BMB
Reports

BMB Rep. 2024; 57(11): 465-471
www.bmbreports.org

Invited Mini Review

Stromal cells and epigenetics: emerging key players of chronic inflammatory skin diseases

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Epigenetic alterations play a crucial role in developmental processes, tissue regeneration, and cellular differentiation. Epigenetic changes are dynamically reversible. Various drugs that target DNA methyltransferases or histone deacetylases have demonstrated their ability to restore normal epigenetic patterns in a number of diseases. While the involvement of epigenetic modifications has been identified in chronic inflammatory diseases, their specific impact on skin inflammation in stromal cells remains unclear. This mini-review explores the role of stromal cells in chronic inflammatory skin diseases, focusing on epigenetic modifications of stromal cells such as fibroblasts, lymphatic, and blood vascular endothelial cells in both healthy and diseased skin. We also provide an overview of recent findings that highlight the contribution of stromal cells, including fibroblasts, to inflammatory and remodeling processes through epigenetic changes in the context of chronic inflammatory conditions. Investigating epigenetic reprogramming of stromal cells might lead to novel strategies for treating chronic inflammatory skin diseases. [BMB Reports 2024; 57(11): 465-471]

INTRODUCTION

Stromal cells are a heterogeneous and indispensable group of cells that provide structural and functional support for various tissues and organs throughout the body. Beyond their conventional structural responsibilities, they play a pivotal role in maintaining the integrity and function of their resident tissues (1). For example, stromal cells can produce and organize extracellular matrix (ECM), a complex network of proteins and carbohydrates crucial for endowing tissues with mechanical resilience and architectural framework (2). Stromal cells can interact with neighboring cells, including epithelial cells and immune cells, thereby contributing to the maintenance of tissue or organ homeostasis (3). Importantly, stromal cells also play a role in various physiological/pathological processes, including inflammation (4-6), wound healing (7), and cancer progression (8). Thus, a comprehensive understanding of the regulation of stromal cell function in both homeostasis and dysfunction is crucial for a better understanding of skin physiology and disease pathogenesis.

Epigenetic changes refer to modifications that affect how genes are turned on/off without changing the genetic code itself. One of the significant features of epigenetic changes is their potential for reversibility. This has implications for therapeutic interventions and strategies to modify gene expression patterns to treat diseases. Thus, drugs targeting epigenetic modifications have been developed and considered as new potential therapeutic tools to ameliorate various diseases, including cancer (9-11) and chronic inflammatory diseases (6, 12-14). The field of epigenetics has grown rapidly in recent years. Ongoing research continues to uncover complexities of epigenetic regulation and mechanisms underlying various biological processes and diseases.

Recently, several studies have discovered the important role of stromal cells in pathological conditions such as cancers and chronic inflammatory diseases that could be regulated by epigenetic modifications (14-16). For example, endothelial cells from pulmonary arterial hypertension show extensive remodeling at active enhancers, while very few transcriptomic changes are observed, indicating an important role of epigenetic changes in disease-relevant stromal cells (15). Thus, it is of great interest to investigate epigenetic changes of stromal cells and their impacts on pathological states that might be reversed by epigenetic reprogramming.

In this mini-review, we will cover the role of stromal cells and epigenetic changes of stromal cells in both healthy skin and chronic inflammatory skin diseases.

ROLE OF STROMAL CELLS IN THE SKIN

Stromal cells in the skin mainly consist of fibroblasts, lympha-

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https://doi.org/10.5483/BMBRep.2024-0039

Received 31 January 2024, Revised 28 March 2024, Accepted 21 May 2024, Published online 8 August 2024

Keywords: Chronic inflammation, Endothelial cells, Epigenetics, Fibroblasts

ISSN: 1976-670X (electronic edition)

tic endothelial cells, and blood vascular endothelial cells. The term "stromal" originates from the Greek word stroma, meaning "bed covering" that refers to a structural or connective role of a tissue or organ. In the skin, stromal cells are positioned in the dermal layer below the epidermis release growth factors that can stimulate cellular division. This process ensures continuous regeneration of the epidermis from its basal layer, while the uppermost skin cells are consistently shedding from the body. The turnover time of healthy human skin is approximately 28 days (17). Furthermore, stromal cells contribute to inflammatory responses and regulate the quantity of cells accumulating in the inflamed region of a tissue (18). For example, extracellular matrix components such as collagen, laminin, and fibronectin derived from stromal cells undergo remodeling in response to external stimuli or during pathological processes (19-22). These stromal cells in the dermis consist of various cell types, including fibroblasts and endothelial cells of lymphatic/blood vessels. Especially fibroblasts, which are among key stromal cell types in the dermis, play an essential role in shaping the microenvironment by synthesizing and remodeling ECM proteins and by secreting cytokines, chemokines, and growth factors (23-26). Stromal cells can impact the homeostasis of adjacent cells such as immune cells through cell-cell communications. They can also modulate inflammatory infiltration (22).

CONTRIBUTION OF STROMAL CELLS TO CHRONIC INFLAMMATORY SKIN DISEASE

Many studies have reported that not only immune cells and epidermal cells, but also stromal cells in the skin, such as dermal fibroblasts and endothelial cells, contribute to the pathogenesis of chronic inflammatory skin diseases such as atopic dermatitis and psoriasis (4, 5, 27, 28). Atopic dermatitis is a Th2 mediated chronic inflammatory disease. In atopic dermatitis, dermal fibroblasts interact with immune cells, triggering a substantial cytokine/chemokine response to NOD2/TLR2 ligands (29). Endothelial cells are highly involved in the pathogenesis of AD since immune cells actively communicate with endothelial cells by releasing and stimulating inflammatory mediators. T cell-endothelial cell interactions are important for establishing acute AD, suggesting that they are pivotal targets for treating AD (30). Psoriasis is a Th17 mediated chronic inflammatory skin disease. In psoriasis, activated fibroblasts can enhance local T-cell persistence (29, 31), alter the expression of ECM proteins (27, 32), and stimulate endothelial cells (33). Activated vascular endothelium then up-regulates adhesion molecules and cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-17 families. Adhesion molecules (e.g., VCAM-1) are important for coordinating the process of leukocyte rolling, attachment, and migration into the skin (34-36). Recently, single-cell analysis has been used to comprehensively characterize specific cell types in atopic der-

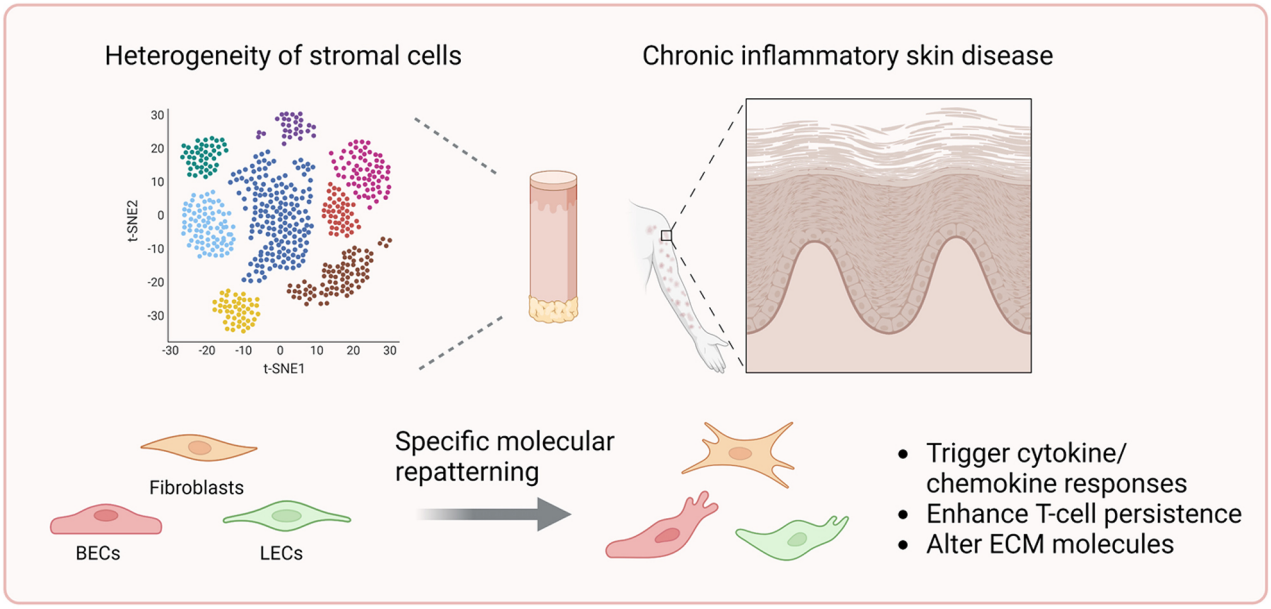

Fig. 1. Heterogeneity of stromal cells in chronic inflammatory disease. Subpopulations of stromal cells, including fibroblasts, blood vascular endothelial cells (BECs), and lymphatic endothelial cells (LECs), identified from single-cell transcriptomics, display specific molecular repatterning, potentially leading to activated states. Activated stromal cells can trigger cytokine/chemokine responses, enhance T-cell persistence, and alter extracellular matrix (ECM) components relevant to the pathogenesis of chronic inflammatory skin diseases.

matitis and psoriasis (Fig. 1). For example, He *et al*. have identified a COL6A5/18A1-positive fibroblast subset that can release cytokines such as CCL2, CCL19, and IL-32 important for AD pathogenesis in AD lesional skin (30). In psoriasis, recent studies have revealed the heterogeneity of fibroblast subpopulation (SFRP2+), showing transition from a profibrotic state to a pro-inflammatory state in psoriatic skin, including producers of ECM components and cytokine-induced, non-matrix producing, pro-inflammatory compartments (38). In addition, He *et al*. (30) have discovered that each endothelial cell subtype shows psoriasis-specific interactions between cis-regulatory enhancers and promoters which reveal dysregulated gene regulatory networks in psoriasis. These results suggest that specific transcriptional responses and epigenetic signatures of endothelial cells lining different vessel compartments are involved in psoriasis (6).

EPIGENETIC MODICIFATIONS IN THE SKIN

Epigenetics is the study of changes in gene expression or cellular phenotype in the absence of changes in underlying DNA sequences. While DNA contains instructions for building and maintaining the body, epigenetic modifications influence how these instructions are interpreted and executed. Changes in DNA accessibility by epigenetic modification can be achieved through various mechanisms such as DNA modification, histone modification, and non-coding RNA (39, 40). DNA undergoes modifications through the addition of methyl groups and consequently influences gene expression (DNA modification). Hypermethylation results in gene silencing, whereas hypomethylation promotes active transcription (41). To study these modifications, various high-throughput techniques are commonly used to profile DNA methylation, including whole-genome bisulfite sequencing and Infinium human methylation beadchip arrays (42) which also have been used to study skin diseases such as psoriasis (43-45). Another epigenetic process that governs chromatin structure and regulates gene expression is histone modification. Histone modifications alter chromatin packaging, determine its accessibility (open) or inaccessibility (closed), thereby influencing gene expression such as activation or repression (39, 46). To study histone modifications, chromatin immunoprecipitation sequencing to analyze histone-DNA interactions and assay for transposase-accessible chromatin (ATAC) sequencing to identify open areas in chromatin packaging are widely performed (47). Epigenetic modifications affect various processes in the skin, such as epidermal homeostasis and differentiation, development, and responses to environmental stimuli (48-52). In chronic inflammatory skin diseases, several histone methylation/acetylation marks have been recently reported in psoriasis, atopic dermatitis, and systemic lupus erythematosus (Table 1). Since epigenetic modifications are modifiable and reversible, epigenetic modifier drugs inhibiting histone acetyltransferases (HATs), histone deacetylases (HDACs), and DNA methyltransferases (DNMTs) that can reverse epigenetic signatures have been drawing attention as a new potential strategy for treating diseases (Fig. 2) (9, 10). There are currently 6 FDA-approved epigenetic modifying drugs, and more than 50 epigenetic drug candidates are being tested in preclinical and clinical trials (53). For examples, trichostatin A, an HDAC inhibitor, ameliorates the development of atopic-like dermatitis by increasing T regs and reducing IL-4 production (54). A485, a HAT inhibitor, has been reported to reduce psoriasis-like skin inflammation *in vivo* (14). Therefore, understanding epigenetic mechanisms in the skin might open avenues for developing novel therapeutic targets and enhancing comprehension of skin biology.

Table 1. Key epigenetic modifications reported in chronic inflammatory skin diseases in recent years

Disease	Modification	Site	Cell types	Ref.
Psoriasis	Histone methylation	H3K9me3	Keratinocytes	Chen C *et al*. (70)
		H3K4me3 H3K4me1	Keratinocytes	Huang S *et al*. (71)
		H3K27me3	Keratinocytes	Zhang T *et al*. (72)
	Histone acetylation	H3K27ac	Skin tissue	Masalha M *et al*. (73) J Kim *et al*. (14)
		H3K27ac	CD4+ T cells	Xia X *et al*. (74)
		H3K9ac	CD4+ T cells	Xia X *et al*. (74)
Atopic dermatitis	Histone acetylation	H3K9ac	Keratinocytes	Traisaeng S *et al*. (75)
Systemic lupus erythematosus	Histone methylation	H3K4me1	CD4+ T cells	Zhao M *et al*. (76)
		H3K9me3	CD4+ T cells	Zhao M *et al*. (77)
		H3K27me3	CD4+ T cells	Tsou PS *et al*. (78)
	Histone acetylation	H3K27ac	CD4+ T cells	Zhao M *et al*. (76)

Recent studies have reported histone modifications at specific sites in different cell types associated with psoriasis, atopic dermatitis, and systemic lupus erythematosus.

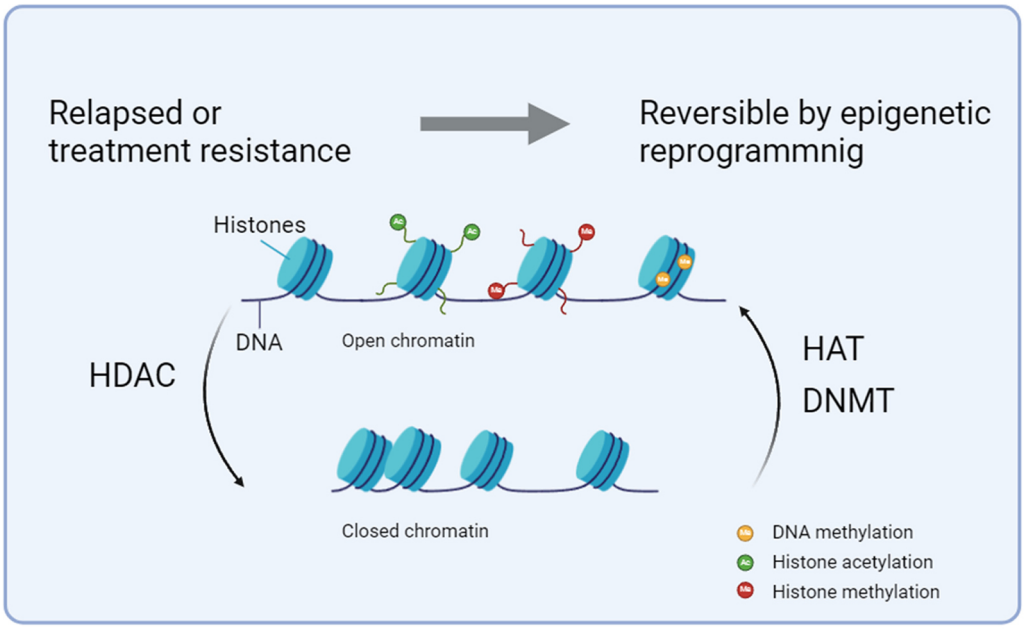

Fig. 2. Flexibility of epigenetic signatures by epigenetic reprogramming. DNA can undergo methylation at cytosine residues in a CpG context (DNA methylation). The DNA wraps around histone proteins to form structures called nucleosomes. Modifications to these histone proteins represent another layer of epigenetic regulations (histone acetylation/methylation). These modifications dictate whether the chromatin structure is open and accessible or closed and inaccessible. Acetylation of histone tails by histone acetyltransferase (HAT) activates genes, whereas histone deacetylation by deacetylases (HDACs) leads to gene silencing. DNA methyltransferase (DNMTs) adds methyl groups to the 5-position of cytosine residues in DNA, crucial for the process of DNA methylation, playing a significant role in maintaining genome stability.

EPIGENETIC CHANGES OF STROMAL CELLS IN CHRONIC INFLAMMATORY DISEASES

Epigenetic changes play crucial roles not only in many biological processes, but also in various diseases, including cancer, chronic inflammatory diseases, and certain genetic disorders (13, 16, 55, 56). Many studies have focused on epigenetic changes of immune cells, keratinocytes, and whole skin tissues in chronic inflammatory diseases such as atopic dermatitis and psoriasis (43, 44, 57-60). However, several studies have recently focused on stromal cells, including fibroblasts and endothelial cells, undergoing epigenetic modifications that contribute to chronic inflammatory conditions in the skin. For example, a recent study has identified psoriatic endothelial cell subtype-specific cis-regulatory element connections (CREs) by 5′ single-cell profiling, providing insights into specific transcriptional responses and epigenetic signatures in psoriasis (6). In this study, MCAM and its binding partners specifically showed upregulation in blood capillaries (CD31+RGCC+ population) in psoriasis, together with vascular remodeling. There was a unique pairing of CREs in psoriasis, suggesting a potent contribution by transcriptomic and epigenetic repatterning of the psoriatic vasculature. Another study has suggested that upregulation of histone deacetylase-1 (HDAC-1) in psoriatic endothelial cells might potentially contribute to overexpression of VEGF that induces proliferation of endothelial cells (61). In addition, Kwon *et al*. have recently investigated interactions between mast cells, keratinocytes, and fibroblasts in an atopic dermatitis model, indicating a regulative role of the HDAC6-CXCL13 axis in the pathogenesis of atopic dermatitis (62). These results on transcriptional and epigenetic changes that underlie responses of stromal cells in chronic inflammatory skin diseases can suggest new therapeutic strategies to overcome limitations of current treatments, including relapse and treatment resistance.

CONCLUSION

Here, we summarized stromal cells and their epigenetic changes known to play a significant role in both healthy skin and chronic inflammatory skin diseases, focusing on atopic dermatitis and psoriasis. Interestingly, recent studies have highlighted disease-specific cell subtypes and their interactions across cell types in healthy and diseased states in the skin by single-cell transcriptomic profiling (6, 31, 38, 63). Single-cell analysis compared to conventional bulk transcriptomics provides a more detailed characterization of various cell types such as stromal and immune cells (64-66), thus uncovering the subtype of each cell that might contribute to transcriptional and epigenetic signatures underlying chronic inflammatory skin

diseases. For epigenetic changes, histone deacetylases (HDACs) can mediate the balance of acetylation/deacetylation together with histone acetyltransferases (HATs). Several studies have shown that aberrant expression of HDACs and HATs in chronic inflammatory skin diseases such as atopic dermatitis and psoriasis (59, 61, 67) might serve as a potential therapeutic target for treatment (68, 69). Therefore, multi-omics profiling, analyzing patterns of transcriptional and epigenetic changes, and their reprogramming via modifier drugs might potentially lead to clinical approaches to improve patient outcomes.

ACKNOWLEDGEMENTS

This work was supported by 2023 Hannam University Research Fund.

CONFLICTS OF INTEREST

The authors have no conflicting interests.

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