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The new era of immune skin diseases: Exploring advances in basic research and clinical translations

1. Introduction

As a vital immune organ, skin performs multiple physiological functions. Immune skin diseases (ISDs) arecharacterized by dysregulated immune responses, manifested as abnormal activation of inflammatory pathways, overexpression of inflammatory factors, and autoimmune responses in the skin. It has been proved immune imbalance dominates the pathogenesis of ISDs, including atopic dermatitis (AD), psoriasis, vitiligo, pemphigus, and systemic lupus erythematosus (SLE) [1–5].

The breakdown of immune homeostasis is crucial to the pathogenesis of ISDs, and abnormal genetics, epigenetics, metabolism, microbiomes, and environment can lead to immune imbalance and aggravate the disease. The development of multi-omics technology has also significantly promoted the pathogenesis research of ISDs, and more targets have been discovered and used for clinical treatment development (Fig. 1) [6]. Studies have shown that abnormal genetic mutations and epigenetic dysregulation can affect the differentiation, activation, and function of immune cells in ISDs, providing new targets for developing novel drugs. Certain metabolites and microbiomes are specifically altered in ISDs and correlated with disease activity.

The above opinions are also included in the articles in our special issue titled “Immune skin disease for the Journal of Translational Autoimmunity”. Here, we summarize the research progress of basic research in ISDs and their clinical translations.

2. Genomics

2.1. Psoriasis

Psoriasis, recognized as a multifactorial disease, involves multiple inherited alleles in genes related to inflammatory pathways [7,8]. Recent progress has been propelled by genome-wide association studies (GWAS), which successfully pinpointed a series of mutation sites of the susceptibility genes. These studies highlight the importance of inherited susceptibility in psoriasis development [9]. One of the most widely recognized susceptibility gene, HLA-Cw*06 locus has been consistently linked to Psoriatic arthritis (PsA) [10,11]. This allele can effectively predict the efficacy of monoclonal antibodies or methotrexate (MTX), but the effects varied in different countries and populations [10,12,13]. These discoveries were instrumental in developing new therapeutic strategies. For instance, the identification of variants in the IL-15 can stimulate T cells expressing IL17 [14]. There have also been reported that IL12B and IL23R genes are crucial to psoriasis [15,16]. Based on these findings, biologics are rapidly being developed and widely used in clinical therapy, including Ustekinumab targeting IL12 and IL23, Ixekizumab targeting IL17A, and Etanercept targeting TNF-α [17]. Meanwhile, GWAS have screened tyrosine kinase 2 (*TYK2*) is a targeting gene of psoriasis. Deucravacitinib, a *TYK2* inhibitor, has shown potential in reducing psoriatic inflammation in clinical trials [18].

2.2. Atopic dermatitis

AD is an allergy-related disorder that can develop in infancy, with the heritability varying from 0.6 to 7.1 % [19]. Genetic variations mainly affect skin barrier functions and stimulation of inflammatory pathways. Filaggrin gene (*FLG*) is a susceptibility gene of AD regulating skin barrier function [20]. Mutations in other genes involved in skin barrier including *SPINK5*, *Cystatin A* and *OVAE* [21,22]. Variations of *RORA*, modifying the function of innate immune cells, may increase the risk of AD [23]. Phosphodiesterase 4 (*PDE4*) is a suspicious gene of AD, and a topical *PDE4* inhibitor called Crisaborole can reduce symptoms in the inflammatory process [24]. GBR 830, an monoclonal antibody targeting suspicious gene *OX40* ligand, is under investigation for its role in modulating the immune response in AD [25]. Genes related to immune function including Toll-like-receptor1(*TLR1*), *TLR2*, IL-4, IL-13, *Foxp3* were found to have mutations in AD [26]. Monoclonal antibodies targeting these cytokines, such as Dupilumab targeting both IL-4 and IL-13 and Tralokinumab targeting IL-13, offer a new approach to treating AD [27,28].

3. Epigenomics

3.1. Systemic lupus erythematosus

Epigenetics refers to modifications that do not change the gene sequence and are associated with environmental exposure and multiple factors. Abnormal epigenetic modifications have been shown to exist in ISDs [29,30]. Alterations in these epigenetic processes affect the differentiation and activation of immune cells and the level of inflammatory factors. Epigenetic markers can be used in the diagnosis of ISDs due to their stable and easily detectable properties, and some microRNAs (miRNAs) inhibitors have therapeutic potential [31,32]. SLE is a highly heterogeneous autoimmune disease with overactivation of immune cells and massive production of autoantibodies. Lu et al. have proved with a series of articles that abnormal DNA hypomethylation leads to the autoimmune of T cells, which is regulated by miRNA and lncRNA, resulting in SLE [33–36]. Genes like CD70, CD11a, and *PRF1* show

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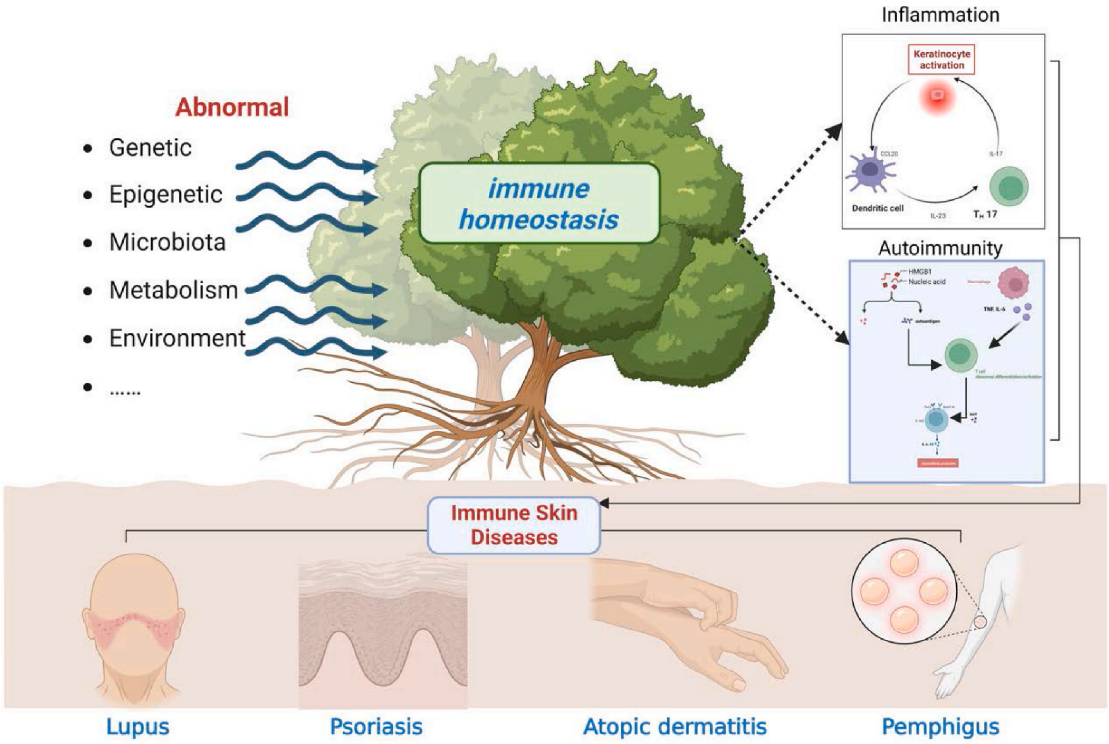

Fig. 1. Disruption of immune homeostasis leads to the development of immune skin diseases, including lupus erythematosus, psoriasis, atopic dermatitis, pemphigus, etc. Abnormal genetic and epigenetic regulation, disturbed gut or skin microbiome, pathological metabolism, and environmental factors are all involved in the development of immune skin diseases. The restoration of immune homeostasis is the goal of treatment (Created with BioRender.com).

hypomethylation in SLE patients, linked with disease activity [35,37]. And changes in methylation of the CD40L gene correlate with clinical features of SLE, which was related to gender differences in morbidity [38]. Among all the differentially methylated genes, *IFI44L* is a highly effective diagnostic marker, and the detection method established by Zhang et enables it to diagnose SLE quickly and easily and distinguish it from other diseases [39]. Meanwhile, *IFI44L* may be related to disease activity [40]. It revealed the potential of methylation markers for early disease prediction. Drugs targeting abnormal DNA methylation in SLE are also being explored. 5-azacytidine and decitabine, which inhibit DNA methyltransferases (DNMTs), are being explored in clinical trials for their potential to reverse aberrant DNA methylation in SLE patients [41]. And HDAC inhibitors such as Vorinostat and Romidepsin are under clinical trials to evaluate their efficacy in treating SLE by modulating epigenetic changes [42,43]. However, these drugs regulate methylation without cell targeting, their safety remains to be further verified.

miRNAs and LncRNAs have affected DNA transcription in SLE. These miRNAs can activate autoimmune genes by influencing DNA methylation and other pathways, offering potential targets for therapeutic intervention. miR-17∼92, miR-146a and miR-148a can stimulate B cells to produce excess autoantibodies, resulting in onset of SLE [44]. miR-155, miR-21, and miR-7 are associated with autoimmunity of B cells by regulating GC Responses in SLE [45,46]. Down-regulating expression of miR-155 can alleviate disease symptoms in mouse models of lupus. Targeting these miRNAs to inhibit B cell autoimmunity is a promising therapeutic approach for SLE, which avoids the risk of tumor and infection after non-selective targeting of B cells. Targeting miRNAs like miR-21 and miR-29 are using in renal fibrosis and myocardial infarctionin. The efficacy and safety of treatment in SLE remain to be explored [47,48]. miRNAs associated with SLE disease activity can be used as markers. A positive correlation was observed between serum miR-21 levels and the SLE disease activity index(SLEDAI) score [49]. Zeng discovered that miR-5100 could potentially serve as serum biomarker to distinguish SLE from rheumatoid arthritis and healthy individuals [50]. In the differential diagnosis of subtypes, notable variations were observed in the expression of miR-150 and miR-30a in cases of lupus nephritis [51]. miRNAs as markers for SLE diagnosis and disease detection remains to be further validated. And more convenient and high-throughput detection technologies need be developed.

3.2. *Psoriasis*

DNA methylation plays an important role in the pathogenesis of psoriasis. Methylation of insulin receptor substrate 1 (*IRS1*) and p16INK4a were significantly changed and can be potential biomarkers [52,53]. A combination of 6 differential methylation sites can be used to distinguish PsA, psoriasis vulgaris, rheumatoid arthritis and healthy individuals with high sensitivity and specificity [54]. The wingless-related integration site (*Wnt*) passway is important in psoriasis, and the methylation of *Wnt* inhibitory factor 1 (*WIF1*) has been proven upregulated in psoriasis. Decitabine can treat IMQ-induced psoriasis mice, proposing the manipulation of DNA methylation as a viable approach for treatment [55].

More epigenetic studies focus on miRNA and psoriasis. miR-21 showed a significant elevation in psoriasis cases and exhibited a positive correlation with the Psoriasis Area Severity Index (PASI) score, while miR-125b was downregulated and negative correlated with PASI score [56]. In another study, locked nucleic acid (LNA)-modified anti-miR-21 compounds demonstrated the ability to treat psoriasis [57]. Upregulated miR-210 can promote psoriasis and its inhibitors are under preclinical study [58]. miR-146a is another important miRNA in psoriasis, and its overexpression can inhibit IL-17-mediated inflammation, so miR-146a mimics could relieve symptoms after delivery to the lesion [59].

4. Microbiomics

4.1. Atopic dermatitis

Recent scientific research has consistently demonstrated considerable dysbiosis in both the skin and gut in ISDs. The abnormal microbiome interacts with the immune cells, further promoting disease development. AD patients have obvious gut microbiome disturbance in both infancy and adulthood [60–62]. AD frequently correlates with a decreased diversity of gut bacteria overall. This reduction is considered a hallmark of dysbiosis and has been linked to the severity of AD symptoms [63]. Specifically, a reduction in the presence of advantageous bacteria such as *Bifidobacteria* and a rise in harmful species like *Clostridia* and *Staphylococcus aureus* have been observed. It was found that the count of *E. coli* is associated with the level of serum IgE, which in turn positively correlates with the severity of the disease [64]. After that, Penders et al. found that high level of *E. coli or C. difficile* in infancy have a higher risk of developing AD or allergic sensitization, suggesting that individual bacterial abundance may show potential for prediagnosis [65]. Besides, a significant alteration in the ratio of *Bacteroides* to *Firmicutes* was found in AD patients, which could serve as a diagnostic marker [66]. Certain strains like *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* have been found to be less abundant in AD patients, also indicating their potential role as biomarkers [67]. At present, the application of dysfunctional intestinal flora in clinical diagnosis is not much. However, it offers a novel concept and target for AD treatment, with the therapeutic intervention of intestinal bacteria demonstrating safety and effectiveness in numerous clinical trials [68–70]. Probiotics, particularly *Lactobacillus* and *Bifidobacterium* strains, have been extensively studied for their potential to alleviate AD symptoms. These beneficial bacteria may modulate the immune system enhancing expression of IL-10 and TGF-β, reducing IL-12, IL-18, and tumor necrosis factor (TNF)-α levels, creating signals for immune tolerance, and reestablishing the equilibrium of gut microbiota [71,72]. AD was treated with the probiotic strain *L. rhamnosus* 19070-2, downregulating the level of IgE [73]. Research has shown that introducing prebiotic oligosaccharide mixtures into the diets of infants before they reach one year of age can decrease the incidence of AD by an average of 44 % [74]. Reduced vitamin D levels in the serum have been linked to gut microbiome dysbiosis. Probiotics that can elevate vitamin D levels or stimulate vitamin D receptor expression are beneficial in supplementary treatment [75,76]. The exploration of dietary prebiotics, known for fostering the growth of advantageous gut bacteria, has shown promise in the management of AD. Kim and colleagues established the potential role of D-galactose as a prebiotic in mitigating AD through the modification of gut microbiota [77]. LactoSporin®, a purified extracellular metabolite derived from the fermented broth of Bacillus coagulans MTCC 5856 (also known as Bacillus ferment filtrate extract in International Nomenclature Cosmetic Ingredient terminology), was used for AD treating. In a study that was randomized, double-blind, and placebo-controlled, researchers found that administering a blend of neutral short-chain galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS) to infants for 6 months post-birth notably decreased the cumulative incidence of AD at the age of two years in infants with a family history of the condition. This finding highlights the importance of FOS and GOS, which are the most commonly researched prebiotics [78]. The transplantation of fecal microbiota, a procedure where fecal bacteria from a healthy individual are transferred to a patient, represents a growing field of study in the therapeutic approaches for AD. It aims to directly alter the gut microbiome and improve AD symptoms. Studies conducted on mice have demonstrated that Fecal Microbiota Transplantation (FMT) enhances the balance between *Firmicutes* and *Bacteroidetes*, as well as increases the population of butyricogenic bacteria. This helps in reestablishing the equilibrium of the gut microbiome and aids in alleviating the symptoms of AD [79]. Clinical trials have also confirmed that FMT can significantly improve skin lesions in AD patients and reduce the use of skin corticosteroids, which is safe and effective. However, the optimum frequency and long-term safety of FMT still need to be validated in more trials [80].

The study of skin microbiota in AD is an evolving field. Patients with AD exhibit a greater proportion of *S. aureus* in their skin microbiome than individuals without the condition. *S. aureus* colonization can antagonize the growth of other skin microbiome, disrupt the stability and diversity of skin flora, destroy the inhibitory activity of Treg cells, activate Th1/Th2 immune response and express a variety of inflammatory cytokines [81,82]. And *S. aureus* in skin is positive related to the serum level of IgE [83]. It was found that the abundance of *Staphylococcus acnes* was negatively correlated with *Staphylococcus aureus*, in which the fermentation products of *Staphylococcus acnes* blocked the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* [84]. In AD, dysregulation of skin flora is also closely related to defective skin barrier function. Filaggrin, which is essential for skin barrier, its deficiency in AD is also associated with *S. aureus* [85]. There are other skin bacterial genera can work as AD biomarkers. *Staphylococcus epidermidis*, typically abundant in healthy skin, is found in lower quantities in AD patients. Its presence might indicate a healthier skin microbiota [86] and a genus of fungi, *Malassezia*, has been linked to AD, especially in cases with head and neck involvement. Monitoring its levels could be relevant for disease management in specific AD subtypes [87]. Rebuilding the skin microbiota ecosystem in AD mainly restores skin microbiome homeostasis by decreasing *S. aureus*. NBUVB therapy can downregulate the *S. aureus* population and increase the diversity of the microbiome [88]. Omiganan, a synthetic analogue of the antimicrobial peptide indolicidin, exhibits effectiveness against *S. aureus*. The application of Omiganan has the potential to markedly decrease the colonization of aureus and reestablish the diversity of the skin microbiome. But the improvement of AD symptoms is not significant, suggesting that anti-aureus therapy alone may not be enough. *Staphylococcus epidermidis*and and other coagulase-negative *Staphylococci* (CoNS) can antagonize *Staphylococcus aureus* colonization. Clinical trials have found that CoNS strain with antibacterial activity can effectively reduce the colonization of *S. aureus* in AD patients, and the disease severity can be significantly improved [89]. Myles et al. applied *Roseomonas mucosa (R. mucosa)*, a type of skin bacteria obtained from healthy people to AD and showed good clinical efficacy [90]. In addition, skin flora metabolites also have inhibitory effects on inflammatory pathways. Propionic acid may alleviate the skin inflammatory response of AD by inhibiting IL33 [91].

4.2. Systemic lupus erythematosus

The link between the gut microbiome and SLE has been extensively established. Research across various ethnic groups reveals slight variations in the intestinal flora of SLE patients from different regions. Generally, there is a reduced diversity in the gut microbiome of SLE patients compared to healthy individuals. Most studies indicate a lower *Firmicutes/Bacteroides* (F/B) ratio in SLE patients, and alterations have been observed in the levels of *Proteobacteria* and *Actinobacteria* [92]. A study found that *L.salivarius* abundances was positively correlated with SLEDAI score, showing the potential to monitor the disease activity [93]. The bacteriophages is another mark for SLE, it was markedly increased in the gut of patients, and these changes in viral species were associated with various clinical indicators [94]. For the disorder of microbiome in SLE, in a single-arm clinical trial, Huang and colleagues demonstrated the safety and efficacy of FMT as a treatment for SLE. They found that FMT notably lowers disease activity, enhances intestinal bacterial diversity, and diminishes inflammatory markers like IL6 [95]. Subsequent study demonstrated that FMT can correct pathologic hypomethylation in SLE patients, particularly interferon-associated gene methylation, which may be a function of microbiota and metabolites [96]. Research into the use of probiotics for treating SLE shows considerable promise. *Lactobacillus fermentum* CECT5716 can improve

lupus disease, reduce cardiovascular complications and kidney damage in SLE mice [97]. Administering fermented *Lactobacillus fermentum* CECT5716a and *Bifidobacterium brevis* CECT7263 was effective in averting hypertension and endothelial dysfunction in lupus mouse models activated by toll-like receptor 9 [98,99]. The skin microbiome of SLE is closely related to the formation of skin lesions. Skin colonization by staphylococcus induces IL-23/IL-17 inflammation pathway, and is involved in the formation of lupus lesions [100]. In comparison to healthy individuals, the skin microbiome in the rash-affected areas of SLE patients showed a reduction in diversity and richness, yet it was more diverse than in the non-rash areas of SLE patients [101]. In patients with SLE, disturbances in the skin microbiome were linked to various clinical characteristics, including reduced serum complement levels, gender, kidney involvement, and muscle inflammation, indicating the disturbed microbiome could monitor the activity of disease. *Staphylococcus aureus* and *Staphylococcus epidermidis*, colonizing on lesions in SLE patients with specificity, are potential biomarkers [102]. The treatment of SLE by targeting the skin microbiome has not been reported, but the local treatment of *Staphylococcus aureus* may be a way worth exploring.

5. Metabolomics

5.1. Psoriasis

Metabolic disorders, including obesity and diabetes, are frequently linked with psoriasis. In a metabolomics study, researchers identified 10 potential biomarkers for psoriasis related to its various subtypes, aiding in diagnosis and clinical use. Additionally, by analyzing the network of metabolite-protein interactions, they identified ESR1, OPRM1, and HSD11B1 as key proteins for potential topical treatments in psoriasis management [103]. The metabolic classification of psoriasis varies with the severity of the disease, and metabolomics helps to classify psoriasis subtypes accurately [102]. Kamleh and colleagues observed that circulating amino acid concentrations could indicate disease severity and the response to anti-TNFα therapy in patients with psoriasis [104]. In PsA, 12-Hydroxyeicosatetraenoic acid was associated with joint disease activity [105].

Metabolomics also provides new ideas for the treatment of psoriasis. In mice, aminooxy acetic acid (AOA) could alleviate psoriasis symptoms by impacting the Th17-associated passway, suggesting a new therapeutic target [106]. Chen et al. found that a higher level of L-carnitine (LC(C0)) can reduce skin thickness and Th17 infiltration in IMQ-induced mice, suggesting that supplementing with LC(C0) could be a viable therapeutic approach for treating psoriasis [107].

6. Conclusions

Immunological homeostasis represents the ideal state for ISDs. However, immune dysregulation occurs when disrupted by abnormal genetic regulation, epigenetic modifications, microbial dysbiosis, or metabolic anomalies, leading to the onset or exacerbation of ISDs. As depicted in Fig. 1, immunological homeostasis is akin to a robust tree swaying in the wind, with the goal of treatment to stabilize the tree.

Basic research utilizing multi-omics approaches has significantly enhanced our knowledge of the causes and development of ISDs, as well as the regulatory mechanisms of the immune system. This research has also provided new diagnostic biomarkers, indicators of disease activity, and prognostic markers while offering novel therapeutic targets. However, the future direction requires contemplation on precisely subtype diagnoses and selecting appropriate diagnostic biomarkers. Furthermore, the optimal dosages of various targeted drugs and new therapeutic technologies, along with their long-term side effects, remain to be explored by real-world studies.

Author contributions

Qianjin Lu, Ming Zhao: Conceptualization editing. **Bo Zhang, Xiaole Mei**: writing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Bo Zhang[a,b,c,d], Xiaole Mei[a,b,c,d], Ming Zhao[a,b,c,d,**], Qianjin Lu[a,b,c,d,*]

[a] *Institute of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Nanjing, 210042, China*

[b] *Key Laboratory of Basic and Translational Research on Immune-Mediated Skin Diseases, Chinese Academy of Medical Sciences, Nanjing, China*

[c] *Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and STIs, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, China*

[d] *Department of Dermatology, Hunan Key Laboratory of Medical Epigenomics, Second Xiangya Hospital, Central South University, Changsha, 410011, China*

[*] Corresponding author. Institute of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Nanjing, 210042, China.

[**] Corresponding author. Institute of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Nanjing, 210042, China.

E-mail addresses: zhaoming301@pumcderm.cams.cn (M. Zhao), qianlu5860@pumcderm.cams.cn (Q. Lu).