Bullous disorders due to hereditary or acquired desmosome or hemidesmosome impairment

A short survey

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SUMMARY

Some aspects of the pathogenetic mechanisms of autoimmune bullous disorders as well as of bullous hereditary disorders are shortly reviewed. The known components of desmosomes and hemidesmosomes, to which specific autoantibodies are directed in autoimmune disorders, are listed. The molecular deficiencies of demosome and hemidesmosome components incriminated to cause hereditary bullous disorders, are also mentioned. The authors believe that clinicians should be familiar with the newest development in basic sciences concerning the pathogenetic role of desmosome and hemidesmosome.

KEY WORDS

bullous disorders, hereditary, autoimmune, desmosome, hemidesmosome, components, targets, pathogenetic role, review

Introduction

Bullous skin disorders especially pemphigus and bullous pemphigoid presented unsurpassed therapeutic problems to dermatologists until the late fifties, when corticosteroids were introduced. The prognosis became additionally more favorable by simultaneous use of corticosteroids and immunosuppressives. Numerous studies have proven that autoimmunity is the main pathogenic mechanism in acquired bullous diseases, whereas DNA mutations are responsible in hereditary bullous disorders. Many details remain however still to be cleared.

In the current literature our readers frequently encounter information on desmosome and hemidesmosome components, which are mentioned as the main targets or pathogenetic factors in bullous skin disorders. In order to make more transparent to our readers, which component is linked to a given bullous dermatosis, we tried to review shortly the problem using a few schemes and tables. We realize that this is a rather difficult task as only the active investigators understand these problems in details and even their opinions sometimes differ. Franke stressed it during his lecture at the 39th ESDR Annual Meeting in Berlin that the physicochemical and immunologic characteristics of an isolated component depend at least partially on the methods applied for its isolation.

Epidermis, basal membrane and associated tissues represent living systems, which are constantly under-

Table 1. Intraepidermal bullous diseases due to autoimmune response to components of the desmosome

Disease	Antigen	Antibody	Author	Reference
Pemphigus vulgaris	Desmoglein 3	IgG	Stanley	1993 (6)
			Amagal	1998 (7)
	Desmoglein 1		Ding	1999 (8)
	Cholinergic receptor		Nguyen	1998 (8)
Pemphigus foliaceus	Desmoglein 1	IgG	Ding	1999 (8)
Pemphigus paraneoplasticus	Envoplakin,	IgG	Kiyokawa	1998 (10)
	periplakin		Kazerounian	2000 (11)
	Desmoglein		Green	2000 (12)
	Desmoplakin 3		Amagal	1998 (7)
	BP 230		Stanley	1993 (6)
IgA pemphigus subcorneal pustulosis	Desmocollin 1	IgA	Tagami	1983 (13)
			Hashimoto	1997 (14)
IgA pemphigus intraepidermalis neutrophilicus		IgA	Huff	1985 (15)
Pemphigus herpetiformis	Desmoglein 1	IgG	Ishii	1998 (16)
	Desmoglein 3			

going changes. In principle the biological processes going on in the epidermis can be divided into *differentiation* and *activation*. During the process of differentiation the epidermal cells are undergoing complicated biochemical processes e.g. transformation of basal cells into corneocytes, whereas in the process of activation the cells react to injuries and to various signaling molecules. Both processes are regulated by complicated signaling mechanisms in which a cornucopia of molecules cooperate: peptides (e. g. interferons), growth factors (e. g. epidermal growth factor, EGF), interleukins (IL 1-12), receptor molecules as well as others (1, 2). Thus desmosomes and hemidesmosomes are too constantly undergoing changes.

Table 2. Hereditary intraepidermal bullous disorders due to deficiency of desmosome components

Disease	Deficiency	Gene	Author	Reference	Lesion
Darier disease	Desmoglein	ATPA2A 12q23-24	Sotoyama	1999 (17)	Acantholysis
			Sakuhtabhai	1999 (18)	
Hailey-Hailey disease	Ergastpl Ca pump	ATP2C1	Mackiewicz	2000 (19)	Acantholysis
Ectoderm dyspl/skin fragil sy	Plakophilin 1		McGrath	1997 (20)	scaling, erythema, blisters
Erythrokerat fig variabilis	Connexin 31	GJB3 1p34-36	Richard	1998 (21)	Papillomatosis, Parakeratosis
Keratodermia palm plant striat	Desmoplakin		Whittock	1999 (22)	Hyperkeratosis
	Desmoglein				
Dysplasia ectod hypohidrotica	transmembrane	X q11-21	Kere	1996 (43)	scaling, sparse
	protein				hair, hypodontia

Legend
ATPA2A - calcium ATP ase isoform 2
GJB3 - Gap junction ß3 protein

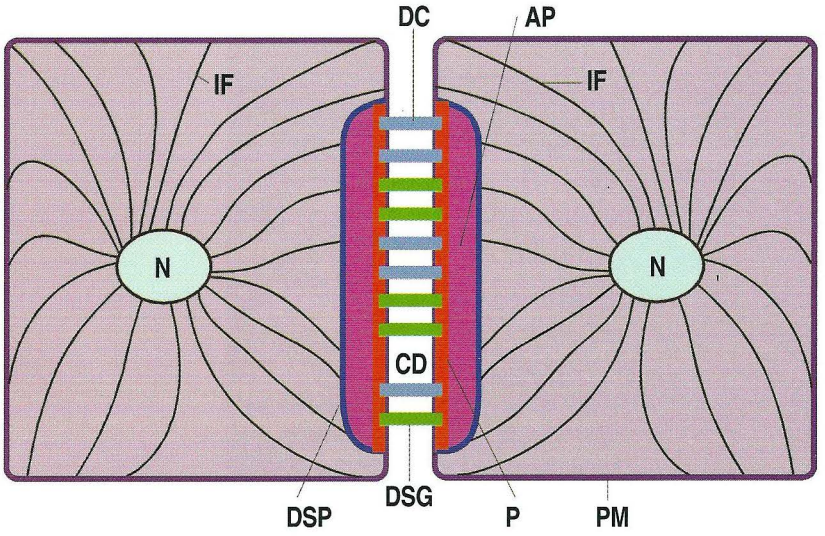
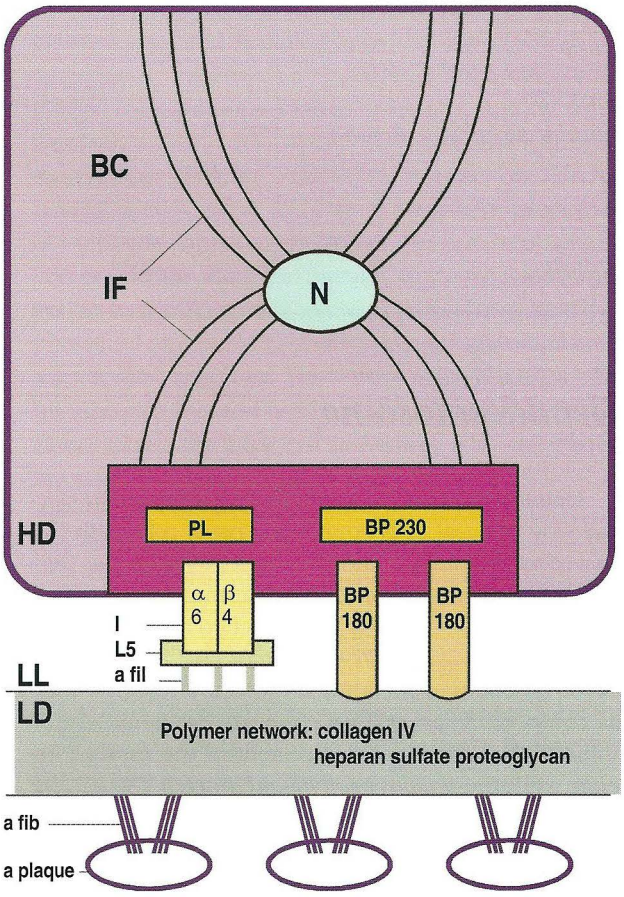


Figure I. Shematic presentation of a desmosome structure.

Legend: DC - desmocollin 1-3 (transmembrane proteins); DSG - desmoglein 1-3 (transmembrane proteins); P - plakoglobins; IF - intermediate filaments; CD - central disc of desmosome; PM - plasma membrane; N - nucleus; AP - attachment plaque; plakoglobin, plakophylin, periplakin, endoplakin, envoplakin DSP - desmoplakin I, II



The main structures responsible for the cohesion between epidermal cells are *desmosomes* and *hemidesmosomes*, but other structures like *adherens junctions, gap junctions* and *tight junctions* also fulfill important functions. We hope that the more biochemical minded readers would understand our didactic intent and accept the simplifications we were constrained to make.

Desmosome

Desmosomes have been visualized long ago by light microscopy and later by electron microscopy. The basic components of the desmosome are the *desmosomal plaque* and the transmembrane adhesion molecules *desmocollins 1-3* and *desmogleins 1-3*, which are connecting two neighboring desmosomes. Plaque components are *plakoglobin, plakophilin, periplakin, desmocalmin, endoplakin* and *envoplakin* as well as *desmoplakins II* and *I*. Plakoglobin seems to be attached primarily to desmocollin and desmoglein, while desmoplakins I and II appear to merge with the intermediate filaments (IF). A schematic presentation of the desmosome, as shown in Figure 1, might be helpful to readers in following the further explanations (3,4,5).

In autoimmune bullous disorders one or more components of the desmosome might become target of specific autoantibodies and thus trigger off the development of the disease. A good example is *pemphigus vulgaris* in which antibodies to desmoglein 3 (6,7) and to a lesser extent to desmoglein 1 (8) or to cholinergic receptors (9) cause the disruption of desmosomes and consequently the formation of intraepidermal clefts, vesicles or bullae (*acantholysis*). Desmoglein 1 is the main antigen in pemphigus foliaceus (8). Antigens responsible for other intraepidermal acantholytic dermatoses of autoimmune origin like pemphigus paraneoplasticus (10,11,12) or IgA pemphigus (13,14, 15,16) are listed in Table 1. It has to be emphasized that sometimes these disorders are characterized by simultaneous presence of autoantibodies directed to more than one desmosome component.

Figure 2. Shematic presentation of the epidermal-dermal junction.

Legend: BC - basal cell; N -nucleus; IF - intermediate filaments; HD - hemidesmosome; LL - lamina lucida; LD - lamina densa; PL - plectin; BP 230 - bullous pemphigoid antigen, BPAg1; BP 180 - bullous pemphigoid antigen, BPAg2 (collagen XVII); I - integrin; L 5 - laminin 5; a fil - anchoring filaments; a fib - anchoring fibrils; a plaque - anchoring plaque

Table 3. Subepidermal bullous disorders caused by autoantibodies directed to components of hemidesmosome and basal membrane

Disease	Antigen	Antibody	Author	Reference
Pemphigoid bullosus	BP180/NC16A	IgG > IgA	Cook	1990 (23)
	BP230		Stanley	1993 (5)
	Desmoplakin		Bedane	1997 (24)
	Plectin		Riou	2000 (25)
Herpes gestationis	BP180/NC16A	IgG	Perriard	1999 (26)
Pemphigoid cicatricans	BP 180	IgG>IgA>IgM	Bernard	1992 (27)
	Laminin5		Domlogue	1993 (28)
			Balding	1996 (29)
	Integrin β4		Mohinen	1993 (30)
Linear IgA dermatosis	285 kD*	IgA > IgG	Wojnarovska	1998 (4)
	97/120 kD*			
	BP180, BP230		Kromings	2000 (32)
	Anch fib			
Lichen planus pemphigoides	BP180/NC16A	IgG	Zilikens	1998 (33)
	200 kD		Braun-Falco	2000 (34)
Epidermolysis bullosa acquisita	Collagen VII/NC1	IgG, IgA	Shimizu	1990 (35)
			Aronsen	1998 (36)

Legend
BP 180 - bullous pemphigoid antigen 2 (BPAG 2, collagen XVII)
BP/NC16A - non-cellular fragment 16A of BP 180, the most immunologic domain
BP 230 - bullous pemphigoid antigen I (BPAG 1)
285 kD, 97/120 kD - specific antigens for linear IgA
anch fib - anchoring fibrils
collagen VII/NC I - non-collagen I domain of anchoring fibrils

Intraepidermal acantholysis is the main symptom also in a number of hereditary disorders which are caused by mutation of genes coding for individual desmosome components. In Darier disease acantholysis was attributed to deficient desmoglein (17), but the latest investigations incriminate the gene for the enzyme ATPase A2A, which is located on chromosome 12q23-24 (18). In the benign familial pemphigus (Hailey-Hailey disease) acantholysis is due to the deficient enzyme ATPase 2C1 (19). In the ectodermal dysplasia/skin fragility syndrome the deficient molecule is plakophilin 1 (20), while erythrokeratodermia figurata variabilis is attributed to to the deficient connexin 31 (21) and in keratodermia palmoplantaris striata to desmoplakin and desmoglein (22). Table 2.

Hemidesmosome

Hemidesmosomes are special structures on the dermal side of basal cells connecting basal cells with the basement membrane and consequently with the dermis. The components of the hemidesmosome to which intermediate filaments (IF) are attached are *plectin* and *bullous pemphigoid 230 kD protein (BP 230 antigen, BPAG1).* The transmembrane molecule *integrin* with its components a6 and b4 connects the hemidesmosome to the *laminin 5* component of the *lamina lucida*, while the *bullous pemphigoid antigen 180 kD (BP 180 antigen, BPAG2, collagen XVII)* links it to the *lamina densa* and its polymer network composed mainly of *type IV collagen* and *heparan sulfate proteo-*

Table 4. Bullous hereditary junctional disorders caused by mutations in components of hemidesmosome and basal membrane

Disease	Deficient component	Gene	Author	Reference
Epidermol hered junct Herlitz	Laminin β3 chain	LAMB 3 LAMA 3	Nakano Uitto	2000 (38) 1998 (39)
Epidermol letalis, atresia pylori	Integrin β4 subunit	Integrin gene	Micheloni	2000 (40)
Epidermol non- Herlitz	Integrin β4 subunit	LAMA 3	Castiglia	2000 (37)
Epidermol dystr	Anchoring fibrils	Collagen VII	Frank	1998 (41)

Legend
Epidermolysis bullosa hereditaria junctionalis letalis Herlitz
Epidermolysis bullosa hereditaria letalis cum atresia pylori
Epidermolysis bullosa hereditaria junctionalis non-Herlitz
LAMB 3 – laminin beta 3 gene
LAMA 3 – laminin alfa 3 gene

glycans. Important constituents of lamina lucida are in addition to laminins also *anchoring filaments*. The basement membrane is connected with the dermis through the *anchoring fibrils* (collagen VII structures). Figure 2.

A number of autoimmune subepidermal bullous skin disorders are linked to specific autoantibodies directed towards components of the hemidesmosome. In blood serum of patients with bullous pemphigoid specific antibodies to *BP 180* (23,24), *BP 230, desmoplakin* and *plectin* (25) were described. In herpes gestationis the autoantibodies are directed to the 16A non-cellular domain of BP 180 (NC16A/BP180) (26), in cicatricial pemphigoid to BP 180 (27), laminin 5 (28) and integrin ß4 (29,30,31). The autontibodies to 285 kD and 97/120 kD hemidesmosome components are specific for the linear IgA dermatosis (4,32), but other antigens like BP180 and BP 230 are also involved. Additionally to IgA, IgG autoantibodies may also be present. In lichen planus pemphigoides the antibodies are directed to the BP180NC16A (33) and to a 200 kD antigen (34), while in the epidermolysis bullosa acquisita the target is the non-collagen domain 1 of collagen VII (35,36).

The main hereditary bullous dermatoses linked to the hemidesmosome and to the basal membrane are the epidermolysis bullosa hereditaria junctionalis (EBHJ, JEB), actually more variants of this disorder are known. For the relatively benign non-Herlitz EBHJ a deficient integrin ß4 molecule expressed by the LAMA 3 gene is responsible (37). For the lethal Herlitz EBHJ the deficient laminin ß3 molecule coded by either LAMA 3, LAMB 3 gene (38) and for the EBHJ with atresia pylori the integrin ß4 expressed by COL7A1 or LAMC 2 gene is responsible (39,40). Further rare variants of EBHJ have been described, but their description would exceed the aim of this short review. At last we would like just to mention the most severe, the dystrophic form of epidermolysis.

Numerous investigations have shown deficient or even absent *anchoring fibrils*, which link the lamina, densa with the dermis and are coded by mutated collagen VII genes (COL7A). This disorder is not directly linked to hemidesmosome, for this reason just refer to two references mentioning mutations of the COL7A1 gene (41,42).

Conclusion

The above mentioned new data will most probably have in the future an impact on treatment. Attempts will be made to find out how to interfere with the reaction between specific autoantibodies and their target antigens, on the other side gene replacement therapy is a subject of intensive studies.

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