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## **Review Article**

### **Desmosomal protein regulation and clinical implications in oral mucosal tissues**

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#### **Abstract**

Cell-adhesion complex within a tissue is important for its stability, structural integrity, functioning, cellular migration and morphogenesis. Disruption of desmosomal cell-adhesions complex results in epithelial conditions such as epidermolysis bullosa and bullous pemphigoid. Desmosome assembly and disassembly is regulated post-translationally by calcium, kinase/phosphatase activity, proteolytic processing, and also through adhesive junctions. Altered functions of desmosomal proteins desmocollin and desmoglein can cause blistering disorders, such as pemphigus foliaceus and pemphigus vulgaris, and non-Hodgkin Lymphoma while defective desmoplakin can cause supra-basal clefting in epithelium and conditions such as Carvajal syndrome, palmo-plantar keratoderma etc. This review summarises major functions of desmosomal complex family and how mis-regulation of desmosomal structural proteins occur in pathogenesis of non-, pre- and malignant oral lesions with disrupted epithelium.

**Key Words:** Desmosomal proteins, Oral mucosal lesion, Junctional complexes, Oral epithelium.

## Introduction

Oral epithelium forms a layer of epithelial cells that provides lining to the mucosa of the oral cavity and variations in its distribution is based on morphological differences and the pattern of differentiation of cells within the oral cavity (Figure 1) (1). Desmosomes are intermediate filaments that serve as a connection between two epithelial cells (2), act as signalling centres and function in cell proliferation, differentiation and morphogenetic processes (3). Trans-membrane adhesion proteins (E-cadherin), cytoplasmic adhesion proteins (desmoplakin, envoplakin, periplakin) and armadillo (desmoplakin, envoplakin, periplakin) family proteins, which act as supporting proteins, are main constituents in the formation of desmosomes (Figure 2) (4). The current literature review was planned to discuss different families of desmosomal proteins, their structures and accurate coupling of these proteins for accurate/appropriate adhesion and functioning of the desmosomal complex. Furthermore, it was planned to focus on the importance of desmosomes and their structural proteins which affect normal keratinised or non-keratinised epithelium in various pre-malignant and malignant lesions of the oral mucosa.

## Structural Disruption of Desmosome and Its Clinical Correlation

Desmosomal complex has intercellular and intracellular components. Intercellular component consists of desmosomal adhesive proteins (E-cadherins), while intracellular component comprises cytoplasmic adhesion molecules and intermediate filaments made of keratin. Failure of connecting intercellular and intracellular components in desmosomes results in blistering disorders, such as epidermolysis bullosa (3). Dys-regulation of desmosomal proteins results in various diseases which affect skin and oral mucosa (Table 1).

The core of desmosomal complex is formed by plasma membrane of adjacent cells having space of 30nm in between and is covered by plaque proteins (2). Ultra-structure of desmosomes has been identified in 2000-year-old skin tissue

signifying that desmosomes are the cornerstones for preserving structural integrity of the epithelium. Gene mutations may interfere with desmosomal protein assembly and function, resulting in blistering disease, such as bullous pemphigoid (3). Structure of desmosomal proteins consists of nitrogen (N) and carbon (C) terminals. Gene mutations can result in alteration of these terminal, such as if the C terminal is changed or removed, it disconnects intermediate filaments from the desmosomal complex. This results in space formation between intermediate filaments and desmosomal complex, resulting in bullous lesions such as pemphigus vulgaris (5). Desmosomal proteins interact through their extracellular domains to hold adjacent plasma membranes together (1). There are two states of adhesion in a desmosomal complex. The high affinity adhesion hyper-adhesive state which is a calcium-independent state, while other with low affinity adhesion is a calcium-dependent state i.e their adhesion may be altered by the disruption of extracellular calcium levels (6). Calcium-dependent and calcium-independent desmosomal complex adhesiveness show no difference in the protein composition of desmosomes (6).

Proteins in desmosomal complex such as desmocollin (Dsc) expression decreases as pre-malignant lesion converts itself to a malignant lesion (4). Anti-cancer therapies affect oral mucosa by disturbing desmosomal protein structure and their number and ultimately result in oral mucositis. Junctional proteins also take part in maintaining signalling molecules such as Slug protein which is essential for the dissolution of desmosomes during epithelial-mesenchymal transformations (2).

### **Cadherin Proteins for Desmosomal Integrity**

The E-cadherin family consists of two proteins named desmocollin (Dsc) and desmoglein (DSG). Dsc and DSG are responsible for maintaining the desmosomal integrity (1, 7). Phosphorylation and de-phosphorylation of E-cadherins is carried out by extracellular calcium levels, growth factors as well as adherents junction (8). It has been suggested that extracellular chelation of calcium creates a hyper-

adhesive state of desmosomal junctions that plays an important role in the persistence of epidermal structure and integrity (6). Genes for these two proteins are present on chromosome 18 in mice as well as humans (9). The cadherin group consists of repeated sequences known as 'domains' which are present in the extracellular portion of the molecules. They are also termed cadherin repeats EI-EIV (extracellular cadherins) (2). Cadherin repeats consist of 110 amino acids along with the calcium component that makes it a stabilised protein complex. It has been suggested that ultra-structure of desmosomes towards cellular cytoplasm shows more conserved structure and is known as intercellular cadherin segment (ICS). ICS further binds to plaque proteins, such as plakoglobin, to form compact structure (8).

### **Desmocollin**

Dsc are of two forms 'a' and 'b'. These forms differ in presence and absence of ICS domains. ICS domains are usually only present in 'a' form which also interact with plakoglobin (2). Cell cytoplasmic components may also play an important role in maintaining desmosomal cadherin function for proper adjacent cell adhesions. Moreover, correct pairing of E-cadherins may be essential for accurate adhesion and functioning of the desmosomal complex (2).

Different isoforms of Dsc express themselves in different epithelial tissues such as desmocollin-1 (Dsc1) which is confined to tongue, lymph nodes and epidermis. Dsc1 is more prevalent in supra-basal layers of oral epithelium which are considered the differentiating cell layers while Dsc3 is prominent in basal and lower spinous layers (10). Dsc having molecular weight 110-115kDa is also responsible for tissue morphogenesis and cell migration. Dsc1 takes part in the onset and differentiation of epithelial cell keratinisation (2) but it is also suggested that Dsc1 does not initiate keratinisation (9). It interacts with keratinocytes of stratified epithelium and induces proliferation and migration of stratifying cells into the spinous cell layer. As Dsc1 is confined to supra-basal cell layer, its

presence in basal or lower spinous keratinocyte layer can alter the desmosomal function and compromise keratinocyte proliferation and differentiation. But a study suggested that Dsc1 is present in both basal and supra-basal layers (9). Normally, low levels of Dsc1 are present in keratinised oral mucosa (4). Keratinised oral mucosa does not show Dsc but non-keratinised surfaces of oral mucosa show abundant Dsc expression (8, 11). Dsc does not regulate keratinocyte differentiation. However, these proteins act as indicators in keratinocyte differentiation process by changing patterns of their expression in the epidermal basal layer. Dsc1 and Dsc3 both are in equal concentration in basal epidermal cells (9).

Lack of Dsc protein expression in keratinised oral mucosal surface makes mucosal surface less prone to progression of any tumour. It is believed that non-keratinised surfaces, such as buccal mucosa and ventral surface of tongue, have increased Dsc expression and these non-keratinised surfaces are more prone to tumour progression (11). Dsc has been studied in oral lichen planus which mainly affects non-keratinised surfaces of oral mucosa by showing dysplastic changes. Lichen planus is a pre-malignant lesion in which Dsc expression reduces as it progresses towards oral cancer (8). Desmosomal adhesion does not allow tumour to spread across epithelium towards the connective tissue which shows E-cadherins performing their role in limiting tumour progression. Exclusively, Dsc1 is the main entity in restricting tumour progression. Decreased levels of Dsc1 protein indicates the onset of cancer within epithelial tissue (4).

### **Desmoglein**

Desmoglein (DSG) is an E-cadherin adhesion molecule in desmosomes and is found in four forms DSG1-4. DSG1 is expressed in supra-basal layer in lesser quantity compared to Dsc, while DSG2 is only present in the basal layer, and DSG3 expresses itself in the basal and immediate supra-basal layers of the stratified epithelium. DSG3 is present in both basal and supra-basal layers of

epidermis. Mainly DSG3 is affected in case of oral epithelium destruction. The expression of DSG4 has been found in all layers except basal cell layer of oral epithelium (2). Para-neoplastic pemphigus is a disease in which DSG1 and DSG3 are affected and this results in blistering and ulceration in the oral cavity and may be associated with cancers such as non-Hodgkin lymphoma (8). It has been proposed that auto-antibodies of DSG1 and DSG3 are present in pemphigus vulgaris and pemphigus foliaceus (12). These auto-antibodies are responsible for the destruction of epidermis and oral epithelium in pemphigus foliaceus and pemphigus vulgaris respectively. This destructive process of DSG family leads to the breakage of intercellular junctions, resulting in acantholysis (2). DSG1 has a molecular weight of 160kDa molecular weight while DSG3 is 130kDa. DSG1-related pemphigus foliaceus affects epidermis but doesn't affect oral mucosa because DSG1 expresses in very low quantity in upper layers of oral mucosa. Disruption of DSG3 by antibodies can be seen in these layers in pemphigus vulgaris and responsible for deep epidermal layer sloughing (2). DSG is unique in structure because it contains different cytoplasmic domains. These DSG domains comprise a proline-rich linker domain (IPL), a DSG-specific repeated unit domain (RUD), and a DSG-specific terminal domain (DTD). These domains establish the position of desmosomal plaque proteins. Other function of these DSG extended domains is not known (2, 4). DSG1 can be affected by toxins produced by staphylococcus aureus and staphylococcus pyogene bacteria, causing blistering disorder of skin termed called bullous impetigo (13).

### **Plaque proteins**

Desmosomal plaque proteins act as communicating proteins between keratin cytoskeleton and cadherin proteins of desmosomal complex. Desmoplakins (DSP), palakoglobin, envoplakin, plectins, desmocalmin, pinin are the important constituents of desmosomal plaque. These are non-glycosylated peptides which have ability to bind with calcium-modulated protein known as calmodulin (8). Dsc

and DSG bind to keratin filaments through desmoplakin(14). Disruption of DSP and keratin filaments of epithelial cells can cause non-epidermolytic palmo-plantar keratodermas (PPK). In PPK, desmosome lacks the capacity to bind to keratin proteins and, overall, DSP content is decreased (8).

### **Desmoplakin**

DSP is an important protein during embryonic development. It belongs to plakin family proteins which also includes envoplakin, bullous pemphigoid antigen-230 (BPA230), periplakin and plectin (8). DSP binds cadherin desmosomal family proteins with keratin intermediate filament proteins. DSPs are present in desmosome as well as hemidesmosome. They are classified as DSP1 and DSP2 (15). DSP1 and DSP2 are present almost in all tissues with the exception of DSP2 which is not expressed in cardiac tissues. DSP consists of alpha-helical central rod and N-C terminals on extremities. The carboxyl C-terminal makes attachment to intermediate filaments while the amino N-terminal gets attached to plakoglobin (2). In DSP, the C-terminal domain differs in having some specific repeats which are able to connect to intermediate filaments (8). These two vary in structure mainly in rod domain lengths, with altered relative molecular weights of 332kDa for DSP1 and 259kDa for DSP2 respectively (16). N-terminal can also bind to  $\beta$ -catenin, but in that case plakoglobin does not adhere to the N-terminal (17). C-terminal of DSP1 interacts with keratin type II and other purified proteins, such as plakoglobin. This C-terminal interaction is important for desmosomal assembly, and N-terminal domain of DSP is important for targeting the protein to desmosomes (4). DSP serves as an important protein for the survival of embryo as mutation in DSP mice results in deficient growth of embryo that does not survive beyond embryonic day 6.5 (18). Defective DSP is responsible for various diseases, such as palmoplantar keratoderma, arrhythmogenic right ventricular dysplasia, skin fragility or woolly hair syndrome, Naxos-like disease, and Carvajal syndrome (13). Disorientation of bonds between desmosomal proteins such as DSP and Dsc may

also result from mechanical stresses over epithelium (16). In pemphigus, DSP mutations can cause supra-basal clefting within spinous layer of squamous epithelium and acantholysis. Intermediate filaments detach themselves from desmosomal junctions due to these supra-basal clefting (7). Loss of DSP is caused by mutation at chromosomal level of 6079CrT (R1934X) and 6370delTT (16). When DSP sub-domains A, B, C are lost, it results in contraction of intermediate filaments in basal and supra-basal epidermal cell layers, resulting in reduced binding capacity to keratin filaments. B and C sub-domains act as recognition site for vimentin rod domains which is a protein in keratin filaments for proper attachment of keratin filaments to form the desmosomal complex (19)

#### **Envoplakin and Periplakin**

These belong to plakin family and are localised in epidermal cells, oral mucosa cells and oesophageal mucosa. They have the same structural properties as DSPs, but have a short C-terminal domain. These are not only components of desmosomes, but also have been found in some epithelial cell cytoplasm. Molecular weight of envoplakin and periplakin is 210kDa and 195kDa respectively (20). During keratinocyte differentiation, both proteins show amplified levels along with other plakin proteins. The levels of these proteins also regress in case of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (21).

#### **Plakoglobin**

Plaque protein is included in the armadillo protein family and helps in nuclear functioning, such as transducing signals which regulate cell growth and differentiation (22). It is found in both desmosomes and adherent junctions. It interacts with cadherin family and also makes contact with the N-terminal of plaque protein such as plectin. Despite being part of wingless-related integration site (Wnt) signalling, it also serves as a structural frame for desmosomal stability. Unlike cadherin that binds to keratin filaments, plakoglobin does not bind to

keratin proteins. Plakoglobin helps in tyrosine phosphorylation which serves as an important enzyme during keratinocyte differentiation of epithelial cell (8).

### **Plakophilin**

Like plakoglobin, plakophilin is also a member of the armadillo family and takes part in nuclear functioning processes, signal transduction for epithelial cell growth and differentiation (15). Plakophilin binds to DSP or Dsc which further attach to keratins, thus giving indirect support towards maintaining structural integrity of the junctional complex. A 75-kDa protein named plakophilin1 in stratified epithelial tissues is also prominent structural protein in desmosomal complex for maintaining epithelial integrity by stabilising desmosomes. It was initially named as Band-6 (2). Mutations in plakophilin1 have been seen in ectodermal dysplasia-I (23). Plakophylin and plakoglobin are structurally similar and connected with each other. Therefore, diseases in which structure of plakophilin is altered, the structure of plakoglobin is also disturbed, such as in lethal congenital epidermolysis bullosa (8)

### **Others Plaque Proteins of Armidillo Family**

Other plaque proteins include plectin, the plectin-related protein called intermediate-filament-associated protein (IFAP-300), a calmodulin-binding protein termed desmoccalmin or keratocalmin, pinin, and desmoyok. They are also significant molecules in making the desmosomal complex. Plectin is mainly found in hemidesmosome (24). Mutations in plectin result in a recessive form of epidermolysis bullosa (25).

A protein named E48 antigen with molecular weight of 20kDa belongs to glycosyl phosphatidyl inositol-linked protein, and is coupled with Ly6 (T cell protein) and helps in conserving stable position of desmosomes. E48 is an important protein in oral squamous cell carcinoma (OSCC) and serves as antigen during antibody-based therapy of OSCC (2)

## **Other Cytoskeletal Proteins**

Proteins such as filaggrin and trichohyalin are also expressed by epidermal and oral keratinocytes and act as differentiation markers of keratinised epithelium. Filaggrin and trichohyalin proteins take part during differentiation of keratin filaments in epithelial cells. Some other proteins, such as loricrin, small proline-rich proteins (SPRPs) and involucrin are also present in keratinised epithelium, such as tongue, gingival and hard palate (1). These proteins are associated with keratinised envelop only in the presence of trans-glutaminase enzyme. Loricrin is responsible for the formation of keratohyalin granules. Decrease in levels of loricrin protein results in increased involucrin and SPRPs concentration in epithelial cells. Increase of SPRPs and involucrin replaces loricrin in cornified epithelium (26). This unbalanced protein formation may change epithelial cell configuration. Altered protein structure and their associated enzymes disturb desmosomal complex and are responsible for various genetic and acquired human defect (8). Enzymes needed for epithelial differentiation processes include trans-glutaminases, kinases or proteinases. Regulation of these supporting proteins and enzymes is still unclear. Some agents such as calcium and retinoids alter epithelium by affecting differentiation process of keratin filaments and desmosomal complex (8).

## **Perp**

A tetra-span protein called 'perp' is an essential desmosomal protein found only in the stratified epithelium. Desmosomal complex that lacks perp protein results in blistering disorder of skin and oral mucosa, and can even result in death (5)

## **Corneodesmosin**

Corneodesmosomes are specialised desmosomes found specifically in stratum corneum of squamous epithelium. Corneodesmosin is a glycoprotein in desmosomal junctional complex of corneodesmosomes. Corneodesmosomes are

converted into cornified layer of epidermis due to continuous turnover within the squamous epithelium. Corneodesmosome is formed by a uniform electron dense plug which is a result of fusion of cornified layer. This cornified layer fused plug acts as protective layer under the plasma membrane. Proteolytic degradation of corneodesmosomes results in desmosomal fragility and can be seen in Netherton syndrome. Dry skin conditions (xeroses) and psoriasis (hyperkeratotic state) are controlled by the persistence of corneodesmosin (27).

‘Neodesmosin’ is a another glycoprotein that is integrated into desmosomes prior to their conversion to corneodesmosomes in the keratinised layers of the epidemis (5).

### **Cyclin-dependent kinase complexes**

The family of cyclin-dependent kinase complexes (Cdks) in desmosomal complex is well known for its role in the cell division cycle. Cdk-1 plays a major role in the homeostatic control, normal cellular replication, repair after damage and apoptotic cell death. Aberrant Cdk-1 expression is seen in cancer cells. They may show increased activity in pre-malignant oral lesions (4).

### **Intercellular adhesion molecule-1**

Intercellular adhesion molecule-1 (ICAM-1) and ligand lymphocyte function-associated antigen-1 (LFA-1) are adhesion molecules in the desmosomal complex which show altered levels in many diseases. Cytokines released from epithelial cells are responsible for regulating these adhesion molecules (28).

### **Conclusion**

Altered desmosomal protein levels may be associated with different oral epithelial diseases, such as epidermolysis bullosa. As altered levels of Dsc protein can be seen in many oral epithelial diseases, such as leukoplakia, epidermolysis bullosa

and erythroplakia, it is important to maintain desmosomal protein levels within the epithelial tissue to avoid disturbances which results in various epithelial diseases.

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**Table: Dys-regulation of desmosomal proteins in diseases affecting skin and oral mucosa**

| Protein       | Desmosomal Protein Family | Disease                                                                                                                                                         | Area affected                |
|---------------|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Desmoglein    | Cadherin                  | Palmoplantar keratoderma, pemphigus foliaceus, pemphigus vulgaris, paraneoplastic pemphigus, bullous impetigo                                                   | Skin epithelium, Oral mucosa |
| Desmocollin   | Cadherin                  | Pemphigus vulgaris                                                                                                                                              | Skin, oral mucosa            |
| Desmoplakin   | Plakin                    | Palmoplantar keratoderma, paraneoplastic pemphigus, arrhythmogenic right ventricular dysplasia, woolly hair syndrome, Naxos-like disease, and Carvajal syndrome | Skin, oral mucosa            |
| Envoplakin    | Plakin                    | Palmoplantar keratosis with increased risk of esophageal cancer (tylosis), paraneoplastic pemphigus                                                             | Skin                         |
| Periplakin    | Plakin                    | paraneoplastic pemphigus                                                                                                                                        | Skin, oral mucosa            |
| Palakoglobin  | Armadillo                 | Pemphigus vulgaris                                                                                                                                              |                              |
| Palakophillin | Armadillo                 | Ectodermal dysplasia, pachyonychia congenita                                                                                                                    | Skin, oral mucosa            |

|                                     |       |                                              |                                   |
|-------------------------------------|-------|----------------------------------------------|-----------------------------------|
| Flaggrin                            | ----- | dry skin, ichthyosis vulgaris, and/or eczema | Skin                              |
| Small proline-rich proteins (SPRPs) | ----- | -----                                        | Skin , oral mucosa (tongue) SPR 1 |
| Involucrin                          | ----- | Atopic dermatitis                            | Skin                              |
| Loricrin                            | ----- | Vohwinkel's syndrome                         | Skin                              |
| Plectin                             | ----- | Epidermolysis bullosa ressesive form         | Skin , Oral mucosa                |
| Perp                                | ----- | ----                                         | Skin, oral mucosa                 |
| Corneodesmosin                      | ----- | Netherton syndrome                           | -----                             |

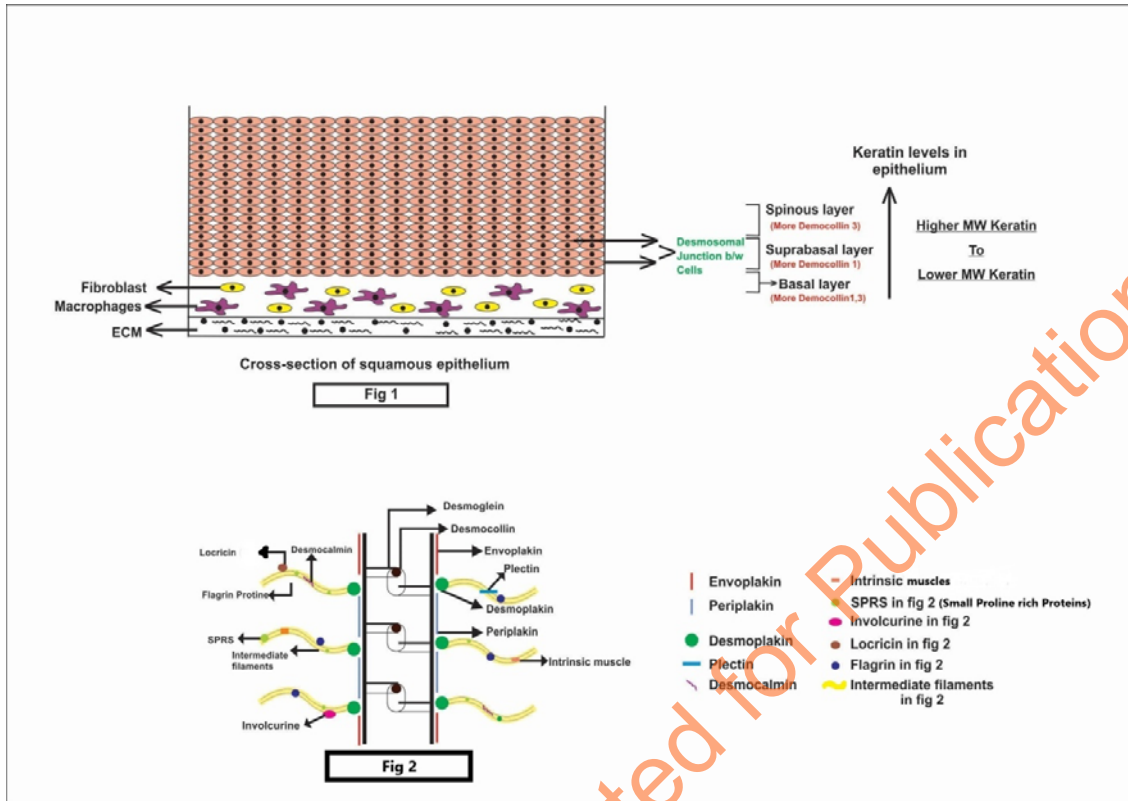
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**Figure 1:** Schematic showing cross-section of a normal non keratinised squamous epithelium with connective tissue containing fibroblasts, macrophages and extracellular matrix (ECM). Cellular localisation of different types of desmocollin (a desmosomal protein) is indicated in epithelial layers. Distribution of keratin protein levels in the epithelium change from low molecular weight to high molecular weight keratins from basal layer to the top layer in oral epithelium.

**Figure 2:** Indicates the localisation of different desmosomal proteins at specific sites in a desmosomal junctional complex.

(ECM: Extra cellular matrix, MW: Molecular weight, SPRPs: Small proline-rich proteins)