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Review Article

AUTOIMMUNE VESICULOBULLOUS LESION OF ORAL CAVITY AND ITS MOLECULAR ASPECT

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A B S T R A C T

One of the remarkable characteristics of the normal immune system is that it is capableof reacting to an enormous variety of microbes, but it does not react against every individual's own antigens. This unresponsiveness to self -antigens, is also called immunological tolerance. Autoantibodies are directed against various constituents of the molecular apparatus that hold epithelial cells together or that bind the surface epithelium to the underlying connective tissue resulting in Autoimmune Vesiculobullous Disorders. An understanding of the basic molecular aspects of these disorders is essential for proper diagnosis. Once a definitive diagnosis is determined, treatment is focused upon the alleviation of clinical signs and symptoms, referral for consultation with other specialists to assess the extent of the disease process, and the prevention of recurrence.

INTRODUCTION

Autoimmune vesiculobullous diseases are rare disorders affecting skin & mucous membranes that are mediated by pathogenic autoantibodies against desmosomal or hemidesmosomal antigens of squamous epithelium.[1] Vesiculobullous (VB) diseases are a distinct group of oral disorders characterized by the formation of vesicles or bullae this includes viral diseases, autoimmune mucocutaneous diseases, diseases that probably have an immunologically mediated mechanism, and genetic diseases.[2]

Autoimmunity and Autoimmune Diseases

Hypersensitivity reactions produce tissue injury as a consequence of an immune response to exogenous antigens. The immune system does not typically respond to autologous antigens due to the induction of tolerance, either through clonal deletion (elimination of autoreactive T and B lymphocytes) or clonal anergy (in which autoreactive lymphocytes persist but are rendered unresponsive). There are instances in which unresponsiveness to self-antigens is altered, resulting in a state termed Autoimmunity. There are mechanisms which are responsible for one of the cardinal features of the immune system, namely, its ability to discriminate between self and nonself (usually microbial) antigens. If these mechanisms fail, the immune system may attack the individuals own cells and tissues.

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Epithelial Biology

The oral epithelium consists mainly of keratinocytes, adherent to each other by desmosomes and adherens junctions and, via hemidesmosomes, to an epithelial basement membrane and thereby to the underlying mesenchyme of the lamina propria/dermis. Desmosomes contain a series of proteins, particularly desmogleins and desmocollins.[Figure 1]

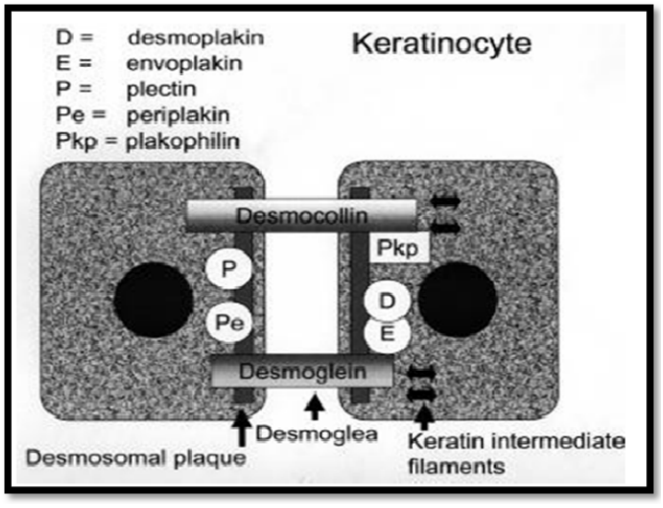

Figure 1 Epithelial structure (Adapted from Scully, 2002).

The hemidesmosome associated proteins are BP antigen1, BP antigen 2, γ6β4 integrin, laminin 5, laminin 6, uncein, type VII, type IV collagen. Damage or defect to any of these epithelial proteins can result in loss of cell to cell adhesion or loss of cellbasement membrane adhesion leading to vesiculation.[4]

Classification

Autoimmune vesiculobullous lesions can be divided into two major subsets.[5] [Table 1]

Table 1

The pemphigus subset	The pemphigoid subset
Pemphigus vulgaris	
Pemphigus vegetans	
Pemphigus vegetans of hallopeau	Bullous pemphigoid (BP)
Pemphigus	Mucous membrane pemphigoid
Pemphigus foliaceus	(MMP)
Pemphigus erythematous	Linear IgA disease (LAD) of
Endemic Pemphigus	childhood & adults
Pemphigus herpetiform	Toxic epidermal necrolysis (TEN)
Immunoglobulin A(IgA) Pemphigus	Bullous systemic lupus erythematous
folaceus	Dermatitis herprtiform& epidermolysis
Paraneoplastic pemphigus foliaceus	bullosa acquisita (BBA)
Drug induced pemphigus foliaceus	
Paraneoplastic pemphigus	
IgA pemphigus	

Pemphigus subset

Pemphigus vulgaris

It is a 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.[6]Molecular cloning of cDNA encoding pemphigus antigens [Figure 2] has indicated that IgG autoantibodies from patients recognize desmogleins (Dsg), which are cadherin-type cell to cell adhesion molecules found in the desmosomes.

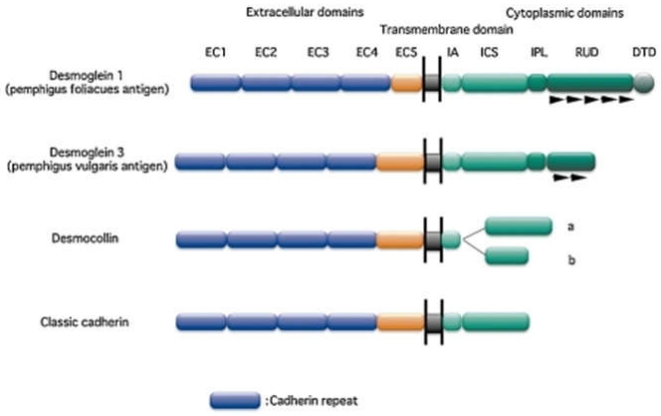

Figure 2 Molecular structure of pemphigus antigen

Patients with pemphigus vulgaris present pathogenic antibodies (IgG1 and IgG4) against desmoglein 1 and desmoglein 3 resulting in mucocutaneous involvement or only against desmoglein 3 resulting in exclusive oral/mucosal involvement. Dsg autoantibodies in active pemphigus vulgaris are predominantly IgG4 polyclonal antibodies and IgG1 is commonly seen in remission. The mechanism of acantholysis after the pemphigus IgG binds to Dsg3 on the cell surface is unknown but may involve proteinases.[7]IgG in PV increases the intracellular calcium and inositol 1,4,5 triphosphate concentration and subsequently activates protein kinase C (PKC) cell lines which in turn activates plasminogen which may involve with apoptosis via Caspase activation. T cell responses to Dsg3 may be critical to the pathogenesis as antibody production is dependent on T cell activation and the strong association with distinct human leukocyte antigen (HLA) class II alleles suggests the involvement of CD4 + T lymphocytes. Most of the T cells are CD45RO which help autoreactive B lymphocytes to produce autoantibodies. T cell recognition of epitopes of Dsg3 may be crucial for the initiation and production of Dsg 3 specific autoantibodies by B lymphocytes. Epitope spreading leading to disease progression may occur in pemphigus vulgaris (PV) in which blistering in the mouth almost always precedes blistering in the skin. The autoantibodies causing the initial damage recognize desmoglein-3 in the mouth mucosae. Subsequently, epitopes on the related desmoglein -1 are exposed. . In both pemphigus vulgaris and foliaceus patients, major epitopes were mapped to the respective N-terminal 161 residues of Dsg1 and 3.[7]However, recent immuno-electron studies demonstrate that desmosomes remain intact till the late stages of acantholysis when they are cleaved behind the desmosomal plaque, due to shearing forces produced by collapsing cells. Hence, the pivotal role of anti-Dsg antibodies in pemphigus is being questioned. In addition to Dsgs, pemphigus auto-antibodies recognize numerous other antigens. In a recently-described model, the proposed initial step is the binding of antibodies to peripheral myelin protein (PERP) and/or cellular acetylcholine receptor (AChR), which leads to dissociation of adhesion molecules and also initiates apoptosis. Subsequently, tonofilaments collapse and keratinocytes shrink with sloughing of desmosomes, which elicits an autoimmune response.[8]

Pemphigus Vegetans

Pemphigus vegetans is a rare variant of pemphigus vulgaris which differs from it by the presence of vegetating erosions, primarily affecting flexural areas. Circulating antibodies have been found in patients with pemphigus vegetans of the Neumann type that precipitate with the 130 and 85 kDa polypeptides of the pemphigus vulgaris antigen (Dsg3). In the Hallopeau type, antibodies to Dsg3 have been detected. The antibodies appear to belong to the IgG2 and IgG4 subclass, with strong complement fixation.[9]

Pemphigus Foliaceus

The pathogenic autoantibodies of PF are of the IgG4 subclass, which has been demonstrated by their passive transfer from human sera to neonatal mice . These IgG4 autoantibodies recognize antigenic epitopes located on the N-terminus of the ectodomain of dsg-1, specifically on extracellular (EC) domains 1 and 2. The binding of pathogenic IgG to dsg-1 triggers the phosphorylation of p38 mitogen-activated protein kinase (MAPK) which is thought to induce apoptosis of the affected keratinocyte. Although complement component 3 (C3) deposition on direct immunofluorescence (DIF) initially suggested that it may play a role in acantholysis in PF, both C5-deficient mice and total complement-depleted mice still develop subcorneal vesicles upon passive transfer of pathogenic human sera.[10]

Paraneoplastic Pemphigus

This IgG-mediated disease is initiated by an obvious or occult lymphoproliferative disorder in most cases. Clinically severe mucositis and polymorphic blistering skin eruptions and histologically acantholysis, keratinocyte necrosis, and interface dermatitis are its hallmark features. Immunoprecipitation and immunoblot testing will detect autoantibodies directed against a complex of four polypeptides (mainly plakin family proteins and desmogleins) with different molecular weights: periplakin (210 and 190 kDa), desmoplakins-I and II (250 and 210 kDa),

bullous pemphigoid antigen-1 (BPAG-I, 230 kDa), and envoplakin-I (210 kDa).[11]

IgA Pemphigus

IgA pemphigus is an autoimmune, intraepidermal vesiculobullous eruption, with variable acantholysis and the presence of intercellular deposits of IgA within the epidermis. There are recurring crops of pruritic papules and vesicles that evolve into eroded and crusted plaques, pustules with a tendency to confluence forming annular and circinate patterns involving the trunk and proximal extremities. Other sites may be involved, but mucous membranes are usually spared.Circulating IgA autoantibodies target specific components of desmosomes between keratinocytes and result in intraepidermal blisters formation. Desmocollin 1 (Dsc1) is confirmed to be the autoantigen of SPD type IgA pemphigus. Desmocollin (Dsc) is an important transmembrane glycoprotein of desmosome and belongs to cadherin supergene family. Similar todesmoglein, there are also three isoforms of Dsc named Dsc1, Dsc2 and Dsc3. The autoantigen of IEN type is still to be determined, although desmoglein 1 and desmoglein 3 have been demonstrated in a few reports. The result of immunoelectron microscopic study revealed that the antigen of IEN type may not be a desmosomalcomponent.[12]

Pemphigoid Subset

Bullous Pemphigoid

Bullous pemphigoid (BP) is a subepidermal blistering skin disease that usually occurs in the elderly population and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone. The pathogenesis of BP is characterized by tissuebound and circulating IgG autoantibodies against two components of the hemidesmosome of stratified epithelia, BP 230 kD (BPAg1) and BP 180 kD (BPAg2, COL17). BPAg1 is a cytoplasmic protein involved in the anchorage of intermediate filaments to the cytoskeleton. BPAg2 is a transmembrane adhesion molecule with several collagenous extracellular domains. Antibodies to BPAg2 appear to be important in subepidermal blister formation. BPAg1 may have a secondary role, and its exact function in the pathogenesis is not fully defined. Autoantibodies against alpha 6 integrin and laminin-5, two other skin basement membrane components, have also been identified in BP. IgG autoantibodies bind to the basement membrane which activates complement and inflammatory mediators. Activation of the complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells release proteases, which degrade hemidesmosomal proteins leading to blister formation. Eosinophils are characteristically present in the blisters as demonstrated by histopathologic analysis, although their presence is not an absolute diagnostic criterion. Cytokines and chemokines like eotaxin, IL16 and IL2 also play an important role. The early urticarial phase in BP seems to be associated with IgE, and IgE autoantibodies against COL17 (BP180Kd Ag) are detected in 86% of untreated BP patients. Iwata et al. reported that the presence of IgE autoantibodies against COL17 was associated with a severe form of BP, and these patients required more intensive and longer treatment period for remission and higher dose of prednisolone.[13]

Cicatricial Pemphigoid

Mucous membrane pemphigoid (MMP) or Cicatricial pemphigoid (CP) is a chronic, subepithelial autoimmune disease, which predominately affects the mucous membranes, including the conjunctiva, and occasionally the skin.The binding of BP 180 specific antibodies to their hemidesmosomal target antigen is not sufficient for blister formation but must be accompanied by the release of proteinases such as collagenases and elastases from neutrophils and eosinophils . The leukocytes release enzymes and cytokines like interleukins, tumour necrosis factor-α (TNF- α), TNF-β, IFN-γ and more eotaxin due to autoantibody induced complement mediated sequestration of these cells. The resultant enzymes and cytokines lead to the detachment of the basal cells from basement membrane zone and causes complement mediated cell lysis. This also contributes to the dermal-epidermal splitting. Autoantibodies directed against BP 180, trigger the expression of IL-6 and IL-8 from human keratinocytes. Dapsone inhibits the BP IgG- induced IL-8 release from cultured keratinocytes by mechanisms at the post-transcriptional level leading to a reduced influx of neutrophils into pemphigoid lesions and the cessation of blister formation. Antibodies to human BP 180 lead to the expression of tissue plasminogen activator from normal keratinocytes which also results in blister formation of BP.[3]In MMP, immunoglobulins are deposited at the epithelial basement membrane zone and IgG (97%), C3 (78%), IgA (27%) or IgM (12%) may be seen. In MMP, IgG to the dermal-epidermal junction (DEJ) between the location of laminin 5 and type VII collagen was found. CP can be characterized by detection of circulating autoantibodies to BP 180. IgG and IgA autoantibodies in CP target epitopes on both extra and intracellular domains of BP 180. Clinical features between CP and BP appear to correlate with distinct target epitopes of BP 180. BP sera react with immundominant membrane proximal non-collagenous domain (NC16a) on the extracellular portion of BP 180, whereas the C-terminal domains of BP 180 were thought to contain the major epitopes in cicatricial pemphigoid. CP sera mainly react with the most C-terminal portion, whereas BP sera react with N-terminal domains.[3]

Linear IgA Disease (Lad) of Childhood and Adults

Linear IgA disease (LAD) is a rare chronic autoimmune subepithelial mucocutaneous bullous disorder that can affect both the skin and the mucous membranes. The condition was originally thought to be a variant of bullous pemphigoid or herpetiform dermatitis. However, during the 1970s LAD was recognized as a distinct entity (1). LAD affects both adults and children (2), the childhood variant being called chronic bullous dermatosis of childhood or juvenile dermatitis herpetiformis. The adult variant has a peak of incidence between 60 and 65 years of age, with a 2:1 predilection for women.The IgA autoantibodies from both variants of LAD are directed against the hemidesmosomal transmembrane glycoprotein BP180 (type XVII collagen). Bullae appear after IgA autoantibodies are deposited, causing neutrophils and other defensive cells to migrate to the basal membrane of the affected connective tissue. This suggests that IgA is responsible for the associated inflammatory events, through an unproven mechanism likely to involve IgA-mediated neutrophil chemotaxis. The connective tissue in the region where IgA antibodies have been deposited becomes necrotic (50% of specimens showing micro-abscesses) and the epithelium separates from the

underlying connective tissue to form bullae. Subsequently, these bullae rupture to produce areas of erosion and ulceration.[14]

Bullous Systemic Lupus Erythematosus

In contrast to SLE bullous systemic lupus erythematosus (BSLE) is a distinctive bullous eruption occurring with SLE, presenting with typical clinical and pathological findings including circulating antibodies to type VII collagen (NC1 [noncollagenous domain 1] domain).The major antigenic epitopes for both BSLE and EBA reside within the fibronectin type III homology region (FN3) of NC1 domain of type VII collagen. This region is important in mediating the interaction between anchoring fibrils and other matrix proteins. Blister formation occurs as a result of antibody-induced interference with normal interactions between type VII collagen and its extracellular matrix ligands; destabilization of anchoring fibrils due to impaired antiparallel dimer formation of type VII collagen; or complement mediated tissue damage.[15]

CONCLUSION

Oral mucosal diseases remain a challenging disease to study because the pathophysiological mechanisms are diverse, and the chronic, unpredictable course of many of these diseases makes it difficult to determine whether the favorable effects of short-term treatment will be sustained. The enormous progress in biotechnology as well as in the improved understanding of the underlying pathomechanisms of several autoimmune diseases has paved the road for the development of more specific and more effective therapeutic strategies. Mucocutaneous diseases cannot be cured until the precise cascade of pathogenetic events and the ultimate molecular mechanism of such diseases are unraveled. Further investigation of epithelial 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.

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