Review

Autoimmune and infectious skin diseases that target desmogleins

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Abstract: Desmosomes are intercellular adhesive junctions of epithelial cells that contain two major transmembrane components, the desmogleins (Dsg) and desmocollins (Dsc), which are cadherin-type cell–cell adhesion molecules and are anchored to intermediate filaments of keratin through interactions with plakoglobin and desmoplakin. Desmosomes play an important role in maintaining the proper structure and barrier function of the epidermis and mucous epithelia. Four Dsg isoforms have been identified to date, Dsg1–Dsg4, and are involved in several skin and heart diseases. Dsg1 and Dsg3 are the two major Dsg isoforms in the skin and mucous membranes, and are targeted by IgG autoantibodies in pemphigus, an autoimmune disease of the skin and mucous membranes. Dsg1 is also targeted by exfoliative toxin (ET) released by *Staphylococcus aureus* in the infectious skin diseases bullous impetigo and staphylococcal scalded skin syndrome (SSSS). ET is a unique serine protease that shows lock and key specificity to Dsg1. Dsg2 is expressed in all tissues possessing desmosomes, including simple epithelia and myocardia, and mutations in this gene are responsible for arrhythmogenic right ventricular cardiomyopathy/dysplasia. Dsg4 plays an important adhesive role mainly in hair follicles, and Dsg4 mutations cause abnormal hair development. Recently, an active disease model for pemphigus was generated by a unique approach using autoantigen-deficient mice that do not acquire tolerance against the defective autoantigen. Adoptive transfer of Dsg3−/− lymphocytes into mice expressing Dsg3 induces stable anti-Dsg3 IgG production with development of the pemphigus phenotype. This mouse model is a valuable tool with which to investigate immunological mechanisms of harmful IgG autoantibody production in pemphigus. Further investigation of desmoglein molecules will continue to provide insight into the unsolved pathophysiological mechanisms of diseases and aid in the development of novel therapeutic strategies with minimal side effects.

Keywords: cadherin, pemphigus, impetigo, SSSS, mouse model, ELISA

What is pemphigus?

The term pemphigus stems from the Greek *pemphix*, meaning blister or bubble, and describes a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell–cell adhesion of keratinocytes through a process called acantholysis. In 1964, Beutner and Jordon discovered that sera from patients with pemphigus contain circulating IgG autoantibodies directed against the cell surface of keratinocytes. The modern history of pemphigus as an autoimmune disease began with this finding (Fig. 1). In the late 1970s to early 1980s, pemphigus autoantibodies were shown to have pathogenic activity in the induction of blister formation in skin organ culture systems as well as by passive transfer of patients’ IgG into neonatal mice. In the mid- to late 1980s, the target antigens of pemphigus were characterized by immunohistochemical methods, such as immunoprecipitation and immunoblotting. In the early 1990s, isolation of cDNA for pemphigus antigens demonstrated that the target antigens in pemphigus are desmogleins.
Clinical picture of pemphigus

Pemphigus has three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. The hallmark of pemphigus is the finding of IgG autoantibodies against the keratinocyte cell surface.

1. **Pemphigus vulgaris.** All patients with pemphigus vulgaris show mucous membrane lesions, which are usually seen as painful erosions (Fig. 2A). Intact blisters are rare, probably because they are fragile and break easily. Extensive erosions and painful lesions in the mouth may result in decreased food and drink intake. Involvement of the throat may produce hoarseness and difficulty in swallowing. The esophagus, conjunctiva, nasal mucosa, vagina, penis, anus, and labia may also be involved. The diagnosis of pemphigus vulgaris tends to be delayed in patients presenting with only oral involvement in comparison to those with skin lesions. The primary skin lesions of pemphigus vulgaris are flaccid, thin-walled, easily ruptured blisters that appear anywhere on the skin surface (Fig. 2C). The blisters arise on normal-appearing skin or erythematous bases. The blisters are fragile and soon rupture to form painful erosions that ooze and bleed easily. Without appropriate treatment, pemphigus vulgaris can be fatal because large areas of the skin lose epidermal barrier function, leading to loss of body fluids or secondary bacterial infection.

2. **Pemphigus foliaceus.** Patients with pemphigus foliaceus develop scaly, crusted erosions, often on an erythematous base in the skin, but do not have apparent mucous-membrane involvement, even with widespread disease (Fig. 2D). The onset of disease is often subtle, with a few scattered
crusted lesions that come and go and are frequently misdiagnosed as impetigo. These lesions are usually well demarcated and scattered in a seborrheic distribution, including the face, scalp, and upper trunk. The disease may remain localized for years or may progress rapidly, in some cases to generalized involvement resulting in erythrodermic exfoliative dermatitis.

3. Paraneoplastic pemphigus. Paraneoplastic pemphigus is a recently described form of pemphigus that occurs in association with underlying neoplasms. Paraneoplastic pemphigus is unique and distinct from the classic forms of pemphigus vulgaris and foliaceus based on clinical, histological, and immunopathological criteria. The most constant clinical feature of paraneoplastic pemphigus is the presence of intractable stomatitis (Fig. 2B). The severe stomatitis is usually the earliest presenting sign; it is also the one that persists after treatment and is extremely resistant to therapy. This stomatitis consists of erosions and ulcerations that affect all surfaces of the oropharynx and characteristically extend onto the vermilion of the lip. Most patients also have severe pseudomembranous conjunctivitis with scarring. The cutaneous lesions are quite polymorphic and may appear as erythematous macules, flaccid blisters and erosions, tense blisters, erythema multiforme-like lesions, and lichenoid eruptions. Extensive cases show clinical resemblance to toxic epidermal necrolysis (TEN).

Paraneoplastic pemphigus is the only form of pemphigus that shows involvement of nonstratified squamous epithelia. Approximately, 30–40% of patients develop pulmonary symptoms. The earliest symptoms are progressive dyspnea, and pulmonary function studies show airflow obstruction involving large and small airways, as seen in bronchiolitis obliterans, which can be fatal through respiratory failure.

Pemphigus is mediated by IgG autoantibodies against desmogleins

Molecular cloning of cDNA encoding pemphigus antigens has indicated that IgG autoantibodies from patients recognize desmogleins (Dsg), which are cadherin-type cell–cell adhesion molecules found in the adhering junctions, the desmosomes (Fig. 3). Cadherins are a family of calcium-dependent cell–cell adhesion molecules that play important roles in the formation and maintenance of complex tissue integrity. The cadherins are divided into two major subgroups based on sequence similarity, i.e., the classic cadherins (e.g., E-, P-, N-cadherins) and the desmosomal cadherins (desmogleins and desmocollins). All members of the cadherin family contain conserved repeated amino-acid sequences (cadherin repeats) with calcium-binding motifs in their extracellular domains. When classic cadherins were introduced by gene transfection into nonadhesive mouse fibroblast L cells, the cells acquired strong cell
adhesion activity.\textsuperscript{13} Furthermore, following transfection with different cadherins, cells expressing identical cadherin types bind to each other, indicating that the classic cadherins mediate homophilic-type interactions.\textsuperscript{14} Cadherins require their well-conserved cytoplasmic domains to associate with plaque proteins, \(\alpha\)-catenin, \(\beta\)-catenin, and plakoglobin, which mediate and regulate binding to the cytoskeleton network. As a consequence of these interactions, cadherins achieve strong cell–cell adhesion with resultant morphological changes of the cells. In contrast, calcium-independent cell adhesion molecules, such as the immunoglobulin superfamily, mediate simple molecular interactions and do not involve morphological changes of cells. The "cell adhesion zipper" model has been proposed as a structural basis of cell adhesion mediated by classic cadherins.\textsuperscript{15} Cadherin molecules form a dimer as a functional unit, and each individual strand dimer interacts with opposing strand dimers on another cell through an adhesion interface of the N-terminal domain (EC1).

Based on morphological and biochemical criteria, there are two major types of adhering junctions in epithelial cells: adherens junctions and desmosomes.\textsuperscript{16,17} Adherens junctions anchor bundles of actin microfilaments and contain classic cadherins as transmembrane components and \(\alpha\)-catenin, \(\beta\)-catenin, and plakoglobin as cytoplasmic components, while desmosomes anchor intermediate filaments such as keratins and contain desmosomal cadherins as transmembrane components and plakoglobin, plakophilin, and desmoplakin as cytoplasmic components. In general, adherens junctions mediate rapid but weak cell adhesion, while desmosomes mediate slow but strong cell adhesion. The establishment of adherens junctions is a prerequisite for desmosomal assembly in keratinocytes.\textsuperscript{18}

Desmogleins have four cadherin repeats in their extracellular domain, as do classic cadherins, and have an extra carboxy-terminal domain containing repeats of 29 \(\pm\) 1 residues (Fig. 3). There are four desmoglein isoforms, designated Dsg1–4. Expression of desmoglein 1 and 3 is restricted to stratified squamous epithelium where blisters are formed in pemphigus, while desmoglein 2 is expressed in all tissues possessing desmosomes, including simple epithelia and myocardia.\textsuperscript{19} Dsg4 plays an important adhesive role primarily in hair follicles.\textsuperscript{20} Desmocollins are another transmembrane glycoprotein of the desmosomes and exist in three isoforms, Dsc1–3. Each isoform has two products derived from alternatively spliced mRNA of a single gene. Desmosomes always have desmoglein and desmocollin as a pair, but the precise nature of their interaction remains to be elucidated at the molecular level. Pemphigus foliaceus and vulgaris antigens are now called Dsg1 and Dsg3, respectively. Thus, pemphigus is an anti-desmoglein autoimmune disease. The basic pathophysiology of pemphigus is that autoantibodies inhibit the adhesive function of desmogleins and lead to loss of cell–cell adhesion of keratinocytes with resultant blister formation.

There is compelling evidence that IgG autoantibodies against Dsg1 and Dsg3 are pathogenic and play a primary role in blister formation in pemphigus. When monitored in individual patients, the titers of serum anti-Dsg1 and anti-Dsg3 IgG autoantibodies, as determined by indirect immunofluorescence or ELISA, are generally correlated with disease activity.\textsuperscript{21,22} Affinity-purified IgG from pemphigus vulgaris sera on the extracellular domain of Dsg3 can cause suprabasilar acantholysis, a typical histological finding of pemphigus vulgaris, when injected into neonatal mice.\textsuperscript{23} Furthermore, when anti-Dsg3 IgG is immunoabsorbed with the extracellular domains of Dsg3 from pemphigus vulgaris sera, these sera no longer have pathogenic activity to cause blisters in neonatal mice.\textsuperscript{24} Similarly, immunoabsorption of pemphigus foliaceus sera with the extracellular domain of Dsg1 eliminates the pathogenic activity of these sera and anti-Dsg1 IgG bound on the column caused superficial blisters in neonatal mice.\textsuperscript{25} Finally, monoclonal antibodies against desmogleins from pemphigus model mice and patients induce blisters that are histologically similar to those seen in patients.\textsuperscript{26,27}

Desmoglein ELISA as a useful diagnostic tool for pemphigus

With a diagnosis of suspected pemphigus based on clinical findings, it is important to perform serum tests to identify IgG autoantibodies against cell-surface antigens of keratinocytes or desmogleins. In the diagnosis of pemphigus, ELISA provides a specific, sensitive, and quantitative means of detecting and measuring circulating IgG autoantibodies.\textsuperscript{28,29} The patient’s serum is tested on ELISA plates precoated with recombinant Dsg1 or Dsg3 proteins produced in the baculovirus expression system. ELISA enables us to serologically distinguish subtypes of pemphigus vulgaris and foliaceus (Fig. 4). In general, if serum is positive against Dsg1 but negative against Dsg3, this suggests a
diagnosis of pemphigus foliaceus. Conversely, serum negative against Dsg1 but positive against Dsg3 suggests a diagnosis of mucosal-dominant-type pemphigus vulgaris. Serum positivity against both Dsg1 and Dsg3 suggests a diagnosis of mucocutaneous-type pemphigus vulgaris. Furthermore, ELISA scores show parallel fluctuation with disease activity. Thus, ELISA is also useful for monitoring disease activity to plan tapering schedules of corticosteroids and to predict flares or relapses before clinical evidence is noted.

Logical explanation for the site of blister formation in pemphigus

Although the disruption of desmoglein-dependent cell adhesion by autoantibodies is the basic pathophysiology underlying blister formation in pemphigus, the clinical spectrum is more complex. This complex clinical feature of pemphigus is now logically explained by the desmoglein compensation theory: Dsg1 and Dsg3 compensate for each other when coexpressed in the same cell. The intraepithelial expression patterns of Dsg1 and Dsg3 in skin and mucous membranes differ. In the skin, Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers, while Dsg3 is expressed in the lower portion of the epidermis, primarily in the basal and parabasal layers. In contrast, Dsg1 and Dsg3 are expressed throughout the squamous layer of the mucosa, but the former is expressed at a much lower level than the latter.

When sera contain only anti-Dsg1 IgG, which interferes with the function of Dsg1, the presence of Dsg3 compensates for the loss of function of Dsg1 in the lower epidermis. In contrast, in the upper epidermis, there is no compensation by Dsg3. Therefore, blisters appear only in the superficial epidermis of the skin. Although anti-Dsg1 IgG binds to the mucosa, no blisters are formed because of the coexpression of Dsg3. Thus, sera containing only anti-Dsg1 IgG cause superficial blisters in the skin without mucosal involvement, as seen in patients with pemphigus foliaceus. Sera containing only anti-Dsg3 IgG do not effectively cause blisters in the skin because the coexpressed Dsg1 compensates for the impaired function of Dsg3, resulting in no or only limited skin blisters. In contrast, in mucous membranes, Dsg1 cannot compensate for the impaired Dsg3 function due to its low level of expression. Therefore, sera containing only anti-Dsg3 IgG cause oral erosions without apparent skin involvement, as seen in patients with mucosal-dominant-type pemphigus vulgaris. When sera contain both anti-Dsg1 and anti-Dsg3 IgG, they interfere with the functions of both Dsg1 and Dsg3, resulting in extensive blisters and erosions in the skin as well as the mucous membranes, as seen in patients with mucocutaneous-type pemphigus vulgaris.

What is bullous impetigo and staphylococcal scaled skin syndrome (SSSS)?

Impetigo is a common and highly contagious superficial skin infection that primarily affects
children. The disease consists of bullous and non-bullous types, and bullous impetigo is caused by *S. aureus*. Staphylococcal scalded skin syndrome (SSSS) is a generalized form of bullous impetigo that most commonly affects children under 6 years of age, particularly neonates, and can occasionally affect adults with chronic renal insufficiency or immunosuppression. The blisters in bullous impetigo and SSSS are induced by exfoliative toxin (ET) released by *S. aureus*. In bullous impetigo, the toxin produces blisters locally at the site of infection; in SSSS, *S. aureus* is present in the pharynx, nose, ear, or conjunctiva, and the ET circulates throughout the body, causing blisters at sites distant from the infection.

Clinically, bullous impetigo commonly begins on any part of the body as small vesicles that enlarge rapidly into superficial flaccid bullae filled with cloudy fluid surrounded by an erythematous rim (Fig. 5A). These bullae rupture easily, leaving shiny erosions with scaly crusts. SSSS begins as erythema, frequently with a proctome of malaise, low-grade fever, irritability, and tenderness of the skin. The rash progresses to a characteristic wet-tissue-paper-like wrinkling due to the formation of flaccid blisters within 24 to 48 h (Fig. 5B). Subsequent generalized involvement elsewhere on the body occurs, but spares the mucous membranes. Histologically, both bullous impetigo and SSSS are characterized by intraepidermal cleavage in the upper layers of the epidermis, i.e., beneath or within the granular layers. In SSSS, the remainder of the epidermis appears unremarkable without keratinocyte necrosis and the dermis contains no inflammatory cell infiltrates in the fresh lesions. In bullous impetigo, however, the blister cavities become filled with neutrophils and the underlying dermis contains mixed infiltrates of neutrophils and lymphocytes in response to the inflammatory reaction to *S. aureus*.

**ETs are Dsg1-specific serine-proteases**

The pathogenic role of ET was first demonstrated by injecting ET into neonatal mice, which developed extensive skin blisters with the typical histology of superficial blister formation in the granular layers as observed in patients (Fig. 5C, D). It was realized that SSSS and pemphigus foliaceus share many similar features. Both diseases involve only the skin, and not mucous membranes or other tissues. The histology of both diseases shows superficial epidermal separation where Dsg3 is not coexpressed. Pathology textbooks actually note that the histology of both diseases is indistinguishable. Neonatal mice injected with IgG from pemphigus foliaceus...
folliculitis or ET develop blisters with essentially identical histology (Fig. 5C, D). These similarities suggested that the molecular mechanism of blister formation in SSSS is similar to that in PF, and we began to investigate the changes in Dsg1 levels after ET treatment.33)

We first stained for Dsg1 and Dsg3 in the skin 1 h after injecting ETA into neonatal mice. ETA caused substantial changes in Dsg1 staining, which was much less intense on keratinocyte cell surfaces, while there were no apparent changes in Dsg3 staining. To demonstrate direct proteolysis of the extracellular domain of Dsg1 by ETA, we then incubated soluble recombinant forms of the extracellular domains of Dsg1 and Dsg3 with ETA in vitro. ETA cleaved the recombinant mouse and human Dsg1 in a dose-dependent manner, while ETA did not cleave Dsg3. Taken together, these findings indicate that ETA specifically recognizes and cleaves the extracellular domains of both mouse and human Dsg1. Other serotypes of ET, ETB and ETD, were also shown to specifically cleave Dsg1 in a manner identical to ETA.34),35) Identification of the physiological substrate of ET also confirmed the function of ET as a trypsin-like serine protease as predicted by structural analysis.36)–38)

When ET reaches the skin and digests Dsg1 in the lower layers of the epidermis, Dsg3 compensates for the loss of function of Dsg1 and manages to maintain cell–cell adhesion, while no compensation by Dsg3 occurs in the superficial layers of the epidermis. Therefore, ET induces superficial blisters on the skin. In mucous membranes, the Dsg3 expressed throughout the squamous layers of the mucosa compensates for the impaired Dsg1 and maintains cell–cell adhesion with no mucosal involvement.30) These dermatological findings on the clinical and histological pictures provide an important framework to understand the molecular mechanisms of blister formation in these diseases, as well as cell–cell adhesion of keratinocytes in the epidermis.

Autoimmune reaction to digested Dsg1 in patients with SSSS

In the pathophysiology of autoimmune disease, triggering of the immune response has been suggested to involve molecular mimicry. In such cases, the antibodies that are produced against the infectious agent are thought to coincidentally crossreact with normal tissues. The observation that an antibody-mediated tissue-specific autoimmune disease, pemphigus foliaceus, and two related infectious diseases, bullous impetigo and SSSS, target the same molecule, Dsg1, also indicates that autoimmunity and infection are connected through Dsg1. These findings suggest that a bacterial toxin may bind to and partially degrade a self-antigen, with the modified self-antigen triggering the immune response.

When paired serum samples were examined from 30 patients with SSSS, 6 of 30 (20.0%) cases with SSSS developed low titers of anti-Dsg1 IgG autoantibodies as detected by ELISA (4/30) or immunoblotting analysis (4/30), although none developed any detectable anti-Dsg3 IgG antibodies.40) Although it was difficult to obtain paired sera because most of the patients were infants or small children, four patients with SSSS showed a shift from negative to positive anti-Dsg1 IgG. No apparent IgM reactivity against Dsg1 or Dsg3 was detected by ELISA. None of 12 patients with bullous impetigo, a localized form of SSSS, showed any detectable IgG production against Dsg1 or Dsg3, as determined by ELISA and immunoblotting.

These findings indicate that a small number of SSSS patients develop low titers of IgG antibodies specific for Dsg1 after binding and systemic digestion of Dsg1 by staphylococcal ETs. Although none of these patients developed pemphigus foliaceus after SSSS, which is not known as a predisposing factor for pemphigus foliaceus, the findings presented here provide evidence that infections that modify self-antigens can trigger the production of IgG autoantibodies against the self antigen. The relevance of this finding to onset of autoimmune diseases remains to be confirmed.

Pathogenic anti-desmoglein IgG autoantibodies preferentially attack the most functionally important part of the molecule

Characterization of the Dsg binding sites of the pathogenic pemphigus autoantibodies is an essential step in understanding the pathophysiology of blister formation in pemphigus, as well as the basic molecular mechanism of Dsg-mediated cell–cell adhesion. This characterization is hindered by the fact that binding of autoantibodies to Dsgs is dependent not only on amino acid sequence but also on molecular conformation. This dependence on molecular conformation is shown by the observation that recombinant Dsg1 and Dsg3, when expressed in baculovirus as secreted proteins, immunoabsorb heterogeneous autoantibodies from the sera of pemphigus foliaceus and pemphigus vulgaris patients, and that this
immunoadsorptive activity is lost upon denaturation by Ca$^{2+}$-chelation, acid or alkaline treatment, or boiling. Therefore, a conventional approach using variously truncated Dsg molecules is inappropriate for definition of the conformational epitopes of Dsgs in pemphigus. Therefore, a strategy based on domain swapping and point mutations was chosen to map regions within Dsg1 and Dsg3 that constitute the conformational epitopes. In both pemphigus vulgaris and foliaceus patients, major epitopes were mapped to the respective N-terminal 161 residues of Dsg1 and Dsg3. These N-terminal 161 residues contained critical epitopes recognized by pathogenic IgG antibodies because the immunoadsorption of pemphigus foliaceus sera with residues 1–161 of Dsg1 blocked their ability to induce blisters in neonatal mice. A pathogenic monoclonal antibody isolated from the adoptive transfer mouse model of pemphigus has been shown to recognize a specific calcium-dependent conformational epitope within the desmoglein adhesive interface, while nonpathogenic anti-Dsg antibodies map to a more carboxy-terminal extracellular domain. Recently, using antibody phage display, repertoires of human anti-Dsg monoclonal antibodies as single chain variable region (scFv) were isolated from patients with pemphigus vulgaris and foliaceus. The isolated scFvs contained both pathogenic and nonpathogenic antibodies as determined by in vitro dissociation assay and passive transfer assay using neonatal mice. The pathogenic scFvs recognized the N-terminal domains of Dsg1 and Dsg3.

Recent high-resolution crystal structure analyses of classic cadherins have provided a mechanistic basis for intermolecular cadherin interactions. This structure provides a new framework for understanding both the cis (same cell) and trans (juxtaposed cell) interactions of cadherin. The trans adhesive interface is a twofold symmetrical interaction that is defined by a conserved tryptophan (W2) side chain at the amino-terminal, membrane-distal end of the cadherin molecule from one cell, which inserts into the hydrophobic pocket at the amino-terminal end of a cadherin molecule on an opposing cell. This simple twofold symmetry provides a rationale for the generally observed homophilic specificity of cadherins, and reveals the molecular determinants of cadherin specificity. Taken together, the structural bases of classic cadherins and the results of the above epitope map studies indicate that the pathogenic autoantibodies in pemphigus are dominantly raised against the N-terminal adhesive interfaces of Dsg1 and Dsg3, which are the functionally important parts of the molecules.

**A novel autoimmune mouse model using mice deficient for the autoantigen**

To investigate the pathophysiological mechanisms and develop therapeutic strategies, animal disease models have played important roles in the study of various conditions, including autoimmune diseases. The conventional approach to develop an autoimmune mouse model is forced immunization of autoantigens in various strains of mice with various types of adjuvant (Fig. 6A). However, this approach is empirical and immune responses are largely dependent on the strain of mouse or type of adjuvant used. Furthermore, any autoimmune reaction in these mice may be transient, unlike that found in patients, and the immune system is systemically stimulated.

The major obstacle in the development of an autoimmune reaction in mice is self-tolerance, which prevents the immune system from reacting destructively against components of the living body. When lymphocytes are exposed to auto-components during the development of the immune system, auto-reacting lymphocytes are eliminated or inactivated. We have taken a novel approach to overcome this obstacle. As self-tolerance is a technical barrier to the development of autoimmune mouse models, we attempted to generate conditions where self-tolerance is not established in an antigen-specific manner (Fig. 6B). If it were possible to remove the antigen during the development of the immune system, or if it were not present from the start, tolerance against the removed or absent molecule would not be acquired. In autoantigen knockout mice, lymphocytes are not exposed to the defective gene product, and self-tolerance against that particular autoantigen is not established. Upon immunization with the autoantigen, the autoantigen knockout mice should elicit an immune reaction against the autoantigen. However, in the immunized knockout mice, no antigen–antibody reaction is expected because the mice lack the target antigen. Therefore, lymphocytes from the immunized autoantigen knockout mice are adoptively transferred into immunodeficient mice that express the autoantigen. The transferred lymphocytes from the autoantigen knockout mice should be persistently stimulated by the endogenous autoantigen in the recipient mice and should therefore produce antibodies against the autoantigen with resultant phenotypes of the human disease.
A. Conventional way by repeated immunization

wild type mouse (tolerance to Dsg3)

B. A novel approach by adoptive transfer of autoantigen-knockout lymphocytes

Dsg3+ mouse (immunodeficient mouse)

Dsg3−/− mouse (no tolerance to Dsg3)

Dsg3 mouse (no tolerance to Dsg3)

adoptive transfer of peripheral T and B lymphocytes

Dsg3−/− mouse (immunodeficient mouse)

Fig. 6. Methods to develop an active disease mouse model for pemphigus vulgaris. In the conventional approach (A), various strains of wild-type mice are repeatedly immunized with recombinant Dsg3 (rDsg3) in various adjuvants to break their immunological tolerance. None of the immunized mice developed IgG that could bind to the native Dsg3 in vivo and showed no IgG deposition on keratinocyte cell surfaces in the skin. In a novel approach (B), splenocytes of Dsg3−/− mice, which do not acquire tolerance against Dsg3, were adoptively transferred into immunodeficient mice expressing Dsg3. Recipient mice persistently produced anti-Dsg3 IgG and developed the pemphigus vulgaris phenotype.

Fig. 7. Phenotype of the active disease model mice for pemphigus vulgaris. A. The recipient mice with Dsg3−/− splenocytes (upper) were smaller than controls with Dsg3+/− splenocytes (lower) because oral erosions inhibited food intake. B. Some recipient mice with Dsg3−/− splenocytes showed crusted erosions on the paws, where constant pressure is applied. C, D. Recipient mice with Dsg3−/− splenocytes showed in vivo mouse IgG deposition on keratinocyte cell surfaces (C) and suprabasilar acantholysis (D) as observed in patients with pemphigus vulgaris.
Development of pemphigus mouse model

We used this novel approach of using autoantigen knockout mice to develop an active disease model for pemphigus vulgaris in mice, in this case, Dsg3−/− mice.42,47 When we immunized Dsg3−/− mice with mouse recombinant Dsg3, anti-Dsg3 IgG was indeed produced. These sera were able to bind to the cell surfaces of living cultured mouse keratinocytes, indicating that the anti-Dsg3 IgG produced in Dsg3−/− mice is capable of binding to the native Dsg3 on living keratinocytes. In contrast, sera from Dsg3−/− littermates or wild-type controls failed to bind to the surface of living keratinocytes. These findings confirmed that Dsg3−/− mice and those expressing Dsg3 have clear differences in their ability to produce anti-Dsg3 IgG that can bind to the native Dsg3.42

Despite the production of anti-Dsg3 IgG, no autoimmune reaction is expected in the immunized Dsg3−/− mice because they lack the target antigen. To allow the anti-Dsg3 IgG to be exposed to the antigen, we isolated splenocytes from the immunized Dsg3−/− mice and transferred them into Rag-2−/− immunodeficient mice that do express Dsg3 (Fig. 6B). Rag-2−/− mice have no mature T or B cells due to the inability to rearrange T cell receptors or immunoglobulin genes and are therefore unable to produce antibodies or reject transferred splenocytes. Circulating anti-Dsg3 IgG was detected in the sera of recipient Rag-2−/− mice as early as day 4 after transfer of Dsg3−/− splenocytes, and its titer increased rapidly without further boosting by recombinant Dsg3, reaching a plateau around day 21. The circulating anti-Dsg3 IgG was detected for as long as 6 months. No significant reactivity against Dsg1 was observed in these recipient mice during this period. In contrast, no circulating anti-Dsg3 IgG was detected in Rag-2−/− mice given Dsg3−/− splenocytes. The persistent anti-Dsg3 IgG production indicates that endogenous Dsg3 in the recipient mice stimulated the transferred Dsg3-specific lymphocytes from the immunized Dsg3−/− mice in vivo.

In recipient mice with Dsg3−/− splenocytes, in vivo IgG deposition was found on keratinocyte cell surfaces in stratified squamous epithelia, including the skin and oral and esophageal mucous membranes, as seen in patients with pemphigus vulgaris (Fig. 7C). In these mice, no IgG deposition was found in other tissues, including heart, lung, liver, kidney, stomach, and the small and large intestine. These IgG binding sites correspond to the known tissue distribution of Dsg3. Histological examination of the recipient mice revealed intracellular loss of cell-cell adhesion just above the basal layers, i.e., suprabasilar acantholysis, in the buccal mucosa, hard palate, oropharyngeal areas, and the upper part of the esophagus, as seen in human patients (Fig. 7D). These oral erosions likely inhibited food intake, resulting in weight loss (Fig. 7A). Some of the recipient mice developed crusted erosions on the skin around the snout, an area that is normally traumatized by scratching, or paws, where constant pressure is applied (Fig. 7B). Close histological examination revealed that the recipient mice with Dsg3−/− splenocytes also exhibited eosinophilic spongiosis, which is often found in patients with early lesions.48 We also observed patchy hair loss in the recipient mice with Dsg3−/− splenocytes (Fig. 7A). Skin biopsy showed intense IgG deposition on the cell surface of keratinocytes surrounding the telogen hair club. Cleft formation was observed between the cells surrounding the telogen club and the basal layer of the outer root sheath epithelium. In contrast, no phenotypic or pathological changes were observed in recipient mice with Dsg3−/− splenocytes.

These results indicate that the Rag-2−/− recipient mice given immunized Dsg3−/− splenocytes developed clinical, histological, and immunopathological phenotypes similar to those of patients with pemphigus vulgaris.42 This active disease model for pemphigus vulgaris provides a useful tool to investigate not only the pathophysiological mechanisms of blister formation by IgG autoantibodies but also immunological mechanisms for tolerance of B cells and T cells to Dsg3.49,50

Loss of tolerance against desmoglein 3 in both T and B cells for efficient production of pathogenic antibodies

Although there is a fundamental difference between Dsg3−/− mice and wild-type or Dsg3+/− mice in their status of tolerance against Dsg3, it was unknown whether such self-tolerance is acquired by B cells alone, T cells alone, or both. Therefore, we attempted to determine whether breakdown of tolerance at the T-cell level or at the B-cell level or both is required to produce pathogenic anti-Dsg3 IgG antibodies.49 T and B cells were purified from Dsg3−/−, Dsg3+/−, or wild-type mice after immunization with recombinant Dsg3, combined in various ways and adoptively transferred into Rag2−/− recipient mice, and the phenotype in each recipient mouse was examined. When the recipient mice with
various combinations of T and B cells were compared, only those with Dsg3−/− T and Dsg3−/− B cells showed apparent weight loss.59) Five of eight recipient mice with Dsg3−/− T and Dsg3−/− B cells showed the weight loss phenotype as well as patchy hair loss, while none of the other recipient mice with different combinations of T and B cells developed either weight loss or hair loss. Sera from all five recipient mice with the phenotype stained the cell surface of mouse keratinocytes when added to culture media. In addition, these five mice showed IgG deposition on the keratinocyte cell surface in vivo and intraepidermal blister formation just above the basal cell layer in histology.59) These findings indicate that loss of tolerance against Dsg3 in T cells as well as B cells is required for efficient production of pathogenic anti-Dsg3 IgG antibodies and development of the phenotype in our mouse model for pemphigus. As our model has characteristics similar to human pemphigus vulgaris, it was also suggested that tolerance against Dsg3 is established in both B- and T-cell populations in humans and breakdown of tolerance in both populations may trigger onset of the disease.

**Isolation and characterization of Dsg3-specific T cells from pemphigus model mice**

Autoreactive T cells are thought to be involved in the pathogenesis of pemphigus vulgaris, but evidence of their direct pathogenicity is lacking. Recently, Dsg3-specific CD4+ T cell lines and clones were isolated from Dsg3−/− mice.51) These Dsg3-reactive CD4+ T cell clones were adoptively transferred into Rag2−/−immunodeficient mice with primed Dsg3−/− B cells purified from immunized Dsg3−/− mice to determine whether all Dsg3-specific T cells are able to help B cells to produce pathogenic antibodies. Dsg3-specific T cells showed pathogenic heterogeneity and only 7 of 20 T-cell lines or clones induced IgG anti-Dsg3 IgG production and the pemphigus phenotype, while the rest did not.51) Comparison of the characteristics between pathogenic and nonpathogenic Dsg3-reactive T-cell clones led to identification of IL-4 and IL-10 as potential factors associated with pathogenic antibody production. Further in vitro analysis showed that IL-4, but not IL-10, promoted IgG anti-Dsg3 IgG production by primed B cells.51) In addition, adenoviral expression of soluble IL-4Rα, but not IL-10Rα or INT-R1, suppressed anti-Dsg3 IgG production and the development of the pemphigus phenotype, indicating the importance of IL4 in this process.51)

Furthermore, single Dsg3-reactive T-cell clones were demonstrated to help polyclonal naïve B cells to produce anti-Dsg3 IgG antibodies and induce the pemphigus phenotype in recipient mice.52) Identification and characterization of this pathogenic subpopulation of T cells will provide valuable tools for the development of efficient therapeutic strategies against the key “commander” T-cell population that may be the source of the harmful autoimmune response.

**Desmoglein isoforms and skin diseases**

Desmoglein exists in four isoforms, Dsg1–Dsg4. In addition to pemphigus, impetigo, and SSSS discussed here, the desmogleins are also targeted in several other skin and heart diseases (Table 1). Mutations in the Dsg1 gene cause striate palmoplantar keratoderma (MIM 148700), which is an autosomal dominant skin disease characterized by linear and focal hyperkeratosis of the palms of the hands and soles of the feet, probably due to haploinsufficiency of Dsg1.53) Mutations in the Dsg4 gene cause impaired hair-follicle development, which results

| Isoform | Tissue distribution | Skin diseases that target desmogleins |
|---------|---------------------|---------------------------------------|
| Dsg1    | Stratified squamous epithelia | PA, PV (MC) | SSSS | PPK |
| Dsg2    | All desmosome-bearing epithelia | None | None | ARVC |
| Dsg3    | Stratified squamous epithelia | PV (MD, MC) | None | None |
| Dsg4    | Hair follicle epithelia | Cross-reactivity of anti-Dsg1 IgG | None | Inherited hypotrichosis |

PF, pemphigus foliaceus; PV, pemphigus vulgaris; MD, mucosal dominant type; MC, mucocutaneous type; PNP, paraneoplastic pemphigus; SSSS, staphylococcal scalded skin syndrome; PPK, striate palmoplantar keratoderma; ARVC, Arrhythmogenic right ventricular cardiomyopathy/dysplasia.
in inherited hypotrichosis in humans (e.g., localized autosomal recessive hypotrichosis) and abnormal hair with bulbous degenerative changes in lanceolate hair mice and rats. It was initially suggested that Dsg4 is the autoantigen targeted in pemphigus vulgaris. However, it was subsequently demonstrated that pemphigus sera show Dsg4 reactivity due to crossreactivity of a subset of anti-Dsg1 IgG, and the Dsg4/Dsg1-crossreacting IgG plays no demonstrable pathogenic role in blister formation. Recently, mutations in the Dsg2 gene were shown to cause arrhythmogenic right ventricular cardiomyopathy/dysplasia, an inherited cardiomyopathy characterized by progressive myocardial atrophy with fibrofatty replacement.

**Perspective**

When we cloned the cDNA for pemphigus vulgaris antigen in 1991, it was not clear how desmogleins were involved in other diseases. In the 20 years since then, as molecular mechanisms have been clarified, desmogleins have been shown to be involved in many diseases. Further studies of desmoglein molecules will continue to provide insight into unsolved pathophysiological mechanisms of diseases and aid in the development of novel therapeutic strategies with minimum side effects.

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Profile

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