

Basic Immunology

28th lecture: Oral mucosal diseases

Zoltán Kellermayer

Oral mucosal diseases

1. Autoimmune ulcerative diseases
2. Recurrent aphthous stomatitis
3. Oral candidiasis
4. Herpes Simplex infection

Autoimmune ulcerative diseases

Mucous membrane pemphigoid



Pemphigus vulgaris



Oral epithelium

Built up of cells (mainly keratinocytes) + Basement membrane

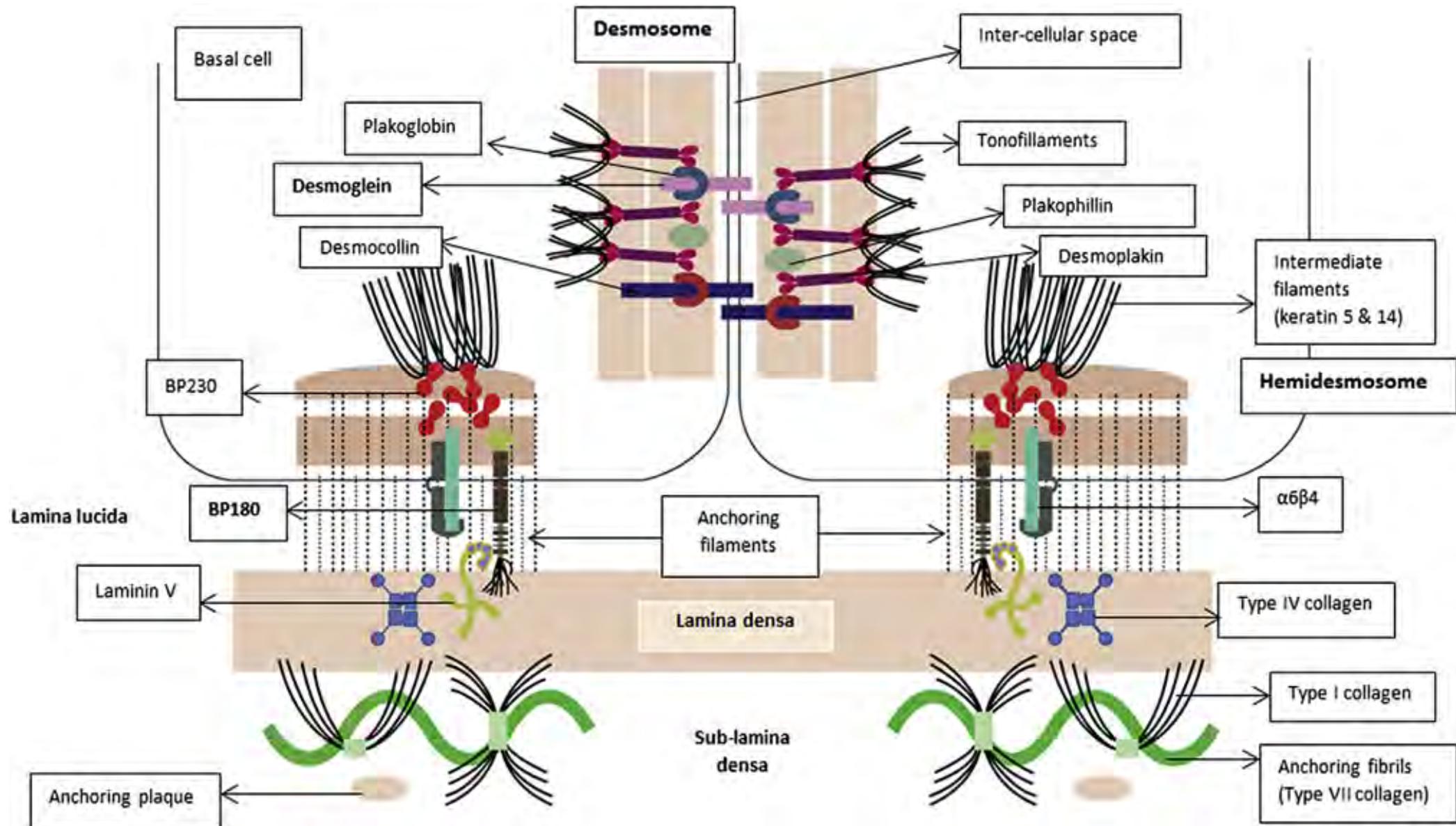
Basement membrane: connects epithelium to lamina propria

Consists of: basal cell plasma membrane + lamina lucida + lamina densa + sublamina densa

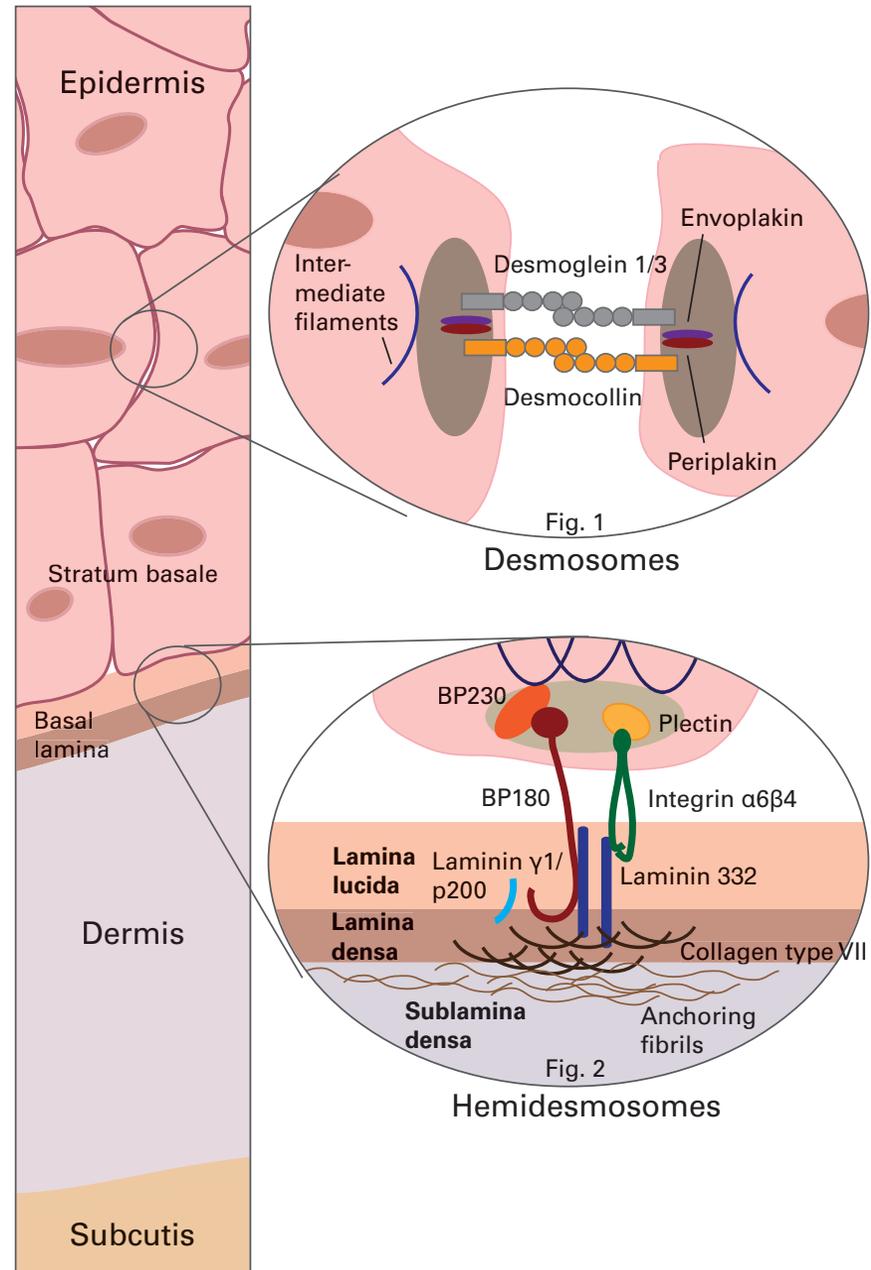
Cell – cell connections: desmosomes + gap junctions, tight junctions

Cell – Basement membrane connection: hemidesmosome

Oral epithelium



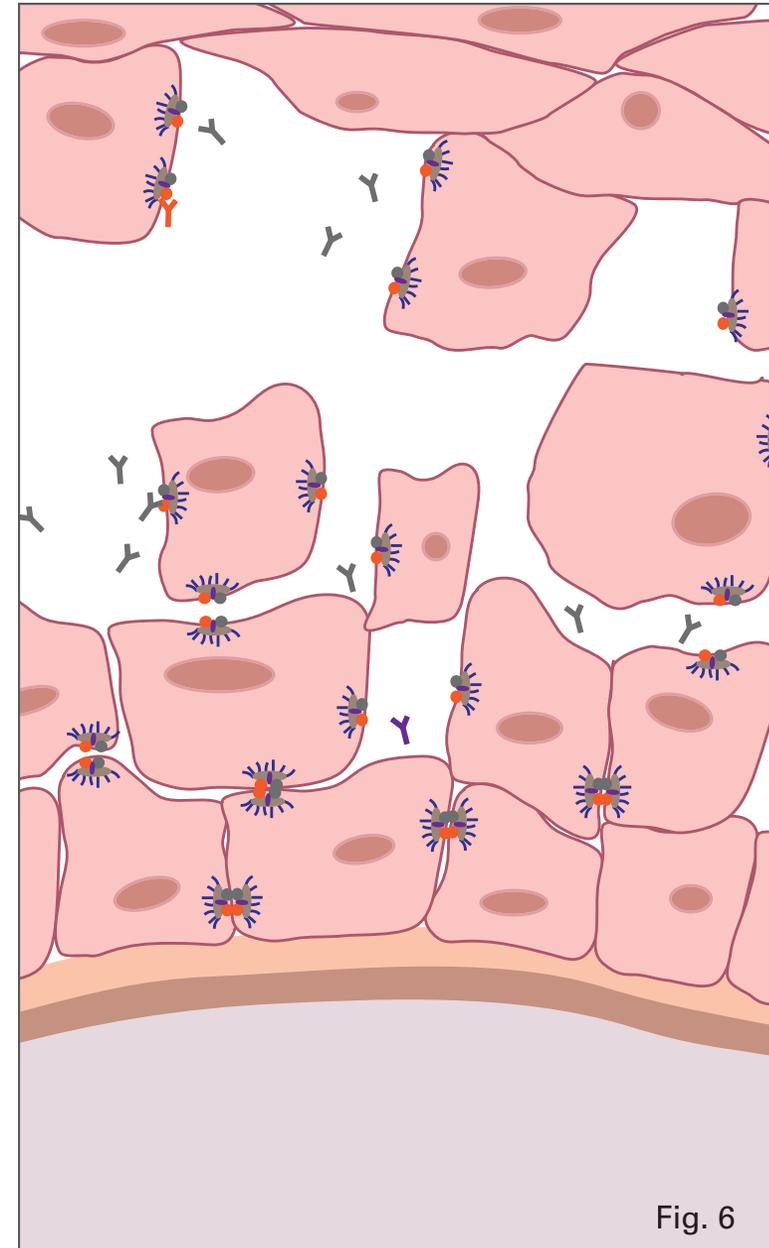
Epithelial and Basement membrane (auto)antigens



Epithelial and Basement membrane (auto)antigens

Pemphigus vulgaris

Desmoglein 3 (important in desmosome)



Epithelial and Basement membrane (auto)antigens

Mucous membrane pemphigoid

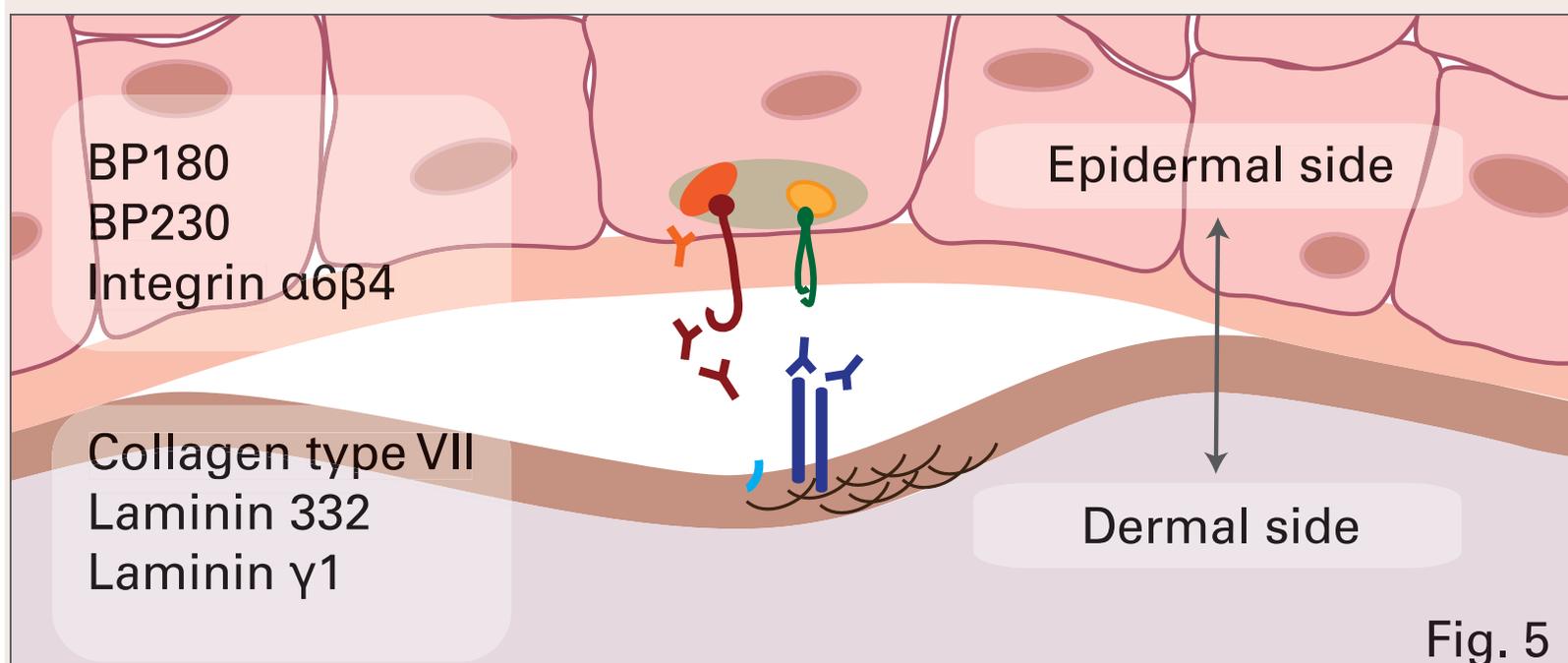
Laminins: non-collagenous glycoproteins

laminin 5, laminin 6

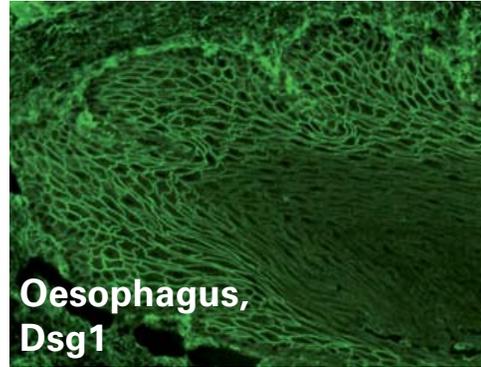
Bullous pemphigoid

BP180: transmembrane molecule

BP230 (=BPAG1, *Bullous pemphigoid antigen 1*): hemidesmosome inner plate



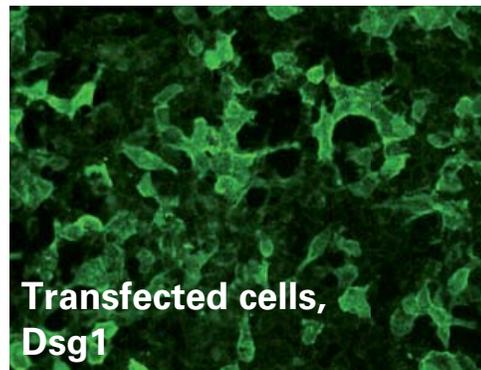
Diagnosis



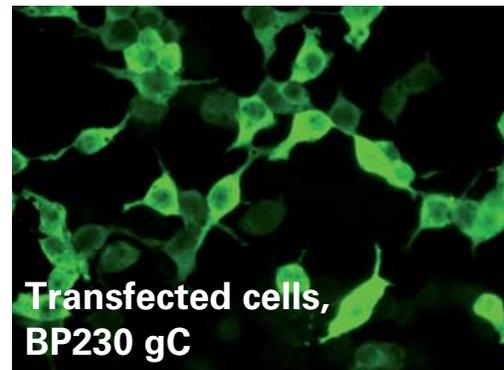
Oesophagus: detection of antibodies against **prickle-cell desmosomes** (pemphigus) and **basal lamina** (pemphigoid).



Salt-split skin: differentiation of autoantibodies against antigens of the epidermal (**BP180, BP230**) and dermal (**collagen type VII, laminin 332, p200**) sides of the skin.



Transfected cells: Monospecific detection of antibodies against **Dsg1, Dsg3** (pemphigus), **BP230 gC** (pemphigoid), and **collagen type VII** (EBA).



Recurrent aphthous stomatitis (RAS)

Characterized by oral ulcers

Heals spontaneously in 7-21 days

Prevalence: ~10%

Genetics:

~90% concordance in identical twins

Possible association with HLA-A2 and HLA-B12

Cause: ~unknown

(Definition: recurrent oral ulceration in the absence of known systemic factors...)

Hypothesis:

Unknown trigger (chemical or infective agent) → decrease in normal suppression → autoimmune response to oral mucosa



Recurrent aphthous stomatitis (RAS)

Findings:

Autoantibodies against epithelial cells (leading to cell death)

Cytotoxic T cells sensitized to oral mucosa

Trigger agent:

Possibly cross-reacting with oral mucosa

Candidate: heat-shock protein (HSP) 60kDa

Microbial HSP → stimulate mucosal Langerhans cells → generation of T-cells that recognize microbial HSP + homologous human HSP

Several other types of (non-aphthous) oral ulcers with underlying causes

(Hematological diseases, gastrointestinal enteropathies, dermatological conditions etc...)

Differential diagnosis is important!

Oral candidiasis

Candida species: present in ~40% of population

Oral candidiasis: usually with underlying causes

Immunosuppression: therapy, HIV

Other oral diseases present

Xerostomia

Main types:

Acute pseudomembranous candidiasis (very young or elderly)

Acute atrophic candidiasis (antibiotics)

Chronic atrophic candidiasis (prosthesis)

Chronic hyperplastic candidiasis (risk of malignant transformation)

Erythematous candidiasis (HIV infection)



Mucosal immune response to Candida

Innate immune response: **polymorphonuclear** cells found in biopsies

Oral candidiasis present in 40% of HIV+, 75% of AIDS patients → role of **T cells**

T_H1 : elevated IL-12, IFN γ observed in patients

T_H17 : elevated IL-17 and IL-23 associated with protection

T_H17 -deficient patients are susceptible to oral candidiasis

IgA-deficiency: increased prevalence of oral candidiasis → role of **B cells**

Secreted aspartyl protease 2 (SAP2): important Candida antigen

Immunization against SAP2 → secretory IgA-type antibodies → protection in mouse model

Herpes simplex

Usually caused by Herpes simplex virus 1 (HSV1)

Prevalence: 58% between ages 14-49

Primary infection: *herpetic gingivostomatitis*

Children or young adults

Pathogenesis: lytic replication of the virus in epithelial cells → lysis of keratinocytes

Immune response: inflammation + adaptive (neutralizing antibodies + CD8+ T_C)

Self-limiting in immunocompetent patients

Characteristic clinical appearance: ulceration of oral mucosa + malaise, fever

Therapy: acyclovir only at beginning of infection + symptomatic treatment



Herpes simplex

HSV1: Rapid transmission to peripheral sensory nerve fibers of n. trigeminus

Retrograde transport of the virus to trigeminal ganglion

Before appearance of neutralizing antibodies!!

Stays latent for years

Reactivation: in 15-40% of seropositive patients; appears as herpes simplex labialis

Trigger factors: UV, stress, illness, immunocompromised conditions

Recurrence: usually in same spot

Herpes simplex labialis

Virus migration from neural cell body to periphery

infects and replicates within keratinocytes

keratinocyte death → inflammation → papule formation → vesicle formation

Resolve spontaneously in 7-10 days

appearance of neutralizing antibodies

T_H: produce IFN γ and IL-12

T_C: cytotoxicity (keratinocyte lysis!)