

# Review on Pathogenesis of Pemphigus

Dr. P. T. Chan

Social Hygiene Service (Dermatology), Department of Health, Hong Kong

## ABSTRACT

*With recent advances in laboratory techniques, the pathogenesis of pemphigus has been better understood. The common mechanism involves the development of antibodies against desmosomal proteins. Different clinical, pathological and immunological features define the subgroups of pemphigus diseases. This review article will summarize the current knowledge on the pathogenesis of pemphigus, with emphasis on the different antigens involved in the autoimmune process. The mechanism of immune intolerance leading to recognition of self-antigens is still unknown.*

**Keywords:** *Antigens, pathogenesis, pemphigus, review*

## INTRODUCTION

Pemphigus (from the Greek *pemphix*, meaning bubble or blister) is a blistering disease involving the skin and mucous membrane. The disease is characterized histologically by acantholysis which means loss of adhesion between keratinocytes, and immuno-pathologically by the presence of immunoglobulin directed towards the cell surface of keratinocytes.<sup>1</sup> The landmark article in the understanding of pathogenesis of pemphigus was published in 1964, which demonstrated the presence of anti-skin antibodies in the sera of pemphigus patients by indirect immunofluorescence staining.<sup>2</sup> Since then, with the improvement in immunological techniques, the antigens responsible for the disease were identified. These medical advances not only provide us with a better knowledge of the pathogenesis of pemphigus but also lead to the development of recombinant proteins, which are employed in enzyme linked immunosorbent assay (ELISA) for the diagnosis of pemphigus.

Pemphigus comprises a group of autoimmune skin diseases. The two major groups are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Their difference lies in the level of acantholysis, with the former in the suprabasilar level and the latter in the subcorneal level. Recently, new forms of pemphigus have been described, namely pemphigus herpetiformis, IgA pemphigus and paraneoplastic pemphigus (PNP).<sup>3</sup> This article reviews the current understanding in the antigens involved (Table 1) and the pathogenesis of these entities.

## THE STRUCTURE OF DESMOSOME

It is essential to have a basic knowledge of the desmosome in order to understand the pathogenesis of pemphigus. Desmosomes (or maculae adherens) are organelles responsible for cell-to-cell adhesion in keratinocytes. The extra cellular part, desmoglea, is composed of transmembrane adhesion glycoproteins belonging to the cadherin superfamily, which includes desmogleins and desmocollins. The intracellular part, desmosomal plaques, has two groups of proteins. The first group, plakin family (desmoplakins, envoplakin, periplakin, plectin), binds to cytokeratin filaments. The second group of proteins, namely plakoglobin and plakophilin, bind to the intracellular domain of cadherins. The pemphigus antibodies bind to the antigens in the desmosome and hence resulting in acantholysis.<sup>4</sup>

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Correspondence address:

Dr. P. T. Chan

Cheung Sha Wan Dermatology Clinic

3/F, West Kowloon Health Centre

303 Cheung Sha Wan Road

Kowloon

Hong Kong

**Table 1.** Antigens in various pemphigus diseases

<b>Pemphigus type</b>	<b>Antigens targeted by antibodies</b>
<b>Superficial pemphigus</b>	
Pemphigus foliaceus	Desmoglein 1 (160 kD)
Endemic pemphigus (Fogo Selvagem)	Desmoglein 1 (160 kD)
<b>Pemphigus vulgaris</b>	
Mucosal involvement	Desmoglein 3 (130 kD)
Mucocutaneous type	Desmoglein 1 (160 kD) and Desmoglein 3 (130 kD)
<b>Paraneoplastic pemphigus</b>	Desmoplakin I (250 kD) Bullous pemphigoid antigen I (230 kD) Desmoplakin II (210 kD) Envoplakin (210 kD) Periplakin (190 kD) Unknown (170 kD) Desmoglein 1 (160 kD) Desmoglein 3 (130 kD)
<b>Pemphigus herpetiformis</b>	Desmoglein 1 (160 kD) Desmoglein 3 (130 kD)
<b>IgA pemphigus</b>	
Subcorneal pustular dermatosis type	Desmocollin I (105-115 kD)
Intraepithelial type	Unknown, some cases desmoglein 3 & 1

## THE PATHOGENICITY OF PEMPHIGUS ANTIBODIES

### Clinical observations

There are several clinical observations that suggest pemphigus is an antibody mediated disease.<sup>1</sup> Firstly, there is a correlation between disease activity and antibody titres in both PV and PF. Secondly, neonates born by women with active PV may develop a self-limiting form of pemphigus disease that terminates spontaneously with the clearance of maternal antibodies. Children of mother with active PF, however, seldom develop neonatal pemphigus because of the difference in desmoglein composition between neonatal and adult skin (see section on desmoglein compensation hypothesis).

### Experimental models

In vitro models utilizing skin explants and cultured keratinocytes have demonstrated the acantholytic effects

of pemphigus antibodies.<sup>5</sup> Animal models have also been developed for the investigation of disease pathogenesis. Anhalt et al was able to reproduce blisters in neonatal mice by daily intraperitoneal injection of pemphigus serum.<sup>6</sup> These blisters were histopathologically similar to the human counterpart. Besides PV, passive transfer of disease by intraperitoneal IgG injection has been performed for PF and PNP.<sup>4</sup> Moreover, by transferring antibodies affinity-purified on different recombinant desmoglein fragments, it was shown that the pathogenic antibodies were directed to the extracellular part of desmogleins.<sup>7</sup> Passive transfer of pemphigus has also been achieved in severe combined immunodeficiency disease mice by grafting with human skin and reconstitution with peripheral blood lymphocyte from patient.<sup>8</sup> The other two animal models belong to the active group, in which pathogenic antibodies are generated by immunization of animals with desmoglein. Thus, BALB/c mice synthesize blister-producing antibodies upon immunization with recombinant human desmoglein 3.<sup>9</sup> And Rag<sup>-/-</sup> mice

developed cutaneous and mucosal disease when they were given splenocytes from desmoglein 3 knockout mice immunized with mouse desmoglein 3.<sup>10</sup> Besides helping us to understand the pathogenesis of disease, these animal models provide us with the opportunity for evaluation of new treatment.

### **The pemphigus antibodies**

Direct immunofluorescence examination of lesional skin from patient with pemphigus shows staining on the surface of keratinocyte, indicating the presence of immunoglobulins on these cells. Patients with PV and PF may display similar direct immunofluorescence findings on IgG on the cell surface throughout the epidermis. Therefore the two diseases cannot be separated by the pattern of immunofluorescence in all cases.<sup>1</sup> The deposited immunoglobulins are mainly IgG, with IgG1 and IgG4 predominate. Indirect immunofluorescence study also revealed that circulating antibodies are mainly IgG1 and IgG4.<sup>4</sup> Support for the pathogenic importance of IgG4 lies on the fact that IgG4 is the major antibody in active PV cases while IgG1 remains detectable in remitted cases.<sup>4</sup> Moreover, in comparing antidesmoglein antibody subclass in pemphigus patients and their healthy relatives, IgG4 was the only one that was found to be significantly lowered in the relative group.<sup>11</sup> But IgG4, unlike IgG1 to IgG3, does not bind complement. As complement deposition is usually present in active cases of PV, a combination of IgG subclasses seems to be necessary in the formation of blister.<sup>11</sup> A more recent finding is the presence of desmoglein 3 reactive IgA and IgE in pemphigus patient with active disease by using baculovirus expressed desmoglein 3 in an immunoblot assay.<sup>12</sup> As the concentration of desmoglein 3 reactive IgA and IgE is much lower than that of IgG1 and IgG4, the pathological importance of these antibody subclasses in blister formation remain to be determined.

In pemphigus herpetiformis,<sup>3</sup> IgG is found primarily in the upper epidermis. The IgG4 subclass is the predominant type of *in vivo* bound and circulating antibody. In IgA pemphigus,<sup>3</sup> IgA is deposited on to keratinocyte cell surface in all cases. In the subcorneal pustular dermatosis (SPD) type of IgA pemphigus, IgA deposition occurs on the upper epidermal cell surfaces, whereas in the intraepidermal neutrophilic (IEN) type of IgA pemphigus, the deposition occurs in the lower epidermis or throughout the entire epidermis. The

subclass of IgA antibody belongs to IgA1. In PNP,<sup>3</sup> direct immunofluorescence of perilesional skin shows IgG deposition along the basement membrane zone and on the keratinocyte surface. The IgG subclasses are found in the following descending order: IgG1, IgG2, IgG4 and IgG3. Unlike PV sera, PNP sera can bind to nonstratified epithelium (such as rodent urinary bladder) as well as stratified squamous epithelium because of their antigens specificity (see section on pemphigus antigens).<sup>13</sup>

## **THE PEMPHIGUS ANTIGENS**

### **Antigens in pemphigus vulgaris and foliaceus<sup>4</sup>**

Immunoprecipitation assays using keratinocyte extracts identified 210 kD complex and 260 kD complex in PV and PF respectively. The 210 kD complex is composed of a 130 kD protein named desmoglein 3 and a 85 kD protein named plakoglobin. The 260 kD complex is composed of a 165 kD protein named desmoglein 1 and a 85 kD plakoglobin. Immunoblotting experiment has shown the desmoglein 1 and 3 are the only part of the complex recognized by patients with PF and PV respectively, and the plakoglobin is coprecipitated. Cloning and sequencing of the desmogleins 1 and 3 genes have confirmed that they has high sequence homology and belong to the cadherin family.

### **The desmoglein compensation hypothesis<sup>14</sup>**

The desmoglein compensation hypothesis has been proposed to explain the localization of lesions of PV and PF. In PF, blisters occur at the granular layer of superficial epidermis, and the mucous membrane is not involved. In PV, two third of the patients develop blisters over the mucous membrane and then the blisters develop over the skin as well, the histological cleavage is located at the basal and suprabasal levels of epidermis. Desmoglein 1 is expressed mostly in the upper epidermis. As antibody to desmoglein 1 is present in PF, acantholysis develops in the superficial epidermis. Because of the coexpression of desmoglein 3 in mucous membrane and lower epidermis of skin, these sites are spared. In PV, the antibody to desmoglein 3 causes acantholysis in the mucous membranes, as desmoglein 3 is the major cadherin expressed in these sites. Later as the disease progresses, many patients will experience cutaneous disease, at the time when antibodies to both

desmoglein 3 and 1 develop.<sup>15</sup> The development of additional antibodies in the disease course may represent an example of 'epitope spreading' seen in autoimmune disease.<sup>15</sup>

The desmoglein compensation hypothesis is also supported by experimental study, in which pemphigus antibodies are passively transferred to normal and desmoglein 3<sup>null</sup> neonatal mice.<sup>16</sup> In areas of epidermis coexpressing both desmoglein 1 and 3, antibodies to either one desmoglein do not induce blister, but antibodies to both desmogleins do. In areas of epidermis where only desmoglein 1 is present, antibody to desmoglein 1 alone can induce blister. This hypothesis explains the clinical and microscopic localization of blister in pemphigus. It also allows the prediction of antibody profile from clinical phenotype:<sup>17</sup> antibody to desmoglein 1 in PF, antibody to desmoglein 3 in mucosal predominant PV, antibody to desmoglein 1 and 3 in mucocutaneous PV.

Desmoglein 1 antibody causes PF in adults, but the transplacental passage of this antibody does not produce disease in neonate. This is different from the case in PV, when transplacental passage of desmoglein antibody causes neonatal disease. Neonates from PF mother are free from the blistering disease because of the presence of both desmoglein 1 and desmoglein 3 on the cell surface of superficial and basal keratinocytes.<sup>18</sup>

### **Pemphigus antigens other than desmoglein**

The pathogenesis of pemphigus has been so well characterized as above with the desmoglein compensation hypothesis that explains the clinical, immunological and pathological aspects of pemphigus. Nonetheless, there are several observations that remain to be explained. There are about 20 self-antigens, the number of which depends on patient status and the detection technique, that react with pemphigus IgGs. In experimental study, PV serum (which only contains anti-desmoglein 3 activity but not anti-desmoglein 1 activity) can induce blisters even in desmoglein 3 deficient mice. Therefore, although desmoglein 1 may compensate for the absence of desmoglein 3, the effect of pemphigus serum cannot be ascribed by a blockade of desmoglein 1 alone.<sup>19</sup>

The presence of antibodies to keratinocyte cholinergic receptors, including pemphaxin and a

50 kD  $\alpha$ -9 acetylcholine receptor, has been recently demonstrated to be present in pemphigus sera.<sup>20</sup> Both antibodies induce acantholysis in keratinocyte culture, but do not induce blister in vivo. Human keratinocytes express cholinergic receptors of both nicotinic and muscarinic classes; stimulation of either receptor can alter the adhesive interaction of keratinocytes at least in part by the regulation of intracellular calcium level. Recent studies showed that calcium mediated actin polymerization is the major driving force for cell to cell adhesion and the assembly of desmosomes is a passive process that occurs when stable cell contact is made.<sup>21</sup> The importance of calcium in mediating cellular adhesion is also demonstrated by two acantholytic disease, Darier's disease and Hailey-Hailey disease. Mutation of the ATP2A2 occurs in Darier's disease<sup>22</sup> and mutation of ATP2C1 occurs in Hailey-Hailey disease,<sup>23</sup> in both diseases the gene products are calcium pumps. Further research is needed to determine whether there is an active role of these non-desmoglein antibodies in the pathogenesis of pemphigus or whether they are just 'bystander' in the phenomenon of epitope spreading.

### **Antigens in the pemphigus variants**

Pemphigus herpetiformis combines the clinical features of dermatitis herpetiformis with the immunologic and histologic features of pemphigus. Patient's sera react most often with desmoglein 1 and sometimes with desmoglein 3. Sera from patients with pemphigus herpetiformis induce spongiosis with eosinophil infiltration, but rarely is acantholysis prominent, in contrast with classical pemphigus. It is thought that sera from pemphigus herpetiformis patients recognize different epitopes on desmoglein molecules and has a different post antigen binding sequelae as compared with classical pemphigus.<sup>3</sup>

The antigens in IgA pemphigus are less well defined.<sup>24</sup> Previous immunoblotting experiment had shown reactivity with bovine desmocollin 1, but not with human skin extracts. This is probably because of conformational dependent epitope for IgA pemphigus antibody. By using a cDNA transfection assay, the antigen in SPD type of IgA pemphigus was shown to be human desmocollin 1. In the IEN type of IgA pemphigus, ELISA demonstrated the presence of reactivity with desmoglein 1 and 3 in a few cases only. Therefore the antigens in IEN type of IgA pemphigus were more heterogeneous.

PNP is an autoimmune disease with a polymorphous mucocutaneous eruption and an underlying neoplasm. The most common association is that of benign and malignant haematological tumours such as lymphomas, chronic lymphocytic leukaemia and Castleman's disease, although other solid tumours have also been described. The diagnostic criteria had been reviewed.<sup>3</sup> The antigens identified by immunoprecipitation include cytoplasmic proteins of the plakin family, desmoplakin I (250 kD), desmoplakin II (210 kD), bullous pemphigoid antigen I (230 kD), envoplakin (210 kD), periplakin (190 kD) and an 170 kD protein, the identity of which remained to be determined.<sup>3</sup> By ELISA, antibodies to desmoglein 1 and 3 are also present in PNP sera. Antibodies from patients with PNP differ from classical pemphigus in their ability to react with nonstratified epithelium. Rat urinary bladder is the preferred substrate as it has a high density of desmosomes. Antibodies from patients with PF and PV do not bind to transitional epithelium as desmoglein 1 and 3 are only expressed in squamous cell epithelia. Plakins are proteins that link keratin filaments to the cell surface and they are inaccessible to antibodies in intact cell because of their intracytoplasmic location. The antibodies against desmogleins (transmembrane proteins) are important in the initiation of PNP based on the observation that: (1) all patients with PNP have anti-desmoglein 3 antibody and about 60% have anti-desmoglein 1 as well by ELISA; (2) passive transfer of whole IgG from PNP sera produce blisters in neonatal mice and (3) immunoabsorption of desmoglein 1 and 3 antibodies from PNP sera prevent blister formation in neonatal mice.<sup>25</sup>

### **ACANTHOLYTIC MECHANISM OF PEMPHIGUS ANTIBODIES**

Although ample evidences are present for the aetiologic role of pemphigus antibodies, there are controversies over the mechanism of acantholysis. Majority of the research work had been concentrated on the classical pemphigus and was reviewed.<sup>4</sup> Release of plasminogen activator has been shown in vitro on addition of pemphigus antibodies to keratinocyte cultures. In vivo, urokinase type plasminogen activator has been demonstrated in blister fluid. But elevation of plasminogen activator has been reported in lesional skin of other non-acantholytic disease and passive transfer of PV and PF IgG to plasminogen activator knockout

neonatal mice can induce acantholysis. Therefore, the plasminogen-plasmin system may act secondarily in the amplification of lesions. The same assistant amplification role has also been proposed for complement. In vitro, pemphigus antibodies alone can induce acantholysis without complement. In vivo, passive transfer of F(ab')<sub>2</sub> fragment, which does not activate complement, into neonatal mice induces blister formation. Cytokines are also possible mediators in acantholysis, with increase in IL-1, IL-6, and TNF- $\alpha$  demonstrated in PV cases,<sup>26</sup> and increase in IL-8 in pemphigus herpetiformis cases.<sup>3</sup> In PNP, some lymphomas and leukemia secrete massive amounts of IL-6 which may drive autoimmune antibody production.<sup>3</sup> However, the nonspecific destruction by proteases and inflammatory cells recruitment is not compatible with the desmoglein compensation hypothesis which predicts the level of acantholysis by the compensation of adhesive function of desmoglein in the presence of another. Thus, a direct inhibitory action of pemphigus antibody on desmoglein adhesive function has been suggested.<sup>14</sup>

### **ROLE OF GENETIC AND ENVIRONMENTAL FACTORS**

Genetic factors may affect susceptibility to autoimmune diseases. Familial cases of pemphigus have been described and relatives of pemphigus patients may have anti-skin antibodies. PV is more common in Ashkenazi Jews and Japanese, and Fogo Selvagem (endemic PF) may have genetic and environmental factors that account for its prevalence in Central and South America. The genetics of pemphigus has been reviewed.<sup>4</sup> In both PV and PF, association with HLA class II genes is found, in particular, DR4 and DR14 genes. Different susceptibility alleles have been described in PV, with the prevalent allele differs in different populations, for example, DRB1\*0402, 0403, 0404, 0406 and DRB1\*1401, 1404, 1405, 1406. In Fogo Selvagem, besides the DR4 and DR14 alleles, a susceptibility allele of DR1 (DRB1\*0102) and protective alleles of DQ class (e.g. DQB1\*0201) are found.<sup>27</sup> The association of HLA alleles with pemphigus is probably related to the ability of susceptible alleles to present desmoglein derived peptides in the antigen presentation process and these alleles have conserved residues at key positions of the DR beta chain.

Environmental factors such as drugs, virus, burns, and irradiation have been described in triggering or exacerbating pemphigus, but their exact importance and pathogenic mechanisms are not well defined.<sup>4</sup> Fogo Selvagem is the endemic form of PF found in Brazil and other parts of South America. While familial clustering of the disease can be explained by genetic association or shared environmental exposure in the same family, other epidemiological data suggest that environmental exposure alone is important. These include geographical clustering, often near to tributaries of river, its occurrence in different ethnic groups and at risk occupation of agricultural work.<sup>27</sup> A case control study demonstrated that insect bite by black fly was a risk factor for development of Fogo Selvagem.<sup>27</sup> Whilst insect bite may act through molecular mimicry in generating an autoimmune reaction, there is no concrete data that suggests how insect bite can lead to Fogo Selvagem.<sup>4</sup>

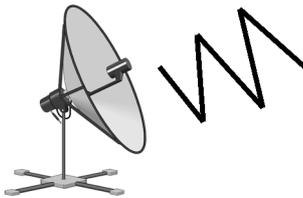
## CONCLUSIONS

In the last few decades, there have been significant advances in the understanding in the pathogenesis of pemphigus. The knowledge has been transformed into improvement in diagnosis (with the use of immunofluorescence, immunoprecipitation, immunoblotting, ELISA), in treatment (with decrease in mortality by the use of immunosuppressant) and disease monitoring (as antibodies titre are related to disease activity). But there are also a number of crucial questions remained to be answered. These include the mechanism leading to immune intolerance of self-antigen, role of acetylcholine antibodies, and mechanism of acantholysis by antibodies.<sup>20</sup> Further research in these areas may provide opportunity for the generation of new treatment strategies and/or prevent the disease occurrence in susceptible individuals.<sup>4</sup>

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