Structure of hemidesmosomes and the epidermal basement membrane zone

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13 Structure of Hemidesmosomes and the Epidermal Basement Membrane Zone

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Introduction and Aims

Learning Objectives

The role of hemidesmosomes and basement membrane in maintaining tissue organization and integrity is demonstrated in several sAIBDs. In this chapter, our aim is to explain the structural complexity and function of hemidesmosomal and basement membrane zone proteins and their relationship to each other and list the sAIBDs that involve them (see Table 13.1).

Facts and Figures

Hemidesmosomes

Hemidesmosomes (HDs) are specialized complexes that provide attachment of the intermediate filament network in epithelial cells to the underlying basement membrane in the skin,

Table 13.1 Targeted molecules and their corresponding autoimmune disease at the site of hemidesmosomes and basement membrane zone

Location	Molecule	Autoimmune blistering disease
Hemidesmosome	Plectin	Anti-plectin pemphigoid Paraneoplastic pemphigus
	BP180 BP230	Bullous pemphigoid Nonbullous cutaneous pemphigoid Brunsting-Perry pemphigoid Lichen planus pemphigoides Pemphigoid gestationis Linear IgA bullous dermatosis Mucous membrane pemphigoid
	LAD-1, LABD-97	Linear IgA bullous dermatosis
	α6β4 integrin	Mucous membrane pemphigoid
Basement membrane	Laminin 332 Laminin 311 (α3 chain)	Mucous membrane pemphigoid
	Type VII collagen	Epidermolysis bullosa acquisita
	p200	Anti-p200 pemphigoid

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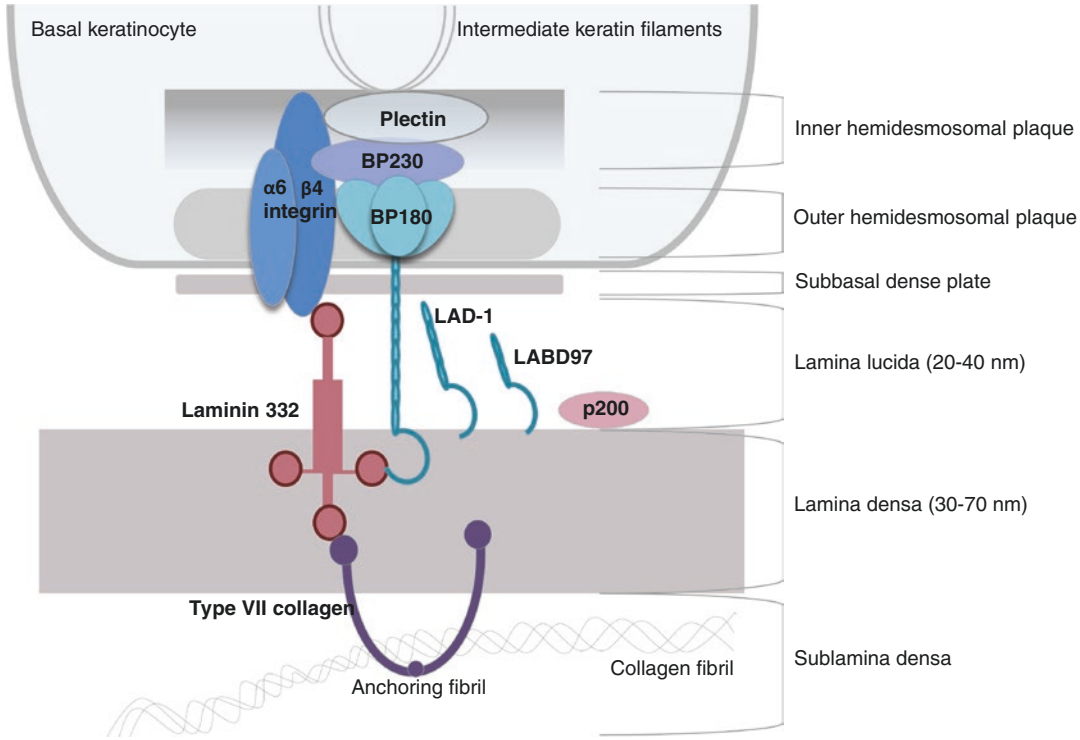

Fig. 13.1 Schematic representation of the hemidesmosome and dermal-epidermal junction including all molecules known to be targeted in autoimmune bullous diseases

mucous membranes of the cornea, pharynx, larynx, esophagus, genitals, and in the amnion. The name originates from its appearance as half of a desmosome, a cell-cell anchoring complex (see Chap. 7). HDs have a tripartite electron-dense plaque structure including the inner hemidesmosomal plaque, the outer hemidesmosomal plaque and the sub-basal dense plaque (Fig. 13.1).

Hemidesmosomes connect intermediate filaments to the basement membrane matrix

Subsequent is a succinct description of the most relevant constituents of HDs.

Plectin is a protein of the plakin family with a molecular mass over 500 kDa. This polypeptide consists of a central coiled-coil rod domain flanked by the globular N-terminal head domain and a C-terminal tail domain at each end, respectively. The N-terminus provides binding sites for integrin β4, BP180 and actin filaments, while the C-terminus connects to intermediate keratin filaments. Furthermore, plectin plays a role in attaching intermediate keratin filaments through association with BP230 [1]. Plectin has many isoforms with a long common rod domain, which are distributed in specific tissues such as stratified squamous epithelia, heart, skeletal muscle, and nerve tissue. Plectin 1a is the dominant isoform in hemidesmosomes in skin. This protein may become target for autoimmunity. Although a rare event, anti-plectin antibodies have been identified in sera from bullous pemphigoid (BP) patients [2]. Plectin has also been implicated as an autoantigen in paraneoplastic pemphigus (PNP).

BP230 is a member of the plakin protein family, like plectin. Also known as BPAG1, this molecule was the first discovered antigen to be targeted in bullous pemphigoid (BP). Structurally, BP230 is composed of a central coiled-coil rod domain flanked by N- and C-termini at each end, respectively. The N-terminus plays an important function in integrating BP230 into the HD and has BP180 and integrinβ4 as ligands; the C-terminus connects to intermediate keratin fila-

ments [3]. Through alternative splicing, the DST gene encoding BP230 generates tissue-specific isoforms expressed in the skin, central nervous system, and muscles, respectively [4]. BP230 has been involved as an autoantigen in several sAIBDs including BP, mucous membrane pemphigoid (MMP), Brunsting-Perry pemphigoid, pemphigoid gestationis (PG), lichen planus pemphigoides (LPP), and linear IgA dermatosis (LAD).

180 kDa bullous pemphigoid antigen or BP180, also known as BPAG1 or type XVII collagen, is a transmembrane hemidesmosomal glycoprotein. The N-terminal is non-collagenous and located intracellular, while the extracellular domain has a triple-helical shape containing collagenous repeats, hence the term type XVII collagen. Intracellularly, BP180 interacts with integrin α6β4 and plectin and aids the integration of BP230 into the HD. The extracellular domain crosses lamina lucida into the lamina densa where it binds laminin 332 [5]. BP180 is expressed in the skin, mucosa, central nerve tissue, teeth, placenta, and umbilical cord. Specific autoimmunity targeting this antigen leads to a spectrum of subepidermal autoimmune disorders such as BP, MMP, Brunsting-Perry pemphigoid, PG, LPP, and LAD. Notably, the ectodomain of BP 180, by means of stepwise proteolytic cleavage, generates the 120-kDa (LAD-1) and 97-kDa (LABD-97) antigens. These shed ectodomains are deposited in the lamina lucida and may become target of IgA autoantibodies in LAD.

Integrin α6β4 is a transmembrane molecule at the heart of the HDs. The integrin β4 subunit has a large intracellular domain which interacts with the intracellular domain of BP180 and links intermediate keratin filaments through plectin and BP230. The extracellular domains of the integrin α6 and integrin β4 subunits bind to laminin 332 in the extracellular matrix [6]. Integrin α6β4 is expressed in stratified squamous and transitional epithelia such as the skin, mucous membranes, gastro-intestinal, and urinary tract. Both α6 and β4 integrin subunits have been suggested as autoantigens in MMP in some studies; the evidence may benefit from more validation.

Epidermal Basement Membrane Zone

The epidermal basement membrane provides architectural linkage and a functional continuity between epidermis and the underlying dermis. Another important task is the maintenance of a barrier for unrestricted passage of chemical or pathological agents into the body or water and electrolytes out of the body. Basement membrane is too small to be visualized with light microscopy and can be identified only by electron microscopy. It contains an electron-lucent 20–40 nm thick layer named lamina lucida and a 30–70 nm thick electron-dense layer named lamina densa. This division is, nevertheless, a tissue preparation and dehydration artifact resulting from the retraction of plasma membrane and thus exposure of lamina lucida [5]. The structural composition of the basement membrane involves supramolecular aggregates that include laminin isoforms, type IV collagen, type VII collagen, perlecan, and nidogen [7].

Basement membrane zone interfaces epithelial and dermal compartment

Following is a succinct description of the most relevant constituents of the basement membrane.

Laminins represent a family of heterotrimeric molecules consisting of three different chains (α, β, and γ), which assemble into cross-shaped polypeptide. It is found in stratified squamous, transition, and simple epithelia [8]. Laminin 332 is a major component of the epidermal basement membrane and by binding integrin establishes a firm linkage to the underlying matrix. An additional function is mediation of keratinocyte migration [9]. Laminin 332 may become a target antigen in MMP. Also, laminin γ1 chain has been involved in some cases of anti-laminin γ1/anti p-200 pemphigoid.

p200 is a 200 kDa polypeptide in the lower lamina lucida, whose exact identity has not yet been fully clarified. The associated sAIBD is anti-p200 pemphigoid.

Type VII collagen is the main, if not the sole, component of anchoring fibrils in the sublamina densa zone. Anchoring fibrils have a semicircular

shape and link the lamina densa to the papillary dermis underneath. Structurally, it consists of three identical α-chains which organize into a triple-helical collagenous structure flanked by globular N-terminus (NC1) and C-terminus (NC2). This molecule is expressed in the basement membrane zone of the skin, cornea, pharynx, larynx, genital mucosa, esophagus, and chorioamnion [10]. Autoantibodies targeting type VII collagen are associated with epidermolysis bullosa acquisita (EBA).

Type IV collagen provides an architectural scaffold for other macromolecules by forming a network of interactions. Autoantibodies against the α3 chain of type IV collagen in the basement membrane of the lungs and kidneys are involved in the pathogenesis of antiglomerular basement membrane disease.

Review Questions

1. Which protein is a structural component of the hemidesmosome?
   (a) Integrin α6β4
   (b) Type IV collagen
   (c) Laminin 332
   (d) Type VII collagen
2. Which protein is a structural component of the basement membrane zone?
   (a) BP230
   (b) Type VII collagen
   (c) Integrin α6β4
   (d) BP180
3. BP180 and BP230 proteins associated with the following sAIBDs:
   (a) BP, MMP, Brunsting-Perry pemphigoid, PG, LPP, EBA
   (b) BP, MMP, Brunsting-Perry pemphigoid, PG, LPP, LAD
   (c) BP, MMP, LPP, PG, p-200 pemphigoid, LAD

Answers

1. (a)
2. (b)
3. (b)

On the Web

https://en.wikipedia.org/wiki/Hemidesmosome
https://en.wikipedia.org/wiki/Collagen,_type_XVII,_alpha_1
https://en.wikipedia.org/wiki/Basement_membrane

References

1. Koster J, van Wilpe S, Kuikman I, Litjens SH, Sonnenberg A. Role of binding of plectin to the integrin beta4 subunit in the assembly of hemidesmosomes. Mol Biol Cell. 2004;15:1211–23.
2. Buijsrogge JJ, de Jong MC, Kloosterhuis GJ, Vermeer MH, Koster J, Sonnenberg A, Jonkman MF, Pas HH. Antiplectin autoantibodies in subepidermal blistering diseases. Br J Dermatol. 2009;161:762–71.
3. Koster J, Geerts D, Favre B, Borradori L, Sonnenberg A. Analysis of the interactions between BP180, BP230, plectin and the integrin alpha6beta4 important for hemidesmosome assembly. J Cell Sci. 2003;116:387–99.
4. Leung CL, Zheng M, Prater SM, Liem RK. The BPAG1 locus: alternative splicing produces multiple isoforms with distinct cytoskeletal linker domains, including predominant isoforms in neurons and muscles. J Cell Biol. 2001;154:691–7.
5. Hashmi S, Marinkovich MP. Molecular organization of the basement membrane zone. Clin Dermatol. 2011;29:398–411.
6. Borradori L, Sonnenberg A. Structure and function of hemidesmosomes: more than simple adhesion complexes. J Invest Dermatol. 1999;112:411–8.
7. Turcan I, Jonkman MF. Blistering disease: insight from the hemidesmosome and other components of the dermal-epidermal junction. Cell Tissue Res. 2015;360(3):545–69.
8. Pierce RA, Griffin GL, Mudd MS, Moxley MA, Longmore WJ, Sanes JR, Miner JH, Senior RM. Expression of laminin alpha3, alpha4, and alpha5 chains by alveolar epithelial cells and fibroblasts. Am J Respir Cell Mol Biol. 1998;19:237–44.
9. Rousselle P, Beck K. Laminin 332 processing impacts cellular behavior. Cell Adh Migr. 2013;7:122–34.
10. Uitto J, Pulkkinen L, Christiano AM. Molecular basis of the dystrophic and junctional forms of epidermolysis bullosa: mutations in the type VII collagen and kalinin (laminin 5) genes. J Invest Dermatol. 1994;103:39S–46S.

Additional Reading

Walko G, Castanon MJ, Wiche G. Molecular architecture and function of the hemidesmosome. Cell Tissue Res. 2014;360(2):363–78.