Bullous disorders due to hereditary or acquired desmosome or hemidesmosome impairment. A short survey

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

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 desmosome 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.

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.
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Epidermis, basal membrane and associated tissues represent living systems, which are constantly undergoing 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.

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).

Shematic presentation of a desmosome structure
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.

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

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

Intraepidermal acantholysis is the main symptom also in a number of hereditary disorders which are caused by the 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
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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 placophilin 1 (20), while erythrokeratodema figurata variabilis is attributed to the deficient connexin 31 (21) and in keratodermia palmoplantaris striata to desmoplakin and desmoglein (22). Table 2.

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

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

Legend:
- ATPA2A - calcium ATPase isoform 2
- GJB3 - Gap junction β3 protein

**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 α6 and β4 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 proteoglycans. 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 strutures). 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
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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 β4 (29,30,31). The autoantibodies 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).

Shematic presentation of the epidermal-dermal junction

![Figure 2](http://ibmi.mf.unl-lj.si/acta-apa/acta-apa-01-2/1-2-01.html)

Figure 2. Schematic 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, BP1Ag1; BP 180 - bullous pemphigoid antigen, BP1Ag2 (collagen XVII); I - integrin; L 5 - laminin 5; a fil - anchoring filaments; a fib - anchoring fibrils; a plaque - anchoring plaque

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 β4 molecule expressed by the LAMA 3 gene is
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For the lethal Herlitz EBHJ the deficient laminin β3 molecule coded by either LAMA 3, LAMB 3 gene (38) and for the EBHJ with atresia pylori the integrin β4 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).

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Antibody</th>
<th>Author</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desmoplakin, Plectin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes gestationis</td>
<td>BP180/NC16A</td>
<td>IgG</td>
<td>Perriard</td>
<td>1999 (26)</td>
</tr>
<tr>
<td>Pemphigoid cicatricans</td>
<td>BP180</td>
<td>IgG &gt; IgA &gt; IgM</td>
<td>Bernard, Domlogue, Balding, Mohinen</td>
<td>1992 (27), 1993 (28), 1996 (29), 1993 (30)</td>
</tr>
<tr>
<td></td>
<td>Lamnin5, Integrin b4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear IgA dermatosis</td>
<td>285 kD*, 97/120 kD*</td>
<td>IgA &gt; IgG</td>
<td>Wojnarovska, Kromings</td>
<td>1998 (4), 2000 (32)</td>
</tr>
<tr>
<td></td>
<td>BP180, BP230, Anch fib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lichen planus pemphigoides</td>
<td>BP180/NC16A, 200 kD</td>
<td>IgG</td>
<td>Zilikens, Braun-Falco</td>
<td>1998 (33), 2000 (34)</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Collagen VII/NC1</td>
<td>IgG, IgA</td>
<td>Shimizu, Aronsen</td>
<td>1990 (35), 1998 (36)</td>
</tr>
</tbody>
</table>

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/NC1 - non-collagen I domain of anchoring fibrils

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deficient component</th>
<th>Gene</th>
<th>Author</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>
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<table>
<thead>
<tr>
<th>Disorder</th>
<th>Protein Target</th>
<th>Genes</th>
<th>Authors</th>
<th>Year (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermol hered junct Herlitz</td>
<td>Laminin b3 chain</td>
<td>LAMB 3 LAMA 3</td>
<td>Nakano Uitto</td>
<td>2000 (38)</td>
</tr>
<tr>
<td>Epidermol letalis, atresia pylori</td>
<td>Integrin b4 subunit</td>
<td>Integrin gene</td>
<td>Micheloni</td>
<td>2000 (40)</td>
</tr>
<tr>
<td>Epidermol non-Herlitz</td>
<td>Integrin b4 subunit</td>
<td>LAMA 3</td>
<td>Castiglione</td>
<td>2000 (37)</td>
</tr>
<tr>
<td>Epidermol dystr</td>
<td>Anchoring fibrils</td>
<td>Collagen VII</td>
<td>Frank</td>
<td>1998 (41)</td>
</tr>
</tbody>
</table>

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 alpha 3 gene

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.

References

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41. Frank J, Cserhalmi-Friedman PB, Paller AS et al. Restoration and open reading frame due to skipping of an exon with an internal deletion in
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