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DYSREGULATED EPIGENETIC MODIFICATIONS IN PSORIASIS.

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ABSTRACT

The observed incidence of psoriasis has been gradually increasing over time[1], but the underlying pathogenic factors have remained unclear. Recent studies suggest the importance of

epigenetic modification in the pathogenesis of psoriasis. Aberrant epigenetic patterns including changes in DNA methylation, histone modifications, and non-coding RNA expression are observed in psoriatic skin. Reversing these epigenetic mechanisms have showed improvement in psoriatic phenotypes, making epigenetic therapy a potential avenue for psoriasis treatment. Here, we summarize relevant evidence for epigenetic dysregulation contributing to psoriasis susceptibility and pathogenesis, and the factors responsible for epigenetic modifications, providing directions for potential future clinical avenues.

KEY WORDS

Epigenetics, Psoriasis, DNA methylation, histone modification, non-coding RNA

INTRODUCTION

Psoriasis is a chronic inflammatory autoimmune skin disorder that affects more than 8 million people in the United States[2]. Due to the nature of visible skin symptoms including, the appearance of skin lesions, characterized by sharply demarcated red scaly plaques, pruritus, skin pain, and often psoriatic arthritis, patients with psoriasis generally have decreased quality of life[3,4]. However, the pathogenic mechanism of psoriasis remains incompletely elucidated and many of the currently available therapeutic approaches still have limited long-term effectiveness[5,6] and substantial patient dissatisfaction[7,8]. As a result, better understanding of the pathogenesis of psoriasis is needed in order to develop better treatment options.

Histological and immunological analyses have revealed that many of the clinical symptoms of psoriasis are related to abnormal epidermal hyperproliferation and differentiation, together with increased infiltration and activation of immune cells[9,10]. Multiple factors, including genetic susceptibility[11-13] and environmental factors[14], contribute to development of psoriasis. Thus, a recent twin study showed that genetic factors may explain up to 68% of the variation in susceptibility, while non-shared environmental factors may explain the rest[15]. Thus, epigenetic changes may play a critical role in psoriasis development as it mediates the mechanisms for both genetic and environmental factors[13,16,17].

Epigenetic modifications are processes that alter genome activity around DNA without changing DNA sequences and are mitotically stable. Alteration of gene expression leads to the differential regulation of cell signaling pathways. Genetic changes, such as single nucleotide polymorphism and copy number variation can affect transcript expression level and are enriched among factors associated with diseases[18]. Recently, epigenetic mechanisms have been shown to regulate gene expression at both transcriptional and post-transcriptional levels[19,20], and contribute to the pathogenesis of various diseases[21-23]. Importantly, similar to genetic alterations, if epigenetic modifications are present in germline cells, the modification can be passed to future generations[24], making epigenetics target for some heritable diseases[25].

The major epigenetic processes include; DNA methylation, histone post-translational modifications and non-coding RNAs (ncRNAs). DNA methylation[26] and histone modifications[27] modulate chromatin structure and are part of transcriptional regulation, while ncRNAs participate in post-transcriptional regulation[28]. The influence of non-hereditary epigenetic changes are best shown by monozygotic twin comparison, with about 4-fold increase in DNA methylation and histone acetylation differences being observed in 50-year-old twins compared to 3-year-old twins[29].

In stark contrast to DNA abnormalities, epigenetic changes can be reversible. This nature of epigenetic processes allows for reprogramming of cellular processes[30], making them feasible targets for therapeutics. Thus, many of the epigenetic machineries have been targeted and applied in cancer therapy[31], and 6 epigenetic drugs have currently been approved by the food and drug administration (FDA) for clinical use[32].

Here in this review, we summarize recent discoveries [Figure. 1] regarding the mechanisms by which epigenetic factors contribute to the pathogenesis of psoriasis, the factors that drive epigenetic modifications, and discuss how epigenetic changes can be targeted therapeutically.

EPIGENETIC ALTERATION IN PSORIASIS

DNA Methylation

DNA methylation is the best studied epigenetic mechanism. DNA methylation is involved in various essential biological processes such as genomic imprinting, X-chromosome inactivation, and silencing of repetitive DNA elements[33]. Dysregulation of DNA methylation has been identified in a wide range of diseases including cancer[34], inflammatory disorders[35] and neurological diseases[36]. In this process, methyltransferases recruit a methyl group to a cytosine or adenine residue at the 5th position on the pyrimidine ring within the CpG dinucleotide[37]. When DNA methylation occurs in the promoter or enhancer region of a gene, it leads to decreased binding of transcription factors that mediate or enhance gene transcriptional activity, leading to repression of gene transcription[38]. On the contrary, loss of DNA methylation, caused by DNA hydroxy-methylation and demethylation, in the promoter or enhancer region of a gene will lead to re-activation or increased gene expression[39,40].

Several whole-genome DNA methylation analyses have shown similar number of hypermethylated and hypomethylated differential methylated regions (DMRs) in whole skin biopsies from patients with psoriasis when compared to normal healthy controls[41,42] , suggesting the existence of altered methylation mechanism in psoriatic skin. A closer look at these differentially methylated genes, such as *S100A9*, *SELENBP1* and *CARD14*, further reveal the relationship of DNA methylation and pathologic features in psoriasis[43].

DNA methylation can also serve as a biomarker for effective psoriasis treatment. Thus, comparison between psoriatic skin prior to and after 1 month of successful anti-TNF treatment (with >75% improvement in PASI score) showed that after TNF inhibitor treatment, methylation status of several methylated loci became more similar to uninvolved skin[42].

In addition, recent studies have identified several male-specific differential methylated sites in psoriatic skin, which regulate genes that are tightly associated with psoriasis[44]. This may provide insights into the mechanisms why psoriasis severity tends to be greater in males[45].

As keratinocytes and immune cells are both playing important roles in the pathogenesis of psoriasis, reports of dysregulated DNA methylome in these cell types, suggest their contribution to altered biological processed related to psoriasis.

Abnormal regulation of DNA methylation in keratinocytes

Hypermethylation

In the epidermis of skin, where 90% of cells are keratinocytes, hypermethylation has been identified in the promoter area of the *p16INK4a* gene in 30% of patients of psoriasis[46]. This leads to decreased expression of *p16INK4a*, which is negatively related to disease severity (as measured by Psoriasis Area and Severity Index (PASI)). p16INK4a is also a tumor suppressor, and its suppression has been demonstrated to promote cell proliferation[47] providing a plausible explanation how hypermethylation relates to increased PASI score.

Hypomethylation

Hypomethylation was identified in 12 CpG sites from epidermal differentiation complex in psoriatic skin, and correlates with enhanced expression of several psoriatic signature genes (including *OAS2*, *S100A7*, and *S100A12*)[42]. Decreased methylation has also been shown in the intragenic area of *CYP2S1* in psoriatic keratinocytes[48]. Further studies have revealed that these methylation loci overlap with the enhancer region of *CYP2S1*, leading to change of *CYP2S1* expression affecting proliferation and immune response in keratinocytes[49].

DMNT dysregulation

DNA methyltransferases (DMNT) are important for the maintenance of DNA methylation in cells. Keratinocytes express *DNMT1*, *DMNT3A* and *DNMT3B*[50]. Under physiological conditions, DNMT1 is important for maintaining epidermal progenitor cell function and suppression of

epidermal differentiation[50,51]. Recent study have shown that inhibition of DNMT1 activity, using indirubin, suppresses *WIF1* promoter hypermethylation, leading to inhibition of proliferation and induction of apoptosis in keratinocytes[52]. This also provides additional mechanism by which indirubin alleviates psoriasis-like skin phenotype in the IMQ-induced murine model[53].

Hydroxyl-methylation

Another group of enzymes that is important for altered DNA methylation profiles in cells is the ten-eleven translocation (TET) dioxygenase family. TET enzymes cause DNA hydroxy-methylation by converting 5-methylcytosine to 5-hydroxymehtylcytosine (5-hmC). The 5-hmC modification leads to recruitment of a different set of binding factors than 5-methylcytosine[54]. In the psoriatic epidermis, and the IMQ-induced mouse model, decreased expression of TET1 and TET2 are observed together with loss of 5-hmC modifications in several genes related to stem cell homeostasis regulations[55]. The loss of 5-hmC leads to accumulation of nestin which contribute to the formation of psoriasis epidermal architecture[55,56]. In addition, *in vitro* modelling suggests that TET2 may regulate inflammatory response in keratinocytes through modulation of expression levels of proinflammatory cytokines and chemokines[57].

Abnormal regulation of DNA methylation in immune cells

In psoriasis, abnormal DNA methylation has been identified in peripheral blood mononuclear cells (PMBC). Thus, PBMCs obtained from psoriatic patients showed global DNA methylation changes, most likely related to the increased DNMT1 activity and decreased MBD2 and MeCP2 mRNA level in psoriatic PBMCs[58]. Naïve psoriatic CD4+ T cells also show distinct methylation profile compared to healthy controls, or patients with atopic dermatitis[59]. These differential methylated sites were found to coincide with histone modifications and transcription factor binding sites, suggesting an active influence on gene transcription regulation. Combinatory analysis of methylation and transcriptome profiles of CD4+ and CD8+ T cells from monozygotic twins discordant for psoriasis, showed effect on multiple immune response related genes such as *IL13*, *TNFSF11*, *PTPN6*, *CCL5*, *NFATC1* and *PRF1*[60,61]. Furthermore, in peripheral blood from psoriasis patients, *FOXP3* gene methylation was significantly higher in Tregs from patients with

psoriasis compared to Tregs derived from normal healthy controls[62]. The hypermethylation may lead to decreased *FOXP3* expression and reduction in the number of Treg cells resulting in unrestrained autoimmune responses.

Histone modification

In eukaryotic cells, octamer of histones is wrapped with 147bp of DNA into nucleosome, which is the fundamental subunit of chromatin. As a result, the alteration of histone influences the nucleosome positioning and unwrapping characteristics, which changes the accessibility of DNA sequences near the nucleosome region[63]. The histone octamer is composed of two copies of the four core histones: H2A, H2B, H3 and H4. Post-translational modifications (PTMs) on these histones, including methylation, acetylation, phosphorylation, ubiquitylation and ADP-ribosylation, have been shown to alter histone-DNA and histone-histone interactions, which then changes the transcription activity[63]. In skin, several histone modifications have been described and implicated in the pathogenesis of psoriasis. Here we summarized some of the more recent discoveries.

Histone Methylation

Histone methylation is normally observed on the side chains of lysine and arginine, and multiple methyl groups could be added to the histones: mono-, di-, and tri-methylation are all observed[64]. Different than DNA methylation, histone methylation can result in either an active or repressed status of transcriptional activity. The result of histone methylation is based on both the methylation site and number of methyl groups added.

Histone methylation is important in regulating cytokine production and drug responses in psoriasis. A recent study showed that H3K9me2 is important in modifying IL-23 expression in keratinocytes, and keratinocytes derived IL-23 is sufficient to drive psoriatic phenotype in a psoriasis murine model[65]. Increased H3K4 methylation has been identified in PBMCs from psoriasis patients compared to controls, potentially contributing to differentially expressed genes in PBMCs[66]. Interestingly, following treatment with biologics, H3K4 and H3K27

methylation level differ significantly between drug responder and non-responder[66], supporting a role of histone methylation marks as potential biomarkers for treatment response.

In psoriasis epidermis, histone H3K27me3 modification and enhancer of zeste homolog 2 (EZH2), a histone H3K27 methylase, are both upregulated[67]. Pharmacological and genetic inhibition of EZH2 leads to downregulation of H3K27me3, suppresses epidermal proliferation and ameliorates psoriatic phenotype in mouse model[67]. However, it still remains unclear if this protective effect is achieved by H3K27me3 downregulation given that EZH2 can also act as a methyltransferase on non-histone targets such as *STAT3*[68].

Histone H3K27me3 modifications are also important for Th17 differentiation. Th17 cells plays a pathogenic role in psoriasis, and inhibition of IL-17 signaling frequently leads to marked clinical improvement[69]. Overexpression of the H3K27me3 demethylase *Jmjd3* leads to reduced H3K27me3 levels and promotes Th17 cell differentiation[70]. Further studies are needed to determine the role of Jmjd3 in the pathogenesis of psoriasis.

Histone Acetylation

Histone acetylation typically occurs on the lysine side chain of the N-terminal tail histone proteins. The addition of acetyl group neutralized the positive charge of lysine, and results in weaker interactions between histone and DNA leading to open chromatin and facilitation of active transcription.

Reduced level of acetylation in H3 and H4 has been observed in psoriatic PBMCs, with H4 acetylation levels correlating negatively with disease severity (as measured by PASI)[66,71]. One of the mechanisms that may link altered histone acetylation in immune cells with psoriasis development involves GLS1-mediated glutaminolysis[72]. In this paper, GLS1 was shown to promote Th17 and γδ T17 differentiation through enhancement of H3K9Ac and H3K27Ac in the *IL17A* promoter region[72].

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two major groups of enzymes that are responsible for histone acetylation. HDAC-1 has been shown to be upregulated in psoriatic skin[73,74]. Previous studies have shown that HDAC inhibition regulates Treg function[75] by increasing *Foxp3* expression[76], and preventing production of IL-17A[77]. As Treg plays an important role in the pathogenesis of psoriasis[78], HDAC may be important for immune regulation in psoriasis. Moreover, HDAC has been shown to suppress expression of inflammatory genes in both macrophages and keratinocytes[79]. Another histone deacetylase, Sirtuin-1 (SIRT1) may also have a role in psoriasis pathogenesis. SIRT1 is regulated by TNF-a and is decreased in psoriatic skin[74,80]. Several studies have shown that SIRT1 activation can induce anti-inflammatory[81] and apoptotic[82] effects in keratinocytes. However, histone substrates of SIRT1 that may contribute to the psoriatic phenotype are yet to be identified.

Recently, inhibition of BET proteins, readers of histone acetylation, have been shown to suppress IMQ-induced psoriatic phenotypes in mice[83]. This study showed that BET inhibition decreases the expression of RORC, IL-17A and IL-22, which are all important pro-inflammatory factors in psoriasis. This further indicates the importance of histone acetylation in the pathogenesis of psoriasis.

Non-coding RNA

Non-coding RNAs (ncRNA) are RNAs that are not translated into protein. Some of the major groups of ncRNAs are microRNA(miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA). These non-coding RNAs are known to perform their role through interacting with RNA, DNA and proteins, leading to changes of their structure and ultimately alteration of gene expression[84,85].

MicroRNA

MicroRNAs are single-stranded, small non-protein coding, endogenous RNAs. miRNAs regulate gene expression primarily by binding to the 3' UTR of mRNA, forming miRNA-mRNA complex and leading to degradation of mRNA. Depending on the binding partners, miRNAs can regulate

various cellular processes. Aside from interacting with mRNA, miRNAs are able to modulate gene expression by influencing epigenetic modifications. miRNAs are able to produce mitotically heritable gene silencing and may contribute to human diseases by modulating DNA methylation in CpG island[86]. In addition, miRNAs are showed to target enzymes that are important for DNA methylation[87,88] and histone modifications[89,90]. Together, these suggest important roles of miRNAs in epigenetic processes.

miRNA125b is one of the most downregulated miRNAs in lesional psoriatic skin. *In vitro* studies have shown that increased expression of miRNA125b suppresses keratinocyte proliferation and promotes differentiation. miRNA125b has been shown regulate expression and translation of fibroblast growth factor receptor 2 (FGFR2)[91] and ubiquitin-specific peptidase 2 (USP2) in keratinocytes[92]. A recent study further suggested that miRNA125b can mediate keratinocyte proliferation through suppression of BRD4 expression, thus influencing Jagged-1/Notch signaling pathway[93].

miR-200c is elevated in plasma and lesional skin from psoriasis patients compared to normal healthy control. More importantly, miR-200c levels are positively correlated with disease severity in psoriasis[94]. One of the confirmed targets of miR-200c is SIRT1[95], a histone deacetylase influencing inflammatory and proliferation process in psoriasis, as mentioned before. Furthermore, circulating miR-200c in psoriasis is positively correlated with cardiovascular risk[94].

microRNAs may also regulate the function of T cells. microRNA-210 (miR-210) is highly expressed in psoriatic CD4+ T cells and psoriatic skin[96]. The inhibition of miR-210, through both pharmacological and genetic methods, results in amelioration of psoriasis-like symptoms in a mouse model, suggesting the crucial role of miR-210 in modulating immune responses[96]. An *in vitro* study further demonstrated that small extracellular vesicles, derived from psoriatic keratinocytes, have an increased expression of miR-381-3p[97]. The increased miR-381-3p was

shown to target several genes including *UBR5*, *FOXO1* and *RORC2*, and influencing the polarization of Th1 and Th17 cells.

Aside from those mentioned above, multiple other miRNAs have been found to influence keratinocyte function in psoriasis. MiR-125b-5p[98], miR-181-5p[98], miR-187[99], miR-145-5p[100], miR-320b[101], miR-20a-3p[102], miR-876-5p[103], miR-99a[104], miR-4516[105], miR-330[106], let-7b[107], miR-155[108], miR-194[109] and miR-138[110] are downregulated in psoriatic keratinocytes. miR-223[111], miR-744-3p[112], miR-31[113], miR-126[114], miR-17-92[115] and miR-146[116] are upregulated in lesional psoriatic skin. In addition, upregulation of miR-31[117] and miR-155[118] have been shown to affect expression of inflammatory mediators in psoriatic skin. Let-7b downregulation is related to increased T cell proliferation and IFN-g secretion through STAT3 targeting[119].

Long non-coding RNA

lncRNAs are non-protein coding RNAs that are longer than 200nt. LncRNAs act as epigenetic modulators through recruitment of transcription factors and chromatin modifying proteins to transcriptionally active loci[120].

Microarray studies have identified around 2,200 lncRNAs that are dysregulated in psoriatic skin[120]. Another study using RNAseq identified over 4,000 differentially expressed lncRNAs in psoriatic skin compared to non-lesional and healthy skin[121]. Further co-expression analysis showed that differentially expressed lncRNAs are involved in immune related functions and epidermal differentiation.

One of the highly upregulated lncRNAs in psoriasis is lncRNA-RP6-65G23.1. By altering the expression of Bcl-xl, Bcl2 and influencing ERK1/2-AKT signaling pathway, RP6-65G23.1 was shown to promote keratinocyte proliferation and suppression of apoptosis[122]. Similarly, lncRNA MIR31HG is upregulated in psoriatic lesions, and influences keratinocyte proliferation through G2/M cell cycle arrest[123]. In addition, lncRNA-MSX2P1 is upregulated in IL-22 treated

keratinocytes, induces increased cell proliferation and expression of S100A7 through suppression of miR-6731-5p[124].

Psoriasis Susceptibility-Related RNA Gene Induced by Stress (*PRINS*) is another important lncRNA that has been implicated in the pathogenesis of psoriasis. Thus, *PRINS* is upregulated in both lesional and non-lesional psoriatic skin[125]. It can induce the expression of the anti-apoptotic protein G1P3 in psoriatic keratinocytes, thus promoting cell proliferation[126].

Another lncRNA, is the maternally expressed gene 3 (MEG3), which is downregulated in psoriatic skin, potentially due to the exposure of TNF-a[127]. MEG3 binds to miR-21 and influences proliferation of skin keratinocytes through the inhibiting effect of miR-21 towards caspase-8[127].

Circular RNA

Circular RNAs are long non-coding RNAs that are covalently linked on the 5' and 3' termini. As circRNAs contain binding motifs for several miRNAs and proteins, they are able to influence biological processes through binding to miRNA and proteins[128].

Transcriptome analysis demonstrated that circRNAs are less abundant in psoriatic skin compared to non-lesional and healthy skin[129]. The circRNAs; ciRS-7 and circZRANB1 are identified as promising psoriasis diagnostic biomarkers. ciRS-7 inhibits miR-7 activity through binding[130]. As miR-7 is known to negatively regulate genes that are involved in cell growth[131], its inhibitor ciRS-7 may contribute to the increased cell proliferation in psoriasis. However, further functional studies are needed to validate the circular RNAs in psoriasis pathogenesis.

ENVIRONMENTAL FACTORS THAT CONTRIBUTE TO THE EPIGENETIC CHANGES IN PSORIASIS

Environmental factors are believed to be important drivers of psoriasis pathogenesis[132]. They are also considered to be a major promoter of epigenetic modifications that lead to transgenerational inheritance and phenotypic variation in human diseases. Here, we

summarized how some of the environmental factors may contribute to psoriasis symptoms through epigenetic modifications.

Microbiota

The skin microbiome population in psoriatic skin differs markedly compared to healthy skin[133]. Activated immune responses, and high expression of various antimicrobial proteins, lead to dysbiosis resulting in reduced population of bacteria such as *Corynebacterium* spp.[134]. Interestingly, gut microbiota is also altered in patients with psoriasis[135]. Using antibiotic that target Gram-positive bacteria in IMQ-induced psoriatic murine model led to decreased IL-17 and IL-22 producing T cells[136], suggesting the importance of microbiota in influencing inflammatory processes central to psoriasis pathogenesis.

Several epigenetic modifiers are strongly influenced by microbiome and their metabolites. For example, short chain fatty acids secreted by gut bacteria are able to inhibit HDAC activities[137]. Another example is that depletion of gut microbiome leads to changes in the methylation of the *TLR4* gene[138]. In addition, different microbiota result in different expression signature of miRNA in mice[138]. Together, these findings suggest the importance of endogenous bacteria in modifying epigenome in cells. However, not much information is available regarding whether skin microbiota directly changes the epigenetic profile in skin, and how different microbiota may contribute to psoriasis pathogenesis. Further research is needed to address this.

Diet

Epidemiology studies have found that different diets influence treatment response in psoriasis. Low calorie and fish oil diet have shown to lead to improvement in disease activity[139]. One of the ways diet may alter epigenetic profile is through dietary intake and the effect of dietary metabolites in influencing microbiota composition[140]. Another way is through direct influence on epigenetic modifying enzymes. Several dietary components, such as butyrate, sulforaphane, curcumin, resveratrol and genistein are able to change the activity of HDAC, HAT and DNMTs[141].

Fish oil that contains omega-3 polyunsaturated fatty acids has been shown to affect DNA methylation profile[142,143].

Smoking

Cigarette smoking has been shown to contribute to the onset of psoriasis, disease severity, response to treatment, as well as increasing incidence of various psoriasis-associated comorbidities[144]. A genome-wide DNA methylation study suggested that, when comparing current smokers with never smokers, that there were 18,760 differentially methylated CpG sites in relation to 7,201 annotated genes[145]. Smoking may also influence histone modifications by decreasing the activity of HDAC[146] and increasing histone methylation[147]. In addition, smoking influences epigenetic modifications through altering the expression of miRNAs[148] and lncRNAs[149].

Cigarette and cannabis smoking have been shown to lead to hypermethylation of two CpGs located in *GPR15* and *AHRR* genes in helper T cells, leading to increased number of $GPR15^{+}CD3^{+}CD4^{+}$ cells in peripheral blood, a well-known marker for autoimmune diseases, including psoriasis[150].

Stress

Epidemiology study suggested that stress contributes to both onset and exacerbation of psoriasis[151,152]. Experiments using IMQ-induced psoriasis-like mouse model found that emotional stress induces higher expression of pro-inflammatory cytokines and resulted in more severe epidermal hyperplasia[153]. Furthermore, other studies have shown that, when under stress, patients with psoriasis experience decreased level of cortisol[154]. Aside from its anti-inflammatory effect, cortisol induces epigenetic modifications including DNA methylation[155-157], histone modifications[158], and miRNA expression[159]. Although no studies have been done to determine whether stress causes epigenetic changes in psoriatic skin, the altered cortisol level[160] and its relationship with epigenetic changes suggest a potential role of stress in contributing to the epigenomic profile in psoriasis.

EPIGENETIC THERAPY

The concept that epigenetic factors play an important role in the pathogenesis of psoriasis is emerging and increasing effort has been put into targeting epigenetic modifiers. For example, 5-azacytidine (5-Za) has been used as inhibitor of DNA methylation[161]. Topical application of 5-Za on mice model shows amelioration of IMQ-induced epidermal thickening, suggesting a potential therapeutic use of methylation inhibitor on psoriasis[162]. Histone acetylation and deacetylation enzymes are another popular target in psoriasis treatment. HDAC inhibitor piperlongumine has been shown to alleviate IMQ-induced skin inflammation and keratinocyte hyperproliferation[79], while another inhibitor trichostatin A has been shown to prevent T cell differentiation towards pathogenic Th17 polarization[163]. Furthermore, clinical trial using SIRT1 activator in treating psoriasis demonstrated significant histological improvement [164].

Several studies have also shown that alteration of non-coding RNA can be effective in treating psoriasis. Topical treatment of miR-210 inhibitor showed decreased acanthosis and inflammatory infiltration in IMQ-induced psoriasis[165]. Interestingly, treatment using ultrasound to target Q-starch and miR-197 resulted in significant improvement in psoriatic histology[166].

CONCLUSION

Emerging importance of epigenetic regulation has been established in the pathogenesis of psoriasis. The specific epigenetic regulations in psoriasis can provide new targets for treatment development, and serve as potential biomarker for diagnosis and treatment response[167]. However, greater understandings of epigenetic modifications in psoriasis are needed. For example, many of the current epigenetic studies have been performed in *in vitro* models that only contains a single cell type, but more complex models are required to fully assess the effectiveness of epigenetic therapies. Combinatorial therapies that utilize epigenetic targeting approaches together with standard psoriasis treatment should be also explored. As medications that target epigenetic modulators are rapidly being implemented in other diseases, a deeper

understanding of the epigenetic mechanism involved in psoriasis pathogenesis will accelerate and facilitate the future use of epigenetic modifiers in psoriasis management.

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Figure legend

Figure 1. Epigenetic regulations in psoriasis.

DNA methylation, histone modifications and non-coding RNAs are the 3 major mechanisms that regulate epigenomic profiles in psoriatic immune cells and keratinocytes. (A) DNA methyltransferases DMNTs are upregulated, while methylcytosine dioxygenases TET1/2 are downregulated in psoriatic cells, leading to change of DNA methylation level in regulatory elements in genes that are important for proliferation, apoptosis, and immune responses. (B) Histone methylation and acetylation regulated by histone methyltransferases (EZH2), demethylases (Jmjd3) and deacetylases (HDAC1). These changes lead to alteration of expressions of genes related to epidermal proliferation and Th17 differentiation. (C) non-coding RNAs (ncRNAs), including microRNA (miRNA), circular RNA (circRNA) and long non-coding RNA (lncRNA) are found differentially expressed in psoriatic cells. These ncRNAs may influence gene expression by interacting with each other, binding to transcription factors, and mRNA. (D)

Microbiota, stress, diet and smoking are some of the common factors that may contribute to epigenetic changes in psoriatic cells.

(This figure is adapted from Zagorac S, Garcia-Bermejo L, Sainz B, Jr. The Epigenetic Landscape of Pancreatic Cancer Stem Cells. Epigenomes. 2018; 2(2):10.)

DATA AVAILABILITY STATEMENT

Research data are not shared

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no conflicts to declare in relation to the topic.

AUTHOR CONTRIBUTION STATEMENT

CZ, LCT and JEG wrote the paper