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Review Article

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Immunopathology and Immunotherapy of Inflammatory Skin Diseases

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Conflicts of Interest
The authors declare no potential conflicts of interest.

Abbreviations
AA, alopecia areata; AD, atopic dermatitis; AIBD, autoimmune bullous disease; Akt, protein kinase B; BP180, bullous pemphigoid antigen 2 (BPAG2); BP230, bullous pemphigoid antigen 1 (BPAG1); BTK, Bruton's tyrosine

ABSTRACT

Recently, there have been impressive advancements in understanding of the immune mechanisms underlying cutaneous inflammatory diseases. To understand these diseases on a deeper level and clarify the therapeutic targets more precisely, numerous studies including *in vitro* experiments, animal models, and clinical trials have been conducted. This has resulted in a paradigm shift from non-specific suppression of the immune system to selective, targeted immunotherapies. These approaches target the molecular pathways and cytokines responsible for generating inflammatory conditions and reinforcing feedback mechanisms to aggravate inflammation. Among the numerous types of skin inflammation, psoriasis and atopic dermatitis (AD) are common chronic cutaneous inflammatory diseases. Psoriasis is a IL-17–mediated disease driven by IL-23, while AD is predominantly mediated by Th2 immunity. Autoimmune bullous diseases are autoantibody-mediated blistering disorders, including pemphigus and bullous pemphigoid. Alopecia areata is an organ-specific autoimmune disease mediated by $CD8^+$ T-cells that targets hair follicles. This review will give an updated, comprehensive summary of the pathophysiology and immune mechanisms of inflammatory skin diseases. Moreover, the therapeutic potential of current and upcoming immunotherapies will be discussed.

Keywords: Atopic dermatitis; Psoriasis; Pemphigus; Pemphigoid, bullous; Alopecia areata; Biologics; Immunopathology

INTRODUCTION

Inflammatory skin diseases, including psoriasis, atopic dermatitis (AD), autoimmune bullous diseases (AIBDs) and alopecia areata (AA), cause major health burdens, deterioration of quality of life, and are associated with various comorbidities. Conventionally, treatment of such skin conditions has focused on controlling symptoms with topical and systemic corticosteroids and other systemic immunosuppressants, which can not only cause dissatisfactory effects, but also occasionally cause serious adverse events.

Dysregulation of the cutaneous immune system leads to various pathogenic outcomes involving inflammatory immune cells and structural tissue cells. Further understanding of the molecular mechanisms and immune biology of cutaneous inflammatory conditions has

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kinase; CAAR, chimeric autoantibody receptor; DC, dendritic cells; DPCP, diphenylcyclopropenone; Dsg, desmoglein; EASI, Eczema Area and Severity Index; EMA, European Medicines Agency; FcRn, neonatal Fc receptor; FcγRIIb, Fcγ receptor IIb; FcεRI, Fcε receptor I; FDA, US Food and Drug Administration; ICOS, inducible costimulator; IDEC, Inflammatory dendritic epidermal cells; ILC2, Innate lymphoid cell group 2; ILC3, Innate lymphoid cell group 3; IVIG, Intravenous immunoglobulin; LC, Langerhans cell; NKG, natural killer group; PASI, Psoriasis Area and Severity Index; SALT, Severity of Alopecia Tool; Tc17, IL-17-secreting CD8+ T cells; Tfh, T follicular helper; TYK, tyrosine kinase.

Author Contributions

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led to identification of the pathways and cytokines involved. These then become molecular targets for the development of immunotherapies including biologic agents that target specific cell-surface molecules or extracellular molecules. Furthermore, small molecule inhibitors can affect intracellular signaling by targeting receptor-associated kinases.

Herein, we present an overview of the molecular immune pathogenesis of inflammatory skin diseases, followed by discussion of approved immunotherapeutic agents and treatments currently under development.

PSORIASIS

Psoriasis is a chronic inflammatory skin disease that appears as demarcated erythematous plaques and silvery-scaled patches. The prevalence of psoriasis ranges between 0.1% and 1.5% across countries (1). Skin lesions vary in size and can occur anywhere on the body, although they are usually located on buttocks, scalp, and extensor areas of knees and elbows. While these clinical features are observed in plaque psoriasis, the most common clinical type, other subtypes also exist, including guttate, erythrodermic, flexural, palmoplantar, nail, and pustular forms. Psoriasis can be associated with other diseases such as psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory bowel diseases, and psychological disorders. Psoriatic arthritis occurs in approximately 20% of patients with psoriasis and presents as seronegative inflammatory arthritis in distal interphalangeal joints, dactylitis, and enthesitis (2).

Histologic findings of psoriasis typically include dermal infiltration of immune cells, including T cells and myeloid cells, under epidermal hyperplasia with neutrophil condensation. In addition, skin lesions in psoriasis patients improve after treatment with immunosuppressive drugs such as cyclosporine and methotrexate. These histologic and clinical findings provide insight into the pathogenic role of immune cells in this disease (3). Numerous immunologic, genetic, and clinical studies have highlighted the involvement of the IL-23/IL-17 axis and IL-17$^+$ T cells, such as Th17 and Tc17 cells, in the central mechanisms of psoriasis (**Fig. 1**) (4-6). The importance of Ag recognition in function of the adaptive immune system is supported by the genetic susceptibility of *HLA-C*06:02* in *PSORS1* locus (7) and the presence of autoreactive and PD-1$^+$ T cells in psoriatic skin (8-10). However, IL-23, a p19 and p40 heterodimer, is the most important stimulator of IL-17$^+$ T cells in psoriasis. After the stimulation of IL-17$^+$ T cells with IL-23, STAT3 is phosphorylated by JAK2 and Tyrosine kinase 2 (TYK2) and then induces the transcription factor RORγt. pSTAT3 and RORγt bind to *IL17A* and *IL17F* promoters and induce the expression of IL-17 (6). A recent study revealed that CD1c$^+$CD14$^+$ classical dendritic cell type 3 (cDC3) is the major source of IL-23 in psoriatic skin (11). Homodimers or heterodimers of IL-17A and IL-17F secreted by T cells primarily target keratinocytes in psoriatic skin, signaling through the IL-17RA-IL-17RC complex (12). IL-17-activated keratinocytes secrete chemokines (e.g., CCL20, CXCL1, and CXCL8) that attract CCR6$^+$IL-17$^+$ T cells, DCs, and neutrophils (13). This feedforward mechanism amplifies disease activity in psoriasis.

Current immunotherapies for psoriasis

For the evaluation of treatment efficacy in psoriasis, disease severity is measured using the Psoriasis Area and Severity Index (PASI), with 75%, 90%, and 100% reductions in PASI scores are referred to as PASI-75, PASI-90, and PASI-100, respectively.

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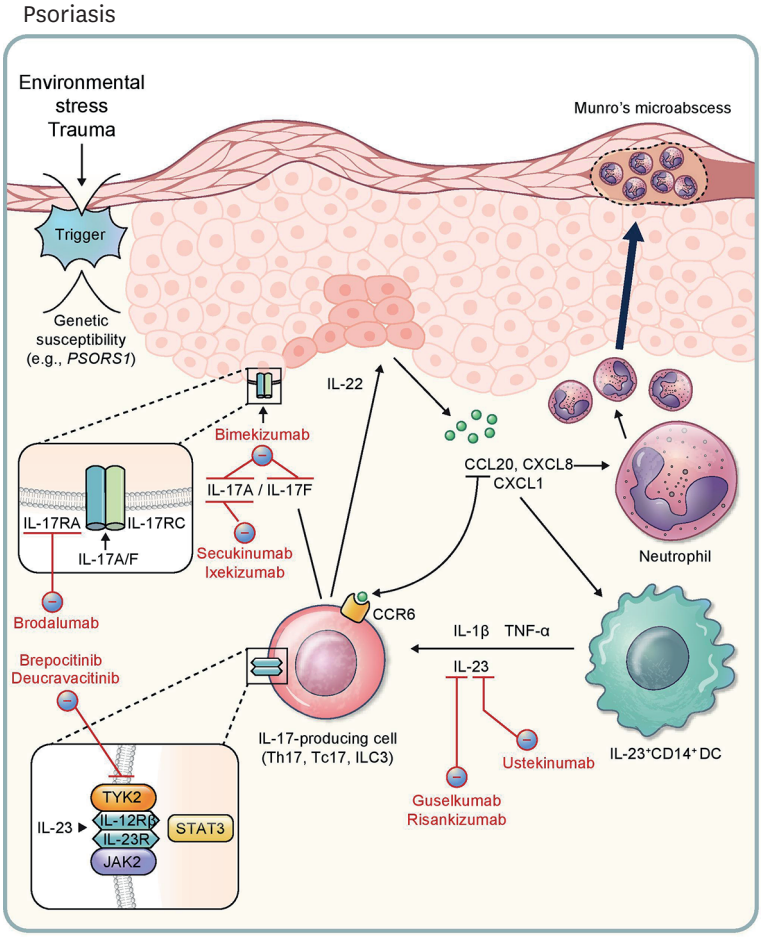

Figure 1. Pathophysiology of and immunotherapeutic agents for psoriasis. External environmental stress and trauma is a possible trigger of psoriasis, especially in individuals with genetic susceptibilities (e.g., *PSORS1*). This leads to the release of CCL20, CXCL8, and CXCL1, stimulating $CCR6^{+}IL\text{-}17^{+}$ lymphocytes, neutrophils, and $IL\text{-}23^{+}CD14^{+}$ DCs, respectively. Release of IL-17A and IL-17F via IL-17-producing cells (Th17, Tc17, and ILC3) results in the activation of the IL-17RA/IL-17RC complex in keratinocytes, further feeding the inflammatory response. Production of IL-22 by ILC3 accelerates hyperproliferation of keratinocytes. DCs induce cytokines like IL-1β, TNF-α, and IL-23. IL-17-producing cells are stimulated by IL-23 through the JAK2/TYK2-STAT3 pathway. Ustekinumab targets the p40 subunit shared by IL-12 and IL-23, and guselkumab and risankizumab inhibit the p19 subunit of IL-23. Secukinumab and ixekizumab are inhibitors of IL-17A. Bimekizumab is a monoclonal antibody targeting IL-17A and IL-17F. Brodalumab is an inhibitor of IL-17RA. With respect to JAK signaling, deucravacitinib acts to inhibit TYK2, and brepocitinib inhibits TYK2 and JAK1 simultaneously.

Although TNF inhibitors were initially approved as biologics for psoriasis (14), they show better therapeutic efficacy in psoriatic arthritis than psoriasis. Ustekinumab, an inhibitor of the p40 subunit shared by IL-23 and IL-12, was approved for the treatment of moderate to severe psoriasis (15). Since ustekinumab targets both Th1 and Th17 immunity, specific IL-23 inhibitors targeting the p19 subunit have subsequently been developed. Among p19 inhibitors, guselkumab (70%–73% of PASI-90 at week 16) and risankizumab (75% of PASI-90 at week 16) are superior to ustekinumab and are well tolerated (16-18). In parallel, IL-17 inhibitors have also been developed for the treatment of psoriasis. Secukinumab (54%–59% of PASI-90 at week 12) and ixekizumab (68%–71% of PASI-90 at week 12) target IL-17A and have shown higher therapeutic efficacy than ustekinumab (18-20). Further, brodalumab, an anti-IL-17RA monoclonal Ab, showed 69%–70% PASI-90 at week 12, which is also superior to ustekinumab (18,21). IL-23 inhibitors are commonly used in severe psoriasis with or without mild psoriatic arthritis because of the convenient dosing interval, whereas IL-17 inhibitors are generally selected when patients have pronounced psoriatic arthritis or require rapid improvement (6).

New immunotherapies for psoriasis

Bimekizumab, a monoclonal Ab targeting IL-17A and IL-17F, is a promising candidate for the treatment of psoriasis. In a phase 3 trial, bimekizumab was superior to secukinumab, showing 86% PASI-90 at week 16 (22). In addition, several oral drug candidates target intracellular signal pathways in IL-17$^+$ T cells. Binding of IL-23 to the IL-23 receptor in T cells induces IL-17 through the JAK-STAT signaling pathway and thus, JAK inhibitors have been developed for clinical use. Deucravacitinib, a TYK2 inhibitor, showed 75% PASI-75 and 43% PASI-90 at week 12 in a phase 2 trial (23). Brepocitinib, a JAK1 and TYK2 inhibitor, was found to provide clinical efficacy in a phase 2 trial with 86% PASI-75 and 52% PASI-90 at week 12 (24). Although the clinical efficacy of JAK inhibitors is well established, the US Food and Drug Administration (FDA) recently expressed concern about an increased risk of serious heart-related events, thromboembolism, cancer, and death with these therapeutics (25). Thus, more clinical studies are warranted.

ATOPIC DERMATITIS

AD is a chronic, recurrent inflammatory skin disease characterized by recurrent eczema and severe itching (26). The prevalence of AD is increasing worldwide and in developed countries, it affects up to 20% of children and 2.1%–4.9% of adults (26). AD can arise at any time in a person's life, but frequently occurs during early childhood. In recent years, its increasing incidence in the adult population has become a serious problem (27,28). Although genetic predisposition is significant in AD, environmental factors are also increasingly known to be of importance (29). AD patients have dry and sensitive skin, and suffer from severe itching arising from eczematous lesions in localized or diffuse areas of the body (30). In cases during infancy, edematous erythema and excoriations are widespread on the face and trunk, and the lesions become localized to flexural areas of dry skin and chronic lichenification in childhood. Adolescents and adult patients often present with focal eczema on eyelids, hands, and flexural areas (26). AD is also considered part of the atopic march that includes food allergy, asthma, and allergic rhinoconjunctivitis (31).

Although the exact pathogenesis of AD remains to be elucidated, it is thought to involve the interaction of three major mechanisms (**Fig. 2**): skin barrier defects, alterations in the skin microbiome, and Th2-biased immune dysregulation (26). Genetic predispositions such as filaggrin mutations and environmental factors disturb physiologic epidermal barrier function, and these dysfunctions contribute to the changes in the skin microbiome and immune system (26). In healthy individuals, *Propionibacterium acnes* and *Staphylococcus epidermidis* are abundant in the skin microbiome (32), and the skin commensal *Staphylococcus* spp. inhibits the growth of *Staphylococcus aureus* (33). In conditions of AD, however, colonization of *S. aureus* increases in the skin microbiome, promoting dysregulation of the skin barrier and immunity (34). In this review, we mainly focus on the skin immune system in the pathophysiology of AD.

Th2-mediated skin inflammation is considered a central pathway in AD. Ag uptake by Ag-presenting cells is increased through loose tight junctions in the AD epidermis (35). These Ags are derived from a variety of sources, including air allergens (e.g., house dust mite), food, and microorganisms (26). Keratinocytes also secrete TSLP, IL-25, and IL-33 due to disruption of the epidermal barrier (36). Increased Ag exposure and signaling from keratinocytes activates Th2 cells to release IL-4, IL-5, and IL-13 and induce IgE production in B cells. IL-4 signals through the type I receptor IL-4Rα/CD132 and type II receptor IL-4Rα/IL-

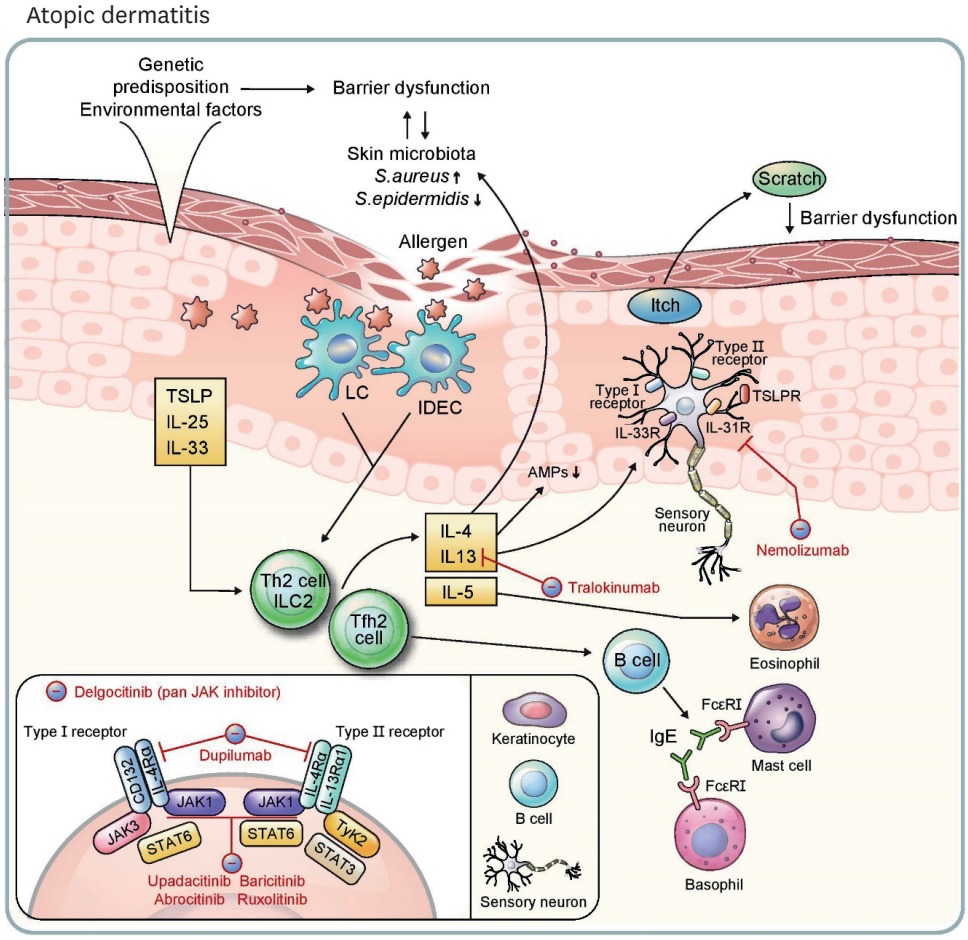

Figure 2. Pathophysiology of and immunotherapeutic agents for atopic dermatitis. Genetic predisposition and environmental factors induce barrier dysfunction. Further, change of surface microbiome diversity, especially decrease of *S. epidermidis* and increase of *S. aureus*, enhances barrier dysfunction and increases vulnerability of skin epidermis to external allergens. TSLP, IL-25, and IL-33 released from keratinocytes promote a type 2 response through ILC2, Th2 cells, and Tfh2 cells, which are induced from activated skin LCs and IDECs. IL-4, IL-13, and IL-5 are released from these lymphocytes. IL-4 and IL-13 activate type I (IL-4Rα/CD132) and type II (IL-4Rα/IL-13Rα1) receptors on B cells, keratinocytes, and sensory neurons, resulting in activation of JAK-STAT pathways. Tfh2 cells induce IgE$^+$ B cells, stimulating mast cells and basophils via FcεRI. AMPs (e.g., human β-defensin 3) are decreased in keratinocytes in response to IL-4 and IL-13. Neuronal itch is induced by IL-4, IL-13, IL-31, IL-33 and TSLP, and the itch-scratch cycle is intensified through the process. Type 2 cytokines also aggravate the imbalance of skin surface microbiota, and IL-5 recruits eosinophils, continuing the vicious circle. Dupilumab inhibits type I and II receptors by blocking IL-4Rα. Tralokinumab neutralizes IL-13 and nemolizumab inhibits IL-31R. Upadacitinib and abrocitinib are oral, selective JAK1 inhibitors, and baricitinib is an oral JAK1 and JAK2 inhibitor. Topical agents ruxolitinib (a JAK1 and JAK2 inhibitor) and delgocitinib (a pan-JAK inhibitor) are approved treatments for atopic dermatitis.

13Rα1. IL-13 shares the type II receptor with IL-4 and can bind to the IL-13Rα2 decoy receptor (37). Binding of cytokines to type I and type II receptors activates the JAK1/STAT6 pathway in hematopoietic and non-hematopoietic cells (37). These type 2 cytokines also cause skin barrier damage and increase the colonization of *S. aureus* (38). Barrier defects also induce keratinocyte production of IL-23, which leads to the activation of IL-23R expressing DCs triggering the Th22 immune response. In addition, CCR6$^+$ Th22 cells promote epidermal hyperplasia and lichenification via the IL-22/IL-22R axis in chronic atopy (39).

Neuronal itch can be induced by the receptors for TSLP, IL-4, IL-13, IL-31, and IL-33 expressed on sensory neurons (40,41). Allergen-induced crosslinking of IgE activates granulocytes, including mast cells and basophils, via Fcε receptor I (FcεRI). Basophils recognize allergen-specific IgE through FcεRI and then release leukotriene C4, which activates CysLTR2 in sensory neurons causing acute atopic pruritus (42,43).

Current immunotherapies for AD

Conventional systemic management of AD consists of corticosteroids and immunosuppressants such as cyclosporine A and methotrexate (44). Topical treatment of AD includes corticosteroids and calcineurin inhibitors (26). However, patients with refractory AD respond poorly to conventional treatments, and long-term usage of systemic drugs carries a risk of side effects.

Recent discoveries in the pathogenesis of AD have enabled the development of biologics and small molecule therapies to target refractory cases. The Eczema Area and Severity Index (EASI) is used to measure disease severity in AD. EASI-75, EASI-90 and EASI-100 indicate reductions of 75%, 90%, and 100% in EASI scores, respectively (45). Currently, dupilumab, a human IgG4 monoclonal Ab blocking IL-4Rα, is the only systemic biologic approved by both the FDA and European Medicines Agency (EMA) (46). Various studies have shown that dupilumab (300 mg every 2 weeks, with a loading dose of 600 mg) is effective in relieving both pruritus and inflammation (47). There are no life-threatening safety concerns with dupilumab, while mild conjunctivitis occurred in 6.5% of patients (48). More than half of AD patients reached EASI-75 at week 16, and 36% of patients achieved EASI-90 at week 16 with dupilumab (45). Tralokinumab, an EMA-approved human IL-13 neutralizing Ab, exhibited 33.2% of EASI-75 in a phase 3 study (11.4% of EASI-75 in the placebo group) (49). Upadacitinib is an EMA-approved oral JAK1 selective inhibitor. A phase 3 study showed that 30 mg/d of upadacitinib is a safe and effective treatment option, with 80% of AD patients reaching PASI-75 at week 16 (50,51). In a randomized clinical trial comparing the efficacy and safety of upadacitinib and dupilumab, 71% of patients achieved EASI-75 with upadacitinib at week 16, whereas 61.1% of patients achieved EASI-75 with dupilumab at week 16 (52). Baricitinib, an oral JAK inhibitor that blocks JAK1/JAK2, is also approved by the EMA for patients with severe adult AD. EASI-75 was achieved in 24.8% of patients taking 4 mg/d of baricitinib for 16 weeks compared to 8.8% of patients in placebo group (53). The topical JAK1/JAK2 inhibitor ruxolitinib is approved by the FDA for patients with mild to moderate AD, and 62% of patients (1.5% ruxolitinib cream, twice daily) achieved EASI-75 at week 8 (54). Delgocitinib is a topical pan-JAK inhibitor approved in Japan. In a phase 3 study, the change in EASI score was −44.3% in the delgocitinib group (0.5% delgocitinib ointment, twice daily) after 4 weeks of treatment, compared with a 1.7% increase in the vehicle group (55).

New immunotherapies for AD

Various biologics and small molecule therapies have shown promise for modulating clinical symptoms of AD. Nemolizumab is a monoclonal Ab that blocks IL-31RA and is known to alleviate itching and the severity of eczema. In a phase 3 study, the visual analogue scale score decreased by 42.8% in the nemolizumab group (60 mg every 4 weeks) compared to a decrease of 21.4% in the placebo group, and EASI score dropped by 45.9% in the nemolizumab group and 33.2% in the placebo group (56). Treatment with abrocitinib, a selective JAK1 inhibitor, resulted in 63% of patients reaching EASI-75 at week 12 with a daily dose of 200 mg (57), and is currently awaiting FDA approval.

AUTOIMMUNE BULLOUS DISEASES

AIBDs are a group of rare, life-threatening blistering diseases mediated by autoantibodies targeting proteins in desmosomes or hemidesmosomes of keratinocytes in epidermis. According to the location of blisters, AIBDs are divided into intraepidermal and

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subepidermal types. Intraepidermal AIBD is called pemphigus, and bullous pemphigoid is the most common subepidermal AIBD.

Pemphigus

Pemphigus is characterized by suprabasal acantholytic blisters on skin and/or mucosa. Autoantibodies in pemphigus are directed against desmoglein 1 (Dsg1) and/or Dsg3, the cell-cell adhesion proteins of desmosomes (58). Pemphigus usually occurs between the ages of 50 and 60 years and is mainly classified as pemphigus vulgaris and pemphigus foliaceus in accordance with the major target Ags and clinical phenotypes. Pemphigus vulgaris caused by anti-Dsg3 autoantibody predominantly affects the oral mucosa, whereas pemphigus foliaceus induced by anti-Dsg1 autoantibody presents with superficial blisters on the skin but not the mucosa. These clinical differences between the two types of pemphigus are thought to be caused by the different expression patterns of Dsg1 and 3 in the oral mucosa and the skin (59). Moreover, the clinical features are similar to those of Dsg1- and 3-deficient patients (60,61).

Titers of anti-Dsg IgG autoantibodies positively correlate with disease activity (62) and pathogenic monoclonal antibodies from pemphigus patients are necessary and sufficient to cause acantholytic blisters (63). These autoantibodies mechanically interfere with the adhesion of Dsg and internalize Dsgs from the cell surface through various cellular signaling mechanisms (**Fig. 3A**) (64). Pathogenic autoreactive B cells are known to undergo somatic hypermutation in patients with pemphigus vulgaris despite the ability of some germline-reverted monoclonal antibodies to bind Dsg3 (65,66). Affinity maturation and isotype switching in B cells requires help from T follicular helper (Tfh) cells. In the mouse model of pemphigus vulgaris, inducible costimulator-positive ($ICOS^+$) Tfh cells are required for disease induction, and Dsg3-specific $ICOS^+$ Tfh cells are associated with anti-Dsg3 Ab production (67). Furthermore, specific subtypes of circulating Tfh cells are associated with anti-Dsg3 autoantibody production in peripheral blood of pemphigus vulgaris patients (67,68).

Current immunotherapies for pemphigus

Systemic corticosteroids and steroid-sparing immunosuppressive drugs such as mycophenolate mofetil are the main treatments for pemphigus; however, achieving clinical remission with these drugs alone takes a long time (69). Intravenous immunoglobulin can reduce pathogenic IgG autoantibody by various mechanisms, including activation of Fcγ receptor IIb (FcγRIIb) inhibitory receptor in B cells and saturation of the neonatal Fc receptor (FcRn), which prolongs the half-life of IgG. Intravenous immunoglobulin was found to significantly, but not dramatically, reduce disease activity and autoantibody titers in a randomized trial for pemphigus (70). Rituximab, a monoclonal Ab against the CD20 Ag of B cells, depletes B cells and has been used to treat pemphigus since the 2000s (71,72). Rituximab was found to strikingly shorten the time to clinical remission and reduce the use of systemic corticosteroid significantly compared to mycophenolate mofetil (71,73). In a meta-analysis, clinical remission was found to be achieved 3 to 6 months after rituximab therapy in 75% of pemphigus patients (74). First-line treatment of rituximab (1,000 mg on days 0 and 14 and 500 mg at months 12 and 18) also showed favorable results (89% of complete remission and 24% of relapse) in a randomized trial (75).

New immunotherapies for pemphigus

Despite the fact that rituximab notably improves clinical outcome in terms of time to remission and use of systemic corticosteroids, the depletion of non-pathogenic B-cells increases the risk of serious infections (75,76). To overcome this problem, T cells expressing

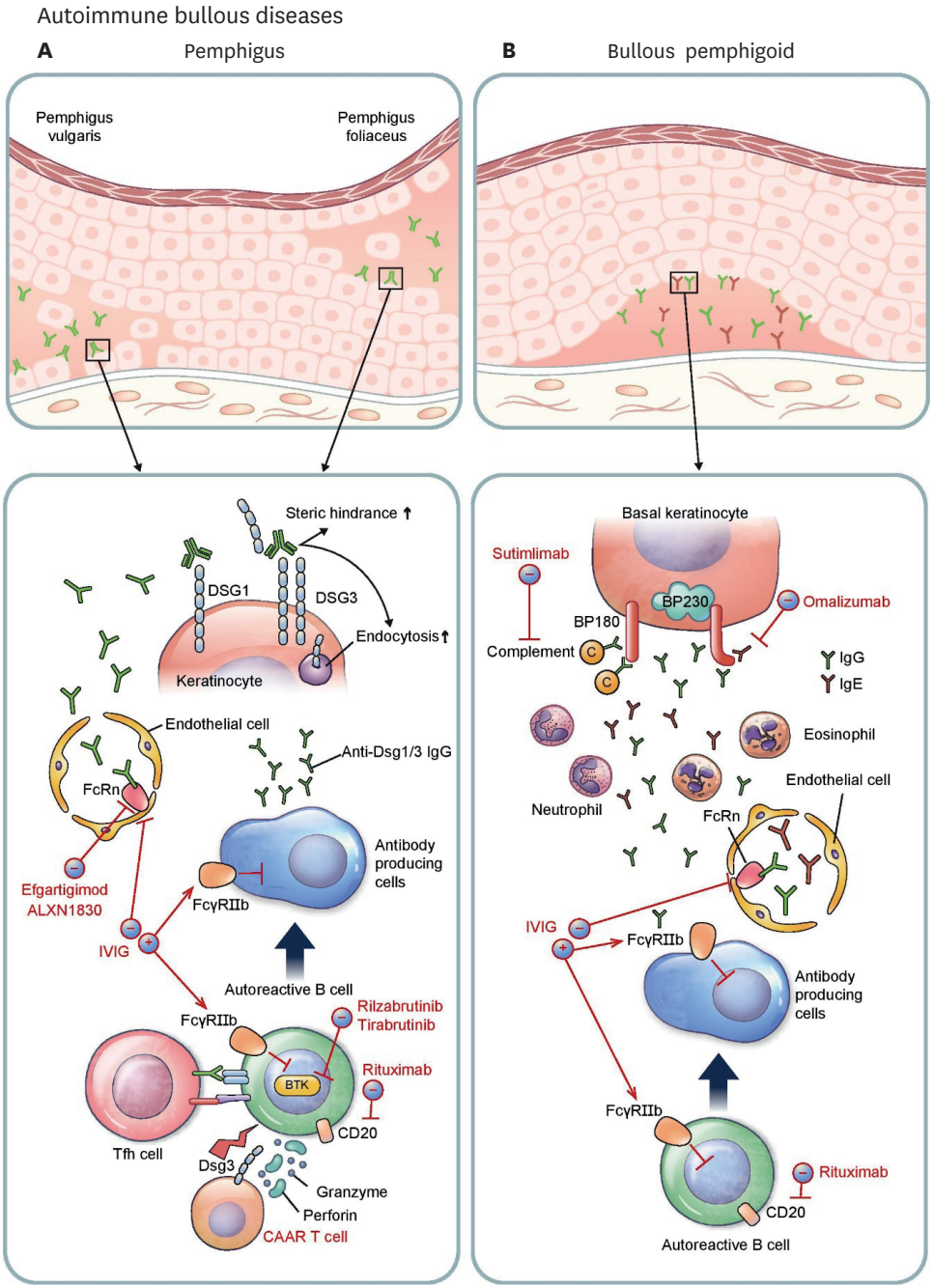

Figure 3. Pathophysiology and immunotherapeutic agents of autoimmune bullous diseases. (A) In pemphigus, Tfh cells activate autoreactive B cells, which differentiate into antibody-producing cells generating pathogenic anti-Dsg1/3 autoantibodies. Autoantibodies circulate through vessels and relocate to the epidermal intercellular space. FcRn expressed on endothelial cells lengthens the half-life of IgG autoantibodies. Binding of autoantibodies to Dsg1/3 induces steric hindrance and enhances endocytosis, leading to loss of cell-to-cell adhesion of keratinocytes. Rituximab depletes autoreactive B cells by targeting cell surface antigen CD20. Rilzabrutinib and tirabrutinib are small molecule drugs that bind BTK in B cells and inhibit aberrant B-cell receptor signaling. Dsg3 CAAR T cells specifically target and destroy Dsg3-specific B cells. ALXN1830 and efgartigimod shorten the half-life of antibodies by blocking FcRn. Intravenous immunoglobulin (IVIG) inhibits antibody-producing cells by activating the FcγRIIb inhibitory receptor and enhances the degradation of autoantibodies by saturating FcRn. (B) In BP, autoreactive B cells switch to become antibody-producing cells resulting in production of pathogenic anti-BP180/BP230 autoantibodies which migrate to dermo-epidermal junction. IgG and IgE autoantibodies against BP180 promote complement activation leading to infiltration of granulocytes such as neutrophils and eosinophils into the dermis. Release of various proteases plays an important role in creating clefts and in blister formation. Along with pemphigus, rituximab depletes $CD20^+$ B cells. IVIG saturates FcRn reducing the life span of autoantibodies, and suppresses antibody-producing cells by activating FcγRIIb. Omalizumab, a monoclonal antibody against IgE, can decrease the level of pathogenic IgE autoantibodies. Sutimlimab decreases complement activation at the dermo-epidermal junction.

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a chimeric autoantibody receptor (CAAR) composed of Dsg3 combined to CD137-CD3ζ signaling domains were developed (77). Preclinical data showed Dsg3 CAAR T cells specifically target and lyse Dsg3-specific B cells, thus preserving non-pathogenic B cells (78). Rilzabrutinib and tirabrutinib, oral Bruton's tyrosine kinase inhibitors that inhibit B-cell activation, were found to decrease the dose of systemic corticosteroid needed and reduce disease activity in pemphigus vulgaris in a phase 2 trial (79,80). In addition, efgartigimod and ALXN1830, FcRn blocking antibodies, showed an early onset of clinical improvement in pemphigus patients in phase 2 trials (81,82).

Bullous pemphigoid

Bullous pemphigoid is the most common subepidermal AIBD clinically featuring pruritic tense bullae with erosions on the skin and/or mucosa. Target Ags of bullous pemphigoid are BP180 (bullous pemphigoid Ag 2; BPAG2) and BP230 (bullous pemphigoid Ag 1; BPAG1), which are the components of hemidesmosomes connecting basal keratinocytes to dermal structures. Several drugs such as dipeptidyl dipeptidase-4 inhibitors and immune checkpoint inhibitors (e.g., PD-1 and PD-L1 inhibitors) may be triggers for bullous pemphigoid (83,84). Bullous pemphigoid is thought to be associated with neurologic disorders including dementia, multiple sclerosis, and Parkinson's disease (85). Because it preferentially occurs in older adults with comorbidities and requires long-term use of systemic corticosteroids and immunosuppressive drugs, patients with bullous pemphigoid have a higher mortality rate (approximately 20%) than healthy older adults (86).

IgG and IgE autoantibodies targeting the extracellular NC16A domain of BP180 (**Fig. 3B**) are associated with disease activity (87,88), and their pathogenicity was confirmed by the passive transfer of human autoantibodies to humanized or human skin-grafted mouse models (89,90). Complement activation and granulocyte infiltration are followed by the autoantibody deposition on the dermo-epidermal junction (91). These factors are known to contribute to blister formation (89-91). In addition to the presence of autoreactive B cells (92), dysfunction of regulatory B cells is observed in peripheral blood of patients with bullous pemphigoid (93). Additionally, a decrease in regulatory T cells might lead to disease since evidence of bullous pemphigoid has been found in Foxp3-deficient mice and humans (94-96).

Current and new immunotherapies for bullous pemphigoid

Bullous pemphigoid is mainly treated with systemic and topical corticosteroids and immunosuppressive agents (97,98). Dapsone and doxycycline can be applied as steroid-sparing agents (99-101). Rituximab treatment showed remission at 5 months after treatment and increased survival rates over a long-term period (102). Intravenous immunoglobulin has also proven beneficial, but with limited therapeutic effects (103). Based on the existence of pathogenic IgE autoantibodies in bullous pemphigoid, omalizumab, a monoclonal Ab against IgE, has been reported to be effective for the treatment of bullous pemphigoid (104). However, clinical results are variable among patients because it cannot reduce pathogenic IgG autoantibodies (104). Sutimlimab, a C1s inhibitor, decreased complement deposition at the dermo-epidermal junctions in patients with bullous pemphigoid in a phase I trial (105).

ALOPECIA AREATA (AA)

AA, a chronic autoimmune inflammatory disease causing sudden hair loss, has a lifetime prevalence of 2% (106). It is characterized by patch-like distribution without scarring, often

in sharply defined areas, with dystrophic hairs called exclamation point hairs (107). There is a genetic predisposition for AA, and several studies have shown up to a 10-fold increased risk for first-degree relatives of AA patients (108). In the early stage of AA, the proportion of telogen hairs and dystrophic hair shafts increase before hair loss (109). Along with the disease progression, peribulbar inflammation takes place, and the hair follicles miniaturize leading to developmental arrest in the anagen phase (110). Affected hair follicles prematurely enter the telogen phase and undergo shortened cycles.

AA is known to be a T-cell-mediated inflammatory disease (**Fig. 4**). Normal anagen hair follicles are considered immune privileged sites with low expression of the MHC (111). This immune privilege is broken in AA lesions, where MHC I and II molecules in the hair follicles

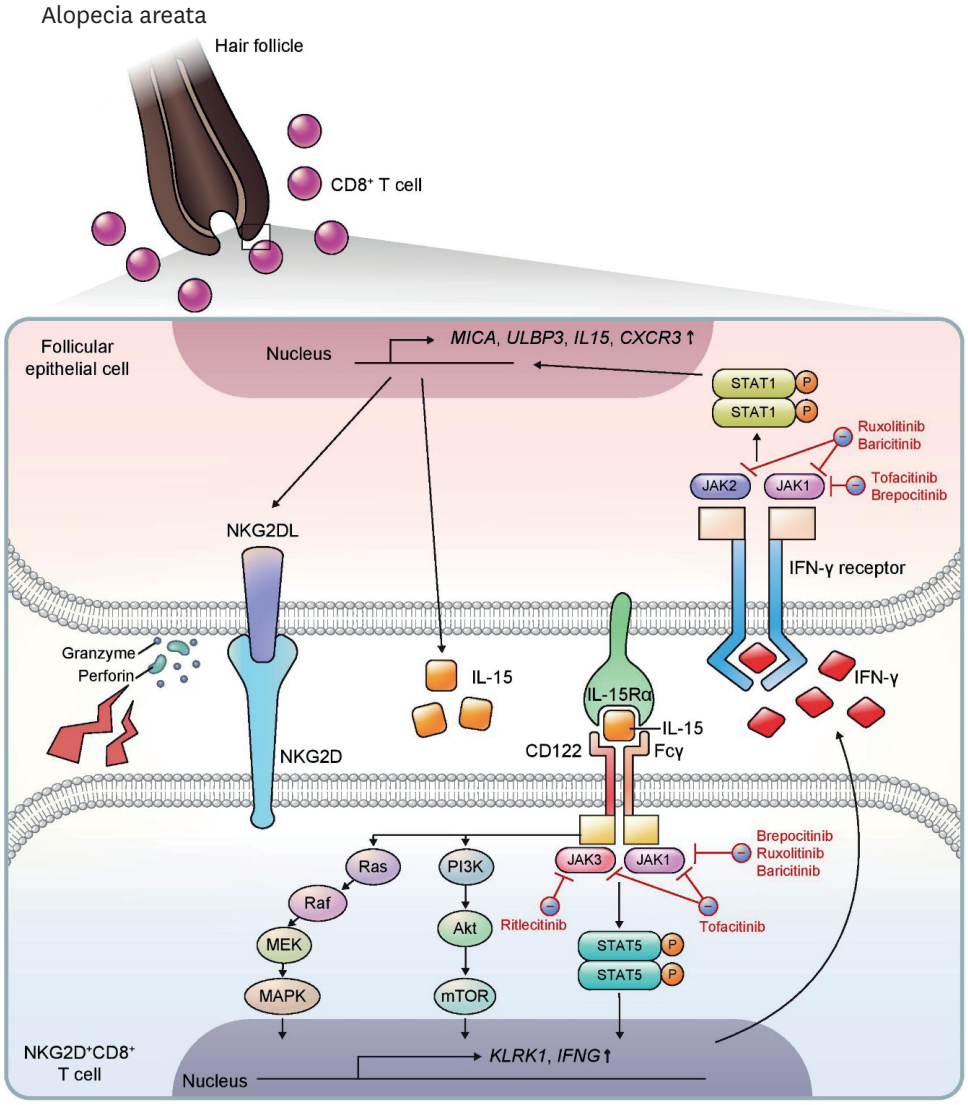

Figure 4. Pathophysiology and immunotherapeutic agents of alopecia areata. In alopecia areata, NKG2D⁺CD8⁺ T cells infiltrate into the dermis and relocate to the hair follicle bulb. IL-15 is an important cytokine for pathogenesis of this disease through activation and proliferation of NKG2D⁺CD8⁺ T cells. The IL-15 receptor complex is composed of IL-15Rα expressed on follicular epithelial cells and CD122 and Fcγ on T cells, and trans-activates CD8⁺ T cells through multiple pathways including Ras-Raf-MEK-MAPK, PI3K-Akt-mTOR, and JAK1/3-STAT5 signaling. These pathways upregulate expression of *KLRK1*, encoding NKG2D, and *IFNG*. IFN-γ binds to the IFN-γ receptor on follicular epithelial cells and triggers JAK1/2-STAT1 signaling, thereby upregulating expression of *MICA*, *ULBP3*, *IL15*, and *CXCR3*. Ruxolitinib and baricitinib inhibit JAK1 and JAK2, and brepocitinib inhibits JAK1. Tofacitinib is a JAK1 and JAK3 inhibitor, and ritlecitinib is a selective JAK3 inhibitor.

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are increased with recruitment of $CD8^+$ and $CD4^+$ T cells and APCs (112). These features first gave rise to the concept that hair follicle autoantigens play a primary pathogenic role in AA. Several autoantigens in AA have been proposed so far, but the exact autoantigens remain elusive (113). In addition to TCR-mediated activation in T cells, a genome-wide association study suggests that a TCR-independent, natural killer group 2D (NKG2D)-mediated pathway is involved in the pathogenesis of AA (114). $NKG2D^+CD8^+$ T cells exert their cytotoxic functions on hair follicles through NKG2D, contributing to pathogenesis in the C3H/HeJ AA mouse model (115). In human AA, ligands of NKG2D, such as MICA and ULBP3, were found to be upregulated in the hair follicle (114,116), and $NKG2D^+CD8^+$ T cells were infiltrated into and activated in perifollicular areas (114,117).

IFN-γ and IL-15 are important cytokines involved in the pathogenesis of AA. IL-15 is known to upregulate NKG2D and drive TCR-independent activation in $CD8^+$ T cells (118). In AA lesions, IL-15Rα and IL-15Rβ are upregulated in the hair follicle and $CD8^+$ T cells, respectively, indicating that trans-presentation of IL-15 activates $CD8^+$ T cells (115). After $CD8^+$ T cells recognize IL-15, downstream signaling pathways, including JAK1/3-STAT5, MAP kinase, and mTOR pathways, are activated (118). Activated $CD8^+$ T cells secrete IFN-γ which upregulates NKG2D ligands, MHC I and II, IL-15, and chemokine ligands of CXCR3 (e.g., CXCL9, CXCL10, and CXCL11) through the JAK1/2-STAT1 pathway in the follicular epithelium (119,120). These subsequent responses induce the recruitment, activation, and effector function of T cells, and this vicious cycle exacerbates inflammation in AA.

Current immunotherapies for AA

Currently, no treatment for AA has been approved by the FDA nor EMA, but various methods have been used for AA treatment (121). Severity of Alopecia Tool (SALT) score, indicating the rate of hair loss, is used to evaluate disease severity and treatment efficacy. Both systemic and local application of corticosteroids were found to be effective, but often resulted in limited curative rates of hair growth in moderate-to-severe AA. Cyclosporine, often used in combination with systemic corticosteroids, showed a hair regrowth rate of up to 76.6% (122). Methotrexate, alone or in combination with systemic corticosteroids, allowed full recovery in 64% of patients with alopecia totalis and universalis (123). Another treatment option for AA is topical immunotherapies such as diphenylcyclopropenone (DPCP) or squaric acid dibutylester, which induce delayed-type hypersensitivity (124). While the exact mechanism underlying the efficacy of this treatment is unknown, DPCP has shown a response rate of up to 72.2% for treatment of chronic and extensive AA (24).

New immunotherapies for AA

In treating AA, about 25% of patients are refractory to conventional therapy and 13.5-33% of patients recur (125). Recent studies suggest that blocking the JAK pathway could be an option for refractory AA (126). Currently, there are several oral JAK inhibitors for treatment of AA, including tofacitinib (JAK 1 and 3 inhibitor), ruxolitinib (JAK 1 and 2 inhibitor), baricitinib (JAK 1 and 2 inhibitor), ritlecitinib (JAK 3 inhibitor), and brepocitinib (Tyrosine kinase 2 and JAK 1 inhibitor). JAK inhibitors can affect both $NKG2D^+CD8^+$ T cells and follicular epithelial cells (115), interrupting the positive feedback loop involving IFN-γ and IL-15 (113,127,128). In a retrospective study of tofacitinib, 58% of patients with at least 40% scalp hair loss achieved greater than 50% change in SALT score over 4–18 months of treatment (129). In a comparative study, tofacitinib (20 mg twice daily) and ruxolitinib (5 mg twice daily) showed similar efficacy after 6 months of treatment (130). In a phase 2 trial, 51.9% of severe AA patients (SALT > 50) taking 4 mg/d of baricitinib achieved SALT ≤ 20 at week 36, while 3.6% of the placebo

group achieved SALT ≤ 20 (131). In a phase 2a study of severe AA (SALT > 50), 50% of patients receiving ritlecitinib (200 mg/d for 4 weeks, then 50 mg/d for 20 weeks) and 64% of patients receiving brepocitinib (60 mg/d for 4 weeks, then 30 mg/d for 20 weeks) achieved a 30% improvement in SALT score (SALT30), while 2% of the placebo group achieved SALT30 (132).

CONCLUSION

Advancements in understanding of skin immunity and molecular pathogenesis have resulted in promising therapeutic approaches for refractory inflammatory skin disorders. Although glucocorticoids and traditional immunosuppressants persist as the most prevalent treatment methods, monoclonal antibodies targeting pathogenic cytokines and their receptors and small molecule inhibitors of cytokine signaling have recently arisen as potential solutions. Still, many inquiries remain unanswered and possible safety issues exist, especially in regard to the FDA's latest drug safety communication on JAK inhibitors. With continuous research in the fields of dermatology and immunology, further understanding of the pathological mechanisms underlying distinct inflammatory disorders will be gained. Along with this, ongoing and future clinical trials will identify novel, more effective targeted immunotherapy approaches for cutaneous inflammatory conditions.

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