Chapter 1

Introduction to Autoimmune Bullous Diseases

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Additional information is available at the end of the chapter

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Abstract

Autoimmune bullous diseases are heterogeneous group of disorders characterized by intraepidermal and subepidermal bullae formation. Autoantibodies to major players of skin integrity cause devastating symptoms in autoimmune bullous diseases that may result with morbidity and even mortality in the affected patients. These group of diseases can be categorized by the level of splitting in the skin and by structural proteins that are targeted by autoantibodies. Autoimmune bullous diseases can be divided into four basic subgroups: pemphigus, pemphigoid, epidermolysis bullosa acquisita and dermatitis herpetiformis, although their different subtypes have been defined. In this chapter, the structure and tasks of desmosomes and basement membrane zone, which consist of the major antigens of the skin integrity targeted by autoantibodies, are examined, and the relation of target antigens and autoimmune bullous diseases is discussed.

Keywords: autoimmune bullous disease, autoantibodies, desmosomes, acantholysis, basement membrane zone

1. Introduction

Bullae are formed as a result of the damage of skin integrity due to various reasons, including bacterial or viral infections, trauma, genetic disorders and autoantibodies and fluid accumulation in the different layers of the skin; subcorneal, suprabasilar, dermal-epidermal junction and upper dermis [1]. Autoimmune bullous diseases (ABD) are a heterogeneous group of rare but fatal or debilitating skin diseases characterized by varying degrees of mucosal and cutaneous blister formation due to autoantibodies directed against the structural proteins of epidermis or the dermal-epidermal junction [2, 3]. ABD are classified according to the location of the bullae in the skin and the antigens targeted by the antibodies. They are simply

examined in four main groups: pemphigus, pemphigoid, acquired epidermolysis bullosa and dermatitis herpetiformis [1].

It is important to know the structure of the skin and antigens targeted by autoantibodies in order to better understand the ABD. The epidermal stratified squamous epithelium is a complex structure which includes several layers of keratinocytes. Cohesion among these cells is needed to preserve the epidermal architecture and function [4]. Epidermal integrity is provided by three types of junctional structures: (1) anchoring junctions (desmosomes and adherens junctions), major adhesive cell–cell junctions of epithelial cells that function with each other to hold epithelial sheets together. Both are connected with the cytoskeleton and represent sites of mechanical coupling between cells. (2) Tight junctions (zonula occludens) that constitute a diffusion barrier. (3) Gap junctions, where intercellular channels allowing for the direct exchange of small molecules between cells [4, 5]. While suprabasal, differentiating keratinocytes adhere to each other, undifferentiated basal keratinocytes are anchored to the dermis and interact with extracellular matrix. Basal cell surfaces not in contact with basement membrane have desmosomes which attach adjacent keratinocytes [1].

2. Desmosomes

Desmosomes are disc-like strong cell–cell adhesion complexes that act as anchors linking the intermediate filament (IF) cytoskeletons of neighboring cells in tissues that undergo large amounts of mechanical strain such as the heart and skin [6, 7]. In addition to their adhesive role, desmosomes are dynamic structures that regulate normal physiological processes such as proliferation and differentiation during development, tissue morphogenesis and wound healing [3, 6, 8–10].

Desmosomes are described as small dense nodules at the contact points between neighboring cells. “Desmos” means “bond” and “soma” means “body.” Electron microscopic investigations and newly developed procedures have supplied detailed knowledge about their structures and major protein components [3].

Desmosomes are 0.2–0.5 μm in diameter in human epidermis and consist of dense plaques located symmetrically on the plasma membranes of adjoining cells. Extracellular domain, a dense midline separates the membranes [8, 11].

Desmosomes, calcium-dependent junctions, have five major component proteins such as the desmosomal cadherins (DCs) [desmoglein (dsg) and desmocollin (dsc)], the plakin family [desmoplakins, (DP)], and the armadillo proteins [plakoglobin (PK) and plakophilin (PP)] [6, 8].

2.1. Desmosomal cadherins

Dsg and dsc are desmosomal adhesion molecules, and there are four dsg (1–4) and three dsc (1–3) in different tissues in humans. Dsg2 and dsc2 are present in all tissues that contain desmosomes such as simple epithelia, myocardium and are present in low amounts in basal layer

of complex epithelia like epidermis [4, 6]. While dsg4 is present in both stratified epithelia and hair, dsg1/3 and dsc1/3 are found only in stratified epithelia. Dysregulation of desmosomal cadherins causes skin, hair, heart and digestive tract disorders and cancer because of their roles in epithelial morphogenesis and differentiation [6].

Extracellular domains of dsg and dsc are highly homologous to those of classical cadherin, E-cadherin, which have five extracellular cadherin repeats containing Ca2+ binding sites and a cell-adhesion recognition (CAR) site [4, 8]. The cytoplasmic domains of dsg have a membrane proximal region, including an intracellular cadherin-typical region and a dsg-specific region [8].

Dsg 1 expression is higher in suprabasal layers in the skin epithelium. Dsg1 can support keratinocyte differentiation. Extracellular regions of dsg1 do not play a role in this function; they are needed for adhesion. In the recent years, mutations in dsg1 that cause severe skin dermatitis, multiple allergies and metabolic wasting syndrome (SAM) have been identified [6].

In the epidermis, dsg1 and 3 show inverse distribution patterns, dsg3 is present in high levels in the basal layer but dsg1 is found in low levels in this layer. However, the upper layers have high levels of dsg1 and low levels of dsg3. Therefore, pemphigus foliaceus causes bullae only in the most superficial layers of the skin while pemphigus vulgaris leads to blisters in the basal layers of the skin. Because dsg1 and dsg3 are both found in the intermediate layers, blisters do not typically occur in these layers (compensation hypothesis) [6].

2.2. The armadillo repeat and plakin families of desmosomal plaque proteins

The armadillo-repeat family members which are PG and the PP are characterized by their central arm-repeat domains. PG, together with PP, provides the adhesion of DP to keratin intermediate filaments and mediates important signal transduction pathways and regulates the clustering of desmosomal components [12].

İ. Plakoglobin: PG has three structural components as an N-terminal and a C-terminal domain which are separated by the central 12 arm-repeat domain and is homologous to *b*-catenin. Despite this homology, PG and *b*-catenin are differently distributed at cell–cell contacts. *b*-catenin normally is not a component of desmosomes and is only present in adherens junctions unlike PG [5]. PG plays an important role in heart, skin and hair development. Pg–/– mice show severe cardiac defects and Naxos disease that presents with arrhythmogenic right ventricular cardiomyopathy, wooly hair and keratoderma due to the mutation in the gene encoding PG [8].

ii. Plakophilins: PP are members of armadillo-repeat family, and PP1 was originally isolated as an accessory desmosomal plaque protein in stratified and complex epithelia binding to keratin. Later, PP2 and 3 and their subtypes were defined. PP are present both at desmosomes and in the nucleus [5]. While PP1 is mostly expressed in the suprabasal layer, PP2 is located in lower layers of stratified epithelia and heart [12]. All PP have diverse biological and pathological roles [6]. PP1 has an important role in desmosomal plaque formation and stability. *PP1* mutation causes ectodermal dysplasia-skin fragility syndrome in which skin fragility,

inflammation, ectodermal development abnormalities such as scant hair, hypohidrosis and astigmatism are seen [8]. Also, PP1 is elevated in the head and neck cancers and Ewing sarcoma. Therefore, it has been thought that PP1 regulates cell proliferation and growth.

PP2 has a role in the regulation of actin cytoskeletal dynamics, cell migration and tumorigenesis in addition to modulation of intercellular adhesion. PP2 is a new positive regulator for EGFR activation. Knockdown of PP2 causes the attenuation of EGFR-mediated signals and tumor development [6].

Also, the mutations in *PP2* have been identified as a cause of arrhythmogenic right ventricular cardiomyopathy.

PP3 mutations have not yet been identified in humans but *pp3* deficient mice developed cutaneous inflammation and hair abnormalities [8]. This protein mRNA expression has been found to be significantly higher in gastrointestinal cancer patients than controls. Also, its level increased in advanced stages and metastatic cancer. Moreover, it was found that PP3 was increased in breast and pancreatic cancers [6].

2.3. The desmosomal plakin family proteins

Plakins presents with a family of very large cytolinker proteins of 200–700 kDa. They have important role in the cross-linking of actin microfilaments, microtubules and/or intermediate filaments to each other and provide the connection of adhesive junctions with the cytoskeleton. There are seven identified plakin proteins and four of them, desmoplakin (DP), plektin, envoplakin and periplakin are localized in the desmosomes [5].

i. Desmoplakin: DP is an essential desmosomal component in the connection of desmosomal proteins with intermediate filament (IF) cytoskeleton. DP has a critical role in the heart and skin. Global knockout of DP in mouse causes lethality at embryonic days leading to a dramatic decrease in the desmosome numbers [6].

The N-terminal plakin domain peptide (DP-NTP) is essential to target DP to desmosomal plaques and contains binding sites for PPs and PG. The carboxy terminal domain of DP is composed of three plakin repeat domains (PRDs) named A, B and C and is responsible for the attachment of IF [5, 12]. The molecular interactions within the desmosomal plaque protein network are much complicated. It has been shown that the PP1 head domain acts as a lateral linker and allows the recruitment of additional DP molecules to the desmosomal plaque. Moreover, there is evidence that DP might bind directly to desmosomal cadherins in the absence of PG and PPs. But, in cells expressing PP1 and PG, DP preferentially binds to PP1. While dsg1 is the only desmosomal cadherin that interacts with the PP1 head domain PP2 interacts directly with dsg1 and 2, and dsc1a and 2a. In contrast to PP1, PP2 binds to PG. Together with the different tissue distribution of the PPs, the different binding specificities may be involved in the regulation of the size and cadherin composition of desmosomes and the efficiency of IF binding to desmosomes [5].

Two major isoforms of DP were identified: DP1 and DP2. Both are widely expressed in numerous tissues but DP2 is absent/reduced in the heart and simple epithelia [12]. The loss of DP2

causes a more severe adhesion defect due to mechanical stress [6]. DP2 has a more significant role than DP1 in maintaining the adhesion of keratinocytes [12]. Sarcoendoplasmic reticulum Ca+2-ATPase isoform 2 (SERCA2) regulates DP translocation to sites of cell–cell adhesion and SERCA2 is often mutated in Darier's disease. If mutation in DP leads to complete loss of protein or loss of the IF-binding C terminus, it results in lethal acantholytic epidermolysis bullosa with or without apparent associated cardiomyopathy. DP missense mutation can lead to Carvajal/Naxos syndrome that is characterized by keratoderma, wooly hair and cardiomyopathy [6, 8]. Consequently, desmosome mutations can lead to aberrant gap junctions and abnormal heart and epidermal functions, abnormal barrier homeostasis of skin. The loss of DP may also be associated with some cancers and/or their local invasion because of the loss of desmosomal function [6].

ii. Plectin: Plectin, a huge protein, was an originally IF-binding protein and was identified in hemidesmosomal and focal adhesion structures in the basal membrane of keratinocytes in the basal layer of the skin and striated, smooth and cardiac muscles. Later, it was shown that plectin is also expressed in desmosomes. However, it has an auxiliary role and is not a major component of desmosomes. It has major function in the organization of microtubules, actin and IF by coordinated cross-linking and the regulation of their dynamics. Plectin gene mutation does not cause blistering in the epidermis but cause blister formation in the epidermal basal layer by affecting hemidesmosomes. Plectin gene mutation causes autosomal recessive epidermolysis bullosa simplex (EBS) associated with muscular dystrophy [5].

iii. Envoplakin: Envoplakin was originally identified as a plakin protein family member. It was found along IFs and is partially colocalized with DP at desmosomes in terminally differentiating keratinocytes. Similar to plectin, envoplakin is not a major component of desmosomes. Envoplakin knockout mice normally develop but they have only a slight delay in barrier acquisition. No disorders due to the envoplakin mutations have been defined in humans yet [5].

iv. Periplakin: Similar to envoplakin, periplakin is upregulated during terminal differentiation of keratinocytes in cornified envelope. It is distributed more extensively than envoplakin, but there is little knowledge about its role in other tissues. Plectin, envoplakin and periplakin play a role as auxiliary factors in strengthening IF attachment to desmosomes at the desmosomal plaque [5].

2.3.1. The specificity of desmosomal adhesion

Data have shown that adhesive binding between dsc2 and 3 and dsg2 and 3 are both homophilic and isoform specific. Dsg3 can mediate weak homophilic adhesion. Dsc3 shows homophilic binding. While there is a heterophilic interaction between dsc3 and dsg1, there is no interaction between dsc3 and dsg3 [8].

2.3.2. Desmosomal hyperadhesion

Hyperadhesion, a strongly adhesive state is a distinctive property of desmosomes from other intercellular junctions. Adoption of hyperadhesion is a property of dsc. Keratinocytes proliferate

in low Ca2+ medium but do not contact adjacent cells. At the early stage of desmosomal development, desmosomal adhesion is Ca2+ −dependent, and chelating agents may induce the loss of adhesion and splitting of desmosomes. A rise in Ca2+ concentration induces assembly of AJ and desmosomes and in the late stage, epithelial desmosome becomes resistant to low Ca2+, and hyperadhesion is characterized by Ca2+ independence [5]. Hyperadhesion is associated with the ordered arrangement of the dsc. Phosphokinase (PK) C*a* may regulate Ca2+ dependence and inhibit hyperadhesion. Phosphorylation of desmosomal plaque components or different cytoplasmic signals may cause rearrangement in the plaque and transmit a signal to EC domains [8].

2.3.3. Desmosome assembly

The cell–cell contact and specific adhesive interaction are essential components for desmosome assembly. Any disorders of these components caused by low extracellular Ca2+, antibodies and blocking peptide inhibit desmosomal assembly. It was shown that intercellular adhesion starts in AJ and then stabilized by desmosomes. Antibodies to E and P cadherin block AJ and also inhibit desmosome formation [5]. PG plays an essential role in desmosomal assembly by providing interaction between AJ and desmosomes (cross-talk). Other components of desmosomal assembly are PP, dsc, dsg and DP [5, 8]. However, desmosomal assembly can also be induced by protein kinase C signaling in case of lacking of AJ. In the first step, dsg3 is transported to the cell surface, and in the second step, IF attached and half-desmosome-like structures are developed and they intermediate desmosome formation. If half desmosomes are not finally stabilized by interactions with half desmosomes on the adjacent cells they undergo endocytosis and degrade [5].

3. Desmosomes in diseases

The role of desmosomes in maintaining tissue integrity is defined by the large number of diseases in which one or more of its constituents are impaired [4]. The impairment of adhesive functions of desmosomal cadherins results from either development of autoantibodies against desmosomal cadherins or by gene mutations. Pemphigus is a family of blistering skin disorders caused by autoantibodies against desmosomal cadherins [5].

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are two most common forms of pemphigus family and potentially fatal disorders characterized by blister formation in skin and mucous membranes (in PV) due to the acantholysis, loss of keratinocytes cell–cell adhesion. Immunochemical studies showed that in PV, autoantibodies are immunoglobulin (Ig) G type and are directed against dsg3, 130 kD glycoprotein, or both dsg3 and dsg1, 160 kD antigen [5, 13], while in PF, they directed to only dsg1 [1, 12–14]. IgG1 and 4 type autoantibodies are indicators for active disorder while IgG2 is found in remission [1, 3]. Dsg3 and dsg1 show different expression patterns throughout epidermis. Dsg1 is expressed throughout epidermis and oral mucosa but it is more predominant in superficial epidermis than in deep epidermis. In contrast, dsg3 is expressed throughout the oral mucosa but it is only present in basal and

lower epidermal cells. In PF, anti-dsg IgG antibodies cause blistering in the superficial epidermis, but not in the mucosa or deep epidermis because dsg3 expression compensates loss of function due to the anti-dsg1 antibodies. In PV, anti-dsg3 antibodies cause blister development in the deepest layer of mucosa, where dsg1 expression is minimal. Mucocutaneous type PV results from both anti-dsg1 and anti-dsg3 antibodies [14–16]. But, in this type, diffuse intercellular blisters throughout epidermis do not occur. A cause of it may be that cell–cell adhesion might be weaker at the basal and intermediate suprabasal layers, where there are fewer desmosomes. Another reason may be that the lower layer of epidermis might have better access for autoantibodies which penetrate from the dermis. The main postulate of this monopathogenic theory (compensation theory) is that anti-dsg3 and 1 antibodies-dependent disabling of cell–cell adhesion is adequate to cause detachment of keratinocytes and form the blisters [3, 17]. However, data demonstrated that inactivation of dsg3 gene or depletion of dsg3 from keratinocytes could not induce gross blistering in the skin. In striate palmoplantar keratoderma which is due to N-terminal deletion of dsg1 acantholysis or skin blisters are not seen. Thus, compensation theory is still controversial [3, 15, 18]. Multipathogenic theory works to explain blister formation by multiple hit hypothesis. According to this hypothesis, a simultaneous and synchronized inactivation of physiological mechanisms of cell–cell adhesion causes disruption of epidermal detachment. Non-dsg antibodies may be pathogenic because they cause cell shrinkage, loss of adhesion at keratinocytes and/or proapoptotic signaling [17]. Additionally, IgA and IgE classes of Anti-dsg3 antibodies have been found in the sera of PV patients [3].

T-helper cells have critical role in the formation of pemphigus autoantibodies. Activation of autoreactive T cells (losing self-tolerance to dsg) responsive to pemphigus antigens lead to induction of IgG antibodies from B cells [3, 19]. Autoimmunity to certain epitopes of dsg3, dsg-reactive T and B cells may be seen in normal individuals particularly, the relatives of PV patients. There are dsg3 reactive Th1 cells in healthy relatives but there are Th2 cells in PV patients. Th2 reactive cells are detected at similar frequencies in the acute, chronic active and remittent phases of the disease but Th1 cells are increased in chronic active PV. It was demonstrated that Treg cells were decreased in the serum of PV patients [3, 18]. However, there is no decrease in Treg cells in PV skin lesions because Treg cells accumulate in the skin lesions and the draining lymph nodes. It has been thought that pemphigus autoimmunity can be triggered by Toll-like receptors (TLR) because of the activation of PF by TLR7 agonist, imiquimod [3].

4. Mechanism of acantholysis

It was shown that the number and size of desmogleins are reduced in PV and PF [19]. Data demonstrated that pemphigus autoantibodies bind to conformational epitopes formed by the N-terminal 161 amino acids and stabilized by calcium on desmogleins, and that these binding areas are responsible for the pathogenicity but C-terminal extracellular domain is not the pathogenic domain [14]. Previous data showed that PV IgG most likely directly cause the loss of adhesion via the disruption of desmogleins by steric hindrance (cis or trans interaction)

[12, 13, 18]. Interestingly, the detachment of keratinocytes from each other first occurs in the interdesmosomal area, and desmosomal detachment is seen in late acantholysis. Recent studies have demonstrated that the loss of desmosomal function is not only related to the steric hindrance, it may be related with other mechanisms [5, 13]. PV IgG bound to unassembled desmosomal cadherins does not prevent desmosomal generation rather, it causes internalization and degradation of IgG-antigen complex [15].

It has been shown that polyclonal PV IgG causes the retraction of keratin IF and intercellular detachment in vitro in keratinocytes obtained from wild type mice. But PG has critical importance for keratin retraction and detachment of cells [14]. PV IgG binding results in the depletion of dsg3 from keratinocytes and is followed by its internalization and degradation and depriving the not yet assembled desmosome of dsg3 [12, 14]. This suggestion was supported by the demonstration of a reduction in dsg3 levels in cell lysates. In contrast, some studies showed that dsg3 levels increase in cell lysates due to the reduction of anchorage of dsg3 to the cytoskeleton caused PV IgG antibodies [15]. Recent studies in mice have not shown the loss of dsg3 in split desmosomes or keratin retraction in acantholytic areas and that dsg3 is not depleted from desmosome before acantholysis [14].

Early studies showed that non-lysosomal proteases like plasminogen activator released by antibody binding caused the development of blisters but later, investigations in mice did not support this hypothesis and demonstrated that plasmin and plasminogen activators were not necessary for IgG-mediated acantholysis in mice in PV. Recent studies in vivo and in vitro have shown that selective proteases such as MMPs disrupt the adhesion of keratinocytes leading to proteolysis of adhesion molecules. While dsg3 is digested by MMP-9, a member of MMPs family, cell adhesion molecules like dsg1 and E-cadherin are digested by members of ADAM family of MMP during apoptosis [15]. In cultured keratinocytes, it has been shown that PV IgG induces apoptosis resulting in acantholysis. Apoptotic keratinocytes, reduced antiapoptotic factors and increased proapoptotic factors were detected in the epidermis in PF. Thus, induction of apoptosis may be a primary factor responsible for acantholysis and loss of intercellular adhesion. Caspases, apoptosis enzymes that have a role in acantholysis, are the other proteases. It was shown that activated caspase 3 was found in the epidermis before the blister formation, and it could cleave desmosomal proteins such as dsg1, dgs2 and dsg3. Caspases also cause the disruption of plaque proteins such as PP and DP1 and DP2, plektin and periplakin [8, 15]. Moreover, caspase inhibitors may block blister formation [8]. Shortly, these data suggested that caspases have fundamental role in apoptolysis [15]. FasL and CytC activate both extrinsic and intrinsic apoptotic signaling pathways in keratinocytes treated with PV IgGs [17]. Tumor necrosis factor alpha receptor superfamily member 5 and NADAH dehydrogenase-like protein are involved in the extrinsic and intrinsic apoptotic pathways, respectively [3].

Acantholysis is an active and complex process. Interaction of cell and PV IgG causes activation of phosphatidylcholine-specific phospholipase C, an increase in inositol 1,4,5 triphosphate (IP3) and diacylglycerol production and protein kinase C (PKC) activity. It also causes an increase in intracellular calcium concentration [15]. It has been shown that PV IgG causes serine-phosphorylation of dsg3, and the phosphorylation leads to the loss of PG binding. Data

suggested that PG, a cytoplasmic plaque constituent, plays a critical role in keratin retraction because PG binding is essential for targeting dsg3 to desmosomes [8, 14]. Recently, a lot of protein kinase and signaling molecules, including p38 MAPK, PKC, c-myc, Src, Rho A, PERK, FAK, Akt/mTOR, and cdk2 have been demonstrated [11, 15]. For example, it was shown that p38 phosphorylation facilitates the retraction of IF and detachment of the cells [13]. Desmocollin genes encoded N-glycosylated type 1 transmembrane proteins belong to Ca-dependent cell adhesion molecules of cadherin family. Similar to dsg3, dsc3 is expressed in the basal and suprabasal layers of the epidermis. It was demonstrated that anti-dsc3 antibodies might induce the loss of adhesion of epidermal cells and contribute to blister development in pemphigus. In addition to dsg and dsc3 antibodies, reactivity to dsc1, several muscarinic and nicotinic acetylcholine receptor subtypes, HLA molecules, a number of mitochondrial proteins, thyroid peroxidase and hSPCA1 encoded *ATP2C1* gene were shown. Moreover, anti-non-dsg antibodies may show the synergistic effects with anti-dsg antibodies, in other words, they may potentially amplify the activity of anti-dsg antibodies [17].

Anti-mitochondrial antibodies (AMA) target the mitochondrial nicotinic acetylcholine receptors that prevent apoptolysis in keratinocytes. AMA with anti-dsg antibodies can induce acantholysis, AMA/anti-dsg1 induces subcorneal splitting and AMA/anti-dsg3 induces suprabasal acantholysis. Recent studies showed that FcRn receptors exist on the keratinocytes and are a single target for PV IgG. PVIgG/FcRn complexes become internalized and are transmitted to mitochondria. Mitochondria are damaged via AMA and apoptotic signals are triggered for cell shrinkage. This shrinkage resulting in cytoskeleton collapse is an outcome of energy failure due to the damaged mitochondria [17].

According to a recent hypothesis, anti-dsg antibodies are not the reason but the result because reactivity to dsg1/3 develops in both extracellular and intracellular domains, and this gives rise to the thought that dsg molecules are released to intercellular space from damaged keratinocytes and become available to antigen presenting cells [3]. Consequently, pemphigus autoimmunity is directed to multiple organ-specific and non-organ-specific proteins.

Paraneoplastic pemphigus (PNP) is a rare and serious form of pemphigus. It is different from other OBD because it can affect multiple organs as well as skin [11, 20]. It has unusual clinical features, including severe mucosal involvement, bronchiolitis and a wide range of skin rash (pemphigus-like, bullous pemphigoid-like, erythema multiforme-like, graft versus host disease-like and lichen planus-like) [21]. It also shows unusual histopathological and immunological findings. PNP lesions are extremely painful and may be localized on the palm and soles, conjunctiva and simple squamous epithelia. The lesions are resistant to therapy. PNP is usually associated with malignancies such as lymphoma and leukemia. The mortality rate of PNP is high (90%) [11]. It may also be associated with myasthenia gravis and thymomas [22]. Because of cutaneous and noncutaneous pathologies associated with neoplasia it is called as paraneoplastic autoimmune multiorgan syndrome [21].

In PNP, targets of autoantibodies are more than one: dsgs, dscs, DP1 and 2, bullous pemphigoid antigen (BPAg)1, PF, PP, envoplakin, plectin, epiplakin and alpha-2-macroglobulin-like-1 (A2ML-1) that is a broad range protease inhibitor expressed stratified epithelia and other damaged tissues in PNP [11, 20, 22]. Characteristic autoantibodies in PNP target

the plakin family proteins that are molecules localized in the intracellular plaque of desmosomes and hemidesmosomes [20]. Also, anti-acetylcholine receptor autoantibodies and acetylcholinesterase autoantibodies were detected in 35 and 28% of PNP patients, respectively. High levels of these autoantibodies correlated with dyspnea in PNP patients. These antibodies target not only epidermal proteins but also other antigens in neural and bronchial tissues [22].

It is currently unclear why there are multiple autoantibodies in PNP. In patients associated with thymoma, it has been thought that defective thymocyte maturation might lead to the production of autoreactive T cells that can induce B-cell proliferation and autoantibody production. In hematologic malign tumors, aberrant immunological conditions caused by tumors might cause the production of many autoantibodies [22]. Another theory is that autoantibodies against the neoplastic antigens cross-react to epithelial antigens [21]. In PNP, responsible immunity is not solely humoral immunity, also cellular immunity plays a role in the pathogenesis. Therefore, histopathology shows individual keratinocyte necrosis with lymphocyte exocytosis in addition to deposits of autoantibodies in direct immunofluorescence (DIF) examination [20].

Lymphoid tumors may produce antibodies to desmosome and hemidesmosome components. But this solely cannot be explained with the pathogenesis of PNP. It is thought that tumors may express proteins that cross-react with epithelial proteins such as plakins. Another mechanism is dysregulated cytokine production by the tumor cells. The levels of interleukin (IL)-6 which promotes B-cell differentiation and Ig production is increased in PNP. Epitope spreading may explain antibodies against multiple proteins found in PNP [20].

In PNP, accumulation of activated CD8+ T cells and increased interferon gamma and tumor necrosis factor alpha levels were shown in the epidermis locally. Also, natural killer cells were detected in the affected tissues. Consequently, both humoral and cellular immunity play a role in the development of PNP [20].

Another subtype of pemphigus is IgA pemphigus characterized by IgA antibodies to desmosomal and non-desmosomal keratinocyte cell surface constituents. It has two subtypes: subcorneal pustular dermatosis type in which there are antibodies to dsc1 and very rarely to dsc 2 and 3, and intraepidermal neutrophilic type in which target antigen is still unknown but in rare cases, anti-dsg1 and 3 antibodies are the target antigens [11, 21, 23]. The mechanism of the development of skin lesions is not clear. It is thought that IgA antibodies might bind to the Fc receptor CD89 on monocytes and granulocytes resulting neutrophil chemotaxis and subsequent proteolytic cleavage of keratinocyte cell–cell junction [21]. Recently, IgG/IgA pemphigus which is an overlapping variant of classic IgG pemphigus and IgA pemphigus has been defined. Histopathological findings are acantholysis, blister formation localized on subcorneal or entire layer of epidermis and neutrophilic infiltration [11].

Pemphigus herpetiformis (PH) is a pemphigus form clinically resembling dermatitis herpetiformis and histopathologically pemphigus. In PH, autoantibodies against dsg1, dsg3, both dsg1 and dsg3 and more recently, dsc1, dsc3 and an unknown 178-kDa protein were

recognized. PH autoantibodies may recognize functionally less important epitopes of dsg1 or 3; therefore, it does not lead acantholysis directly. It is thought that autoantibodies cause the attraction of the inflammatory cells to tissue inducing by signaling pathway of cytokine production by keratinocytes [21] (**Table 1**).

Pemphigus form	Target antigens
PV	dsg3 or dsg3 and 1, dsc1, muscarinic and, nicotinic acetylcholine receptor, several HLA molecules, hSPCA mitochondrial proteins, thyroid peroxidase subtypes
PF	dsg1
PH	dsg1, dsg3, dsc 1, dsc3, unknown 178-kDa protein
PNP	dsgs, dscs, DP1 and 2, BPAg1, PF, PP, envoplakin, plectin, epiplakin and A2ML-1
IgA pemphigus	
SCP	mostly dsc1 rarely dsc2,dsc3
IEN	mostly unknown, some dsg1, dsg3

Table 1. Pemphigus forms and target antigens.

5. Basement membrane zone

Basement membranes are highly specialized forms of extracellular matrix composed of a distinct set of glycoproteins and proteoglycans [24]. They underlie all epithelia and endothelia, enveloping nerves, muscle fibers, distinct cell compartments and whole organs [24]. Basement membranes of various tissues differ ultrastructurally, biochemically and functionally. They act as substrates for attachment of cells, templates for tissue repair, matrices for cell migration, substratum to influence differentiation, morphogenesis and apoptosis of epithelial cell layers and permeability barriers for cells and macromolecules [25]. Basement membranes consist of *lamina densa*, a central electron-dense region, adjacent to a less dense area which is *lamina lucida* or *lamina rara* [24].

Human skin is the body's largest organ, which provides mechanical and immunological barrier against the external environment [26]. The interface between the lower part of the epidermis and the top layer of dermis is the dermoepidermal basement zone (BMZ) which maintains the structure and integrity of the skin by anchoring the overlying epidermis to the dermal matrix below [27]. The importance of the correct assembly of the components of BMZ for skin integrity is apparent from the multiple skin blistering disorders caused by mutations in genes coding for proteins associated with the epidermal BMZ and from autoimmune

disorders where autoantibodies target these molecules. These proteins are also important in tissue homeostasis, repair and regeneration [28].

The epidermal BMZ can be divided into four zones. The first zone contains the cytoskeleton, hemidesmosomes and plasma membranes of basal keratinocytes. The second zone is lamina lucida which contains filaments connecting hemidesmosomes in basal keratinocytes to the lamina densa. The third zone is lamina densa and the fourth zone is sublamina densa region which contains anchoring fibrils, anchoring plaques and fibrillin containing microfibrils [25, 29]. The biochemical components of BMZ are synthesized by basal keratinocytes and dermal fibroblasts [30]. Molecular components of epidermal BMZ are shown in **Table 2**.

The basal keratinocytes are anchored to the basal lamina via the keratin intermediate filaments and hemidesmosomes. The molecules within the basal lamina connect the basal keratinocyte to the basal lamina which anchors the BMZ to the underlying collagenous matrix of the superficial dermis [31]. Hemidesmosomes are small, regularly spaced electron dense structures on the inner surface of the basal pole of the keratinocytes [32]. They extend from the intracellular compartment of basal keratinocytes to the lamina lucida in the upper portion of the dermal epidermal basement membrane. The intracellular domains within the basal keratinocytes attach to the keratin intermediate filament network, and within the lamina lucida, they are contiguous with anchoring filaments [30]. The anchoring filaments transverse the lamina lucida and insert it into the lamina densa. Beneath the lamina densa, the anchoring fibrils extend beneath the basement membrane within the papillary dermis. The hemidesmosomes, anchoring fibrils and anchoring filaments form the hemidesmosome-anchoring filament complex [25, 32]. The hemidesmosome-anchoring filament complex forms a continuous link between the basal keratinocyte intermediate keratin filaments and the underlying BMZ and dermal components [32, 33].

5.1. Molecular components of epidermal basal membrane zone

5.1.1. Cytoskeleton of basal keratinocytes

5.1.1.1. Keratin 5 and 14

There is a structural framework known as the cytoskeleton within each basal keratinocyte which is composed of three main types of filaments: microfilaments, microtubules and intermediate filaments [31]. Basal keratinocytes express intermediate filament keratins 5 and 14 which are the major keratins in the adult epidermis [32]. Intermediate filaments form an intracellular cytoskeletal network throughout the epidermis and help to maintain the cell shape and epithelial structural integrity both through the formation of a cell scaffold and through their connection to desmosomes and hemidesmosomes [27, 32]. Mutations in genes coding *K5* and *K14* interfere with the assembly of the tonofilament cytoskeleton and connection of intermediate filaments to desmosomes and hemidesmosomes [27]. Autosomal dominant mutations in *K5* and *K14* underlie epidermolysis bullosa simplex (EBS) localized to hands and feet [26].

Cytoskeleton of basal keratinocytes
Keratin 5
Keratin 14
Hemidesmosome-anchoring filament complexes
Plectin
230 kDa bullous pemphigoid antigen (BP230/BPAG1)
Type XVII collagen (180 kDa bullous pemphigoid antigen/BP AG2)
$\alpha 6\ ß_4$ integrin
Tetraspan CD151
Laminin 332
Type XIII collagen
Syndecans 1 and 4
$\alpha 3\ ß_1$ integrin
Lamina densa
Laminin 332 (formerly laminin 5)
Laminin 311 (formerly laminin 6)
Laminin 511(formerly laminin 10)
Nidogen
Type 4 collagen
BM-40/SPARC
Perlecan
Sublamina densa region
Type VII collagen
Type IV collagen
Elastin
Fibulins
Fibrillins
Latent TGF-ß-binding proteins
Linkin
Type III collagen
Type I collagen

Table 2. Molecular components of epidermal BMZ.

5.1.2. Hemidesmosome-anchoring filament complexes

5.1.2.1. Plectin

Plectin is an epidermal plakin protein and is a component of hemidesmosome [34]. In the epidermis, the N-terminal of plectin includes binding sites for the cytoplasmic region of integrin ß4, BP180 and actin filaments and the C-terminal connects to keratin filaments [27]. It plays a key role in linking the keratin filament network to hemidesmosomes at the plasma cell membrane [34]. Mutations in plectin gene lead to various forms of EBS, including EBS associated with muscular dystrophy or with pyloric atresia and EBS-Ogna [27].

5.1.2.2. 230 kDa bullous pemphigoid antigen (BP230/BPAG1e)

The first specific target antigen of circulating autoantibodies identified in bullous pemphigoid patients, 230 kDa bullous pemphigoid antigen, which is also called the bullous pemphigoid antigen (BPAG) 1 isoform e (BPAG1e) is an intracellular, hemidesmosomal protein and a member of plakin family [33].

It is the major component of the hemidesmosomal inner dense plaque [29]. BPAG1e interacts with cytoplasmic domain of type XVII collagen, keratin intermediate filaments, erbin and integrin ß4. It links the keratin intermediate cytoskeleton to multiple hemidesmosome components [32]. The N-terminal of BP230 has a role in the integration of BP230 into the desmosomes and has binding sites for BP180 and ß4 integrin, and the C-terminal has binding sites for intermediate keratin filaments [27].

Though BP230 is a major target antigen in BP, the pathogenic relevance of BP230 in BP is not clear due to its intracellular localization [35]. In a study in 1995 in BPAG1e knockout mice, hemidesmosomes were otherwise normal, but they lacked the inner plate and had no cytoskeleton attached. The cell growth or substratum adhesion was also not affected indicating that BPAG1e was not absolutely essential for hemidesmosome or BMZ assembly. The mice also developed severe dystonia and sensory nerve degeneration [36]. In 2014, Feldrihan et al. demonstrated that antibodies against BP230 were nonpathogenic in experimental models of bullous pemphigoid [37].

5.1.2.3. Type XVII collagen (180 kDa bullous pemphigoid antigen/BP AG2)

Type VII collagen, which is also known as 180-kDa bullous pemphigoid antigen, is a transmembrane collagenous protein which is located within the hemidesmosome and lamina lucida [26, 30]. Its intracellular ligands are plectin, BPAG1e and ß4 integrin, and the extracellular ligands are α6 integrin and laminin 332 [29]. Collagen XVII spans almost the entire length of the BMZ and it is a major component of the hemidesmosome [31]. It is thought to play a role in the structure or stability of anchoring filaments, and it has an important function in maintaining the integrity of dermoepidermal junction [32].

Autoantibodies from patients with BP, pemphigoid gestationis (PG) and linear IgA bullous disease (LABD) target the NC16a domain of BPAG2 and from patients with mucous

membrane pemphigoid (MMP) tend to target the distal carboxy terminus of BPAG2, which extends deeper into basement membrane as well as NC16A [25].

The ectodomain of BP180 can be proteolytically shed from the cell surface through cleavage within the NC16A domain generating neoepitopes and the resulting 120 kDa fragment is LAD-1 that can be further processed into a 97 kDa fragment, which is targeted in linear IgA disease and also in BP and pemphigoid gestationis [35].

Mutations in *COL17A1* gene encoding type VII collagen cause non-Herlitz subtypes of junctional EB [27].

5.1.2.4. $\alpha 6\beta_4$ integrin

Integrins are a family of cell adhesion receptors, which have important roles in ligand binding and signaling [11]. The primary integrin in the cutaneous BMZ is $\alpha 6\beta_4$ integrin, which is critical in the adhesion of basal cells to the underlying BMZ [30]. It links the intracellular hemidesmosomal plaque to the extracellular matrix and plays an important role in initiating signaling pathways involved in cell migration, differentiation and survival. The large intracellular domain of β_4 integrin interacts with cytoplasmic domain of BP180 and provides linkage to keratin filaments via plectin. The extracellular domain of $\alpha 6$ and β_4 integrins provides binding sites for various laminin isoforms, including laminin 332 [27]. Mutations in either $\alpha 6$ or β_4 chains result in autosomal recessive junctional EB associated with pyloric atresia [31].

Autoantibodies against $\alpha 6$ and β_4 integrins have been detected in a subgroup of patients with MMP. Autoantibodies recognizing the $\alpha 6$ subunit were found in patients with oral lesions, and autoantibodies recognizing the ß4 subunit were found in patients with ocular involvement [35].

5.1.2.5. Tetraspan CD151

CD151 is a member of the tetraspanin family of cell surface proteins [28]. It is expressed on the basolateral surface of basal keratinocytes concentrated within desmosomes [27, 28]. The possible interaction partners of CD151 are the $\alpha 3\beta 1$ and $\alpha 6\beta 1$ integrins [32]. CD151 is thought to play a role in the organization and stability of hemidesmosomes by facilitating the formation of stable laminin-binding complexes with integrin $\alpha 6\beta 4$ as well as being involved in cellular signaling [27, 28].

5.1.2.6. Laminins

Laminins are a heterogeneous family of noncollagenous glycoproteins within the lamina lucida/lamina densa of all basement membranes. The laminin molecule is formed by three different polypeptide subunits: α, β and γ [38]. Laminins have a cruciform structure containing both globular- and rod-like segments which are implicated in interactions with other extracellular matrix molecules, like the hemidesmosomal components and type VII collagen, as well as in cell attachment [30]. Laminins are the major components of all the basement membranes along with collagen IV and exist in several isoforms which have been shown to self-assemble

into independent networks that are cross-linked by nidogen and perlecan [38]. To date, 16 laminin isoforms have been identified, and some of the laminin isoforms are expressed in the epidermal BMZ [30, 32]. Laminins 5,6 and 10 are the main epidermal BMZ-specific laminins [32]. Laminins promote basement membrane assembly and maintain cell and tissue integrity. Laminins within basement membranes serve as ligands for overlying cell surface receptors, thereby providing signals regarding the epithelial microenvironment [25]. The integrins, a family of cellular receptors, are major receptors that mediate cell adhesion to laminins [38].

Previously known as laminin 5, laminin 332 (epiligrin, kalinin, nicein, GB3 antigen, BM600) is the major laminin within the cutaneous BMZ [25, 30]. It consists of α3, ß3 and γ 2 laminin polypeptide chains [26]. It is found at the upper lamina densa/lamina lucida border at the base of anchoring filaments [32]. It plays an essential role in dermal-epidermal attachment and can be regarded as a bridge between hemidesmosomal proteins (α6ß4 integrin and type XVII collagen) and the anchoring fibrils (Type VII collagen) on the dermal site [27, 35].

The mutations in *LAMA3*, *LAMB3* and *LAMC2* genes encoding laminin 332 cause Herlitz type of junctional EB [35].

Autoantibodies against laminin 332 mainly directed against the α3 chain and can be detected in 20% of patients with MMP. This subgroup is termed anti-laminin 332 MMP, and it is associated with a solid malignancy in 30% of the cases [35].

Laminin γ 1 is a component of various laminin heterotrimers, including laminin 311, 321 and 511. It has been described as a target in anti-laminin γ1 pemphigoid, previously known as anti-p200 pemphigoid [35].

5.1.2.7. $\alpha 3 ß_1$ integrin

The integrin α3 subunit may dimerize with ß1 integrin in the dermoepidermal junction and contribute to epithelial-mesenchymal signaling [27]. Integrin α3 is a transmembrane integrin receptor subunit that mediates signals between the cells and their microenvironment. Mutations in the gene for the integrin α3 subunit causes an autosomal recessive multiorgan disorder characterized with interstitial lung disease, nephrotic syndrome and junctional EB [39].

5.1.2.8. Nidogen

Nidogens (previously known as entactin) are ubiquitous BM glycoproteins [24, 25]. The predominating nidogen is nidogen-1, and nidogen-2 was discovered as second mammalian isoform [24]. They interact with many other BMZ molecules, in particular with laminin and collagen IV, and their primary function appears to be stabilizing interactions between laminins and collagen IV with the lamina densa [35].

Nidogens are not required for epidermal BMZ formation because of the overlapping functions of many of the BMZ components [31].

5.1.2.9. Type IV collagen

Type IV collagen is found only in basement membranes and consists of three α-chain subunits which can be identical or genetically distinct but structurally related [25, 31]. Collagen IV's

primary role in the basement membrane is structural, as its three-dimensional lattice superstructure forms the basal lamina [31]. It is linked to laminins 5/6/10 complex by nidogen [32]. Collagen IV also has been associated with angiogenesis, tissue remodeling and cancer progression. There are many genetic diseases attributed to collagen IV, including Goodpasture syndrome, Alport syndrome, diffuse esophageal leiomyomatosis, benign familial hematuria [25].

5.1.2.10. Heparan sulfate proteoglycans

Heparan sulfate proteoglycans are glycoproteins which are found at the cell surface and in the extracellular matrix, where they interact with a plethora of ligands [40]. Characteristically, three proteoglycans are present in vascular and epithelial basement membranes, including perlecan, agrin and collagen XVIII [29]. They are present within, just above and just below the lamina densa of the epidermal basement membrane [25]. They can interact with various components of lamina densa, including type IV collagen and nidogen, and they are believed to contribute to the overall architecture of the basement membrane as well as tissue-specific functions [25, 29]. Their high sulfate charge contributes to the negative charge of basement membranes and restricts the permeability of these matrices [25].

5.1.2.11. Type VII collagen

Type VII collagen is the major component of anchoring fibrils, and it provides mechanical strength by linking the basal lamina and the underlying connective tissue [35]. Anchoring fibrils lie beneath the basal lamina, and they are fan-like, cross-banded structures extending into the papillary dermis that form semicircular loops [32]. They extend from the lower part of the lamina densa to the upper reticular dermis [25].

Type VII collagen consists of three identical α-chains that self-organize into a triple-helical collagenous structure. Each triple helical domain is flanked by a noncollagenous N-terminal and a C-terminal [27]. It contains a large globular noncollagenous domain termed NC1 in the amino terminal and a smaller domain termed NC2 in the carboxy terminal [25].

A large number of type VII collagen molecules laterally aggregate to form anchoring fibrils in which NC1 domains bind the lamina densa at one end and either loop back into lamina densa or else connect to anchoring plaques in sublamina densa region [25, 30]. The anchoring plaques are electron-dense structures which contain collagen IV and laminin 332 [29]. Specific subdomains within the NC1 domains have affinity for type I fibrillar collagen in the dermis and type IV collagen in the lamina densa and anchoring plaques. It also interacts with laminin 332 [25].

The importance of anchoring fibrils in securing the adhesion of the dermal-epidermal basement membrane to the underlying dermis is seen in mutations in *COL7A1* encoding type VII collagen which underlie both autosomal dominant and autosomal recessive forms of dystrophic EB in which the blister formation occurs in the sublamina densa region [34].

IgG autoantibodies directed against type VII collagen also results in epidermolysis bullosa acquisita which is a severe, acquired autoimmune bullous disease [41].

Type VII collagen has also been described as autoantigen in a small subgroup of patients with MMP, bullous systemic lupus erythematosus and LABD [35] (**Table 3**).

Basement membrane zone molecules	Acquired subepidermal blistering disease
BPAG1e	Bullous pemphigoid
	Mucous membrane (cicatricial) pemphigoid
	Pemphigoid gestationis
	Linear IgA disease
	Lichen planus pemphigoides
Collagen XVII	Bullous pemphigoid
	Pemphigoid gestationis
	Mucous membrane (cicatricial) pemphigoid
	Lichen planus pemphigoides
	Linear IgA disease
Laminin 332	Mucous membrane (cicatricial) pemphigoid associated with malignancy
Laminin 311	Mucous membrane (cicatricial) pemphigoid
Laminin γ1	Anti-laminin γ1 pemphigoid,
	(anti-p200 pemphigoid)
Integrin α6β4	Mucous membrane (cicatricial) pemphigoid
Type VII collagen	Epidermolysis bullosa acquisita
	Bullous lupus erythematosus

Table 3. Targeted molecules and the corresponding acquired subepidermal blistering disease.

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