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# Latest Advances in Inflammatory Skin Disease

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## Abstract

Inflammatory skin disorders are chronic diseases that present with redness, itching, and plaques and occur due to the interaction between genetic and environmental factors. The immune basis of the disease involves the action of proinflammatory cytokines and overexpression of CD4+ and CD8+ T-cells.

**Objective**
To discuss the developments in chronic inflammatory disease pathogenesis and treatments using single-cell RNA sequencing and spatial transcriptomics.

**Approach**

Single-cell RNA analysis and spatial transcriptomics allow one to study a cell individually and identify the cell-to-cell differences and the mutations that can be found within individual cells in a pool. It aids in improved understanding of disease pathogenesis and helps identify the distinct mutations that arise in every disease which can be targeted for therapy. However, this technology is quite new and requires improvements on cost reduction and standardization of methods. Nevertheless, this approach has opened new avenues to studying disease pathogenesis and creating drugs targeting the active inflammatory pathway.

**Conclusion**
This review focuses on chronic inflammatory skin conditions like psoriasis, atopic dermatitis, acne, lichen planus, and alopecia. This review provides insight into their pathogenesis and targeted therapy using the latest advances in the field of single-cell RNA sequencing and transcriptomics

**Keywords:** Biologic, JAK Inhibitors, Gene Therapy, Combination Therapies, Biomarkers, Tissue Engineering.

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## *Introduction*

Inflammatory skin diseases are the largest class of chronic skin disorders. It includes diseases such as eczema, dermatitis, psoriasis, and acne (Liu et al., 2022). Most of these diseases present with hallmark symptoms of inflammation including erythema, pruritus, pain, and dryness. Each of these disorders is also accompanied by a specific rash, for example acne presents with comedones and psoriasis presents with a scaly silvery rash. These multifactorial disorders have a specific genetic predisposition that is triggered by environmental stimuli. Epidemiology has proven an 80% heritability of the diseases. These diseases are caused by the synergistic or additive effects of

multiple loci rather than a single gene mutation (Rodriguez et al. 2011). Environmental factors play a major role in all inflammatory skin disorders. They alter the homeostasis and functioning of the skin to keep it well adapted to the external environment and thus may occasionally cause an inflammatory reaction. Sawada and colleagues (2021) explained that the lifestyles of patients play an important role in the pathogenesis of inflammatory skin conditions. Excessive intake of protein in the form of gluten, disruption in sleep pattern, obesity, smoking, and alcohol regulate the helper T cell response leading to increased production of pro-inflammatory cytokines which cause skin inflammatory disorders. Decreased intake of dietary fiber and omega-3 fatty acids has been associated with an increase in cytokine production which mediates the proinflammatory response of the skin (Sawada et al. 2021).

### *Known Causes of Inflammatory Skin Disorders*

Inflammatory skin disorders are most caused by the interaction of genetic factors with environmental stimuli. Many immune factors responsible for these diseases have been studied in detail.

Psoriasis is a chronic inflammatory skin condition associated with plaque formation on the extensor surfaces of the body. Liu and his colleagues (2020) identified Interleukin-17 as the major pro-inflammatory cytokine involved in the pathogenesis of psoriasis and other inflammatory disorders like atopic dermatitis, pemphigus, or alopecia. Genetically altered mouse models have identified IL-4, IL-12, and IL-13 to be the major cause of severe pruritus and eczema which are the hallmarks of atopic dermatitis (Nakajima et al. 2019). Acne vulgaris is caused by the hypersensitive response of sebaceous glands to normal androgen levels, triggered by the bacterium *P. acnes* (Motosko et al. 2019). Lichen planus is a chronic inflammatory skin condition with possible precancerous origin and an unclear etiology (Wang et al. 2021). Drug eruption is an inflammatory response associated with erythema and pruritus after intake of a drug against which the immune system is sensitive, usually sulfa drugs (Zhang et al. 2021).

### *Recent Advances in Studying Inflammatory Disorders*

Most of the research in dermatology is based on animal models. While these models can mimic human skin, further clarity is needed to determine how closely they can imitate human skin. As a result, there is a gap in the proper understanding of inflammatory diseases such as eczema, psoriasis, dermatitis, etc.

With the advent of recent technologies like single-cell RNA sequencing, it is now possible to study every single type of cell individually and have an idea about the functioning of the cells. Each cell can now be studied as a single unit and the information it provides in the form of genetic material and protein codes can be used to study different diseases. Single-cell RNA-sequencing and spatial transcriptomics are potent assays that help in the determination of cellular components and their spatial orientation (Houser et al. 2023).

They have also aided in determining the immunological disturbances in inflammatory disorders which can help to target therapy according to the specific mutation (Liu et al. 2022). Chronic inflammatory disorders of the skin are usually treated with topical corticosteroids which reduce inflammation, immunomodulators to reduce the hyperactive response of the immune system, antifungals, and antibiotics. Rare cases also require isotretinoin, methotrexate, and biologics. With the described treatments, these skin conditions remit but are not completely cured. Single-cell RNA sequencing and spatial transcriptomics allow for targeted therapy that will prove more beneficial for a cure while reducing the chances of drug resistance. It also provides information regarding cell heterogeneity and a small population of cells that are found within the lesions different than the rest of the cells. These small populations are often more susceptible to targeted therapy. Cell-to-cell differences and individual characteristics of different cells can be identified. Moreover, new mutations occurring in any disease can be studied most efficiently with these new technologies and therapy can be targeted to them.

## Discussion

### *Single-cell RNA Sequencing and Spatial Transcriptomics*

The first study on single-cell RNA sequencing was published in 2009. This new technique gave the advantage to study the sequencing and composition of mRNA in a cell that controls the properties and functioning of the cell. Previously used sequencing techniques were carried out on samples that had up to millions of cells but this held back the direct inspection of the unit of life- the cell (Haque et al. 2017). Genomic DNA, mRNA, and protein expression has been studied previously to comprehend the molecular knowledge of the cells. The available genetic material is usually in small quantities, so many millions of cells are analyzed simultaneously for practical reasons. The data on protein expression is required to understand the cell responses. The absolute complement of proteins that are expressed in a single cell is called a ‘proteome’. As an alternative method to studying the entire proteome, the researchers now study

the mRNA molecules that are used for protein-coding. These mRNA molecules are collectively called a 'transcriptome'. The expression of these mRNA molecules can bring about changes in the traits and functioning of the cells (Haque et al. 2017).

Single cell sequencing of mRNA allows the comparison of cellular proteins of various cells which helps to understand their heterogeneity. Rare populations of immune cells have also been identified which are more responsive toward various stimuli (Shalek et al. 2014). It has also provided valuable information for studying gene expression at the cellular level which can be applied to understand the regulation of gene modules, heterogeneity, and specification of the cell type (Wagner et al. 2016).

### *Applications of Single-cell RNA Sequencing in Inflammatory Skin Diseases*

Single-cell RNA sequencing has been used to classify inflammatory disorders into subgroups. However, the process is still in nascency. It has been used to understand the pathogenesis, characteristics of lesions, gene signatures, and cellular mechanisms involving different stages of the disease.

The use of single-cell mRNA sequencing in the understanding of inflammatory skin diseases is discussed below;

### *Atopic Dermatitis*

Atopic dermatitis is the most common form of eczema that leads to redness, dryness, itching, and resulting lichenification. The global burden disease study has ranked atopic dermatitis as the 15th most common non-fatal disease and as the most common chronic inflammatory skin disease (Laughter et al. 2021). The study collected data from 1990 to 2017 and showed a bimodal distribution with increased incidence in children and older individuals. Disease prevalence is 20% in children and 10% in adults (Stander et al. 2021).

Genetic predisposition weakened skin barrier, abnormalities in skin flora and immune disturbances have been identified as the primary causes of atopic dermatitis (Langan et al. 2020). The pathogenic mechanisms for atopic dermatitis are unclear and primarily involve dysfunctional T-cells (Th2 and Th17).

RNA sequencing has provided valuable information regarding the pathogenesis of the disease. The data extracted by carrying out skin biopsies of 6 patients with atopic dermatitis confirmed the presence of Th2 cells in skin lesions (Nomura et Al., 2023).

Helen and colleagues (2020) carried out single–cell RNA sequencing on the 4 lesional and 5 non-lesional samples obtained from 5 patients with atopic dermatitis that were compared with samples from 7 healthy controls. 39,042 transcriptomic profiles were created. The researchers identified a specific subpopulation of fibroblasts COL6A5+COL18A1+ and a specific dendritic cell population LAMP3+ unique to the lesions. These cells expressed special cytokine receptors CCL2, CCL19, and CCL7. Lesions showed high populations of T-cells as well. However, further research is required to evaluate if fibroblasts initiate the lesion or are in their healing phase.

Innate lymphoid cells, particularly type 2 also play a role in the pathogenesis of atopic dermatitis. Single-cell RNA sequencing conducted on mouse models has shown that the innate lymphoid cells can be of two types: skin-localized or circulating. The skin-localized cells are responsible for the synthesis of proinflammatory cytokines like IL-4, IL-5, and IL-13 which play a significant role in skin inflammation of atopic dermatitis (Nakatani et al. 2021).

Knowledge about the pathogenesis of atopic dermatitis can help in creating targeted therapies for the disease. 27 Japanese patients were given a 600 mg loading dose and then a weekly 300 mg dose of dupilumab for 16 weeks. Dupilumab is an antibody targeted against the IL-4 receptor which plays a major role in the pathogenesis of atopic dermatitis. Single-cell RNA sequencing carried out in the 16th week showed a remarkable decrease in the circulating levels of Th2 cells and innate lymphoid cells which proves the efficacy of the drug (Imai et al. 2021).

### *Psoriasis*

The global burden study evaluated data from 1990 to 2019 and identified the prevalence rate of psoriasis between 2-3% around the globe. People of ages 60-69 are the most affected population (Damiani et al. 2019).

Alwin (2015) identified the Il-17/Th23 pathway playing a predominant role in psoriasis progression. Antibodies that specifically target these pathways have been used in the treatment of psoriasis. Risankizumab is an IL-23 inhibitor is used for the treatment of moderate to severe cases of chronic plaque psoriasis (Haugh et al. 2018). The IL-17 inhibitor ixekizumab has shown a 75% reduction in the psoriasis-area-and-severity-index (PASI) at 12 weeks with a 150 mg dose given after every 2 weeks (Leonardi et al. 2017).

Single-cell RNA sequencing on emigrating cells of the skin has shown that psoriatic lesions are rich in IL-10 and have a decreased CCL27-CCR-10 interaction because of the impairment of basal keratinocytes (Kim et al. 2021).

Single-cell transcriptomics carried out on lesion biopsies from 11 patients was compared with skin biopsies of 5 healthy controls. The researchers found two types of Th17 cells which are a type of cytotoxic CD8+ cells. The cells expressing CXCL-13 were associated with severe symptoms (Liu et al. 2021). Almost 30% of the patients suffering

from psoriasis can develop psoriatic arthritis. Single-cell sequencing carried out on synovial fluid has shown increased expression of the chemokine receptor CXCR3 on CD8+ cells and upregulation of CXCL9 and CXCL10 in the synovial fluid (Penkava et al. 2020).
30 patients diagnosed with moderate to severe chronic plaque psoriasis was given monoclonal antibodies secukinumab (18 patients) and brodalumab (12 patients) which bind with IL-17 blocking its actions. 75% of the patients attained a 75% improvement in their PASI score after 3 months with 18.3% reductions in CXCR3 and 11.5% reductions in Th17 cells after therapy. The use of methotrexate and other interleukin inhibitors will augment the results, achieving remission much sooner in the disease process.

### *Lichen Planus*

Oral lichen planus is a common chronic inflammatory skin disorder. The exact pathogenesis of the disease is unknown but it has been associated with a possible precancerous etiology (Wang et al.2021).
RNA sequencing has identified 153 differentially expressed genes that could be the possible cause of the lesion (Wang et al., 2021).
Qionghua and his colleagues (2023) took four biopsy samples of oral lichen planus with their peripheral blood mononuclear cells. These samples were contrasted with two healthy biopsy samples and three healthy samples of peripheral blood mononuclear cells. Single-cell RNA analysis revealed activated memory CD8+ T-cells (Th17) in lichen planus samples. Other identified varieties of the cells include dendritic cells, macrophages, and fibroblasts; all of which work together to create the proinflammatory environment in the lesion of lichen planus. This specific immune environment could serve as a means for the early diagnosis and targeted treatment of the disease.

### *Drug Eruption*

Drug eruption is a damaging inflammatory reaction with an increased risk of mortality and is accompanied by reddish, pruritic plaques all over the body. There is an increase in eosinophils in the blood and damage to multiple organs in severe conditions. The reaction is often accompanied by the reactivation of the latent herpes virus and the onset of autoimmunity in the body (Zhang et al. 2021).
Kim and his colleagues (2020) performed single-cell RNA sequencing on blood and skin biopsy samples obtained from a 44-year-old patient who had a hypersensitivity reaction to sulfamethoxazole/trimethoprim and remained unresponsive to high doses of cyclosporine, mycophenolate mofetil. It was compared with samples from 5 healthy controls. A total of 14 clusters were sampled on which the transcriptomic analysis was carried out. Analysis showed that JAK/STAT pathways were the most active in the mediation of inflammation. Herpes virus 6b was also found in the patient's samples that were enriched with CD4+ T-cells. The researchers then used the JAK kinases inhibitor totafinicib which inhibited the JAK/STAT pathway and also led to a remarkable decrease in the CD4+ T-cell population. Other antivirals that helped in the treatment were ganciclovir and artesunate which decreased the T-cells according to their doses. This study implies the role of single-cell RNA sequencing in determining the active pathways of inflammation in different skin diseases and then targeting the drugs in those pathways.

### *Acne*

Globally, 1 in 10 persons suffers from acne. It is a chronic inflammatory disorder of the skin that causes permanent disfigurement and scarring. Acne is associated with excess sebum production which are unsaturated fatty acids, thickening of stratum corneum, and inflammation of the skin (Wen-Hua et al. 2017).
Benzoyl peroxide has proven useful in the treatment of chronic acne due to its antibacterial and anti-inflammatory properties. Topical application of 5% benzoyl peroxide for 10 to 16 weeks has shown a remarkable decrease in inflammation by killing the polymorphonuclear lymphocytes that release reactive oxygen species responsible for the inflammation in acne (Warner et al. 2002).
To understand the pathogenesis of acne and the action of benzoyl peroxide, single-cell RNA sequencing, and spatial transcriptomics were done by Tran H. Do and his colleagues (2022) on early acne lesions. They found that macrophages expressing TREM2 were found near the hair follicles on the acne-inflicted areas of the skin. These macrophages were also rich in the enzyme squalene oxidase which was responsible for the induction and decrease in the antibacterial activity of the TREM2 macrophages. The addition of benzoyl peroxide in vitro led to the inactivation of the enzyme and restored the antibacterial action of macrophages. The results determine the proinflammatory pathways of skin diseases which can be targeted by medications to control the spread of acne lesions.

### *Alopecia Areata*

Alopecia Areata is an inflammatory disease where the immune system of the host attacks the hair follicles leading to

chronic inflammation; however, there is no scarring. The major cytokine involved is interferon gamma with an increase in CD8+ T-cells which are the major drivers of chronic inflammation (Markus et al. 2020).
Borcherding and his colleagues (2020) used single-cell mRNA sequencing to identify the differences between the skin affected with alopecia and normal skin. 18,321 immune cells were separated from the experimental set of mice affected with alopecia. CD11b+ and CCD2+ were the dominant receptors on the dendritic cells with an over-activation of the JAK/STAT pathway. CD8+ T-cells were also identified with an increase in interferon-gamma which was needed for disease induction. The research was then conducted on the lesional and nonlesional skin biopsies of human subjects and the previous results were mirrored. This work gives an understanding of the immune basis of the disease and also provides knowledge of the pathways that can be targeted to cure the disease.

### *Limitations*

There is a tiny amount of genetic material to perform the analysis on which creates a higher bias in the final results. The overall procedure is very expensive putting the cost around $5000 for one analysis. There is a lack of standard guidelines for the comparison of data. Most of the programs do not support live cell visualization and have a high doublet rate.

### *Drawbacks and Future Directions*

Single-cell RNA sequencing is like bulk RNA sequencing but it uses genetic material from a single cell and therefore gives transcriptomics of that cell only. The sequenced data is noisier and therefore precise annotation is difficult. Cell viability decides the accuracy of the data generated. Drop-seq which is the most commonly used program does not support live cell visualization and has a high doublet rate.
The cost has decreased over the past few years, but it continues to be a major drawback in the use of single-cell sequencing.
There is a lack of standardized methods for carrying out the analysis. Standardized methods need to be mapped out. This should involve the state of the tissue in which the analysis is carried out, the addition of chemicals, the physical conditions under which the analysis is being carried out and the settings of the equipment.
More advanced research is required in technological advancements to open new avenues for healthcare practices. Also, an effort needs to be made to integrate the recent advances in the healthcare system.

### *Conclusion*

Inflammatory skin conditions are chronic disorders that usually take a long time to recover. One basic hurdle in the timely recovery of these disorders is the lack of knowledge available about their etiology and pathogenesis. Single-cell RNA sequencing is a tool that provides useful insight into the functioning of the cells. It identifies cell-to-cell variations, new mutations, rare cell populations and cells that are more responsive to treatment.
By visualizing the transcriptomics of the cells, it has provided valuable information regarding the pathogenesis of chronic inflammatory skin disorders like atopic dermatitis, psoriasis, lichen planus, acne, etc. Specific transcriptomics can then be used to synthesize the drugs that target the immune factor or the mutation responsible for the condition. Targeted therapy can prove useful because it will reduce the chances of drug resistance and improve the quality of life. More progressive research is required to understand disease pathogenesis and develop optimal treatments for patients.

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