stem cells. Recently, more and more studies have focused on the mechanisms of inflammatory memory. Inflammatory memory has now been found to be characterized by several features:1) Inflammatory memory is independent of innate and adaptive immune memory, and experiments have shown that the rate of healing of skin wounds experiencing inflammation is enhanced in the absence of immune cells.2) This memory is not specific to a particular type of inflammation, and is prevalent in models of psoriasis or atopic dermatitis, as well as in models of sterile wounds or Candida albicans infections.3) It is long lasting, at least 6 months in experimental settings. 4) Although long-lived epithelial stem cells

Received: 19 May 2024
Accepted: 24 August 2024
Published: 21 September 2024

have the ability to continuously differentiate, they retain a "memory" that has transgenerational effects. The memory effect is only present in localized EpSCs undergoing an inflammatory response and is not transmitted through the circulation, and has not been found in distal parts of the skin. 5) The root cause of inflammatory memory is the alteration of EpSCs chromatin dynamics after the inflammatory response, which belongs to epigenetic memory. These surprising findings hold the promise of unraveling the mystery of skin "memory" from the perspective of skin tissue cells, which could become a new target for the treatment of recurrent inflammatory skin diseases. Here, we review the process of inflammatory memory discovery and focus on the mechanism of inflammatory memory in epidermal stem cells, which will help us to further precise intervention in the future.

What is Inflammatory Memory

Descriptions of inflammatory memory were first found in immune cells, such as the protective effect of macrophages experiencing Staphylococcus aureus infection against Candida albicans infection.[10] Subsequently, immunological memory properties for past insults have also been described in monocytes, natural killer cells.[11,12] In 2011 Netea et al referred to the ability of innate immune cells to retain insult experience to enhance resistance to secondary stimuli as trained immunity (or innate immune memory). Presently, it is believed that training immunity occurs by experiencing semi-specific changes in the number and/or function of inflammatory immune cells, leading to increased resistance to a broad spectrum of secondary infectious agents.[13] This finding challenges the previous privileging of memory phenotypes as adaptive (acquired) immunity and expands the scope of immune memory.

In higher biology, there are two main forms of immune response, innate immunity and acquired immunity. Innate immunity is a nonspecific rapid defense mechanism that recognizes conserved pathogens through pattern recognition receptors, which are phagocytosed and lysed by innate immune cells (eg, monocytes, macrophages), and which used to be thought to lack immune memory.[14] Acquired immunity, also known as adaptive immunity, is manifested by the formation of a highly specific long-term immune memory in the form of T and B lymphocytes upon recognition of a pathogen. Upon a second attack by the same pathogen, a rapid response is induced by clonal expansion of memory T and or B cells, which is referred to as classical immune memory.[15] And these two types of immunization do not fully explain the complex immune mechanisms. For example, Bacillus Calmette-Guérin (BCG)-vaccinated mice are resistant to Candida albicans, Mycobacterium tuberculosis.[16] The proposal of training immunity complements the explanation of this nonspecific cross-protection phenomenon. Unlike classical immune memory mediated by gene rearrangements, training immunity relies on epigenetic reprogramming that induces changes in transcriptional programs and belongs to the category of epigenetic memory.[17] Innate immune cells undergo activation induced by primary stimulation, which activates gene transcription accompanied by the acquisition of specific chromatin marks (eg histone modifications). Most of these marks persist when the stimulus is removed, leaving the chromatin in a "standby state", which leads to faster and enhanced transcription of genes with specific marks upon secondary stimulation, resulting in altered physiological functions of the immune cells. NK cells recovering from CMV virus infection differ from typical NK cells in DNA methylation patterns, transcription factor levels, associated gene promoter levels, and at least 30% of the chromatin is in a state of significant accessibility, rendering these adaptive NK cells altered in their ability to secrete cytokines.[18]

Although this ability to respond more rapidly and strongly is attractive, this memory effect in short-lived monocytes and macrophages lasts only a few days or weeks, which is in contrast to epidemiologic studies that show that the nonspecific anti-infective effects of vaccines such as BCG or measles last for months or even years.[19] Some scholars have proposed that training immunity may be at the stem or progenitor cell level. Kaufmann et al found that hematopoietic stem cells cultured with BCG vaccine produced epigenetically modified macrophages that provided better protection against tuberculosis viral infection than initial macrophages.[20] De Laval et al reported that after bacterial lipopolysaccharide (LPS) exposure, hematopoietic stem cells undergo expansion and myeloid differentiation to acquire epigenetic memory and increase protective responses against the Gram-negative bacterium Pseudomonas aeruginosa.[21] This extends the scope of trained immunity to the tissue stem cell level. In 2017 by Naik et al it was proposed that epithelial stem cells "trained" by inflammation enhance anti-inflammatory capacity through epigenetic memory, the first time a non-immune cell has been found to retain inflammatory memory.[7] Subsequently, bronchial epithelial cells, microglia, and hair follicle stem cells have also been reported to have inflammatory epigenetic memory.[22–24]

Inflammatory memory mechanisms have been applied to cancer, cardiometabolic diseases, neurodegenerative diseases, systemic sclerosis, and vaccine development.[25–27]

How Inflammatory Memories are Formed

Skin responds to external stimuli through self-renewing epithelial stem cells (EpSCs) by fine-tuning gene expression - epigenetic and transcriptional reprogramming - to maintain epidermal homeostasis.[28] Epigenetic modifications synergize complex mechanisms that regulate chromatin adaptation and regulate heritable changes in gene expression through molecular interactions that affect chromosome structure and gene activity with no alterations in DNA sequence.[29] Among them, microRNAs, histone modifications, and DNA methylation regulate cell differentiation, proliferation, and apoptosis in skin tissues.[30] Epigenetic modifications play an important role in many inflammatory skin diseases, contributing to susceptibility, onset, and progression of inflammatory skin diseases by participating in the inflammatory cascade, transcription of pro-inflammatory factors, and establishment of an inflammatory setting.[29,31,32] S For example, Ghaffarinia et al found in resolved psoriasis lesions that epigenetic mechanisms may be involved in localized recurrence 34.[33] Nedoszytko et al found that the epigenome of AD patients differed from that of healthy individuals in innate immunity and epidermal structural protein genes.[34]

Naik et al used ATAC sequencing (ATAC-seq)—A high-throughput sequencing method for obtaining chromatin accessibility at the genome-wide level[35]—to analyze inflammation's alteration of the chromatin landscape of epithelial stem cells, and found that epigenetic memory exists in post-inflammatory (PI) epithelial stem cells, with >1000 peaks still maintaining the accessibility pattern (>44,000 peaks at IMQ induction 6 days).[3] Subsequently, Larsen et al built on this foundation by further analyzing and clarifying the extent of the memory domains in which epithelial stem cells retain chromatin accessibility after an inflammatory response, and defined the regions of chromatin that gained access during the inflammatory response and remained accessible after it subsided as memory structural domains.[36] Although the memory domains remain "on standby", their genes are rarely transcribed after the inflammatory response subsides. This retention of the chromatin-open state after the inflammatory response is a key mechanism for our study of inflammatory memory (Figure 1). When trauma was used as a secondary attack, this upregulated 73 (52%) of the 140 genes that were upregulated within 12h post-trauma, which were associated with ATAC seq spikes that were acquired and sustained during IMQ treatment of inflammation. This suggests that genes associated with the memory domain are rapidly transcribed during secondary attacks, which is why we see a rapid and strong response to secondary stimuli, and the memory domain is the vehicle that carries the "memories". Although RNA polymerase II (RNA Pol II) prevents

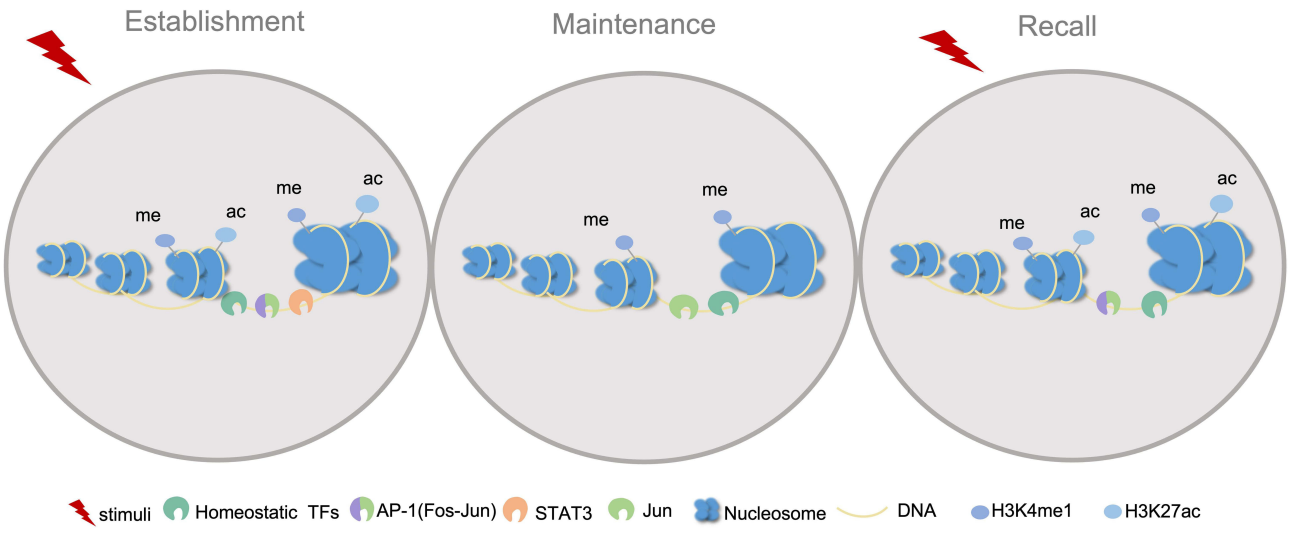

Figure 1 Mechanisms of inflammatory memory in epidermal stem cells. Epidermal stem cells undergoing inflammatory stimulation establish epigenetic memory by regulating chromatin accessibility through histone modifications (H3K4me1, H3K27ac) and the binding of specific transcription factors (AP-1, STAT3); after inflammation subsides, homeostatic transcription factors and JUN are involved in inflammatory memory; and upon secondary stimulation, FOS rapidly bind to the memory domains and reactivate transcription.

transcription and keeps chromatin open, it is not a factor in keeping the memory domains open in the PI state without active gene transcription. How then does this memory domain retain chromatin accessibility, and understanding the formation of memory domains is key to our solving this mystery.

Upon inflammation triggering, inflammation-associated chromatin undergoes histone modification, which results in a "loose" open and interrogable state of inflammation-associated chromatin, followed by the rapid recruitment of transcription factors and RNA polymerase II, resulting in the transcriptional expression of the associated genes. Using CIP-seq sequencing, it was found that H3K4me1 and H3K27ac are more strongly expressed in enhancers and promoters of genes where inflammatory memory domains are located than in non-memory regions, and >90% of memory domains are located in enhancers at the site of transcriptional initiation. H3K4me1 and H3K27ac are common histone modifications, which are often thought to be reflective of the state of the already open chromatin.[37] H3K4me1 is monomethylated on lysine (K) residues of histone H3 and is usually highly enriched in chromatin enhancer regions, suggesting that the gene is in an initiation state.[38,39] H3K27ac is acetylated on the lysine (K) residue of histone H3, and H3K27ac is enriched at promoters and enhancers of active transcribed genes, which can form large extensive structural domains, so-called super-enhancers, in the intergenic region, suggesting that the gene is in an active state.[37] Sahlén et al. By labeling H3K27ac could screen for enriched regions of differentially expressed genes and associated transcription factors in psoriasis and AD.[40] Histone modifications play an important role in the regulation of chromatin state, mainly through the deposition or removal of histone modifying enzymes, histone acetyltransferases, and histone kinases dynamically and reversibly regulating the expression of chromosomally structurally activated or silenced genes to produce different cellular functions.[41]

The effects of histone modifications on inflammatory skin diseases are focused on two main areas: immune cells and histiocytes.[42] The study showed that histone deacetylase (HDAC) is dominantly expressed in epidermal stem cells.[30] Markova et al found that histone deacetylase (HDAC) is involved in the regulation of epidermal differentiation.[43] In addition, 60% of the regions of genes overexpressed in psoriasis were detected to be significantly enriched for H3K27ac.[44] Among them, elevated levels of histone acetylation were detected in the promoter region of the IL-17A gene (an inflammatory factor characteristic of psoriasis).[45] Ovejero-Benito et al found that after treatment with biologics H3K27ac and H3K4me1 could be significantly changed in psoriatic lesions.[46]

After the inflammatory response subsided (PI), histone modifications in most inflammation-associated chromatin structural domains (except the memory domain) returned to their original state, the chromatin-accessible state was turned off, and most genes ceased transcription. However, the memory domains H3K4me1 and H3K27ac were still highly expressed, suggesting that the gene repression state H3K27me3 remained largely unchanged during and after the inflammatory response. H3K27me3 is a trimethylated lysine (K) residue of histone H3.[39] This suggests that histone modifications of memory domain-related genes persist after inflammation subsides. This phenomenon was also observed in immune cells.[16,47] Long-term persistence of some histone modifications in bone marrow cells observed after removal of the initial activating stimulus.[48] However, whether histone modifications are responsible for memory domains remaining accessible after inflammation subsides, the persistence of histone modifications may reflect the continued activation of signaling and transcription factors that control their upstream signaling, in addition to the fact that more stable modifications (histone methylation) may be better suited to maintain functional changes than modifications with the typical short half-life (histone acetylation).[18] These are critical in advancing our understanding of epigenetic transcriptional memory.

Transcription factors are also critical in maintaining chromatin in an open state and promoting transcriptional activity, binding to a number of histone modifying enzymes, as well as acting as heralds that bind to nucleosomes and directly open chromatin,[49,50] For example, AP-1 (activator protein-1 is a universally important transcriptional regulator) is required for open chromatin formation during T cell activation.[51] AP-1 has been shown to be enriched in the inflammatory memory domain of hematopoietic stem cells (HSC).[21] EpSCs undergoes an inflammatory response many key epidermal transcription factors (TFs) are involved in the transcriptional activity of inflammatory genes, like AP-1 (member of Jun, Fos, ATF), AP2γ, KLF5, ETS2, GRHL2/3, p63, as well as nuclear factor kB (NF-kB) and STAT1/3 are enriched in inflammation-related genes. However, not all of the above transcription factors are involved in the establishment of memory structural domains, in which AP-1 (Fos and/or Jun) and STAT3 were identified to be involved in the establishment of memory domains using CUT&RUN a high-resolution, high-throughput strategy for reflecting TF-DNA interactions. Both AP-1 and STAT3 are key transcription

factors in the development of inflammatory skin diseases, regulating keratinocyte proliferation, differentiation and apoptosis.[52–54] For example, in several studies it has been shown that AP-1 is an initiator of the etiology of psoriasis.[54–57] More importantly, the finding that AP-1 binds extensively to genes related to the pathogenesis of psoriasis (especially genes in terms of histopathological features) was revealed by sequencing techniques in the presence of increased chromatin accessibility.[58] In addition to psoriasis, AP-1 also plays an important role in AD lesion development.[59,60] As the most widely studied transcription factor in inflammatory dermatoses, STAT3 is directly involved in the inflammatory response to keratin formation. In epidermal keratinocyte-specific Stat3-deficient mice more severe psoriasis-like and AD-like lesions are produced.[61,62] AP-1 (Jun, Fos member) and STAT3 are strongly expressed during inflammation and are significantly enriched and bound in the memory domains, but not C/EBP, NF-kB, p63, MAF, and ETS family members (homeostatic IFs, with homeostatic roles in naive EpSCs in the absence of inflammation). If loss of AP-1 or STAT3 severely affects the accessibility of the memory domains, global chromatin remains in an accessible state. This suggests that AP-1 and STAT3 are necessary for, but not exclusive to, the "opening" of the memory domain. In addition, there is a hierarchical synergy between the two, with STAT3 playing a major role in memory domains and FOS-JUN promoting chromatin remodeling and transcription of relevant inflammatory response genes. Because in the absence of STAT3, the failure of FOS and JUN to bind and open the memory domains not only significantly attenuates chromatin accessibility on the structural domains of memory, but also attenuates the sustained transcription of genes hosted by the memory domains in the PI state (eg, genes such as Runx1, Tmprss11g, and Tnfaip2, which represent a high level of transcription that remains high long after the inflammation subsides few genes).

After inflammation subsides only JUN remains among the transcription factors STAT3, FOS, and JUN, and the static EpSCs TFs (AP1 homologs) ATF3 and P63 bind to the memory structural domain. Surprisingly, while FOS-JUN is essential for establishing the memory domain, the other homeostatic transcription factors TFs are sufficient to maintain chromatin accessibility. In the absence of JUN ATF3 was still able to bind to the ATF3-binding motifs that are prevalent in memory domains, as well as with AFOS (dominant-negative form of FOS), and memory domains remained accessible during the PI state. It is suggested that the maintenance of inflammatory memory is a joint effort of multiple homeostatic transcription factors, reflecting the complex mechanisms of organismal adaptation.

The Effector Role of Inflammatory Memory

We know that chromatin that opens after an inflammatory response retains the ability to sense tissue damage, so how does it function when faced with a secondary attack. This would explain the rapid response of cells experiencing inflammation in the face of a secondary attack. Larsen et al found that components involved in the establishment of inflammatory memory were not necessary for inflammatory memory to return.[36] In other words, the steps and components required for a cell that has already experienced inflammation to experience the inflammatory response again are reduced or different. At the time of the secondary attack trigger, the memory domain chromatin genes, which are already in the initiation state, express H3K4me1 and H3K27ac faster and more intensely, although the transcription factor STAT3 is still expressed, and FOS does not need STAT3 to redirect its homologous binding partner JUN to bind significantly to the memory domain-associated genes and rapidly activate the transcription of memory-associated genes. In the absence of STAT3, FOS was present in wound-edge EpSCs, and memory-related genes remained rapidly upregulated. This identifies a central role for AP-1 (FOS-JUN) that not only drives memory establishment and associated gene expression during the inflammatory response, but also nonspecifically controls memory return in response to secondary stimuli.

We know that rapid transcription of genes associated with memory domains is key to the protective or pathogenic utility of inflammatory memory. These genes are mainly focused on gene motif enrichment related to inflammation-regulated cytokine production, regulation of immune system processes, response to peptides, response to TGF beta, hematopoietic regulation, regulation of catabolic processes, response to insulin, and regulation of ROS metabolic processes. By pathway analysis of fast-response transcripts of memory domain-associated genes containing these chromatin elements, it was found that the transcript of the AIM2 gene, the AIM2 inflammatory vesicle, and its downstream components, caspase-1 and IL-1β, are central regulators of the memory effects of inflammation.[63] And after a series of failures to show wound repair advantage using depleted RORC populations, AIM2-deficient mice, and AC-YVAD-cmk29 (blocking CASP1) EpSCs, it was determined to show that AIM2 and its downstream effectors, CASP1 and IL-1β, are central regulators of the enhanced wound repair response in inflammatory memory skin (Figure 2).

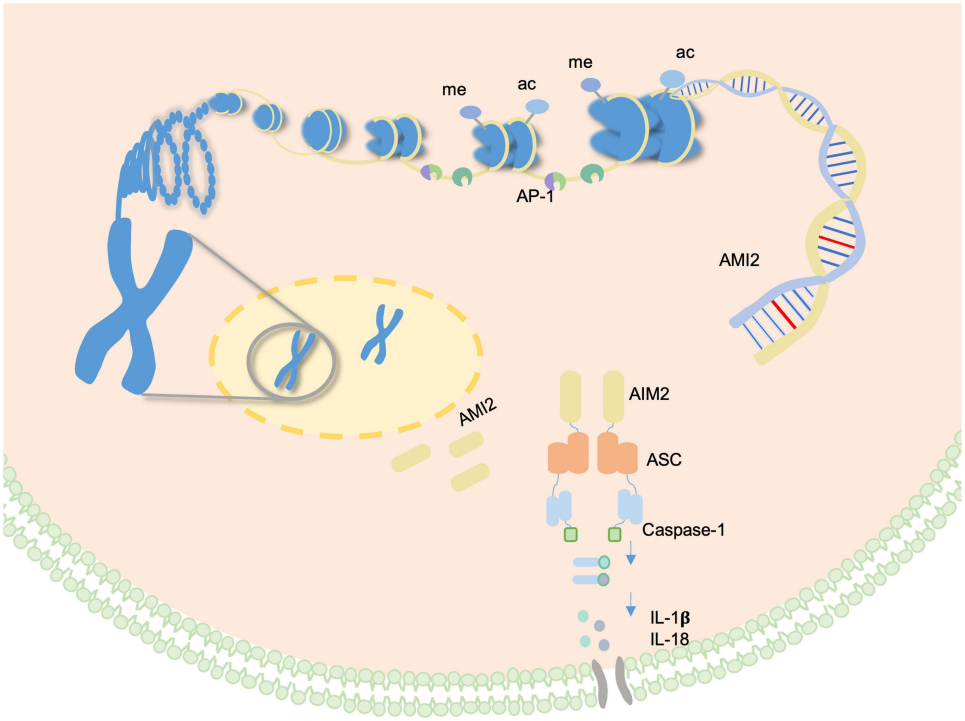

Figure 2 Mechanism of inflammatory memory effects; upon secondary stimulation, due to histone modification and transcription factor binding to keep chromatin in an accessible state, memory domain genes are rapidly expressed, of which AIM2 is the main expressed gene, and its downstream AIM2/Caspase-1/IL-1β signaling axis performs cell proliferation effects.

AIM2 is strongly expressed in many inflammatory skin diseases and plays a pathogenic role.[64] For example, AIM2 is a susceptibility gene locus for psoriasis.[65] Expression is increased in psoriatic keratinocytes.[66–68] And ATAC sequencing analysis of skin tissue samples from patients with psoriasis revealed that AIM2 is in chromatin-accessible regions and is a direct target of Fra-1 and or activator protein-1.[69] In addition, studies have found that caspase-1 and IL-1β are involved in the inflammatory response of keratinocytes in psoriasis.[55,70] This evidence suggests that the AIM2/Caspase-1/IL −1β axis may play an important role in inflammatory skin diseases.[71]

Prospects

The potent effect of cellular inflammatory memory in skin tissues demonstrates its potential research value in recurrent inflammatory skin diseases. However, there are several points that require more research in the future. First, inflammatory memory can last for months in limited experimental designs, whereas how long can the inflammatory memory acquired by skin tissue cells last when humans are exposed to a multifactorial and complex environment. This requires observational studies in more humans. Secondly, inflammatory memory has two sides, protective and destructive. Manipulating "memory" is a complex challenge, and it is clear that it is not feasible to inhibit or promote it. The balance between targeted elimination and selective recall will be more helpful for us to accurately intervene in "memory". Thirdly, we already know that skin "memory" is the result of the joint action of immune cells and skin tissue cells, so is the collaboration between the two or is there a sequence. In addition, the maintenance of inflammatory memory in skin tissue cells and the rapid response value-added during memory recovery require a large amount of energy metabolism, which also has a "memory", so it can be seen that the skin "memory" is a multi-mechanism interaction of the common alliance. "Memory linkage" may be the key to unraveling the skin's "memory". Lastly, despite these advances, we still have not fully revealed the link between the inflammatory memory phenotype and the corresponding signals, especially the possible crosstalk between them. Thus, information on the signals regulating inflammatory memory generation is insufficient and there is still a long way to go.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Sichuan Provincial Science and Technology Department Foundation (Grant No:2020YJ0436).

Disclosure

The authors declare no conflict of interest.

References

1. Benezeder T, Wolf P. Resolution of plaque-type psoriasis: what is left behind (and reinitiates the disease). *Semin Immunopathol*. 2019;41(6):633–644. doi:10.1007/s00281-019-00766-z
2. Lee A-Y. Fixed Drug Eruptions. *Am J Clin Dermatol*. 2000;1(5):277–285. doi:10.2165/00128071-200001050-00003
3. Uttarkar S, Brembilla NC, Boehncke W-H. Regulatory cells in the skin: pathophysiologic role and potential targets for anti-inflammatory therapies. *J Clin Immunol*. 2019;143(4):1302–1310. doi:10.1016/j.jaci.2018.12.1011
4. Ali N, Zirak B, Rodriguez RS, et al. Regulatory T cells in skin facilitate epithelial stem cell differentiation. *Cell*. 2017;169(6):1119–1129.e11. doi:10.1016/j.cell.2017.05.002
5. Eidsmo L, Martini E, Fan L, Wu M. Human Langerhans cells with pro-inflammatory features relocate within psoriasis lesions. *Front Immunol*. 2018;9:9. doi:10.3389/fimmu.2018.00300
6. Pham J, Wark KJL, Woods J, Frew J. Resident cutaneous memory T-cells: a clinical review of their role in chronic inflammatory dermatoses and potential as therapeutic targets. *Br J Dermatol*. 2023;189(6):656–663. doi:10.1093/bjd/ljad303
7. Clark RA. Gone but not forgotten: lesional memory in psoriatic skin. *J Invest Dermatol*. 2011;131(2):283–285. doi:10.1038/jid.2010.374
8. Suárez-Fariñas M, Fuentes-Duculan J, Lowes MA, Krueger JG. Resolved psoriasis lesions retain expression of a subset of disease-related genes. *J Invest Dermatol*. 2011;131(2):391–400. doi:10.1038/jid.2010.280
9. Naik S, Larsen SB, Gomez NC, et al. Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. *Nat*. 2017;550(7677):475–480. doi:10.1038/nature24271
10. Bistoni F, Vecchiarelli A, Cenci E, Puccetti P, Marconi P, Cassone A. Evidence for macrophage-mediated protection against lethal candida albicans infection. *Infect Immun*. 1986;51(2):668–674. doi:10.1128/iai.51.2.668-674.1986
11. Quintin J, Saeed S, Martens JHA, et al. Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes. *Cell Host Microbe*. 2012;12(2):223–232. doi:10.1016/j.chom.2012.06.006
12. Sun JC, Beilke JN, Lanier LL. Adaptive immune features of natural killer cells. *Nat*. 2009;457(7229):557–561. doi:10.1038/nature07665
13. Netea MG, Quintin J, van der Meer JWM. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9(5):355–361. doi:10.1016/j.chom.2011.04.006
14. Medzhitov R, Janeway CJ. Innate immune recognition: mechanisms and pathways. *Immunol Rev*. 2000;173(1):89–97. doi:10.1034/j.1600-065x.2000.917309.x
15. Bonilla FA, Oettgen HC. Adaptive immunity. *J Clin Immunol*. 2010;125(2):S33–S40. doi:10.1016/j.jaci.2009.09.017
16. Chen L, Ozato K. Innate immune memory in hematopoietic stem/progenitor cells: myeloid-biased differentiation and the role of interferon. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.621333
17. Fanucchi S, Domínguez-Andrés J, Joosten LAB, Netea MG, Mhlanga MM. The intersection of epigenetics and metabolism in trained immunity. *Immunity*. 2021;54(1):32–43. doi:10.1016/j.immuni.2020.10.011
18. Netea MG, Joosten LAB, Latz E, et al. Trained immunity: a program of innate immune memory in health and disease. *Science*. 2016;352(6284):6284. doi:10.1126/science.aaf1098
19. Benn CS, Netea MG, Selin LK, Aaby P. A small jab – a big effect: nonspecific immunomodulation by vaccines. *N a In Immun*. 2013;34(9):431–439. doi:10.1016/j.it.2013.04.004
20. Kaufmann E, Sanz J, Dunn JL, et al. BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. *Cell*. 2018;172(1–2):176–190.e19. doi:10.1016/j.cell.2017.12.031
21. Laval de B, Maurizio J, Kandalla PK, et al. C/EBPβ-dependent epigenetic memory induces trained immunity in hematopoietic stem cells. *Cell Stem Cell*. 2020;26(5):657–674.e8. doi:10.1016/j.stem.2020.01.017
22. Bigot J, Guillot L, Guitard J, et al. Respiratory epithelial cells can remember infection: a proof of concept study. *J Infect Dis*. 2019. doi:10.1093/infdis/jiz569
23. Zhang X, Kracht L, Lerario AM, et al. Epigenetic regulation of innate immune memory in microglia. *J Neuroinflammation*. 2022;19(1). doi:10.1186/s12974-022-02463-5
24. Gonzales KAU, Polak L, Matos I, et al. Stem cells expand potency and alter tissue fitness by accumulating tderse epigenetic memories. *Science*. 2021;374(6571). doi:10.1126/science.abh2444
25. Funes SC, Rios M, Fernández-Fierro A, Genaro MSD, Kalergis AM. Trained immunity contribution to autoimmune and inflammatory disorders. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.868343

26. Xing Z, Afkhami S, Bavananthasivam J, et al. Innate immune memory of tissue-resident macrophages and trained innate immunity: re-vamping vaccine concept and strategies. *J Leukoc Biol*. 2020;108(3):825–834. doi:10.1002/jlb.4mr0220-446r
27. Zhong C, Yang X, Feng Y, Yu J. Trained immunity: an underlying driver of inflammatory atherosclerosis. *Front Immunol*. 2020. doi:10.3389/fimmu.2020.00284
28. Wagner R, Hofbauer JP, Wally V, et al. Epigenetic and metabolic regulation of epidermal homeostasis. *Exp Dermatol*. 2021;30(8):1009–1022. doi:10.1111/exd.14305
29. Yi JZ, McGee JS. Epigenetic-modifying therapies: an emerging avenue for the treatment of inflammatory skin diseases. *Exp Dermatol*. 2021;30(8):1167–1176. doi:10.1111/exd.14334
30. Saldanha S, Royston K, Udayakumar N, Tollefsbol T. Epigenetic regulation of epidermal stem cell biomarkers and their role in wound healing. *Int J Mol Sci*. 2015;17(1):16. doi:10.3390/ijms17010016
31. Akhtar S, Alsayed RKME, Ahmad F, et al. Epigenetic control of inflammation in atopic dermatitis. *Semin Cell Dev Biol*. 2024;154:199–207. doi:10.1016/j.semcdb.2023.04.005
32. Dopytalska K, Ciechanowicz P, Wiszniewski K, Szymańska E, Walecka I. The role of epigenetic factors in psoriasis. *Int J Mol Sci*. 2021;22(17):9294. doi:10.3390/ijms22179294
33. Ghaffarinia A, Ayaydin F, Póliska S, et al. Psoriatic resolved skin epidermal keratinocytes retain disease-residual transcriptomic and epigenomic profiles. *Int J Mol Sci*. 2023;24(5):4556. doi:10.3390/ijms24054556
34. Nedoszytko B, Reszka E, Gutowska-Owsiak D, et al. Genetic and epigenetic aspects of atopic dermatitis. *Int J Mol Sci*. 2020;21(18):6484. doi:10.3390/ijms21186484
35. Sun Y, Miao N, Sun T. Detect accessible chromatin using ATAC-sequencing, from principle to applications. *Hereditas*. 2019;156(1). doi:10.1186/s41065-019-0105-9
36. Larsen SB, Cowley CJ, Sajjath SM, et al. Establishment, maintenance, and recall of inflammatory memory. *Cell Stem Cell*. 2021;28(10):1758–1774.e8. doi:10.1016/j.stem.2021.07.001
37. Crusio WE, Dong H, Fang D, Han J. Histone mutations and cancer. *Histone Mutations N a*. 2021. doi:10.1007/978-981-15-8104-5
38. Santos-Rosa H, Schneider R, Bannister AJ, et al. Active genes are tri-methylated at K4 of histone H3. *Nat*. 2002;419(6905):407–411. doi:10.1038/nature01080
39. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. *Nat Rev Genetics*. 2012;13(5):343–357. doi:10.1038/nrg3173
40. Sahlén P, Spalinskas R, Asad S, et al. Chromatin interactions in differentiating keratinocytes reveal novel atopic dermatitis– and psoriasis-associated genes. *J Clin Immunol*. 2021;147(5):1742–1752. doi:10.1016/j.jaci.2020.09.035
41. Kim JJ, Lee SY, Miller KM. Preserving genome integrity and function: the DNA damage response and histone modifications. *Crit Rev Biochem Mol Biol* 2019;54(3):208–241. doi:10.1080/10409238.2019.1620676
42. Zhang L, Chai R, Tai Z, et al. Noval advance of histone modification in inflammatory skin diseases and related treatment methods. *Front Immunol*. 2024:14. doi:10.3389/fimmu.2023.1286776
43. Markova NG, Karaman-Jurukovska N, Pinkas-Sarafova A, Marekov LN, Simon M. Inhibition of histone deacetylation promotes abnormal epidermal differentiation and specifically suppresses the expression of the late differentiation marker profilaggrin. *J Invest Dermatol*. 2007;127(5):1126–1139. doi:10.1038/sj.jid.5700684
44. Masalha M, Ben-Dov IZ, Ram O, et al. H3K27Ac modification and gene expression in psoriasis. *J Dermatol Sci* 2021;103(2):93–100. doi:10.1016/j.jdermsci.2021.07.003
45. Xia X, Cao G, Sun G, et al. GLS1-mediated glutaminolysis unbridled by MALT1 protease promotes psoriasis pathogenesis. *J Clin Invest*. 2020;130(10):5180–5196. doi:10.1172/jci129269
46. Ovejero-Benito MC, Reolid A, Sánchez-Jiménez P, et al. Histone modifications associated with biological drug response in moderate-to-severe psoriasis. *Exp Dermatol*. 2018;27(12):1361–1371. doi:10.1111/exd.13790
47. Saeed S, Quintin J, Kerstens HHD, et al. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science*. 2014;345(6204):6204. doi:10.1126/science.1251086
48. Aoyama K, Itokawa N, Oshima M, Iwama A. Epigenetic memories in hematopoietic stem and progenitor cells. *Cells*. 2022;11(14):2187. doi:10.3390/cells11142187
49. Efroni S, Duttagupta R, Cheng J, et al. Global transcription in pluripotent embryonic stem Cells. *Cell Stem Cell*. 2008;2(5):437–447. doi:10.1016/j.stem.2008.03.021
50. Fang R, Chen F, Dong Z, et al. LSD2/KDM1B and its cofactor NPAC/GLYR1 endow a structural and molecular model for regulation of H3K4 demethylation. *Molecular Cell*. 2013;49(3):558–570. doi:10.1016/j.molcel.2012.11.019
51. Yukawa M, Jagannathan S, Vallabh S, et al. AP-1 activity induced by co-stimulation is required for chromatin opening during T cell activation. *J Exp Med*. 2019;217(1). doi:10.1084/jem.20182009
52. Calautti E, Avalle L, Poli V. Psoriasis: a STAT3-centric view. *Int J Mol Sci*. 2018;19(1):171. doi:10.3390/ijms19010171
53. Andrés RM, Hald A, Johansen C, Kragballe K, Iversen L. Studies of <scp>J</scp>ak/<scp>STAT</scp>3 expression and signalling in psoriasis identifies <scp>STAT</scp>3-<scp>S</scp>er727 phosphorylation as a modulator of transcriptional activity. *Exp Dermatol*. 2013;22(5):323–328. doi:10.1111/exd.12128
54. Wagner EF. Bone development and inflammatory disease is regulated by AP-1 (Fos/Jun). *Ann Rheumatic Dis*. 2009;69(Suppl 1):i86–i88. doi:10.1136/ard.2009.119396
55. Johansen C, Möller K, Kragballe K, Iversen L. The activity of caspase-1 is increased in lesional psoriatic epidermis. *J Invest Dermatol*. 2007;127(12):2857–2864. doi:10.1038/sj.jid.5700922
56. Novoszel P, Holcmann M, Stulnig G, et al. Psoriatic skin inflammation is promoted by c-Jun/AP-1-dependent CCL2 and IL-23 expression in dendritic cells. *EMBO Mol Med* 2021;13(4). doi:10.15252/emmm.202012409
57. Swindell WR, Johnston A, Voorhees JJ, Elder JT, Gudjonsson JE. Dissecting the psoriasis transcriptome: inflammatory- and cytokine-driven gene expression in lesions from 163 patients. *BMC Genomics*. 2013;14(1):527. doi:10.1186/1471-2164-14-527
58. Xu X, Tang X, Zhang Y, et al. Chromatin accessibility and transcriptome integrative analysis revealed AP-1-mediated genes potentially modulate histopathology features in psoriasis. *Clin epigenetics*. 2022;14(1). doi:10.1186/s13148-022-01250-6

59. Pastore S, Giustizieri ML, Mascia F, Giannetti A, Kaushansky K, Girolomoni G. Dysregulated activation of activator protein 1 in keratinocytes of atopic dermatitis patients with enhanced expression of granulocyte/macrophage-colony stimulating factor. *J Invest Dermatol*. 2000;115 (6):1134–1143. doi:10.1046/j.1523-1747.2000.00149.x
60. Sasakura M, Urakami H, Tachibana K, et al. Topical application of activator protein-1 inhibitor T-5224 suppresses inflammation and improves skin barrier function in a murine atopic dermatitis-like dermatitis. *Allergol Int*. 2024;73(2):323–331. doi:10.1016/j.alit.2023.12.006
61. Wang Z-Y, Zheng Y-X, Xu F, et al. Epidermal keratinocyte-specific STAT3 deficiency aggravated atopic dermatitis-like skin inflammation in mice through TSLP upregulation. *Front Immunol*. 2023:14. doi:10.3389/fimmu.2023.1273182
62. Sano S, Chan KS, DiGiovanni J. Impact of Stat3 activation upon skin biology: a dichotomy of its role between homeostasis and diseases. *J Dermatol Sci* 2008;50(1):1–14. doi:10.1016/j.jdermsci.2007.05.016
63. Naik S. The healing power of painful memories. *Science*. 2018;359(6380):1113. doi:10.1126/science.aat0963
64. Koning de HD, Bergboer JGM, Bogaard van den EH, et al. Strong induction of AIM2 expression in human epidermis in acute and chronic inflammatory skin conditions. *Exp Dermatol*. 2012;21(12):961–964. doi:10.1111/exd.12037
65. Zuo X, Sun L, Yin X, et al. Whole-exome SNP array identifies 15 new susceptibility loci for psoriasis. *Nat Commun*. 2015;6(1). doi:10.1038/ncomms7793
66. Zhang Y, Xu X, Cheng H, Zhou F. AIM2 and psoriasis. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1085448
67. Wang J, Gao J, Huang C, et al. Roles of AIM2 gene and AIM2 inflammasome in the pathogenesis and treatment of psoriasis. *Front Genetics*. 2022:13. doi:10.3389/fgene.2022.929162
68. Ciążyńska M, Olejniczak-Staruch I, Sobolewska-Sztychny D, Narbutt J, Skibińska M, Lesiak A. The role of NLRP1, NLRP3, and AIM2 inflammasomes in psoriasis: review. *Int J Mol Sci*. 2021;22(11):5898. doi:10.3390/ijms22115898
69. Tang L, Wang M, Shen C, et al. Assay for transposase-accessible chromatin using sequencing analysis reveals a widespread increase in chromatin accessibility in psoriasis. *J Invest Dermatol*. 2021;141(7):1745–1753. doi:10.1016/j.jid.2020.12.031
70. Cai Y, Xue F, Quan C, et al. A critical role of the IL-1β–IL-1R signaling pathway in skin inflammation and psoriasis pathogenesis. *J Invest Dermatol*. 2019;139(1):146–156. doi:10.1016/j.jid.2018.07.025
71. Sharma BR, Karki R, Kanneganti T. Role of AIM2 inflammasome in inflammatory diseases, cancer and infection. *Eur J Immunol*. 2019;49 (11):1998–2011. doi:10.1002/eji.201848070