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Autoimmune Blistering Diseases

–Pathophysiology and Serological Diagnosis–

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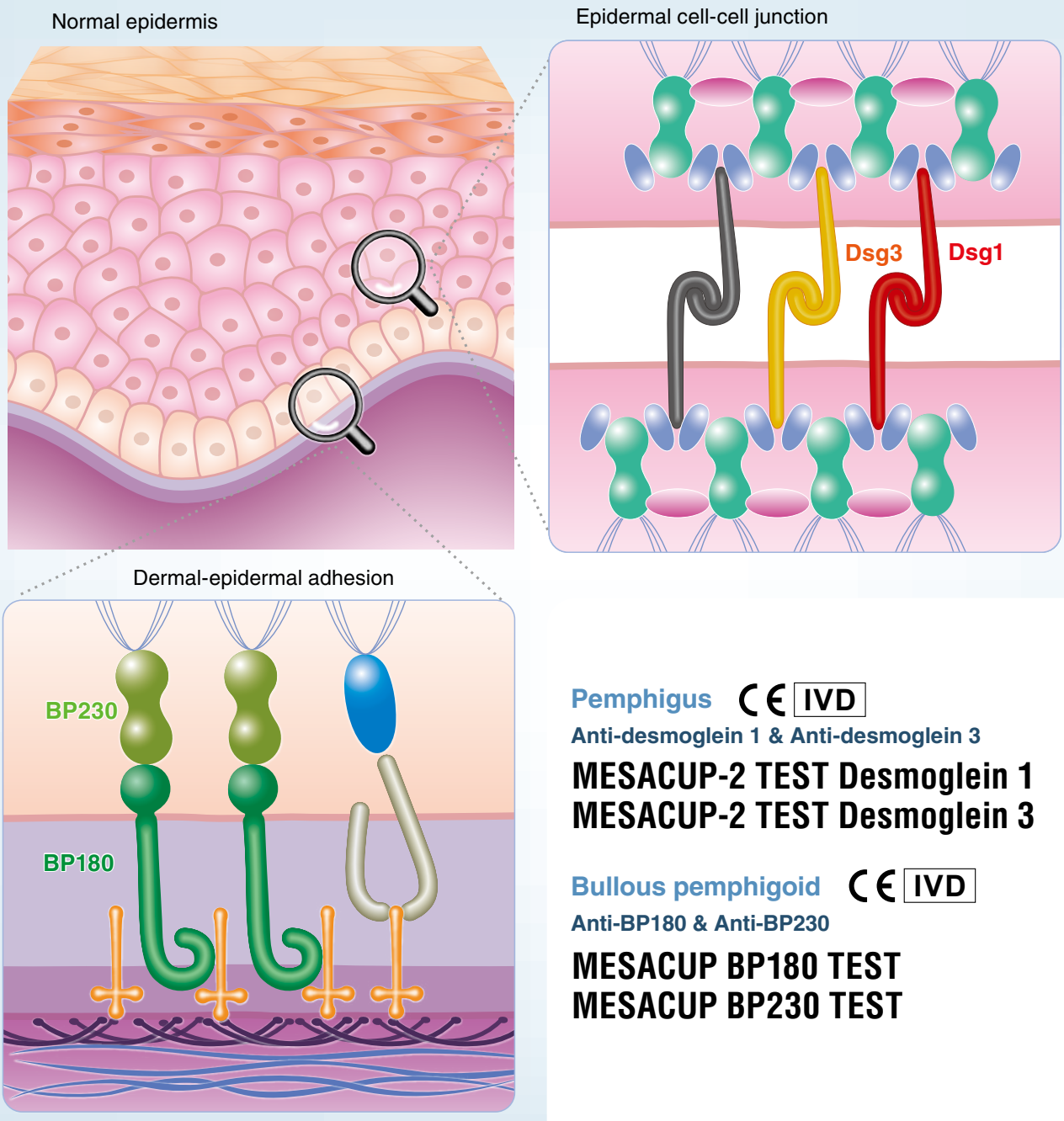


Pemphigus CE IVD

Anti-desmoglein 1 & Anti-desmoglein 3

MESACUP-2 TEST Desmoglein 1
MESACUP-2 TEST Desmoglein 3

Bullous pemphigoid CE IVD

Anti-BP180 & Anti-BP230

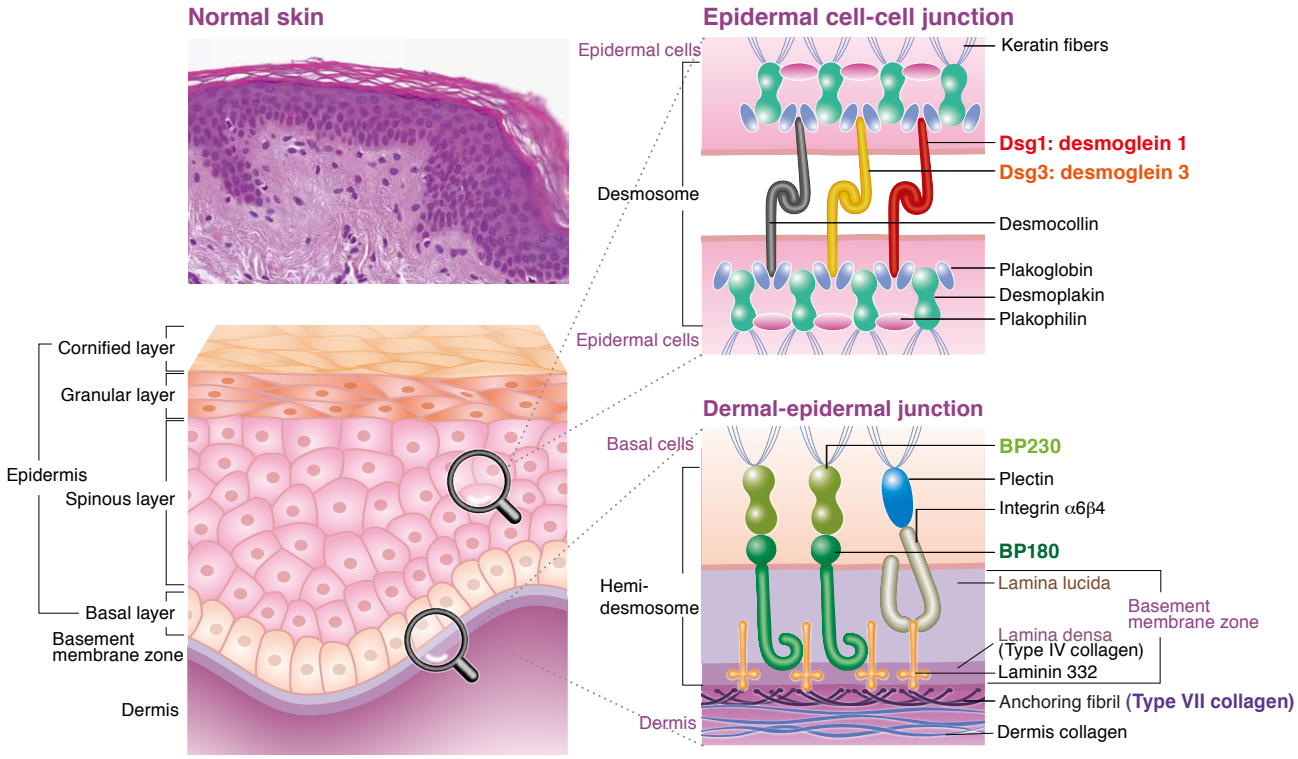
MESACUP BP180 TEST
MESACUP BP230 TEST

CONTENTS

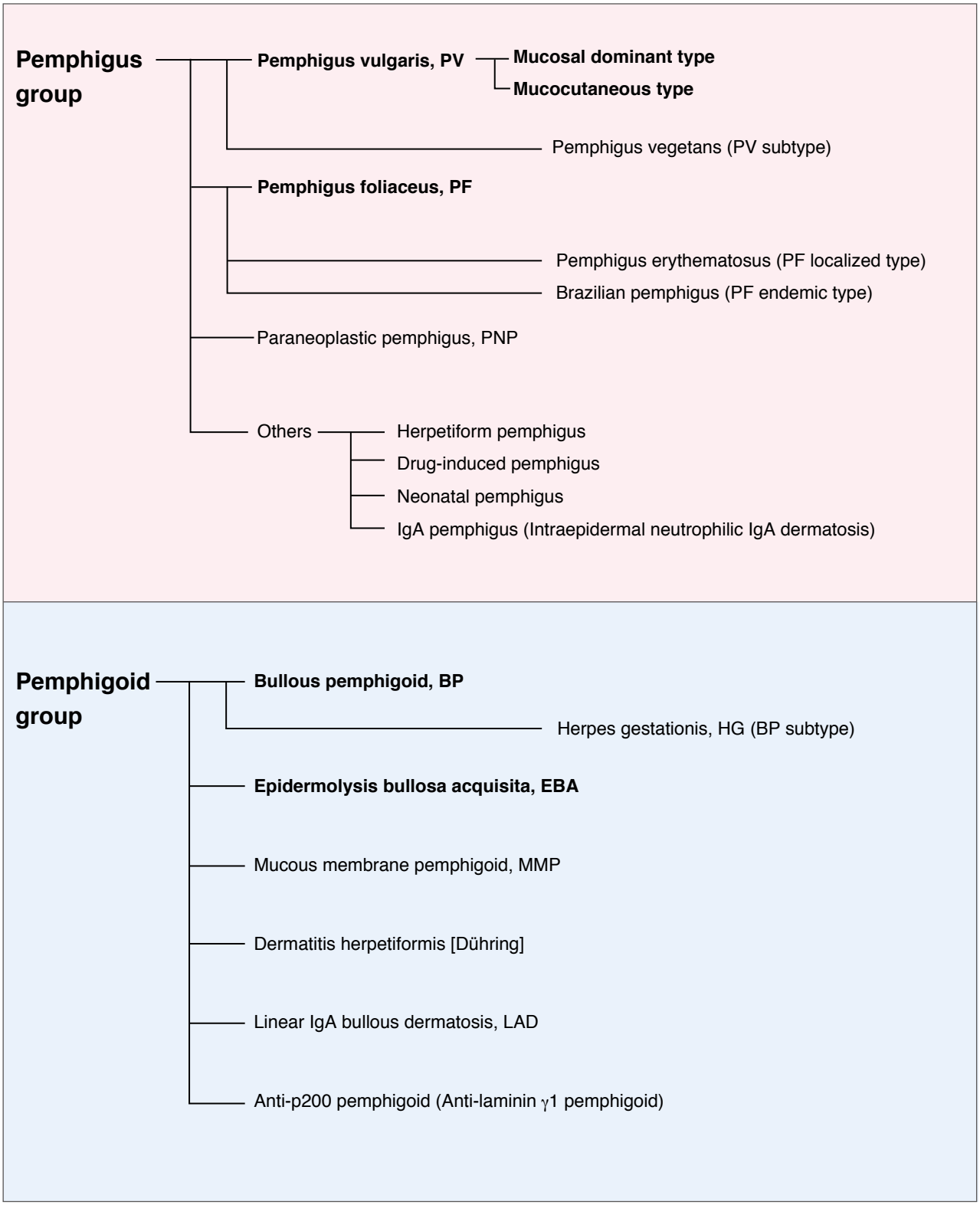
Structure of the epidermis

The epidermis generally consists of four layers: basal layer (stratum basale), spinous layer (stratum spinosum), granular layer (stratum granulosum), and cornified layer (stratum corneum). Keratinocytes are the major component of the epidermis. These cells progressively differentiate from basal cells to the finally differentiated, cornified layer, the outermost layer of the epidermis. Several types of intercellular junctions in the epidermis, such as desmosomes and tight junctions, are involved in protection against mechanical stress, physical stimulation or infectious agents. Desmosomes are composed of transmembrane proteins (*e.g.*, desmoglein [Dsg] 1, Dsg3, and desmocollin) and intracellular proteins (*e.g.*, desmoplakin). Desmogleins and desmocollins, which are the cadherin family proteins, maintain epidermal cohesion in a Ca^{2+}-dependent manner. Basal layer, the deepest layer of the epidermis, rests upon the basement membrane zone (BMZ) of dermal-epidermal junction (DEJ). Keratinocytes in basal layers have hemidesmosome, a structure comparable to a half of desmosome, being involved in adhesion in DEJ. Two hemidesmosomal components, BP180 (BPAG2, [bullous pemphigoid antigen 2], or type XVII collagen) and integrin $\alpha6\beta4$ are transmembrane proteins which link to the basal membrane zone. BP230 (BPAG1) and plectin (HD-1) are cytoplasmic proteins involved in the organization of the cytoskeleton. BMZ is divided into the lamina densa and the lamina lucida. The major component of the lamina densa is type IV collagen. The lamina lucida contains heparan sulfate proteoglycan, fibronectin and Laminin 332 (laminin 5). Laminin 332 serves as a major anchoring protein between the lamina lucida and the lamina densa and connects BP180 and integrin $\alpha6\beta4$ in the lamina lucida with type VII collagen. Type VII collagen secures the lamina densa to the dermis through association with dermis collagens.

Blistering disease is the general term for several diseases with blisters and erosion on the skin and mucous membrane caused by congenital or acquired interruptions of epidermal or epidermal-dermal cohesions [1-3]. This brochure summarizes the clinical manifestations, the mechanism of the blister formation, and the serological diagnosis on various autoimmune blistering diseases.



Classification of autoimmune blistering diseases



Pemphigus

Overview

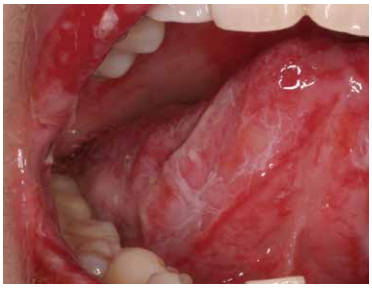
Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes which are characterized histologically by intraepidermal blisters due to acantholysis (*i.e.*, disruption of the intercellular connections between keratinocytes of the epidermis) and immunopathologically by *in vivo* bound and circulating immunoglobulin G (IgG) antibodies directed against the cell surface of keratinocytes. The mean age of the onset of diseases is about 40 to 60 years. Nikolsky's sign (*i.e.*, blistering induced by lateral pressure to the normal-appearing skin) is also a characteristic feature of pemphigus. The target antigens in pemphigus are Dsg1 and 3 [4, 5], members of the cadherin super family. Pemphigus can be classified into pemphigus vulgaris (PV), pemphigus foliaceus (PF), paraneoplastic pemphigus (PNP), and others. The blisters in PV and PF occur in the deeper region of the epidermis (just above the basal layer) and the upper layer, respectively.

Clinical characterization

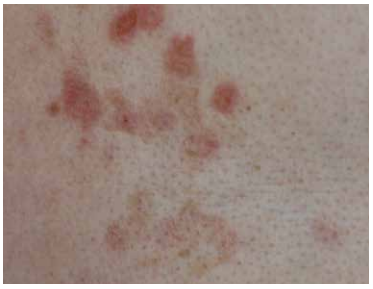
- **Pemphigus vulgaris (PV)**

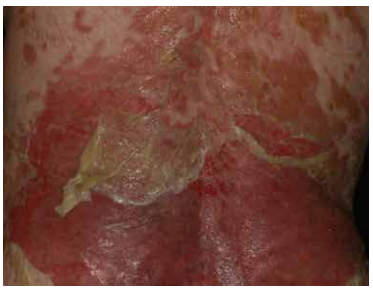
PV is the most common of pemphigus diseases. The majority of patients have painful mucous membrane erosions, especially in the oral cavity. While mucous membranes are mainly affected in mucosal dominant PV (MDPV), in mucocutaneous PV (MCPV), blisters and erosions are not only present on the mucosal area but also on the skin, predominantly the regions prone to pressure and friction, such as scalp, axilla, groin, upper part of back, and buttock. Pemphigus vegetans, a rare form of PV, is characterized by vegetating granulomatous lesions.

Oral lesion

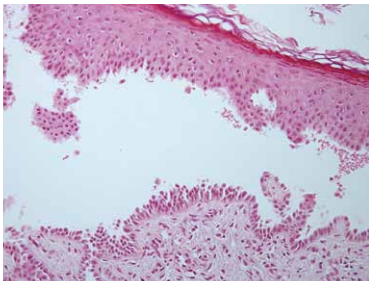


Skin lesion



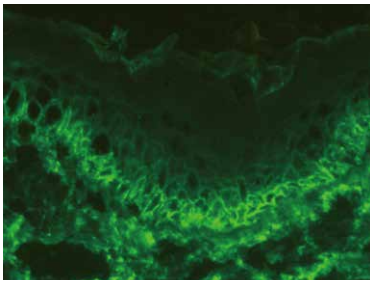


Histopathology



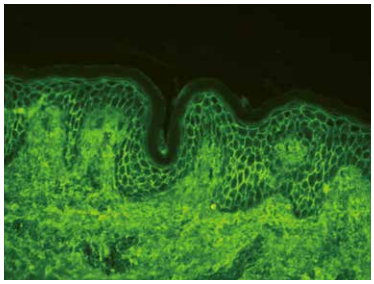
Acantholytic blisters in the epidermis are formed just above the basal layer.

Direct immunofluorescence staining of the skins taken from patients with PV



Mucosal dominant PV

IgG deposits on the cell surface of the epidermis, and stronger staining in the deeper layers than the upper layers.



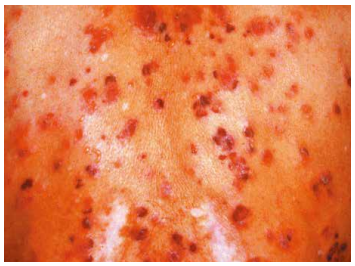
Mucocutaneous PV

IgG deposits on the cell surface throughout the epidermis.

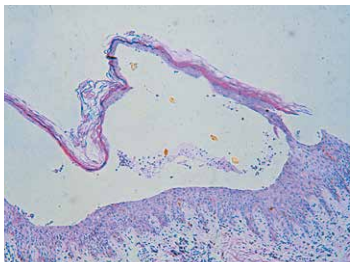
Pemphigus foliaceus (PF)

PF is characterized by scaly crusted erosions. These lesions are scattered in seborrheic regions such as the scalp, face, and upper trunk, while the mucous membranes are never affected. Symptoms of patients with PF are generally not as serious compared to those of PV. Pemphigus erythematosus (Senear-Usher syndrome), the localized form of PF, is associated with butterfly rash on the face. Fogo selvagem (Brazilian pemphigus foliaceus) is the endemic type of PF in the area of South America, especially Brazil.

Skin lesion

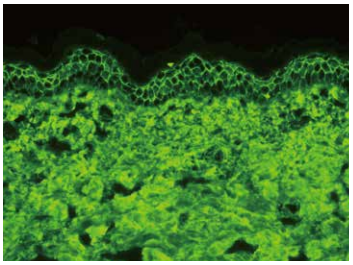


Histopathology



Acantholytic blisters in the epidermis are formed in the superficial epidermis.

Direct immunofluorescence staining of the skin taken from a patient with PF



IgG deposits on the cell surface of the epidermis, and stronger staining in the upper layers of the epidermis than the lower layers.

Paraneoplastic pemphigus (PNP)

PNP is an autoimmune mucocutaneous disease associated with underlying malignancy, particularly lymphoproliferative neoplasms. Painful erosions and ulcerations occur in the oral mucous membrane. In addition, many patients with PNP have ocular mucosal lesions and pseudomembranous conjunctivitis, resulting in ankyloblepharon in severe cases [6].

Other types of pemphigus

Herpetiform pemphigus is characterized clinically by erythematous urticarial plaques and vesicles that present in a herperiform arrangement, histologically eosinophilic spongiosis with minimal or no acantholysis, and serologically IgG autoantibodies against cell surfaces of keratinocytes. Drug-induced pemphigus is induced by drugs such as D-penicillamine or captopril. Neonatal pemphigus is a disease that rarely occurs in infants born to mothers with PV. IgA pemphigus is characterized by tissue-bound and circulating IgA autoantibodies that target the desmosomal proteins or unidentified cell surface antigens in the epidermis.

Pemphigoid

Overview

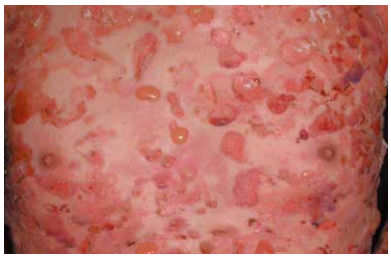
Pemphigoid is a group of diseases characterized histologically by subepidermal blisters and immunopathologically by linear deposition of IgG and complement C3 at basement membrane zone (BMZ) in the skin from patients with circulating IgG against the molecules within the dermal-epidermal junction (DEJ). The target antigens recognized by autoantibodies in patients with bullous pemphigoid (BP) are BP180 (a 180-kDa transmembrane protein), and BP230 (a 230-kDa intracellular protein). The target antigens recognized by autoantibodies in other diseases of this group include type VII collagen in epidermolysis bullosa acquisita (EBA); laminin 332 (laminin 5, epiliglin), one of the target antigens in mucous membrane pemphigoid (MMP); a 97-kDa protein (BP180 degradation product) in linear IgA bullous dermatoses (LAD); and laminin γ1 in anti-p200 pemphigoid [7–9].

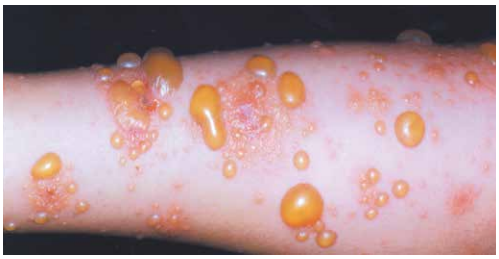
Clinical characterization

- **Bullous pemphigoid (BP)**

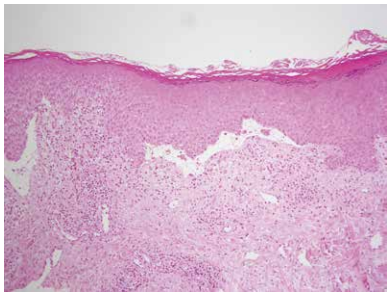
The skin lesions of BP are characterized by tense blisters with significant pruritus. Histopathological analysis detects subepidermal blisters and superficial dermal infiltrations of eosinophils, lymphocytes, and macrophages. Mucous membrane erosions are occasionally found in some patients with BP. BP usually occurs in elderly individuals.
Herpes gestationis (HG, pemphigoid gestationis), a subtype of BP, occurs during pregnancy and the immediate postpartum period [10]. Histopathology of HG shows subepidermal blisters with eosinophil infiltration.

Skin lesion



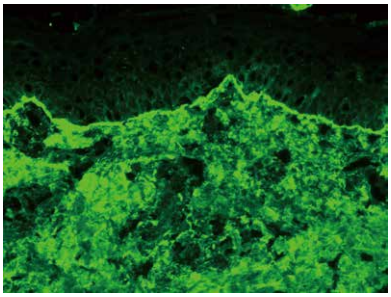


Histopathology



Subepidermal blister formation.

Direct immunofluorescence staining of the skin taken from the patient with BP



Linear deposition of IgG along BMZ.

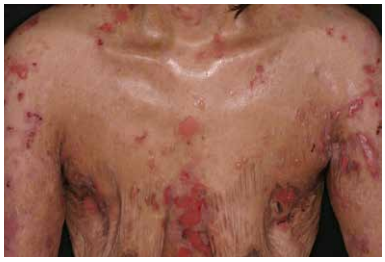
Mucous membrane pemphigoid (MMP)

MMP had been called cicatricial pemphigoid due to scar formation after blisters and erosions. However, not all of the patients have scarring. MMP is a rare autoimmune blistering disease, involving oral and ocular mucous membranes. Linear depositions of IgG and/or complement C3 along BMZ can be detected by direct immunofluorescence assay. A major MMP target autoantigen is BP180. Other target antigens include laminin 332 and BP230 [11].

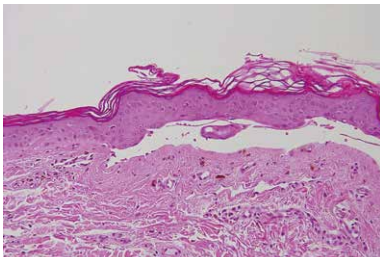
Epidermolysis bullosa acquisita (EBA)

EBA is subepidermal autoimmune skin diseases associated with autoimmunity to type VII collagen, which is the major component of anchoring fibrils. The classic presentation of EBA is noninflammatory blistering on the extremities that heal with scarring and milia formation. However, the clinical manifestation is varied and inflammatory blisters and eruptions can also be observed on any part of the body including the mucous membrane. Histopathology shows subepidermal blisters with different degrees of inflammation and neutrophil infiltration. Direct immunofluorescence assay reveals IgG deposition along BMZ [12, 13].

Skin lesion

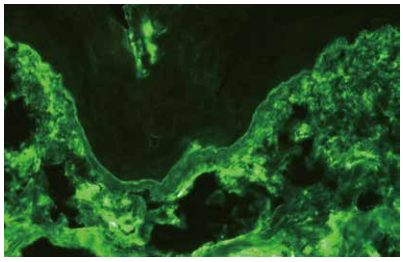


Histopathology



Sub-epidermal blister formation.

Direct immunofluorescence staining of the skin taken from the patient with EBA



IgG deposits in BMZ.

Dermatitis herpetiformis (Dühring disease)

Dermatitis herpetiformis (DH) is characterized by chronic eruptions typically on elbows, knees, and back with intense pruritus. The granular deposits of IgA are detected in the papillary dermis by direct immunofluorescence assay. Circulating IgA autoantibodies against transglutaminase have been identified in patients. However, the exact mechanisms on the IgA deposition in the skin remain unclear. In addition, it has been reported that the IgA deposits may be reduced in the patients who go on a long-term gluten-free diet [14].

Linear IgA dermatosis (LAD)

LAD is a rare blistering disease with the onset over 40 years or under 10 years of age (chronic bullous diseases of childhood [CBDC]). The clinical manifestations of LAD are itchy erythematous papules and blisters. Direct immunofluorescence of perilesional skin from the patient with LAD reveals IgA linear deposition along BMZ. A target antigen is the 97-kDa protein, an extracellular domain of BP180 [15].

Anti-p200 pemphigoid (Anti-laminin γ1 pemphigoid)

Anti-p200 pemphigoid is a blistering skin disease occasionally seen in patients with psoriasis. Recently, laminin γ1 was identified as the target antigen [9].

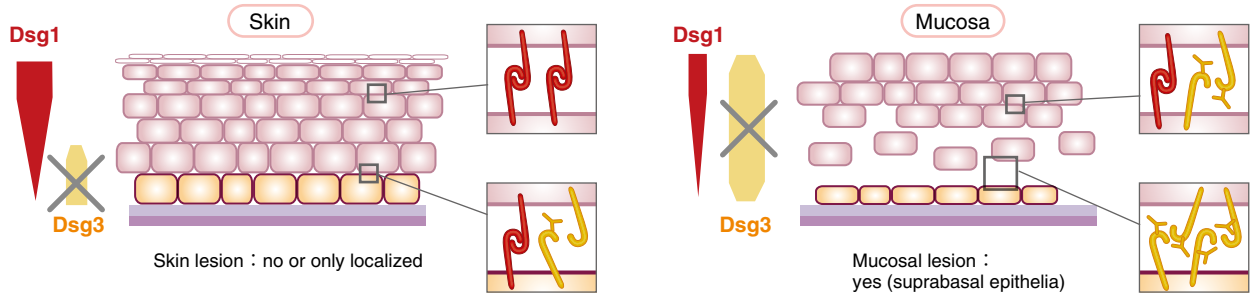
Autoimmune blistering diseases and associated autoantibodies

Pemphigus (PV/PF) and anti-desmoglein 1 & 3 IgG autoantibodies

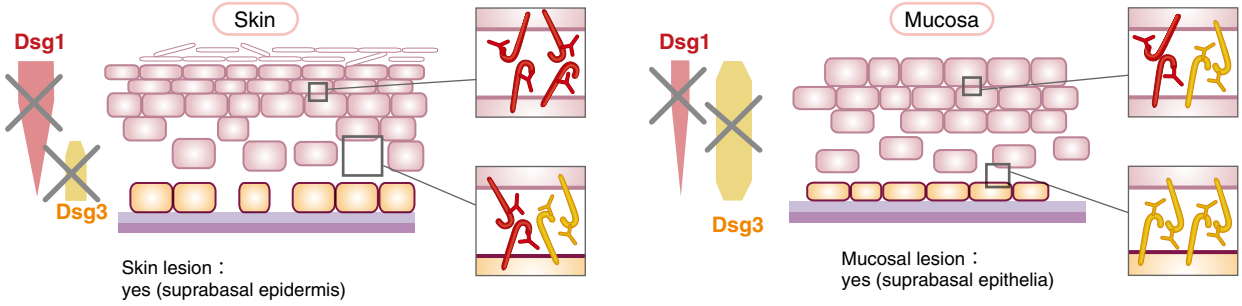
Dsg1 and Dsg3, the pemphigus target antigens, have different intraepidermal expression patterns in the skin and mucous membranes. In the skin, Dsg1 is distributed throughout the epidermis, but more strongly in the superficial layers, whereas Dsg3 is expressed in the lower part of the epidermis (basal or parabasal layers). In the mucous membranes, on the other hand, Dsg1 and Dsg3 are expressed throughout the mucous membrane, but the expression level of Dsg1 is much lower than that of Dsg3. The clinical features of pemphigus can be explained by "desmoglein compensation theory", *i.e.*, these antigens can compensate their adhesive functions when they co-expressed in the same cells [16, 17].

In cases of PV, when only anti-Dsg3 antibodies are present, the blister formations occur only in the deep layers of mucous membranes that lack the compensation by Dsg1 (mucosal-dominant type of PV). In the patients who have both anti-Dsg1 and anti-Dsg3 antibodies, the blisters are formed in mucous membranes as well as the skin (mucocutaneous type of PV). On the other hand, in cases where antibodies are present only against Dsg1, the blisters are formed only in the upper epidermis of skin, where Dsg1 is present without compensation by Dsg3 (PF) [18].

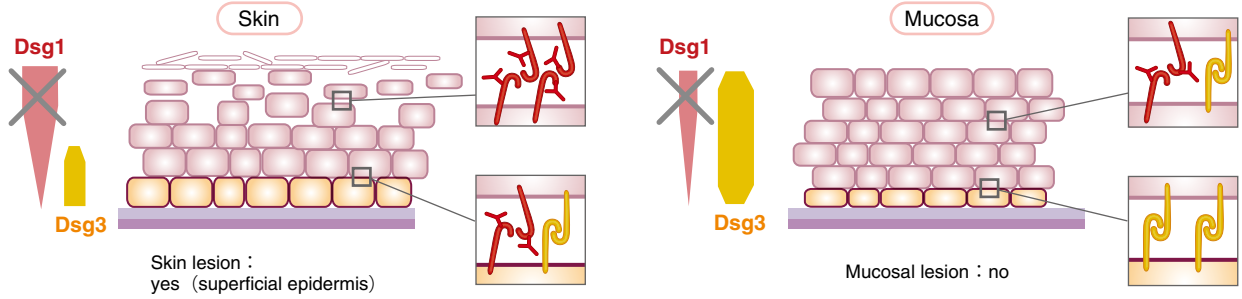
Pemphigus vulgaris (PV, Mucosal dominant type)



Pemphigus vulgaris (PV, Mucocutaneous type)



Pemphigus foliaceus (PF)



Bullous pemphigoid (BP) and anti-BP180 and anti-BP230 IgG antoantibodies

Anti-BP180 autoantibodies in patients with BP are generally considered to be pathogenic. *In vitro* studies indicate that BP IgG activates the classical complement pathway, thereby causing activation of inflammatory cells with the degranulation and resulting dermal-epidermal separation [19]. However, some reports suggested the non-inflammatory mechanism of the blister formation; anti-BP180 antibodies cause conformational changes of BP180, to reduce functional BP180 molecules [20]. The autoantibodies from most patients with BP recognize the NC16a domain, which is a non-collageneous region of BP180, located just outside the cell membrane.

In contrast, anti-BP230 antibodies may not directly cause the blister formation because it is unlikely that the antibodies can access to BP230 localized in the cytoplasm. Nevertheless, anti-BP230 antibodies are a useful diagnostic marker for BP with high specificity. Anti-BP230 antibodies are detected only in some patients with BP [21].

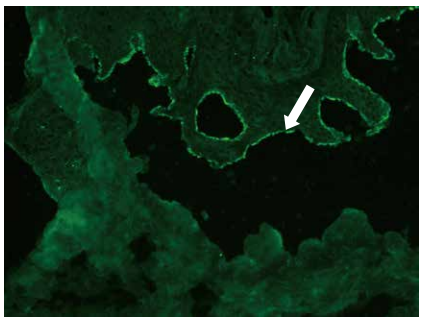
Epidermolysis bullosa acquisita (EBA) and anti-type VII collagen IgG autoantibodies

Autoantibodies against type VII collagen are associated with dysfunction of anchoring fibrils in dermal-epidermal junctions. Direct immunofluorescence staining shows IgG deposition within the sub-lamina densa of the skin. The localization of autoantibodies is distinct from the deposition in BP. To differentiate EBA from BP, salt-split skin technique (*i.e.*, skin incubated with 1 M NaCl to fracture dermal-epidermal junctions) followed by direct immunofluorescence assay is allowed to discriminate EBA from BP. The antibodies from the EBA patients are localized at the dermal side of the separation.

Type VII collagen is composed of three identical alpha-chains (290 kDa). Each chain consists of a 145-kDa non-collagen (NC1) domain, a typical collageneous domain, and a 34-kDa non-collagen (NC2) domain. Epitopes recognized by autoantibodies from EBA patients is mainly on NC1. NC2 is also considered to contain minor epitopes [22].

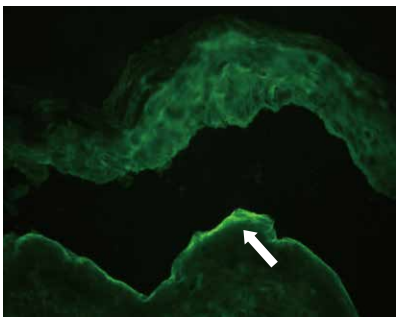
Salt-split skin immunofluorecence

BP



IgG binds to the epidermal side of the split skin (indicated by arrow).

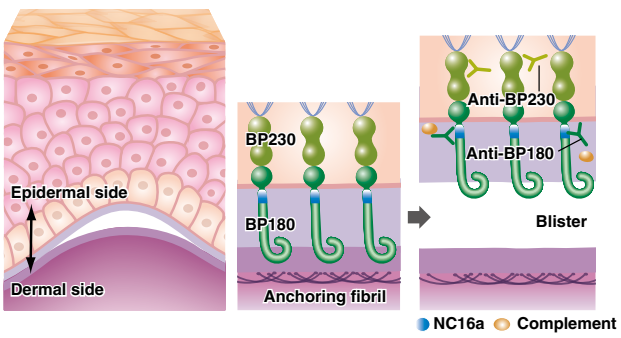
EBA



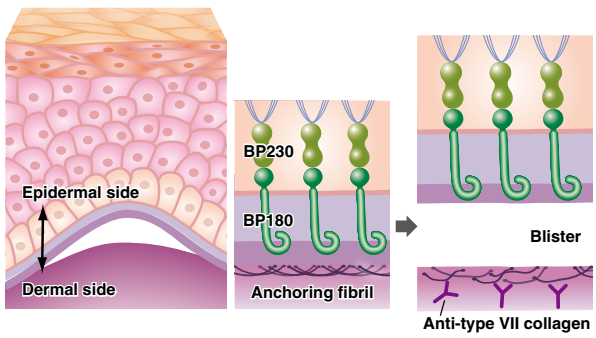
IgG binds to the dermal side of the split skin (indicated by arrow).

Sites of the skin blister formation in BP and EBA

BP



EBA

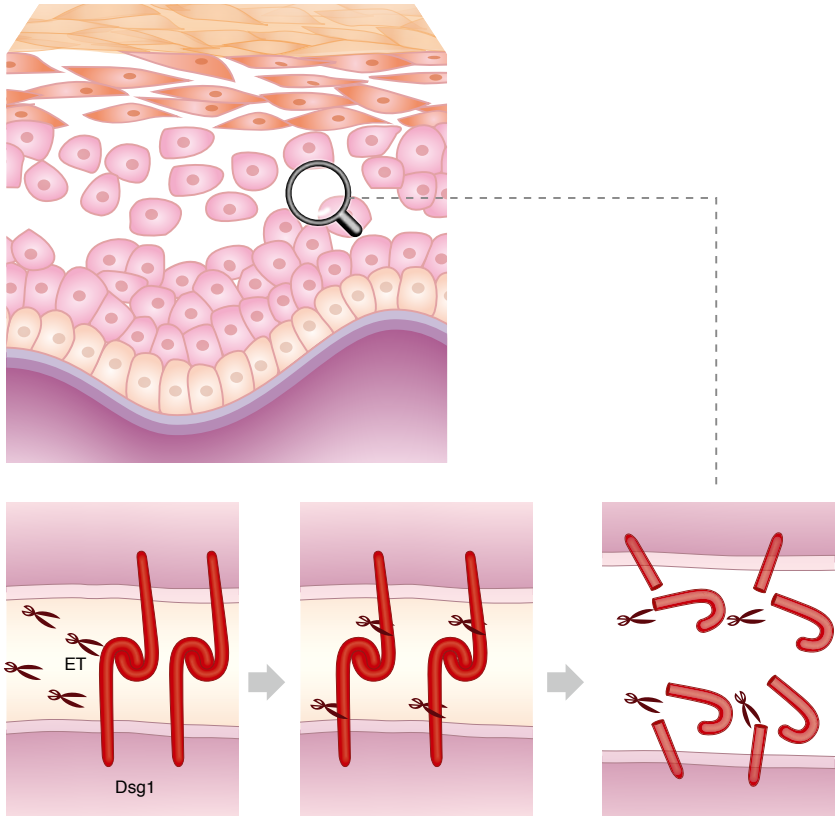


Topic

-Desmoglein 1 is a target in infectious blistering diseases-

Staphylococcal scalded skin syndrome (SSSS) and bullous impetigo are blistering diseases caused by exotoxins (exfoliative toxin, ET) produced by *Staphylococcus aureus*. SSSS is common in newborns, infants, and patients with renal failure or immunodeficiency. It is considered that ET disseminated through the blood stream causes erythema and blisters throughout body. Nikolsky's sign is also detected. In contrast, in bullous impetigo, ET produces the blisters locally at the infected area. The mechanisms of blister formation in both diseases had remained unclear until recently, although classic studies showed that ET could induce blisters in neonatal mice in 1970's.

SSSS and pemphigus foliaceus (PF) share many similar features; 1) only the skin is affected, but not the mucous membrane, 2) the blister formation occurs in the upper epidermis, 3) no necrotic keratinocytes precede the blisters, and 4) injections of ET into neonatal mice induce superficial blisters whose histology is identical to PF. In addition, various experiments indicated that several ET subtypes (exfoliative toxin A, B, and D) induced the blister formation by a cleavage of Dsg1 at Gul381 through their serine protease activity, while they do not cleave Dsg3. This reflects the histological manifestation in SSSS, of which the lesion is localized in the skin. It is clinically significant that the inactivation of Dsg1 causes superficial skin blisters in two different skin diseases, PF and SSSS [23, 24].



ET: Exfoliative toxin

ELISA for diagnosis and monitoring of autoimmune blistering diseases

Pemphigus CE IVD

ELISA for detection of anti-desmoglein 1 antibodies in human serum

MESACUP-2 TEST Desmoglein 1

ELISA for detection of anti-desmoglein 3 antibodies in human serum

MESACUP-2 TEST Desmoglein 3

Bullous pemphigoid CE IVD

ELISA for detection of anti-BP180 antibodies in human serum

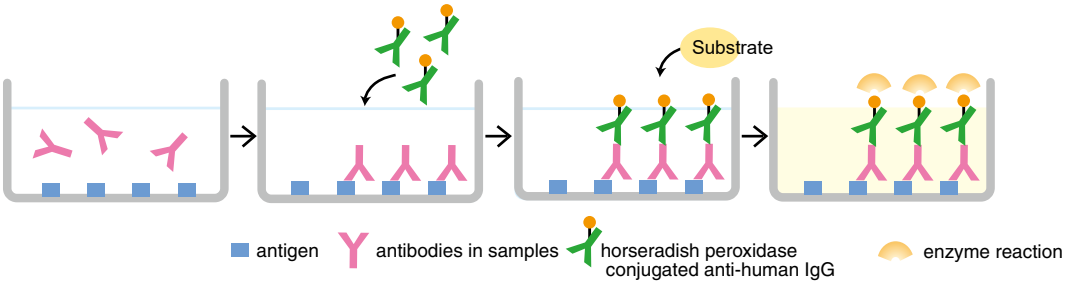
MESACUP BP180 TEST

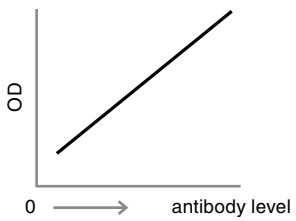
ELISA for detection of anti-BP230 antibodies in human serum

MESACUP BP230 TEST

- High sensitivity and specificity for differential diagnosis
- Objective evaluation of disease transition and progression
- Performance sufficient for monitoring disease activities
- Shared reagents and assay protocol

Principles of enzyme-linked immunosorbent assay (ELISA)-based measurement of autoantibodies





Autoantibodies in sera react with the antigen immmobilized on the surface of microtiter wells. After incubation with sera, unbound materials are washed out. Next, horseradish peroxidase (HRP)-conjugated anti-human IgG antibody is added to each well, to form immune complexes, consisting of autoantibodies, antigen and HRP-conjugated antibody. After unbound materials are washed out again, substrates for HRP are added to each well. A chromogenic reaction is allowed to proceed. The reaction is terminated by adding the stop solution. The titer of antibodies in each sample is calculated from the resulting signal read with a plate reader.

Differential diagnoses of autoimmune blistering diseases with ELISA

Differential diagnosis of pemphigus

Immunofluorescence assay could reveal differences in staining patterns between PV and PF according to the tissue distribution of Dsg1 and 3 (see page 3). However, the immunofluorescence patterns of tissues are difficult to clearly discriminate two diseases.

MESACUP-2 TEST Desmoglein 1 and MESACUP-2 TEST Desmoglein 3 are ELISA kits for measurements of anti-Dsg1 and anti-Dsg3 antibodies in serum, using the recombinant Dsg1 or Dsg3 as the solid-phase antigen. These ELISA kits provide sensitive and specific assays for the differential serological diagnosis between PV and PF on the basis of their characteristic profiles of autoantibodies [25]. The positive predictive values of anti-Dsg1 antibodies were 69% in PV (n = 39) and 100% in PF patients (n = 31). The positive predictive values of anti-Dsg3 antibodies were 100% in PV (n = 39) and none in PF (n = 31).

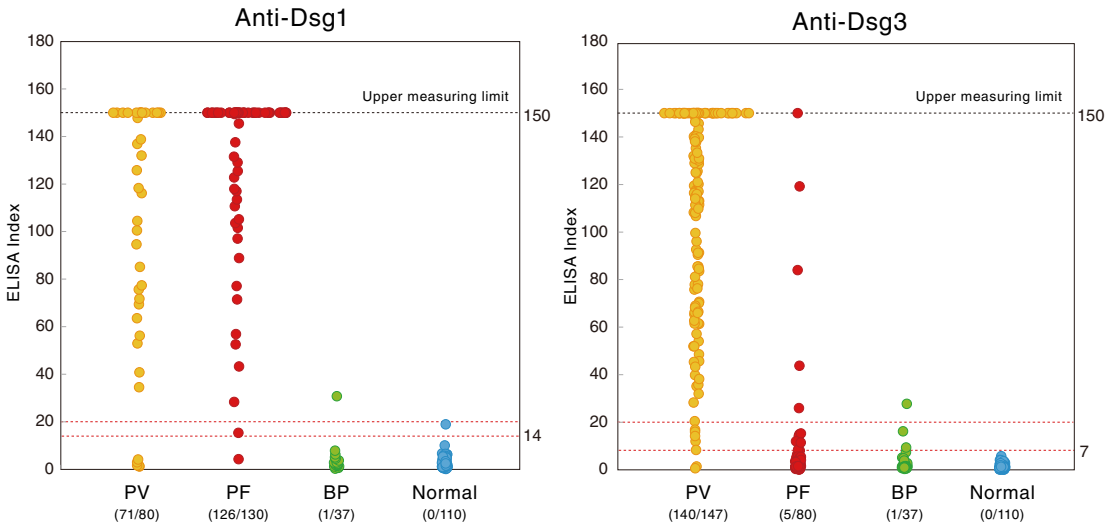
Interpretation of results with MESACUP-2 TEST Desmoglein 1 and MESACUP-2 TEST Desmoglein 3

	ELISA Index (U/mL)		
	Negative	Indeterminate	Positive
MESACUP-2 TEST Desmoglein 1 *1	< 14	14 ≤ – < 20	≥ 20
MESACUP-2 TEST Desmoglein 3 *2	< 7	7 ≤ – < 20	≥ 20

*1: Values were established by assaying 110 normal sera, sera from 130 pemphigus foliaceus (PF) patients, and sera from 117 patients with diagnoses other than PF. When results are categorized as indeterminate, it is recommended to further investigate the possible transition of diseases.

*2: Values were established by assaying 110 normal sera, sera from 147 pemphigus vulgaris (PV) patients, and sera from 117 patients with diagnoses other than PV. When results are categorized as indeterminate, it is recommended to further investigate the possible transition of diseases.

■ Presence of anti-Dsg1 and anti-Dsg3 antibodies in PV, PF, BP, and normal sera



■ Disease classification of pemphigus by anti-Dsg antibody profiling

Sensitive and specific measurements of anti-Dsg1 and anti-Dsg3 antibodies, using ELISA, can differentiate between PV and PF, because each type of pemphigus has a particular antibody profile.

Types of pemphigus	Anti-Dsg3 antibody	Anti-Dsg1 antibody
Mucosal-dominant PV	Positive	Negative
Mucocutaneous PV	Positive	Positive
PF	Negative	Positive

Differential diagnosis of BP

MESACUP BP180 TEST is an ELISA kit for measurement of anti-BP180 antibodies in human serum, using the recombinant BP180 NC16a protein as the immobilized antigen. The sensitivity of the kit is 84% (54/64) in patients with BP in the active stage.

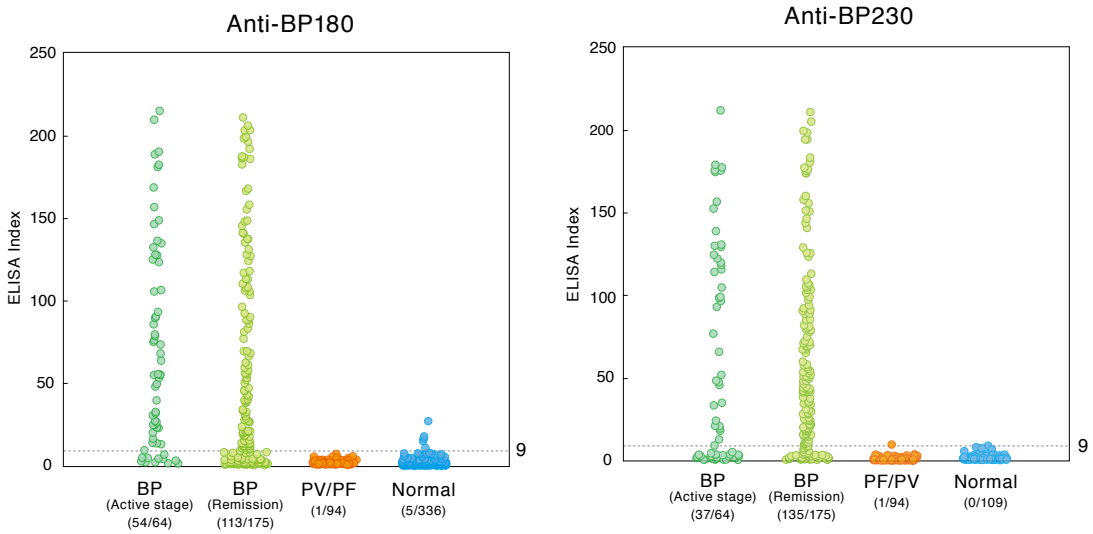
MESACUP BP230 TEST is an ELISA kit using both the recombinant *N*-terminal and *C*-terminal domains of BP230 for detection of anti-BP230 antibodies in human serum. The sensitivity is 58% (37/64) in patients diagnosed with BP in the active stage. Most significantly, higher clinical sensitivity (97%) can be achieved by combining the results of both BP180 and BP230 TEST [26].

Interpretation of results with MESACUP BP180 and MESACUP BP230

	ELISA Index (U/mL)	
	Negative	Positive
MESACUP BP180 TEST *1	< 9	≥ 9
MESACUP BP230 TEST *2	< 9	≥ 9

*1: Values were established by ROC analysis with 64 BP samples and control samples (42 PF, 69 PV and 336 normal samples).
*2: Values were established by ROC analysis with 72 BP samples and 109 normal samples.

■ Presence of anti-BP180 and anti-BP230 antibodies in BP, PV/PF, and normal sera



These data were kindly provided by Prof. T. Hashimoto (Department of Dermatology, Kurume University School of Medicine, Japan.)

■ Clinical sensitivity of anti-BP180 and anti-BP230 ELISA for BP sera

	Active stage	Remission	Total
MESACUP BP180 TEST	84% (54/64)	65% (113/175)	70% (167/239)
MESACUP BP230 TEST	58% (37/64)	78% (136/175)	72% (173/239)
MESACUP BP180 TEST + MESACUP BP230 TEST	94% (60/64)	98% (172/175)	97% (232/239)

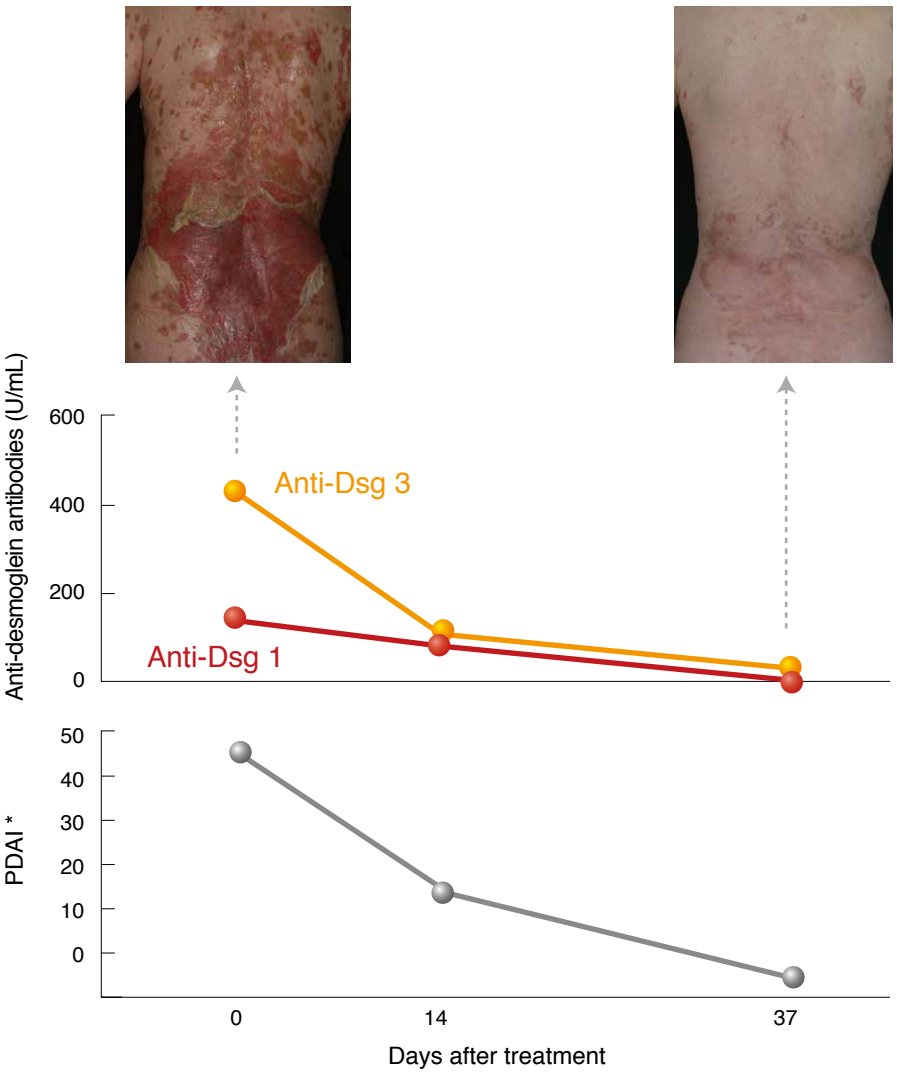
Monitoring disease activities by ELISA

ELISA is a convenient tool for monitoring disease activity in autoimmune blistering diseases.

Monitoring disease activity in mucocutaneous PV with MESACUP-2 TEST Desmoglein 1 and MESACUP-2 TEST Desmoglein 3

Clinical data using MESACUP-2 TEST Desmoglein series indicate that amounts of anti-Dsg1 and anti-Dsg3 antibodies decrease during the improvement, correlating with the improvement of cutaneous erosions. Amounts of autoantibodies also correspond to the pemphigus disease area index (PDAI).

■ **Time courses of PV disease activities and amounts of anti-desmoglein antibodies**

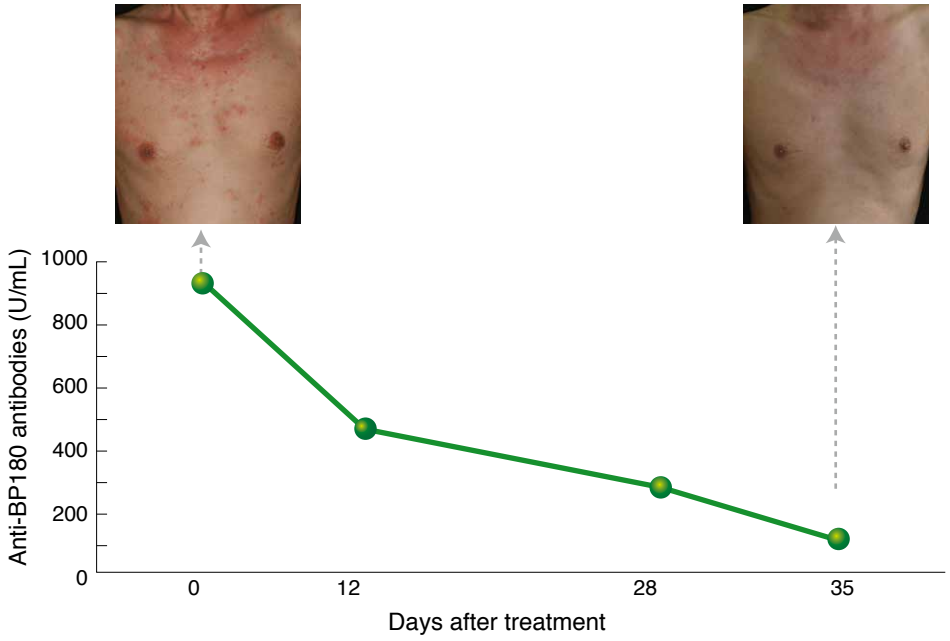


* PDAI: Pemphigus Disease Area Index

Monitoring disease activity in BP with MESACUP BP180 TEST

Clinical data using MESACUP BP180 TEST demonstrate that the disappearance of blisters correlates with decrease in the amount of anti-BP180 antibody. Additionally, in a previous report on one patient with herpes gestationis (HG), the amount of anti-BP180 antibodies was consitent with the severity of the erythema and blisters of mothers and neonates in the peripartum period [27]. These findings strongly suggest the clinical importance of periodic measurements of the autoantibodies in patients with BP.

■ Time courses of BP disease activities and the amount of anti-BP180 antibodies



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Code No.	Product	Volume	Range	Storage	Antigens	
7881E	MESACUP-2 TEST Desmoglein 1	48 wells	5–150 U/mL	2–8℃	recombinant human Dsg1	CE IVD
7886E	MESACUP-2 TEST Desmoglein 3	48 wells	5–150 U/mL	2–8℃	recombinant human Dsg3	CE IVD
7697E	MESACUP BP180 TEST	48 wells	7–150 U/mL	2–8℃	recombinant human BP180 NC16a	CE IVD
7614E	MESACUP BP230 TEST	48 wells	5–150 U/mL	2–8℃	recombinant human BP230 (NT and CT)	CE IVD

Research reagents related with bullous diseases

◎ Antibodies : Anti-Desmoglein 1, Anti-Desmoglein 2, Anti-Desmoglein 3

◎ Kit : Mouse Desmoglein 3 Antibody ELISA Kit

This product is intended for *in vitro* diagnostic use only. Classification of this product may differ from the status of approval in each country. Please read the data sheet carefully before use.
The information is as of February 2023. Please contact us for the latest information. The term of validity: From February 2023 to September 2023.

2023.02 254252-23021000PDF20230930

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