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Autoimmune Skin Diseases: Origin, Classification, Progression, and Advanced Therapeutic Strategies

Jiayi Du

Ningbo Binhai International Cooperative School, Zhejiang, Ningbo, China, 315800
2283562164@qq.com

Abstract:

Globally, the incidence of complex skin diseases such as psoriasis and lupus erythematosus is continuously increasing, and current therapies often fail to achieve complete disease remission. This review explores the pathogenesis, classification, and progression of autoimmune skin diseases, as well as several promising emerging treatment strategies, including JAK-STAT inhibitors, gene and cell therapies, microbiome regulation, and the application of nanotechnology. These strategies aim to enhance disease management efficacy and improve patients' quality of life. However, several challenges remain, such as safety concerns, high treatment costs, and interindividual variability in treatment response. Although these challenges mean that a complete cure for many stubborn skin diseases will still take some time, the current progress has brought new weapons for more effective control of the disease and improvement of quality of life. For instance, JAK(Ruxolitinib) inhibitors and biologics are now integral to managing atopic dermatitis and psoriasis. While stem cell therapy demonstrates potential in addressing autoimmune conditions like systemic sclerosis and lupus.

Keywords: autoimmune skin diseases, JAK-STAT inhibitors, microbiome regulatio, Nanotechnology applications

1. Introduction

Socioeconomic development, changes in pharmaceutical use, and environmental shifts have led to an increase in skin disorders across all age groups, with a particular rise in complex autoimmune skin diseases. Autoimmune skin diseases have become a global issue. However, there are gaps in people's understanding of the disease mechanism and in the comparative analysis of emerging treatment methods. For instance, psoriasis is a complex disease with multiple causes, such as genetics and the immune system. At the same time, it is also a very common skin disease. Approximately 2% of Americans suffer

from this condition. In a study conducted in the United States, researchers found that 3.6% of whites, nearly 2% of African Americans, and 1.6% of Hispanics have psoriasis[1]. As a result, it is prone to recurrence and requires long-term treatment[1]. Systemic Lupus Erythematosus(SLE) remains incurable; patients can prevent and monitor organ damage through long-term strategies such as regular follow-ups [1]. At present, the medical community has not yet fully grasped the complex mechanisms involved. Although previous studies mainly focused on traditional immunosuppressive therapies and their clinical efficacy, the complex mechanisms underlying these diseases have not been fully elucidated. Unlike earlier studies that mainly focused on symptom control, this review aims to deeply explore the causes, classification, and progression of autoimmune skin diseases, with particular attention to emerging cutting-edge treatment methods. These methods include small molecule inhibitors (such as JAK-STAT pathway inhibitors), gene therapy, cell-based interventions, microbiome regulation, and nanotechnology. By combining the insights of the article with advanced treatment approaches, new ideas and methods for clinical treatment are provided. Through a better understanding and treatment of complex skin diseases, researchers can improve the treatment outcomes for patients.

2. Pathogenesis and Etiology of Autoimmune Skin Diseases

The skin, as the largest organ of the human body, is composed of water, proteins, lipids, and minerals. It serves as the first line of defense, protecting internal tissues from pathogens, harmful substances, and bacteria. Autoimmune skin diseases arise when the immune system mistakenly targets the body's own skin cells, leading to chronic inflammation and tissue damage. For instance, vitiligo is a chronic autoimmune disease characterized by the immune system attacking melanocytes, leading to their loss of function or apoptosis. This condition often has a strong genetic component, with many patients having family members who also suffer from it[2]; Similarly, psoriasis is a hereditary disease with a genetic predisposition. Research has shown that certain genes increase the likelihood of developing psoriasis. However, not all individuals with a family history of the disease will develop it. Common triggers of psoriasis include skin damage, certain medications, tobacco, weather, and stress[3]. Additionally, estrogen levels contribute to gender differences in lupus incidence: women are more susceptible to lupus than men. Studies have found that women with rheumatoid arthritis often experience exacerbated symptoms during periods of high estrogen levels, such as premenstrual phases and pregnancy.

3. The main classifications of skin diseases

The causes of these diseases are complex, ranging from external pathogen invasion to internal immune system abnormalities, as well as genetic factors, etc. Currently, there are mainly three of the most core and common classifications.

3.1 Infectious Skin

The first type is infectious skin conditions, which are mainly caused by bacteria, viruses, fungi, and parasites. Bacterial infections include abscesses, carbuncles, pustular dermatitis, folliculitis, and pustular eruptions; viral infections include herpes simplex virus infection, infectious mollusks, and warts, as well as chickenpox and measles, which can cause skin symptoms; fungal infections include common athlete's foot and candida infection; parasitic infections include hookworm, lice, and mite infections [4].

3.2 Autoimmune Skin

Autoimmune skin diseases are characterized by immune system dysfunction, where the immune system mistakenly attacks normal skin tissues, leading to chronic inflammation and tissue damage. They are usually not contagious, but the condition may recur and require long-term management. Psoriasis is a chronic disease, where the immune system is overly active, causing accelerated growth of skin cells, with red patches covered by silver-white scales, which often occur between the ages of 10 and 35 or as people age. It has a hereditary component, and factors such as infection can trigger it. Scleroderma is a connective tissue disease, divided into local and systemic types. The former mainly affects the skin, bones, and muscles, while the latter also involves internal organs. It is more prevalent in women, with occupational exposure to silica dust identified as a risk factor. Cutaneous lupus causes the immune system to attack skin cells, and about two-thirds of systemic lupus erythematosus patients will suffer from it. Although it cannot be cured, it can be treated. Dermatomyositis mainly affects muscles and skin, is related to polymyositis, and can be distinguished by rashes. The pediatric type and adult type are different. Behcet's disease is rare, causing inflammation of systemic blood vessels, with diverse symptoms. It is common in the 20-30 age range, and the severity of the condition varies from person to person. Erythema nodosum and bullae affect the skin and mucous membranes of the eyes, requiring long-term

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treatment; otherwise, it may lead to vision loss[5].

3.3 Genetic Skin

This category encompasses a broad group of chronic, recurrent, non-infectious inflammatory diseases that are typically triggered by a combination of genetic susceptibility and environmental factors (such as allergens and irritants). Genetic skin diseases are a type of skin disorder caused by genetic mutations. They reside in an individual's genome and can be passed on to offspring through genetic means, such as vitiligo and psoriasis. Dermatitis refers to skin irritation and rashes caused by various factors such as genetics, immunity, and infection.

3.4 Inflammatory Skin

Common symptoms include dry skin, redness, and inflammation. It is not contagious. There are numerous subtypes of dermatitis, affecting individuals of all ages, with distinct risk factors for each subtype. Different types of dermatitis have different risk factors. For example, atopic dermatitis is related to family history and gender, while contact dermatitis is associated with exposure to chemicals in the workplace environment. The initial signs of dermatitis are usually inflammation and redness, which vary depending on the type[6].

Inflammation is a defensive response of the body to damage (such as pathogens, damaged cells, and irritants), with the main purpose of eliminating harmful stimuli and initiating the repair process. The process can be summarized as "redness, swelling, heat, pain, and dysfunction"[7]. Leukocyte exudation is divided into four stages. The rolling and adhesion stage: During the movement of white blood cells in the blood, they temporarily bind to the ligands on the surface of vascular endothelial cells through surface adhesion molecules, causing a slowdown and rolling along the vessel wall. For example, when vascular endothelium is stimulated by inflammatory factors, it expresses selectins that bind to the sugar ligands on the surface of white blood cells, forming an "adhesion- de-adhesion" cycle. The activation and strong adhesion stage: Cytokines at the inflammatory site bind to the receptors on the surface of white blood cells, causing the integrins on the surface of white blood cells to change from low affinity to high affinity, and then strongly bind to the adhesion molecules on the surface of endothelial cells. The white blood cells stop rolling and tightly adhere to the vessel wall. The transendothelial migration stage: White blood cells pass through the intercellular connections between vascular endothelial cells or directly penetrate the endothelial cells by deforming. They rely on the reorganization of the cytoskeleton and proteolytic enzymes to degrade the basement membrane, and the endothelial cells express related molecules to guide the migration direction. The chemotactic movement stage: The white blood cells entering the tissue move directionally towards the inflammatory or injured site under the guidance of the chemotactic gradient, and exert functions such as phagocytosis after reaching the site[7]. At the same time, anyone, regardless of age, can suffer from dermatitis. Atopic dermatitis typically begins in childhood but can occur at any age; it is commonly seen in individuals with a personal or family history of allergies, such as asthma or allergic rhinitis, and often affects areas like the hands and antecubital fossa. Contact dermatitis is triggered by exposure to external substances, with risk factors including handling chemicals such as dyes, solvents, or detergents in industrial, culinary, or gardening settings. Seborrheic dermatitis (including cradle cap in infants) frequently occurs in babies but may also develop in adults, influenced by warm climates, excessive sebum production, and Malassezia colonization. Xerotic dermatitis (also known as dry skin dermatitis) is associated with risk factors such as female sex, age between 15 and 45, frequent bathing, and arid environments[8].

3.5 The JAK-STAT pathway and its inhibitors

The JAK-STAT signaling pathway plays a critical role in mediating numerous inflammatory and immune responses, making it a significant therapeutic target for various dermatological conditions. Dysregulation of this pathway is implicated in chronic inflammatory skin diseases such as eczema and psoriasis. Recently, LEO Pharma announced that the FDA approved ANZUPGO (delgocitinib) cream, the world's first topical JAK inhibitor specifically indicated for moderate to severe chronic hand eczema (CHE) in adults. For many patients, CHE is a persistent and debilitating condition characterized by chronically rough, thickened, scaly skin, painful fissures, intense pruritus, and recurrent flares, significantly impairing hand function, daily activities, and quality of life. Hand eczema is a common chronic disorder, with a global incidence of approximately 5.5-8.8 per 1000 person-years, an annual prevalence of 5.2%-10%, and a lifetime prevalence reaching up to 14.5%. Chronic hand eczema constitutes about 63.8% of cases, most of which are moderate to severe in severity. Currently, two JAK inhibitors are notably used in dermatological applications: ruxolitinib and delgocitinib. Table 1 summarizes their profiles, clinical trial results, and applications:

Table 1. The differences of various JAK inhibitors in dermatology

Name	Developer	Targets Inhibited	Original Indication	Dermatologic Application
Ruxolitinib	Incyte Corporation	JAK1, JAK2	Myelofibrosis, GVHD	Atopic Dermatitis, CHE
Delgocitinib	Japan Tobacco Inc. (JT)	JAK1, JAK2, JAK3, TYK2	N/A (New Topical)	Chronic Hand Eczema (CHE)

Ruxolitinib was initially developed by Incyte Corporation for hematologic conditions such as myelofibrosis and graft-versus-host disease (GVHD). It inhibits JAK1 and JAK2, thereby reducing inflammatory cytokine signaling. Its cream formulation has been repurposed for dermatological conditions including atopic dermatitis and chronic hand eczema, showing significant efficacy in reducing inflammation and pruritus. In clinical trials, ruxolitinib demonstrated markedly superior response rates compared to control groups—29.1% versus 6.9% in GVHD and 49.5% versus 18.2% in myelofibrosis ($p<0.001$). By 2024, its global sales reached $4.728 billion, reflecting its broad applicability and clinical acceptance.

Delgocitinib, developed by Japan Tobacco Inc. (JT), is a broad-spectrum JAK inhibitor that targets JAK1, JAK2, JAK3, and TYK2. It potently blocks signaling of multiple pro-inflammatory cytokines, including IL-4, IL-13, and IL-23, effectively reducing skin inflammation and itching. Although not yet approved in China, delgocitinib cream has shown promising results in clinical trials for moderate to severe CHE. At week 16, patients using delgocitinib achieved significantly higher rates of meeting the primary endpoint—Investigator's Global Assessment for chronic hand eczema (IGA-CHE) score of 0 or 1 with ≥2-point improvement from baseline—and the key secondary endpoint (HECSI-75 improvement ≥75%) compared to those using a placebo[9].

4. Gene editing technology

Inflammatory skin diseases (ISDs) are extremely stubborn diseases, characterized by the activation of innate and adaptive immune responses driven by pro-inflammatory cytokine production. Inflammatory skin diseases such as psoriasis and atopic dermatitis (AD) are becoming increasingly prevalent and have become a major threat to public health. Current treatment options are limited: for example, long-term use of glucocorticoids often leads to drug resistance, progressing the disease to a chronic state and severely impairing patients' quality of life. The soluble microneedle technology was designed by the team led by Professor Ping Yuan from the School of Pharmacy of Zhejiang University. This technology combines a nano-formulation carrying the Cas9 ribonucleoprotein (RPN) gene editing agent with high specificity targeting NLRP3 and glucocorticoids for in situ treatment of ISDs. This technology has two key features: one is the design and invention of a soluble microneedle loading nano-formulation technology, and the other is the in situ combination of NLRP3 gene editing and glucocorticoid administration and transdermal delivery, which can effectively treat ISDs[10].

5. Cell Therapy

Cell therapy, especially chimeric antigen receptor T-cell (CAR-T) therapy, modifies the patient's own T cells through genetic engineering, enabling them to specifically recognize and attack tumor cells. It has achieved revolutionary success in certain recurrent or refractory hematological cancers. In the second phase of the ZUMA-1 trial, Axicabtagene Ciloleucel (a CD19-targeting CAR-T cell therapy) recruited 111 adult patients with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, or transformed follicular lymphoma. Prior to this, all patients had been resistant to previous treatments (i.e., treatment failure). Eventually, 101 patients were injected. From the therapeutic outcome, namely the proportion of patients achieving the predetermined standard of tumor shrinkage (complete or partial remission) after treatment: objective response rate (ORR): 82% (83/101); complete response rate (CR): 54% (55/101). Among the patients who remained in remission during the subsequent 15.4-month follow-up, 42% maintained remission at the end of the follow-up period. From the survival results, 59% of the patients survived for 12 months. For patients with refractory large B-cell lymphoma who are ineffective to traditional chemotherapy and have a very poor prognosis, a single infusion of Axicabtagene Ciloleucel (Yescarta) achieved an ORR of 82% and a CR of 54%. This is an unprecedented breakthrough achievement. However, its safety still cannot be ignored. The successful application of axicabtagene ciloleucel has demonstrated that CAR-T cell therapy can be an effective treatment option for fatal cancers, bringing new hope to countless patients who have failed traditional end-of-life treatments and completely transforming the treatment paradigm for hematological malignancies.

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6. Microbiome regulation and NT (Nanotechnology)

The occurrence and development of atopic dermatitis (AD) are closely related to the imbalance of the skin microecology. Its characteristic is the imbalance of the ratio between pathogenic bacteria and commensal bacteria. Specifically, the abnormal proliferation of Staphylococcus aureus and the expression of its virulence factors form a vicious cycle with skin barrier damage and immune inflammatory response; meanwhile, the commensal bacteria with barrier protection and anti-inflammatory effects (such as Staphylococcus epidermidis) are significantly reduced, further aggravating the disease. Currently, some biological agents not only alleviate the clinical symptoms of AD but also show potential effects in regulating the skin microbiota. Based on this mechanism, a variety of new treatment strategies targeting microorganisms are emerging, mainly including: local antibacterial drugs specifically targeting the clearance of Staphylococcus aureus, self-transplantation of beneficial microorganisms to restore the balance of the microbiota, and the use of immunomodulatory bacterial preparations such as heat-killed Lactobacillus johnsonii NCC533. In addition, quorum-sensing inhibitors, as a promising strategy, inhibit the expression of virulence factors and biofilm formation of Staphylococcus aureus by blocking its group communication system, thereby reducing its pathogenicity rather than directly killing it, providing a new idea for mitigating drug resistance development [11].

Liposome transdermal drug delivery system (TDDS) has attracted widespread attention due to its non-invasive nature, ease of use, and avoidance of first-pass metabolism. However, the strong barrier effect of the stratum corneum (SC) limits its application. In recent years, the synergistic strategy of nanocarriers and physical assistance techniques has brought significant breakthroughs in this field. The main barrier to the skin is the stratum corneum, and drugs can penetrate through the transdermal or accessory pathways (such as hair follicles). Nanocarriers can enhance penetration by adjusting particle size (e.g., <500 nm) and surface properties (e.g., positive charge modification)—with flexible nanocarriers (e.g., liposomes) showing particularly strong performance. There are mainly two design strategies for nanocarriers: soft nanocarriers, rigid nanoparticles, and nanoliposomes and polymer nanoparticles. Through the synergistic enhancement of physical assistance techniques, such as microneedle arrays, iontophoresis, and laser and magnetic response technologies. Significant achievements have been made in acne, hair loss, pain management, and infection treatment. Some formulations have shown excellent efficacy and sustained efficacy in animal or clinical models. In the current era of rapid development of AI, artificial intelligence can be used to predict drug transdermal behavior and optimize formulation design, such as improving penetration models with deep learning and microneedle printing. In the future, it will be necessary to further develop penetration kinetics models, develop intelligent patches with integrated sensing functions, and combine AI to achieve personalized TDDS design, promoting the development of precise transdermal treatment[12].

7. Conclusion

Due to the complex pathogenesis of autoimmune skin diseases, which involves genetic, immune, environmental and microbiome-related factors, some emerging therapies show promising results. For instance, JAK-STAT inhibitors (such as ruxolitinib and delgocitinib), and gene editing (such as the CRISPR-Cas9 technology targeting NLRP3) can improve the symptoms of conditions like chronic hand eczema. Gene editing techniques like CRISPR-Cas9 offer the possibility of curing stubborn inflammatory diseases by targeting genes such as NLRP3. Cell therapies, including mesenchymal stem cells and exosomes, exhibit anti-inflammatory and regenerative properties in psoriasis and scleroderma. Regulating the microbiome through probiotics, antimicrobial agents or metabolites helps restore the skin's ecological balance. Nanotechnology-based delivery systems (such as liposomes and microneedles) can enhance drug penetration and precision. These novel approaches significantly improve treatment efficacy and patients' quality of life. For instance, JAK inhibitors and biologics are increasingly integral in managing atopic dermatitis and psoriasis, while stem cell therapy holds promise for systemic sclerosis and lupus. However, challenges remain in safety (e.g., infection risks with JAK inhibitors, potential off-target effects in gene editing), high costs, interpatient variability, and technical scalability. Many therapies are still in early research stages with limited clinical data. Despite these hurdles, advances in targeted treatments provide new tools for better disease control and symptom management, paving the way for more personalized and effective dermatological care.

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