Review Article

Current concepts of pemphigus with a deep insight into its molecular aspects

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Abstract

Pemphigus vulgaris is an autoimmune bullous disease involving both the skin and mucosal areas, which is characterized by intraepithelial flaccid blisters and erosions. The pathogenesis of this disease is not yet completely established, but novel intuitions into its pathogenesis have recently been published. An unanswered question in its pathophysiology is the mechanism of acantholysis or loss of keratinocyte cell adhesion. Acantholysis seems to result from a communal action of autoantibodies against numerous keratinocyte self-antigens, of which desmogleins 1 and 3, desmocollins and nondesmosome components, such as the mitochondrion, might take part in the disease initiation. Lately, apoptosis was described as a possible underlying mechanism of acantholysis. Likewise, apoptolysis is assumed to be the association between suprabasal acantholytic and cell death pathways. Hence, the present review focuses on the current concepts in the pathogenesis of the pemphigus in a nutshell.

Keywords: Acantholysis, apoptolysis, apoptosis

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INTRODUCTION

Vesiculobullous diseases are a distinctive group of oral disorders characterized by the formation of vesicles or bullae of which pemphigus group of disease is more common. Pemphigus belongs to a group of potentially life-threatening organ-specific autoimmune blistering diseases. It affects the skin, oral mucosa and may also affect the mucosa of the nose, conjunctiva, genitals, esophagus, pharynx and larynx.[1] Pemphigus is classically characterized by the damage to the desmosomes by antibodies, against the extracellular domains of the desmogleins (Dsgs) with immune deposits intraepithelially. It is known that these autoantibodies play an imperative role in the pathogenesis and development of pemphigus vulgaris (PV).[2] This lesion also exhibits morphologically characteristic acantholysis due to loss of cell–cell adhesion among the keratinocytes.[3] However, novel insights into Dsg biology and pemphigus pathology have been recommended, and new questions are evolving as the conventional concepts of the pathogenesis of pemphigus are being confronted. Hence, the present review focuses on the earlier and the current concepts with an insight into acantholysis and cell junctions, with a view to understand the immunopathogenesis of pemphigus.

FACTS OF CELL JUNCTIONS

Before understanding the pathophysiology of the pemphigus, it is of prime importance to have the idea

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about the cell junctions and the concept of acantholysis in general and their affect in vesiculobullous lesions, i.e., pemphigus in particular.

Desmosomes are the cell junction molecules which contribute to epidermal cell–cell adhesion. The desmosomal proteins (Dsg1 and Dsg3) are the autoantigens for various groups of immune-mediated disorders. Hemidesmosome is a membrane-associated protein complex that extends from the intracellular area of basal keratinocyte to the extracellular area. It links the cytoskeleton of the basal keratinocyte to the connective tissue.[1]

Any disturbance generated in the desmosomal and hemi-desmosomal cell junction molecules will lead to the immune-mediated vesiculobullous disorders. It is stated that targeted cell junctions in different immune-mediated diseases are the desmosomes and hemidesmosomes. In pemphigus, the cell junctions which are targeted are desmosomes, more precisely Dsg1 and Dsg3.[4]

ACANTHOLYSIS AS A MAINSTAY

In the year 1881, the term acantholysis was coined by Auspitz, and it is derived from the Greek words Akantha, meaning a thorn or prickle, and lysis, i.e., loosening.[5] Acantholysis means loss of coherence among epidermal cells due to the breakdown of intercellular bridges. The cells remain intact but are no longer attached to each other; they tend to acquire the smallest possible surface area and become rounded up, resulting in intra-epidermal clefts, vesicles and bullae. It is the primary pathological change occurring in pemphigus.[6] Putting the context of acantholysis in a nutshell, it can be categorized to primary and secondary acantholysis.

Primary acantholysis refers to the dissociation and disintegration of desmosomes leading to the separation of keratinocytes which may be either due to the direct injury to desmosomes or due to the hereditary defects in their assembly. It is of key pathogenetic relevance in diseases of the pemphigus group.[7]

Secondary acantholysis denotes to the acantholysis which is secondary to alteration or damage to keratinocytes by various factors.[8] In another context, keratinocytes are damaged first followed by a subsequent breakdown of desmosomes.[7,8] It is seen in several benign and malignant skin diseases such as herpes simplex and herpes zoster lesions, epidermolytic hyperkeratosis, certain variants of epidermolysis bullosa, solar keratoses, acantholytic acanthoma and adenoid squamous cell carcinoma.[8,9]

Linking the idea of the acantholysis to the pathophysiology of pemphigus few conventional concepts were suggested. They are as follows.

EARLIER CONCEPTS

Steric hindrance theory

According to this theory, immunomapping of pemphigus antibodies has demonstrated that the pathogenic antibodies bind the amino-terminal extracellular domain of Dsgs that is predicted to form the trans-adhesive interface between cells, based on the crystal structures of classical cadherin molecules.[10] However, this theory could not explain the exact mechanism of pathogenesis of pemphigus.

Desmoglein compensation theory

This theory is stated by Amagai *et al*. in 1999 based on the distribution of Dsg1 and Dsg3 in the skin and mucosa.[11] They stated that the presence of any one Dsg type is appropriate to sustain the integrity of the epidermis and mucosa.[12]

Usually, Dsg3 is preferentially expressed in the parabasal region of the epidermis and oral epithelium, whereas Dsg1 is found chiefly in the superficial portion of the epidermis. Hence, patients who develop autoantibodies directed against Dsg3 with or without the involvement of Dsg1 will histopathologically show intraepithelial clefting just above the basal layer, and clinically oral mucosal blisters of pemphigus will form. Persons who develop autoantibodies directed against Dsg1 will histopathologically show superficial intraepithelial clefting of the epidermis, but oral mucosa will not be affected.[12]

This concept has elucidated the basic pathophysiology of pemphigus and has been widely used in diagnosis and assessment of efficacy and prognosis. Nevertheless, this theory cannot clarify the epidermal-blister formation satisfactorily.

"Multiple hits" hypothesis

Current evidence states that a part from the anti-Dsg1 and anti-Dsg3 antibodies, additional desmosomal, and nondesmosomal proteins such as cell-membrane receptors (nicotinic acetylcholine receptor, pemphaxin, thyroperoxidase and some other annexins) can be a target for the pemphigus.[13]

Spindler *et al*. stated that desmocollin 3 (Dsc3) is expressed all through the basal, spinous and lower granular layers. He stated that blocking of Dsc3 function with a monoclonal antibody, directed to the formation of intraepidermal blisters.[14]

Few researches stated that a part from the desmosomal antigens, nondesmosomal autoantigens such as pemphaxin, alpha 9-acetylcholine receptor also deliver relative contributions to pemphigus.[15] Few stated that there exists development of anti-mitochondrial antibodies, which could penetrate keratinocytes and react with mitochondrial proteins.[16] These facts specify that pemphigus is a complex disease, instigated by at least three classes of autoantibodies directed against desmosomal, nondesmosomal, mitochondrial and other keratinocyte autoantigens.

Recently, investigated subclasses of specific IgG found that the IgG4 subclass was dominant in the acute stage, whereas IgG1 was in remission of pemphigus. Therefore, although the involvement of other autoantigens in the pathogenesis of pemphigus has been explored, the relative contributions of these proteins remain a matter of debate.[17]

Antibody-induced apoptosis theory

The current pemphigus research is clarifying new mechanisms of keratinocyte detachment in Pemphigus. Researches have put forward that apoptosis may possibly be responsible for the causal mechanisms of acantholysis.[18] They also stated that under experimental conditions, the activation of apoptotic signaling can be induced by pemphigus IgG and anti-Fas receptor (FasR) antibody.

The pathway involves the secretion of soluble Fas ligand (FasL), an increase in the level of intracellular FasR, FasL, Bax and p53 and a decrease in the level of Bcl-2, enrichment of caspase-8, and activation of caspases 1 and 3 and the death-inducing signaling complex as a result of the aggregation of FasL, FasR and caspase-8. Inhibitors of caspases 1 or 3 were effective in suppressing IgG-mediated apoptosis and blocking acantholysis, supporting the idea that apoptosis contributes to the cell dissociation.[19]

The mechanisms of apoptosis in PV may be based on the PV IgG-triggered activation of signaling pathways, such as:[20]

- Epidermal growth factor receptor (EGFR) activation-dependent intracellular signaling (extracellular signal-regulated kinase) pathway
- Apoptosis (FasR) pathway.

NEWER CONCEPTS

Basal cell shrinkage theory

This theory came into progress later explaining that the acantholysis mainly occurs in the superior basal layer, and is generally characterized by the tombstone-like transformation of basal cells. In the year 2006, Bystryn and Grando proposed a new hypothesis of pemphigus pathogenesis, which suggests that after the binding of pathogenic pemphigus autoantibody to the keratinocyte receptor, a series of signal transduction pathways trigger the rupture of the cytoskeleton, resulting in the collapse and shrinkage of the keratinocytes.[21] This hypothesis elucidates why pemphigus acantholysis mainly occurs at the basal layer, even though the keratinocytes in the superior basal layer remain connected.

Apoptolysis: Relating the apoptotic pathways to basal cell shrinkage and suprabasal acantholysis

In the year 2009, a novel term, "apoptolysis," was suggested by Grando *et al*., which relates the suprabasal acantholytic and cell death pathways to basal-cell shrinkage.[22] The fundamental difference between apoptolysis and apoptosis is that the basal cells shrink but do not die, rendering a "tombstone" appearance to the pemphigus lesions.[23]

Quite, a lot of researches stated that PV IgG-induced caspase-8 activation and acantholysis can be prevented by anti-FasL antibody, which suggests that the structural damage (acantholysis) and death (apoptosis) of keratinocytes in pemphigus are intervened by the same set of cell death enzymes. This novel concept distinguished the unique pattern of cell damage and detachment in pemphigus.

So, here is the pathologic mechanism of apoptolysis, emphasizing that apoptotic enzymes contribute to acantholysis development both in terms of molecular events and chronologic sequence.[24]

First event starts with the binding of pathogenic antibodies to Dsgs, acetylcholine receptors and other members of the pemphigus antigen family to the plasma membrane of keratinocytes via a receptor-ligand type of interaction and mobilization / aggregation of these "survival receptors," directing an array of signals. Then, the activation of EGFR, Src, mammalian target of rapamycin, p38 MAPK and other signaling elements and elevation of intracellular Ca2+, together initiate the programmed cell death enzymatic cascades essentially in keratinocytes of the basal and the lowermost suprabasal cell layers.

Early acantholysis is established by basal cell shrinkage due to collapse and retraction of the tonofilaments cleaved by executioner caspases and dissociation of interdesmosomal adhesion complexes caused by both phosphorylation of adhesion molecules and cleavage of the cytoplasmic tails of transmembrane cadherins by caspases. Advanced

acantholysis is due to the continuous degradation and collapse of structural proteins, including Dsgs, by the same cell death enzymes.

This results in the separation and splitting of preexisting desmosomes from the cell membrane by shear forces, thus entirely separating the collapsing cells and stimulating the production of scavenging antibodies. Then, rounding up and apoptotic death of acantholytic cells in the lower epidermal part result from the irreversible destruction to mitochondrial and nuclear proteins by the same cell death enzymes.

CONCLUSION

In conclusion, Dsgs are the key target antigens, though other autoantigens are also being explored. It is important that these autoantigens cannot elicit pemphigus alone without the presence of anti-Dsg antibodies; nonetheless, they may worsen the disease. Hence, this review summarizes that the structural damage (acantholysis) and death (apoptosis) of keratinocytes in pemphigus are intervened by the same set of cell death enzymes. Collectively, our understanding of the pathogenesis of pemphigus continues to be improved by newly found molecules, and antigenic targets, which it is hoped will enable the identification of precise therapies for pemphigus.

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