

## Review

# The molecular aspects of oral mucocutaneous diseases: A review

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**Most of the mucocutaneous diseases are confined to the stratified squamous epithelium and thus may involve skin, oral and other mucosae like the nasal, ocular, genital mucosa. Some patients present with oral lesions only whereas in others there may be involvement of skin and other mucous membranes. 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.**

**Key words:** Mucocutaneous disease, desquamative gingivitis, vesiculobullous disorder, pemphigus vulgaris, pemphigoid.

## INTRODUCTION

Mucocutaneous lesions of skin and oral mucosa commonly manifest as vesicular and/or ulcerative lesions. Various etiological factors contribute to the development of these lesions and encompass autoimmune/immune mediated, infectious, neoplastic, hematologic, reactive, nutritional and idiopathic causes (Rinaggio, 2007). Approximately, 50% of oral mucosal diseases are localized to gingiva causing desquamative gingivitis, although other intraoral and extraoral sites may be involved. Most of these diseases have a dermatologic genesis. Immunologically, mediated conditions that can

manifest as desquamative gingivitis are lichen planus, bullous pemphigoid (BP), pemphigus vulgaris (PV), linear IgA disease, dermatitis herpetiformis and lupus erythematosus. A predilection for females is generally seen.

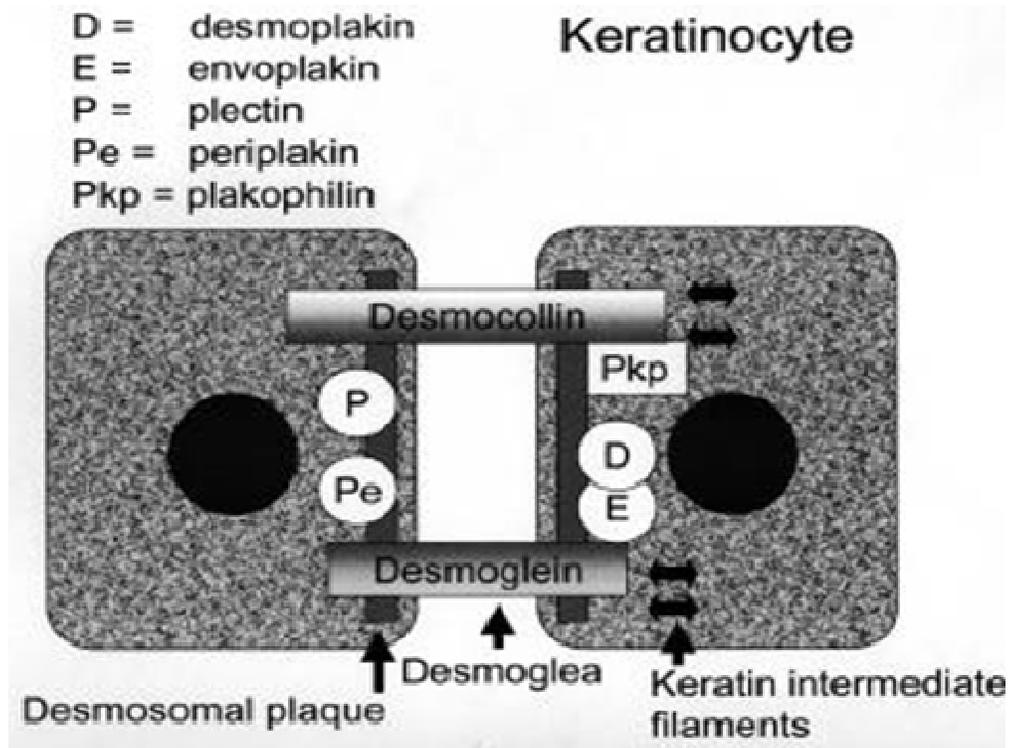
An immunologic phenomenon termed epitope spreading has been increasingly recognized as an important pathogenic mechanism responsible for the initiation and/or progression of autoimmune diseases such as mucocutaneous lesions. Epitope spreading could be defined as a specific autoreactive lymphocyte (T- or B-cell) response to endogenous epitopes, which are distinct from and non-cross-reactive with the disease-inducing epitopes, on the (same or different) proteins secondary to the release of such a self-protein during an autoimmune response. The diagnosis of mucocutaneous lesions is difficult and requires the correlation of thorough history, clinical, histological and immunopathological criteria (C Scully, 1998) as shown in Figure 1.

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**Abbreviations:** **Dsg**, Desmogleins; **BP**, bullous pemphigoid; **CP**, cicatricial pemphigoid; **HLA**, human leukocyte antigen; **ELISA**, enzyme linked immunosorbent assay; **PV**, pemphigus vulgaris; **MHC**, major histocompatibility complex; **TNF**, tumour necrosis factor; **IFN- $\gamma$** , Interferon-gamma; **LABD**, linear IgA bullous dermatosis; **HAEM**, herpes associated erythema multiforme; **ICAM-1**, inter-cellular adhesion molecule 1; **VCAM-1**, vascular cell adhesion molecule-1; **ELAM- 1**, Endothelial Leukocyte Adhesion Molecule 1; **RANTES**, regulated upon activation, normal T-cell expressed, and secreted; **IP-10**, interferon gamma-induced protein 10; **NF-KB**, nuclear factor kappa B.

## EPITHELIAL PROTEINS

Stratified squamous epithelium present in skin and oral mucosa is a complex structure which requires various molecules to maintain its integrity and health. The oral epithelium consists mainly of keratinocytes, adherent to each other by desmosomes and adherens junctions and



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

it is connected to an epithelial basement membrane and thereby to the underlying mesenchyme of the lamina propria/dermis via hemidesmosomes (Scully, 2005) as shown in Figure 2. Each component consists of several proteins with important functions like cell to cell recognition and signaling. Desmosomes contains proteins like desmogleins and desmocollins. Desmogleins are glycoproteins of the cadherin-supergene family which link to cytokeratins via desmoplakins and plakoglobin. Cadherins are a family of calcium-dependent cell to cell adhesion molecules that play important role in the formation and maintenance of complex tissue integrity. They are composed of an extracellular domain involved in calcium dependent binding to adjacent cells, a transmembrane and an intracellular domain that binds to catenins and thence to actin (Masayuki, 2010). There are four desmoglein isoforms, designated as Dsg1–4. Expression of desmoglein 1 and 3 is restricted to stratified squamous epithelia. Dsg 1 and 3 are both expressed in skin but in oral epithelium only the 130 KDA molecule Dsg 3 is preferentially expressed. The intraepithelial expression patterns of Dsg 1 and 3 in skin and mucous membranes differ. In the skin, Dsg 1 is expressed throughout the epidermis, but more intensely in the superficial layers, while Dsg 3 is expressed in the lower portion of the epidermis, primarily in the basal and parabasal layers.

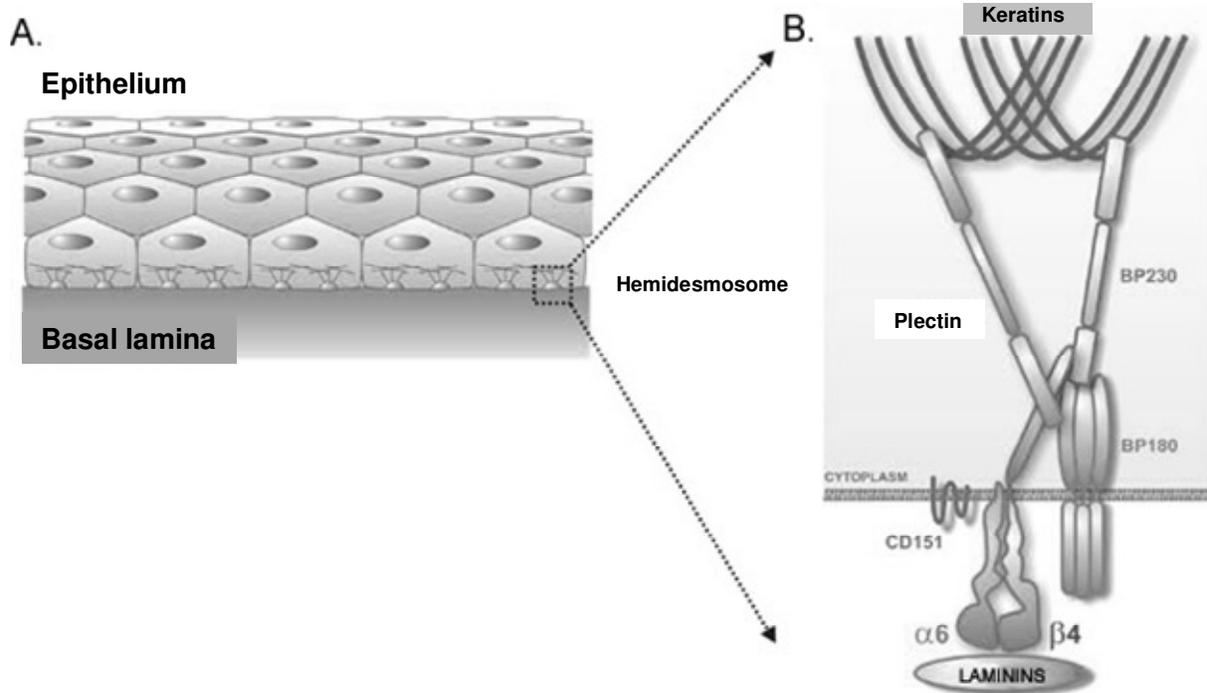
Cell-epithelial basement membrane contact is largely via hemidesmosomes, which link the keratinocyte

cytoskeletons to the lamina lucida. Lamina densa is anchored to the underlying papillary dermis by anchoring fibrils. The epithelial basement membrane and the adjacent area are termed the epithelial basement membrane zone. The hemidesmosome associated proteins are BP antigen1, BP antigen 2,  $\gamma 6\beta 4$  integrin, laminin 5, laminin 6, uncein, type VII, type IV collagen (Daniela, 2007).

Damage or defect to any of these epithelial proteins can result in loss of cell to cell adhesion or loss of cell-basement membrane adhesion leading to vesiculation. Many of the disorders damaging the protein molecules have autoimmune causes and may have systemic manifestations.

## PEMPHIGUS VULGARIS

Pemphigus is a group of potentially life threatening autoimmune diseases characterized by mucocutaneous and/or mucosal blistering. Pemphigus affects the skin and oral mucosa and may also affect the mucosae of the nose, conjunctiva, genitals, oesophagus, pharynx and larynx. In pemphigus there is damage to desmosomes by antibodies against the extracellular domains of the desmogleins with immune deposits intraepithelially. There is loss of cell to cell contact (acantholysis) which results from damage to the intracellular area leading to separation of keratinocytes and thereby intraepithelial



**Figure 2.** A. The epithelium is connected to the lamina propria/demis via hemidesmosomes. B. Antigens of hemisomesomes. Courtesy: xtal.cicancer.org.

vesiculation (Scully, 2002).

Pemphigus vulgaris has a strong genetic background. Associations of pemphigus vulgaris with human leukocyte antigen (HLA) class II alleles are found with HLA-DR4 (DRB1\*0402), DRw14 (DRB1\*1041) and DQB1\*05030 (Loiseau, 2000). The HLA class II alleles appear critical to T lymphocyte recognition of Dsg 3 peptides. Genes in the HLA class I region may also have a role in the development or progression of pemphigus vulgaris (Gazit, 2004). The HLA DRB1\*14/0406 molecules may present both Dsg1 and Dsg3 peptides leading to mucocutaneous clinical phenotypes (Loiseau, 2000).

### The molecular aspects

Molecular cloning of cDNA encoding pemphigus antigens has indicated that IgG autoantibodies from patients recognize desmogleins (Dsg), which are cadherin-type cell to cell adhesion molecules found in the desmosomes (Amagai, 1991). The autoantibodies inhibit the adhesive function of desmogleins and lead to loss of cell to cell adhesion of keratinocytes with resultant blister formation.

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 mucosal involvement (Andreadis, 2006). The titers of serum anti-Dsg1 and anti-Dsg3 IgG autoantibodies, as determined

by indirect immunofluorescence or enzyme linked immunosorbent assay (ELISA), are generally correlated with disease activity. The proportion of Dsg 1 and 3 antibodies appears to be related to the clinical severity of pemphigus vulgaris and those with only Dsg 3 antibodies have oral lesions predominantly (Harman, 2000). Oral lesions appear at an early stage and antibodies against Dsg 1 marks the involvement of skin and mucosae other than oral. Other pemphigus variants such as pemphigus foliaceus, pemphigus erythematosus and pemphigus vegetans only rarely affects the oral mucosa.

Loss of tolerance against Desmogleins 3 (Dsg 3), in both B and T cells appears important for the development of pemphigus vulgaris (Tsunoda, 2002). Dsg autoantibodies in active pemphigus vulgaris are predominantly IgG4 polyclonal antibodies and IgG1 is commonly seen in remission (Ayatollahi, 2004). The mechanism of acantholysis after the pemphigus IgG binds to Dsg3 on the cell surface is unknown but may involve proteinases.

Pemphigus vulgaris-IgG (PV) increases the intracellular calcium and inositol 1,4,5 triphosphate concentration and subsequently activates protein kinase C (PKC) cell lines. The phosphatidyl choline specific phospholipase pathway plays a major role in PV-IgG induced transmembrane signaling by causing long term activation of PKC (Seishima, 1999). Plasminogen activation may also be involved with apoptosis via caspase activation (Puviani, 2003). 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 (Nishifuji, 2000). T cell recognition of epitopes of Dsg3 may be crucial for the initiation and production of Dsg 3 specific autoantibodies by B lymphocytes (Hertl and Riechers, 1999).

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. The autoantibodies against desmoglein-1 are produced and skin blistering commences. The autoimmune response thus appears to spread from epitopes of desmoglein-3 to include epitopes of desmoglein-1.

With the 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, enzyme linked immunosorbent assay (ELISA) provides a specific, sensitive, and quantitative means of detecting and measuring circulating IgG autoantibodies (Ishii, 1997). In both pemphigus vulgaris and foliaceus patients, major epitopes were mapped to the respective N-terminal 161 residues of Dsg1 and 3.

## PEMPHIGOID

Pemphigoid is a family of diseases which includes conditions such as bullous pemphigoid which generally affect the skin and have only minor oral involvement and cicatricial pemphigoid (CP) which mainly involves the mucous membranes most frequently the ocular and oral mucosa (Bagan, 2005).

Subepithelial vesiculobullous disorders are mucous membrane pemphigoid, bullous pemphigoid, pemphigoid gestationis, anti- P 200, anti-P105, anti-P 450 pemphigoid, dermatitis herpetiformis, linear IgA disease, bullous systemic lupus erythematosus and paraneoplastic pemphigus (Verdolini and Cerio, 2003).

In pemphigoid, the autoantibodies damage the hemidesmosome associated proteins which might lead to subepithelial vesiculation resulting in the various clinical phenotypes of pemphigoid. The immune deposits at the basement membrane zone were shown to consist of predominantly of IgG and C3.

### The molecular aspects

The pathogenesis of bullous pemphigoid (BP) is characterized by tissue bound and circulating IgG autoantibodies against two components of the hemidesmosome of stratified epithelia, referred to as BP 230 kDa

(BPAg1) and BP 180 kDa (BPAg2) (Labib, 1986). 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 (Borradori, 1998).

Common major histocompatibility complex (MHC) class II markers and extended MHC haplotypes have been found in distinct clinical variants of mucous membrane pemphigoid (MMP), including HLADR4,-DR5, -DQw3, -A2, -B8, -B35, and -B49. Since 1989, it has been recognized that the presence of the HLADR4 allele substantially increases the risk of ocular disease. Furthermore, a prevalence of HLA-DQB1\*0301 was first described in patients with pure ocular mucous membrane pemphigoid (Chan, 1997). This allele, however, was later found to be associated with all clinical sites of involvement and possibly to be linked to antibasement membrane IgG production. Interestingly, these studies also suggested a role for this allele in disease severity (Setterfield, 2001). Epidemiological evidence to support the premise of an underlying genetic factor comes from the observation that patients with mucous membrane pemphigoid have a higher prevalence of other autoimmune diseases (Nayar, 1991). However, studies have shown that monozygotic twins are discordant for mucous membrane pemphigoid which argues against genetic susceptibility as the only major risk factor of the disease (Bhol, 1995). The nature of putative environmental factors remains unclear in most cases.

The human leukocyte antigens DQB1\*0301 allele confers a predisposition to all subgroups of MMP and may have a role in T cell recognition of basement membrane antigens (Setterfield, 2001). HLA DQ7 positivity is seen in cicatricial pemphigoid (CP) and ocular CP. Occasionally, they are triggered by drugs like furosemide.

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 (Liu, 2000). The leukocytes release enzymes and cytokines like interleukins, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), TNF- $\beta$ , IFN- $\gamma$  and more eotaxin due to autoantibody induced complement mediated sequestration of these cells (Verdolini and Cerio, 2003). 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 (Schmidt, 2001). Antibodies to human BP 180 lead to the expression of tissue plasminogen activator from normal keratinocytes which also results in

blister formation of BP.

Plasma cells are predominant in mucosal lesions. The production of autoantibodies should be preceded by presentation of self-antigens leading to T helper (Th) cell activation and secretion of antibodies. Langerhans cells are the group of antigen presenting dendritic cells involved in bullous skin diseases. Increased numbers of dendritic cells are detected in the epidermis of patients with pemphigus and pemphigoid (Venning et al., 1992).

BP 180 and BP 230 proteins are internalized by dendritic cells of individuals who do not develop the disease, but the low affinity of the HLA class II binding groove with the peptide will circumvent the expression of these immunogenic peptides, avoiding activation of Th cells (Oostingh et al., 2002). BP 180-specific T lymphocyte clones were detected in patients with BP and in patients with IgA bullous dermatosis. T cells, autoreactive to specific epitopes help B cells to differentiate into antibody producing plasma cells.

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 (Egan et al., 1999). 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 immunodominant 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 (Lee et al., 2003).

### Target antigens

Ten different basement membrane components have been identified as autoantigens in various subepithelial blistering disorders. Antigens like BP 180 KDA, BP 230 KDA, 105 KDA, laminin 5 or laminin 332, laminin 6, ucein,  $\beta 4$  subunit of  $\alpha 6$ ,  $\beta 4$  integrin and type VII collagen are the antigens implicated in BP, MMP (Stoopler et al., 2003).

The specific reactivity of MMP autoantibodies is with the lamina lucida/lamina densa interface particularly with the carboxyterminal region of BP Ag2, a site positioned deeper within the epidermal basement membrane zone, while the BP autoantibodies label the upper lamina lucida to the BPAg2NC16A domain (Bedane et al., 1997). CP can be characterized by circulating autoantibodies specific for BP 180. The sera of patients with linear IgA bullous dermatosis (LABD) contain IgA autoantibodies

reactive with a 97/120 KDA protein, linear IgA bullous dermatosis (LABD) antigen 1, which is highly homologous to the extracellular portion BP 180.

The different clinical manifestation of autoimmune bullous diseases suggest that variable epitopes of BP 180 are targeted by the different autoantibody isotopes like IgA and IgG resulting in the distinct clinical pictures. This suggest that the autoantibody response may be more epitope-specific than antigen specific (Christophoridis et al., 2000). Diseases such as CP, BP or anti-laminin 5 MMP share the same molecular target but have very different clinical manifestations. This may be probably linked to different expression of major histocompatibility complex (MHC) (Bagan, 2005) Table 1.

### ERYTHEMA MULTIFORME

Erythema multiforme is a reactive mucocutaneous disorder that comprises variants ranging from a self-limited, mild, exanthematous, cutaneous variant with minimal oral involvement (EM minor) to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis such as Stevens-Johnson syndrome (Farthing, 2005). It is characterized by cutaneous target lesions and satellite cell or more widespread necrosis of the epithelium. These features are the sequelae of a cytotoxic immunologic attack on keratinocytes expressing non-self antigens. These antigens are primarily microbial or drugs (Ayangco and Rogers, 2003).

Erythema multiforme is triggered by viruses like herpes simplex virus, varicella-zoster virus, cytomegalo virus, Epstein barr virus, hepatitis virus and influenza virus. Less commonly bacteria such as mycoplasma pneumonia, diphtheria, haemolytic streptococci and certain fungal infections, food additives or chemicals and drugs such as sulphonamides, cephalosporins, quinilones could trigger erythema multiforme (Scully and Bagan, 2004). Viral infections appear to trigger erythema multiforme minor or major but drug ingestion triggers Stevens-Johnson syndrome. This is characterized by sub-and intraepithelial vesiculation.

Genetic predisposition could be an etiology implicated in erythema multiforme. Recurrent erythema multiforme is related with HLA B15, HLA-B35, HLA-A33, HLA-DR53 and HLA DQB1\*O3O1. HLA DQ3 is a helpful marker for Herpes associated erythema multiforme (HAEM). HLA allele DQB1 \*0402 is seen patients with extensive mucosal involvement (Farthing, 2005).

### The molecular aspects

The aetiology appears to be an immunologically hypersensitivity reaction with the appearance of cytotoxic effector cells, CD8+T lymphocytes in epithelium including

**Table 1.** Target antigens of hemidesmosomes implicated in subepithelial blistering disorders (Bagan, 2005).

Proteins	Diseases
BP Ag1	Cicatrical pemphigoid
BP Ag 2	Cicatrical pemphigoid, bullous pemphigoid
$\alpha 6 \beta 4$	Cicatrical pemphigoid, junctional epidermolysis bullosa
Laminin 5	Cicatrical pemphigoid, junctional epidermolysis bullosa
Type VII collagen	Epidermolysis bullosa dystrophica, Epidermolysis bullosa acquisita

apoptosis of keratinocytes leading to satellite cell necrosis (Ayangco and Rogers, 2003). They are characterized by a lichenoid infiltrate in the basement membrane zone of the epidermis or epithelium. Vacuolar alteration of basal cell layer occurs and T lymphocytes, mononuclear cells are present in the dermis and lamina propria and extend into the epithelium or epidermis appears obscuring the basement membrane zone. The epithelium or epidermis is oedematous and spongiotic and there is necrosis both of basal and suprabasal epithelial cells resulting in both intra and sub-epithelial bullae formation.

Erythema multiforme appears to be the result of a cell-mediated immune reaction to the precipitating agents. In HAEM, HSV-DNA fragments and in particular DNA polymerase has been detected in the basal and suprabasal cell layers of the epidermis (Imafuku et al., 1997). CD4+T cells accumulate in active lesions and produces IFN- $\gamma$  leading to tissue damage (Kokuba et al., 1999). This cytokine amplifies the immune response and stimulates the production of additional cytokines and chemokines which aids the recruitment of further reactive T cells to the area. These cytotoxic T cells, natural killer cells or chemokines can induce epithelial damage.

The mechanisms of tissue damage in EM appear to differ between virally-induced and drug-induced EM. In drug induced erythema multiforme, the reactive metabolites of the initiating drug induce the disease. T cells do not produce IFN- $\gamma$  in drug induced lesions but rather the lesions are characterized by TNF- $\alpha$  present in keratinocytes, macrophages and monocytes. In contrast, TNF- $\alpha$  has not been detected in HAEM and it has even been proposed that its presence may be used as a laboratory test to distinguish drug-induced lesions from HAEM. In HAEM tissue damage appears to be the result of delayed type hypersensitivity.

## ORAL LICHEN PLANUS

Oral lichen planus is a chronic inflammatory disorder affecting stratified squamous epithelia and is potentially premalignant. It rarely undergoes spontaneous remission (Eisen, 2005). Oral lichen planus may manifest in one of the three clinical forms: reticular, erythematous and erosive. The reticular forms are the most common form of

oral lichen planus which appear as a network of connecting and overlapping white lines or plaques. Unlike erythematous or erosive lesions patient rarely do complain of any symptoms. In erythematous or erosive lichen planus patient has discomfort because of ulcerations (Thorn et al., 1988). Extraoral mucosal sites of involvement includes genital, ocular, bladder, nasal, laryngeal and auricular mucosae, although these sites of involvement are not common.

## The molecular aspects

Oral lichen planus is a cell mediated autoimmune disease in which auto-cytotoxic CD8+ T cells trigger apoptosis of oral epithelial cells (Eversole, 1997). Cell mediated immunity possibly initiated by endogenous or exogenous factors results in the production of TNF- $\alpha$  and IFN- $\gamma$  (Lodi et al., 2005). These cytokines induce the expression of HLA-DR on the basal keratinocytes and also activates dendritic cells including langerhans cells and attract more lymphocytes (Walsh, 1990).

Oral lichen planus lesional T-cells do not secrete IL-4 and 10 or TGF- $\beta$ . CD8 + T cells in oral lichen planus play an important role and are evident by the expression of the chemokines like CR5, CCR3 and their respective ligands. Regulated upon activation, normal T-cell expressed, and secreted (RANTES) and IP-10 / CXCL10 is increased (Iijima et al., 2003). There is upregulation of endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) by endothelial cells in the subepithelial vascular plexus (Regezi et al., 1996). Activated T cells in the oral lichen planus infiltrate migrate to oral epithelium mediated by intracellular adhesion molecules like ICAM-1, VCAM-1.

Genetic polymorphism of the first intron of the promoter gene of IFN- $\gamma$  was associated with the development of lichen planus whereas an increase in the frequency of the -308 A TNF- $\alpha$  allele was demonstrated in patients who displayed lichen planus of mouth and skin (Carrozzo et al., 2004).

TNF- $\alpha$  also stimulates the activation of nuclear factor kappa B (NF-KB) whose increased expression is seen in oral lichen planus (Santoro et al., 2003). NF-KB translocation in keratinocytes may induce the production

of many inflammatory cytokines which could contribute to the chronic course of oral lichen planus. There is upregulation of epithelial basement membrane extracellular matrix proteins like collagen types IV and VII, laminin, few integrins serving as pathways for T cell migration (Eversole, 1997). T cells then bind to keratinocytes and apoptosis is implicated in the basal cell destruction of lichen planus (Tanda et al., 2000).

## 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 management of mucocutaneous lesions involves not only the control of the disease process but also the treatment of complications and the restoration of function in cases with disabilities or mutilation. 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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