Immunopathogenesis of pemphigus vulgaris: A brief review
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Abstract
Pemphigus vulgaris is an autoimmune blistering disease of the skin and mucous membrane. It is mediated by autoantibody against desmoglein 3, an intracellular adhesion glycoprotein that forms a part of desmosome. Loss of tolerance to this autoantigen happens for a still unknown reason. However, this disease has a very strong association with some human leukocyte antigen molecules whose structure favors the binding of certain peptide of desmoglein 3. The mechanism of the action of autoantibody has turned out to be more complicated than it was thought, and it is not well established yet. Nevertheless, in the past few years, important discoveries have been made that point to a role of autoantibodies in staining different signaling cascades that lead to loss of adhesion between keratinocyte and death of these cells resulting in acantholysis as histologic manifestation and blister as clinical manifestation.

Keywords
Acantholysis, apoptolysis, desmoglein, pemphigus vulgaris

Introduction
Immunobullous diseases are a group of conditions characterized by severe blistering of the skin and mucosal surfaces, one among which is pemphigus. Pemphigus vulgaris is a rare autoimmune disease that causes painful blistering on the skin and mucous membrane. It is classified as a Type II hypersensitivity reaction, with the formation of antibodies against desmosomes which results in blisters. The term pemphigus was derived from a Greek word “pemphix” which means blister. Pemphigus is a group of chronic vesiculobullous, mucocutaneous lesions caused due to the autoantibodies formed against intercellular attachments of keratinocytes leading to the loss of cell-cell epithelial adhesion, and thus mediating the process of acantholysis. The two major variants of pemphigus are pemphigus vulgaris and pemphigus foliaceus. In most of the cases, oral mucosa is one of the first sites of attack. However, there are 10-15% of cases that show only cutaneous manifestations. Clinically, the diseases present with rapid appearance of vesicles and bullae of varying diameter filled with thin watery fluid in the initial stages, and the fluid may soon become purulent. Oral manifestations include ill-defined, irregular erosions in the palate, buccal mucosa, or gingiva which are painful and extensive. An intact bulla is rarely seen. Such erosions cause difficulty to the patients in terms of eating or drinking.

It has been accepted that pemphigus vulgaris is an autoimmune disease as there are evidences suggesting the presence of circulating IgG antibodies in the patients with the disease. This review deals in detail about the theories put forward to explain the pathogenesis of pemphigus vulgaris and also enlists the various laboratory investigations that can be done to confirm the diagnosis.

Various Theories of Immunopathogenesis
It has been found that pemphigus vulgaris is caused due to the autoantibodies directed against the desmoglein 1 and/or desmoglein 3. However, many theories have been put forward to understand the biology of desmoglein and pemphigus vulgaris. Four theories have been put forward to explain the pathogenesis of pemphigus vulgaris which are as follows:
1. The desmoglein compensation theory
2. Multiple hits hypothesis
3. The antibody-induced apoptosis theory
4. The basal cell shrinkage hypothesis and the apoptolysis theory.

The Desmoglein Compensation Theory
The desmoglein compensation theory was given by Mahoney M.G in the year 1999 based on the differential antigenic
distribution and generation of autoantibodies. Desmoglein comprises a family of cadherins that play a major role in the formation of desmosomes, whose basic function is adhesion of one cell to another. Proteins such as desmogleins 1-4 come under this family of cadherins. The theory puts forward that the presence of even a single type of desmoglein is enough to maintain the continuity of the epithelium.

This theory was proposed based on two crucial experimental evidences:

1. There exists a difference in the expression patterns of desmoglein 1 and 3 in the skin and mucous membranes. Desmoglein 1 is found to be expressed in the epidermis and oral mucosa with intense expression in the subcorneal layers and weak expression in deeper layers.

2. There also exists a clinical correlation of pemphigus with the anti-desmoglein antibody profile in regard to clinical phenotypes. Patients affected by pemphigus foliaceus have only anti-desmoglein 1 IgG in their autoantibody profile, and lesions were predominantly seen on the skin. Patients with pemphigus vulgaris have only anti-desmoglein 3 IgG in the autoantibodies profile and lesions were predominantly seen in mucosal surfaces. However, mucocutaneous variant of pemphigus vulgaris consisted of both anti-desmoglein 1 and anti-desmoglein 3-IgG autoantibodies.

Compiling these two evidences, it was assumed that anti-desmoglein IgGs are highly required and sufficient to cause pemphigus vulgaris and that desmoglein 1 and 3 can reciprocally compensate for their adhesive functions. Thus, it was stated that the serum of pemphigus vulgaris patients would contain only anti-desmoglein 3 IgG and that it does not cause blisters on the skin because of the compensation of impaired desmoglein 3 function by desmoglein 1 co-expression. However, in mucous membranes, desmoglein 1 is unable to compensate for the impaired desmoglein 3 function due to its decreased expression. In patients whose serum contains both antibodies against desmoglein 1 and desmoglein 3, results in extensive blisters as well as erosions on the skin and mucous membranes [Figure 1].

Limitations

This theory does not give a proper explanation of epidermal blister formation.

Multiple Hits Hypothesis

Evidences indicate that apart from anti-desmoglein 1 and anti-desmoglein 3 antibodies, patients also develop antibodies against other desmosomal proteins such as desmocollins and plakins and non-desmosomal proteins such as cell-membrane receptors such as nicotinic acetylcholine receptor, pemphaxin, thyroperoxidase, and other annexins. It was found by Volker et al. that desmocollin 3 is expressed in the basal, spinous, and lower granular layers of the epithelium. Moreover, further, blocking of its function will give rise to the development of intraepidermal blisters. Non-desmosomal autoantigens such a pemphaxin also contributed to pemphigus vulgaris. All these data suggest that pemphigus is a complex disease which is started by at least three classes of autoantibodies which are directed against desmosomal, mitochondrial, and other keratinocyte autoantigens. Multiple hits hypothesis puts forward a mechanism that explains acantholysis in the disease. However, the desmogleins are still thought to be an important factor in the disease. Clinically, the titer of anti-desmoglein antibody directly correlates with disease activity. The involvement of other autoantigens in the pathogenesis of pemphigus vulgaris has been explored, but the relative contributions of these proteins in the disease process remain controversial.

The Antibody-induced Apoptosis Theory

Research on pemphigus has been trying to elucidate new mechanisms to explain acantholysis in pemphigus vulgaris. Researchers have suggested that apoptosis could be the reason for acantholysis. On activating the apoptotic signaling, there is induction by pemphigus IgG and anti-Fas receptor (anti-FasR) antibody. The pathway consists of secretion of soluble Fas ligand (FasL), followed by an increase intracellular FasR, FasL, Bax, and p53 levels which leads to decreased levels of Bcl-2, enrichment of caspase-8 as well as activation of caspases 1 and 3 and also the death-inducing signaling complex. Inhibition of caspases 1 or 3 was found to be effective in suppression of IgG-mediated apoptosis, and thereby blocking acantholysis. However, the recent studies have shown that keratinocytes that are cultured in vitro with pemphigus vulgaris IgG underwent acantholysis without the presence of any detectable apoptotic-like nuclear fragmentation. Therefore, apoptosis may not prove to be a prerequisite as far as skin blistering in pemphigus vulgaris is considered, but rather it could occur secondary to acantholysis. Thus, pemphigus vulgaris is a disease that is caused due to reduced cell adhesion as well as apoptosis, which takes place in association with a detachment of cell and triggered by pathogenic IgG antibodies.
The Basal-cell Shrinkage Hypothesis and the Apoptolysis Theory

Studies have found that acantholysis occurring in pemphigus vulgaris is primarily confined to the superior basal layer and is characterized by “tombstone” appearance of basal cells. Claude et al. suggested a new theory for pemphigus pathogenesis in 2006. Based on the theory, soon after the binding of the pemphigus vulgaris autoantibody to the keratinocyte receptor, there is rupture of the cytoskeleton through a downstream of signal transduction pathways, leading to the collapse and shrinkage of keratinocytes. This hypothesis was successful in explaining the reason why acantholysis is confined to the basal layer. The term, “apoptolysis,” was formulated by Grando et al. in the year 2009. The main principle difference of apoptolysis and apoptosis in pemphigus vulgaris lies in the fact that the basal cells shrink, but they do not die, which renders a “tombstone” appearance.[5] It has been found that pemphigus vulgaris IgG-induced caspase-8 activation and acantholysis can be inhibited by anti-FasL antibody suggesting the role of the same set of enzymes in causing structural damage and death of keratinocytes. The concept of apoptosis vividly links the cell apoptosis with the basic pathological features. However, it remains unsure of whether apoptosis occurs before acantholysis or whether apoptosis is a step occurring midway in the pathogenesis of PV. Further research is required to uncover this mechanism.[6]

Conclusion

These theories help in better understanding about the pathogenesis of pemphigus vulgaris which is much needed in this age. These theories mostly suggest that it is autoimmune in nature. Various precipitating factors are there which leads to pemphigus vulgaris. The more the understanding of the disease better is the chances of diagnosis and treatment. Further research is necessary in this topic to aid in providing better prevention and treatment.

References
