Basic Immunology

26th lecture:
Oral mucosal diseases

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Oral mucosal diseases

1. Autoimmune ulcerative diseases

2. Recurrent aphthous stomatitis

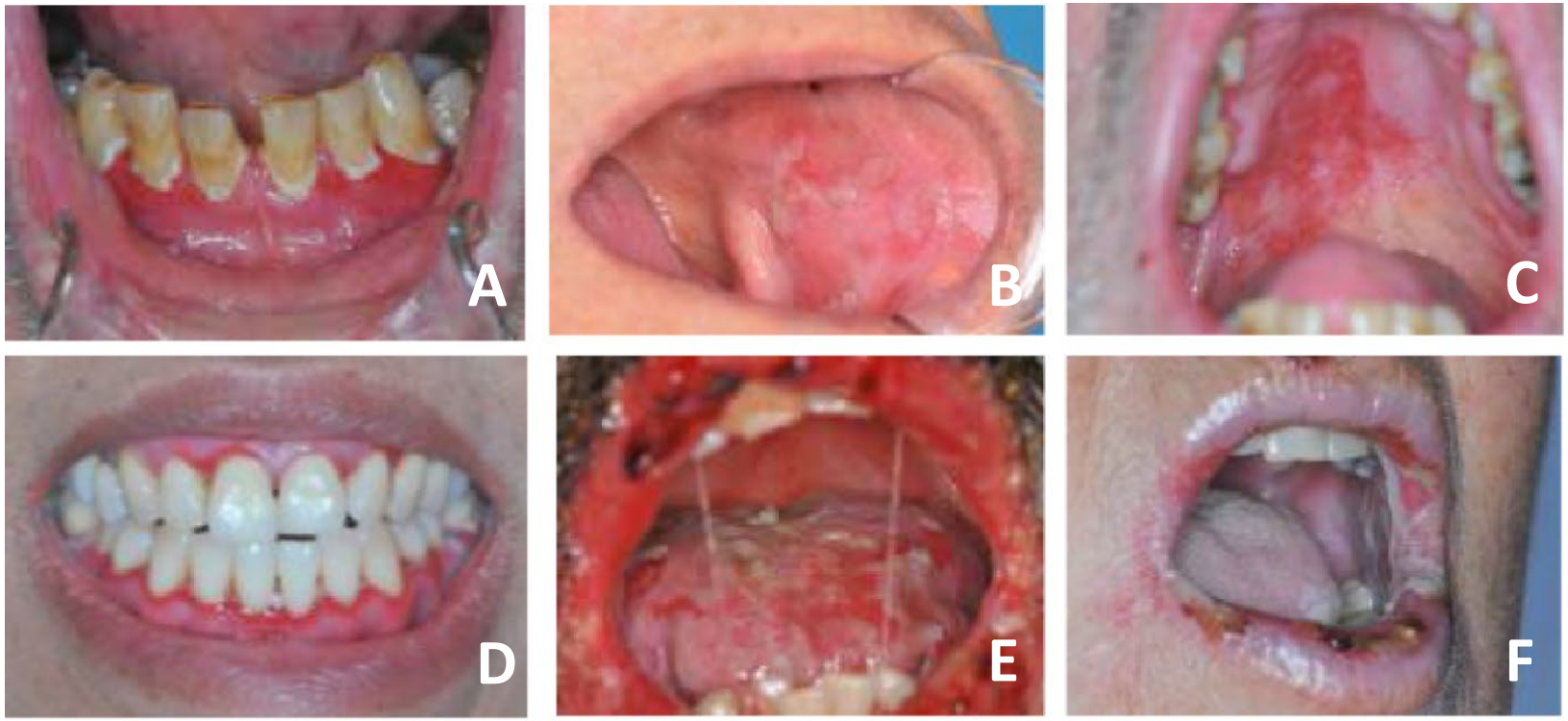
3. Oral candidiasis

4. Herpes Simplex infection

Autoimmune ulcerative diseases

Mucous membrane pemphigoid

Pemphigus vulgaris



Rashid H et al. 2019. American Journal of Clinical Dermatology

Oral epithelium

Built up of cells (mainly keratinocytes) + Basement membrane

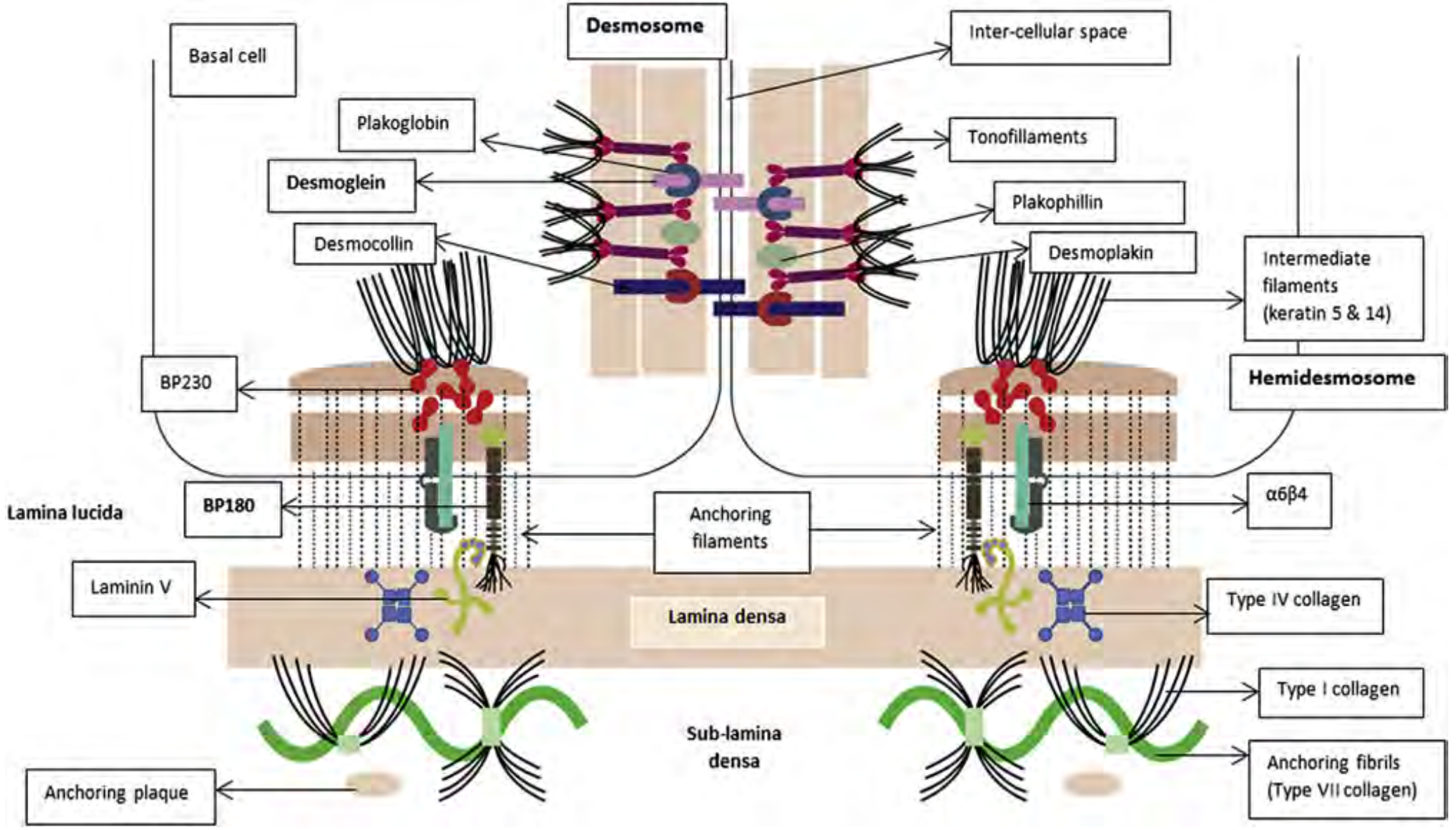
Basement membrane: connects epithelium to lamina propria

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

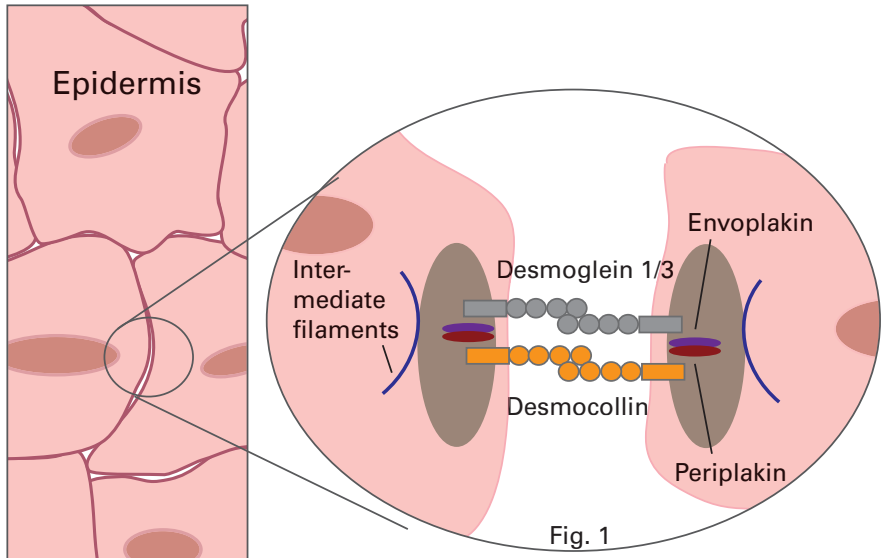


Fig. 1
Desmosomes

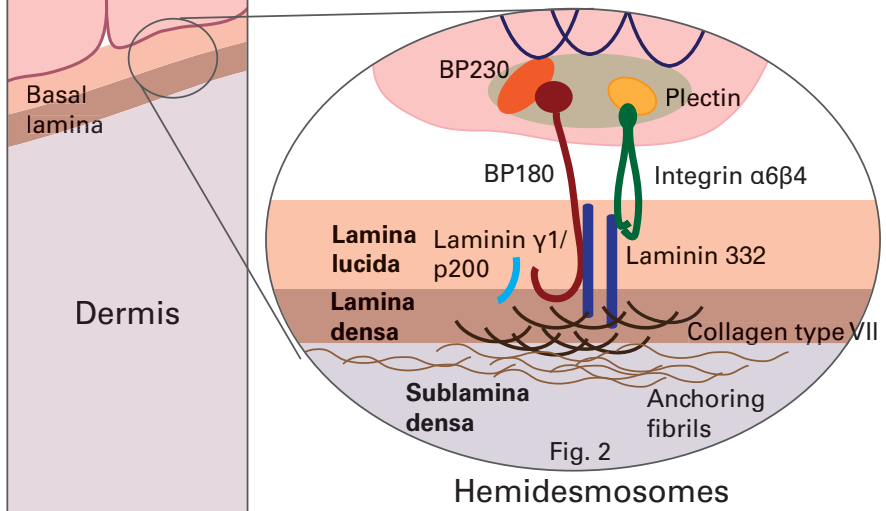


Fig. 2
Hemidesmosomes

Epithelial and Basement membrane (auto)antigens

Pemphigus vulgaris

Desmoglein 3 (important in desmosome)

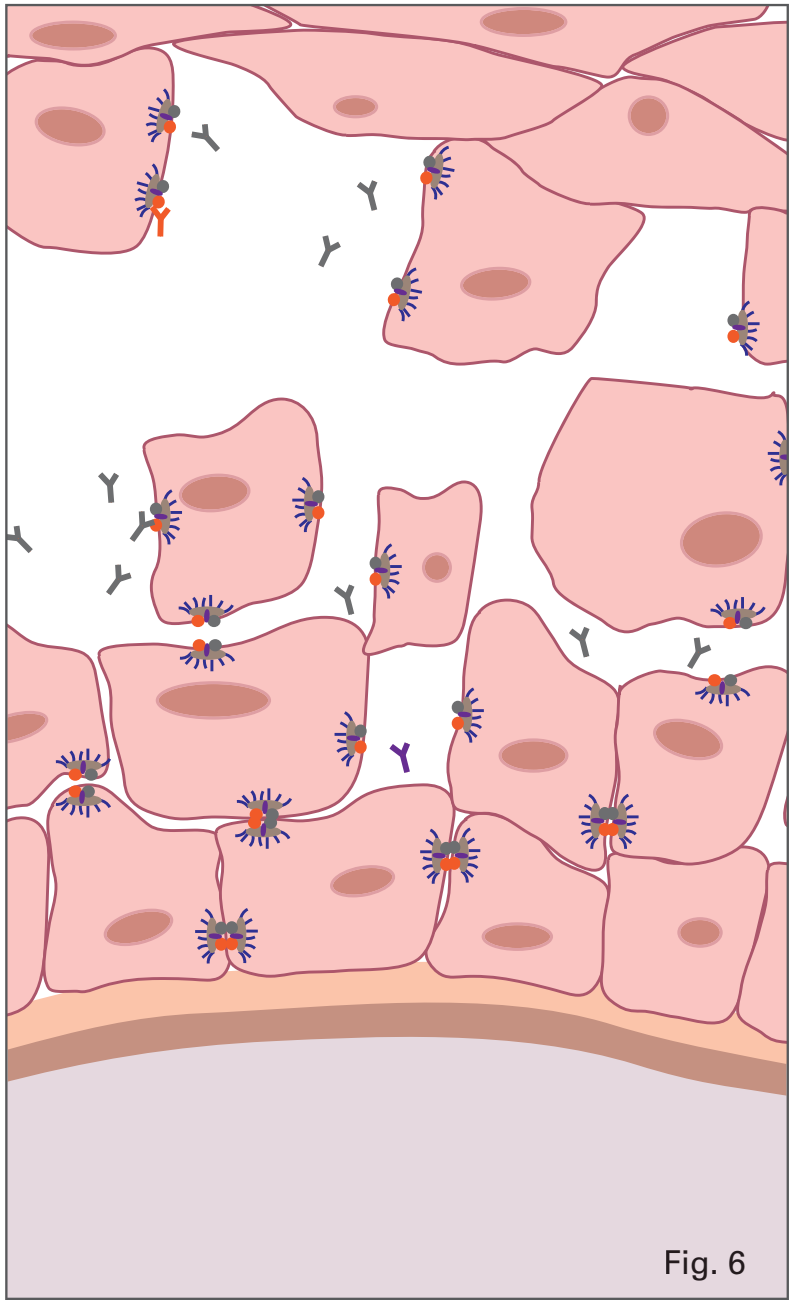


Fig. 6

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

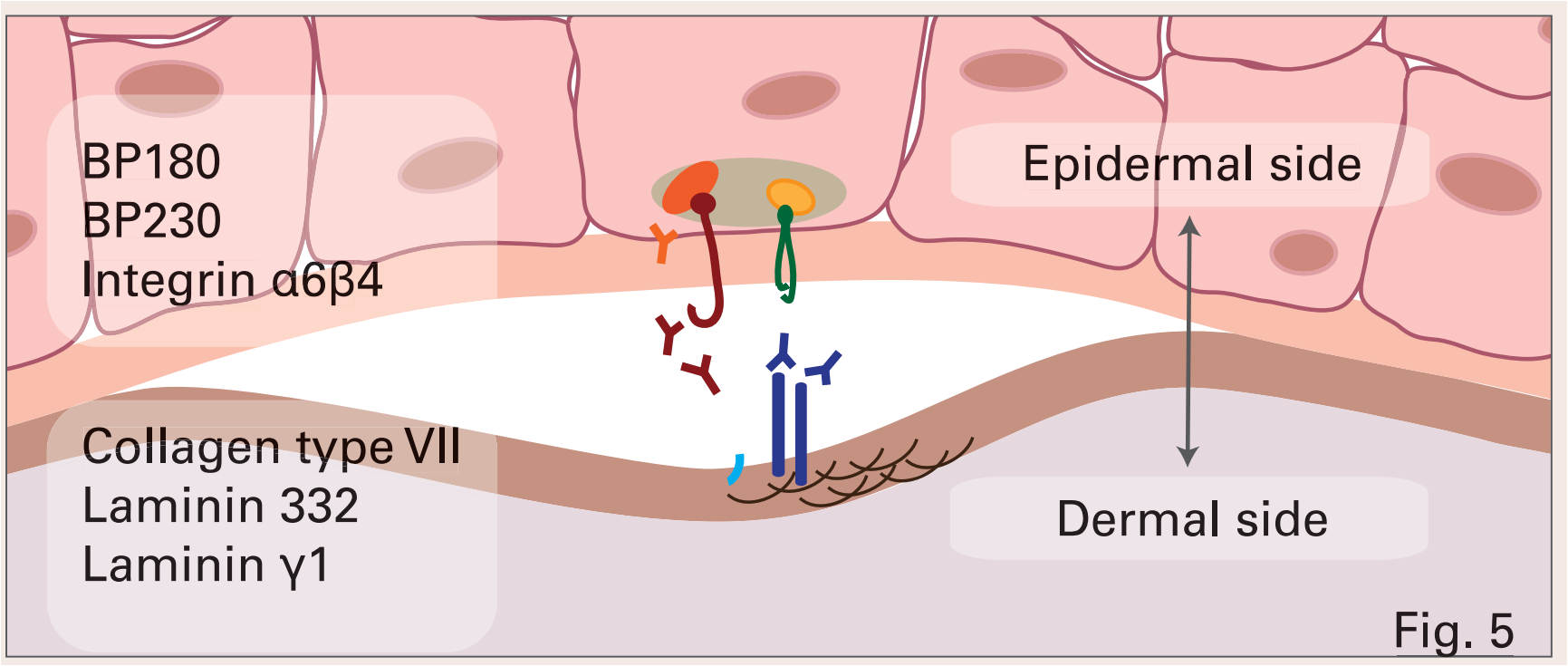
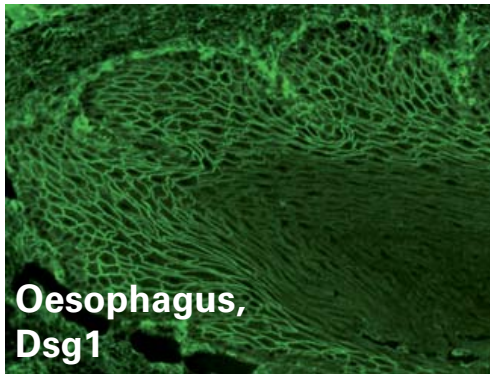


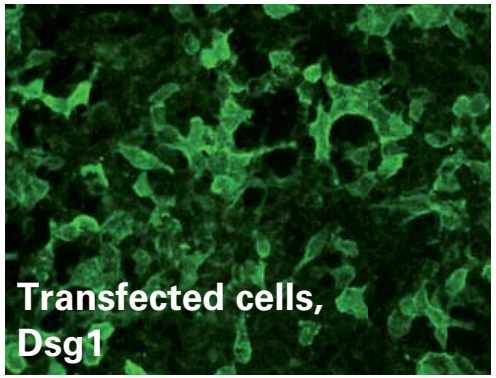
Fig. 5

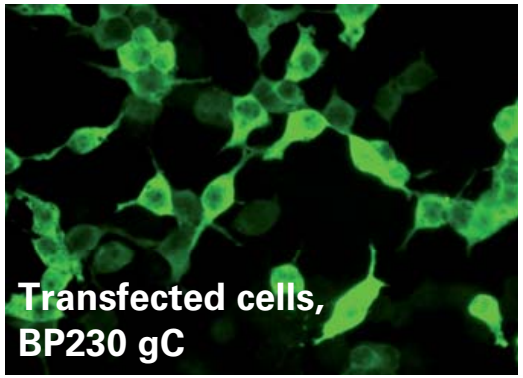
Diagnosis



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

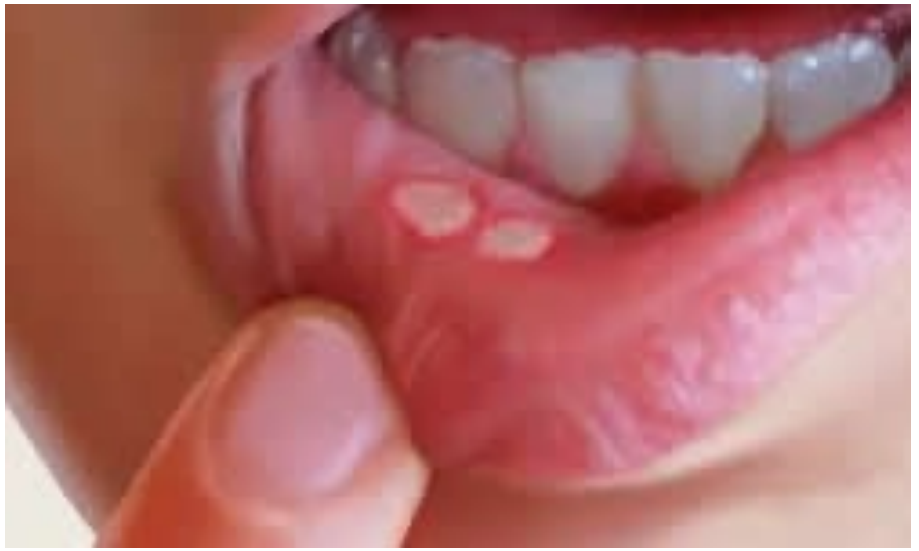
Salt-split skin: differentiation of autoantibodies against antigens of the epidermal (**BP180, BP230**) and dermal (**collagen type VII, laminin 332, p200**) sides of the skin.





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…)*

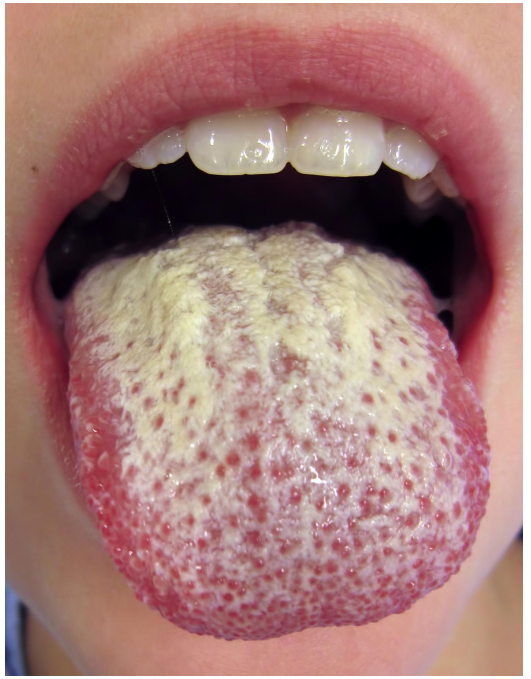
Differential diagnosis is important!

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, IFNγ observed in patients

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

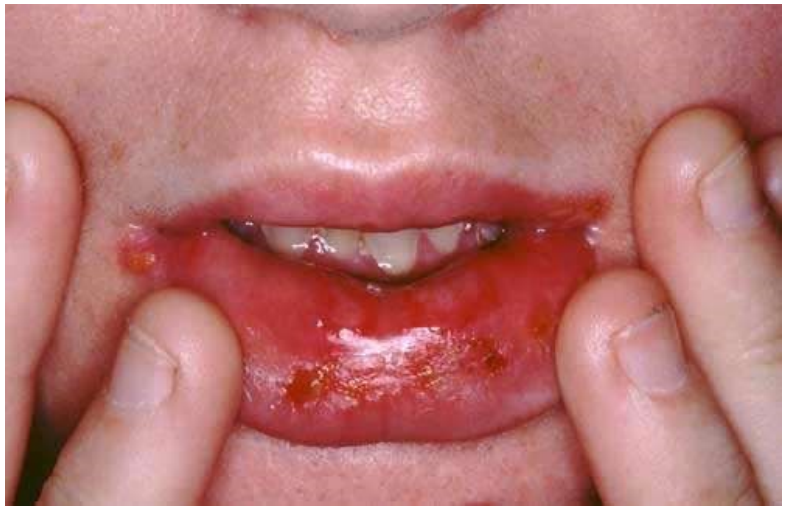
T_H17-deficient patients are susceptible to oral candidiasis

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

Secreted aspartyl protease 2 (SAP2): important Candida antigen

Immunization agatinst 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 simples 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 IFNγ and IL-12
- T_C: cytotoxicity (keratinocyte lysis!)