PRIMEVIEW

PEMPHIGUS

nature REVIEWS DISEASE PRIMERS

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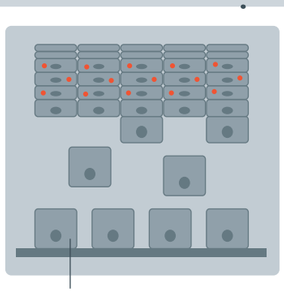
Pemphigus is a group of autoimmune disorders characterized by blisters and erosions in stratified squamous epithelia, such as the skin and oral mucosa. The three most common types are pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus.

DIAGNOSIS

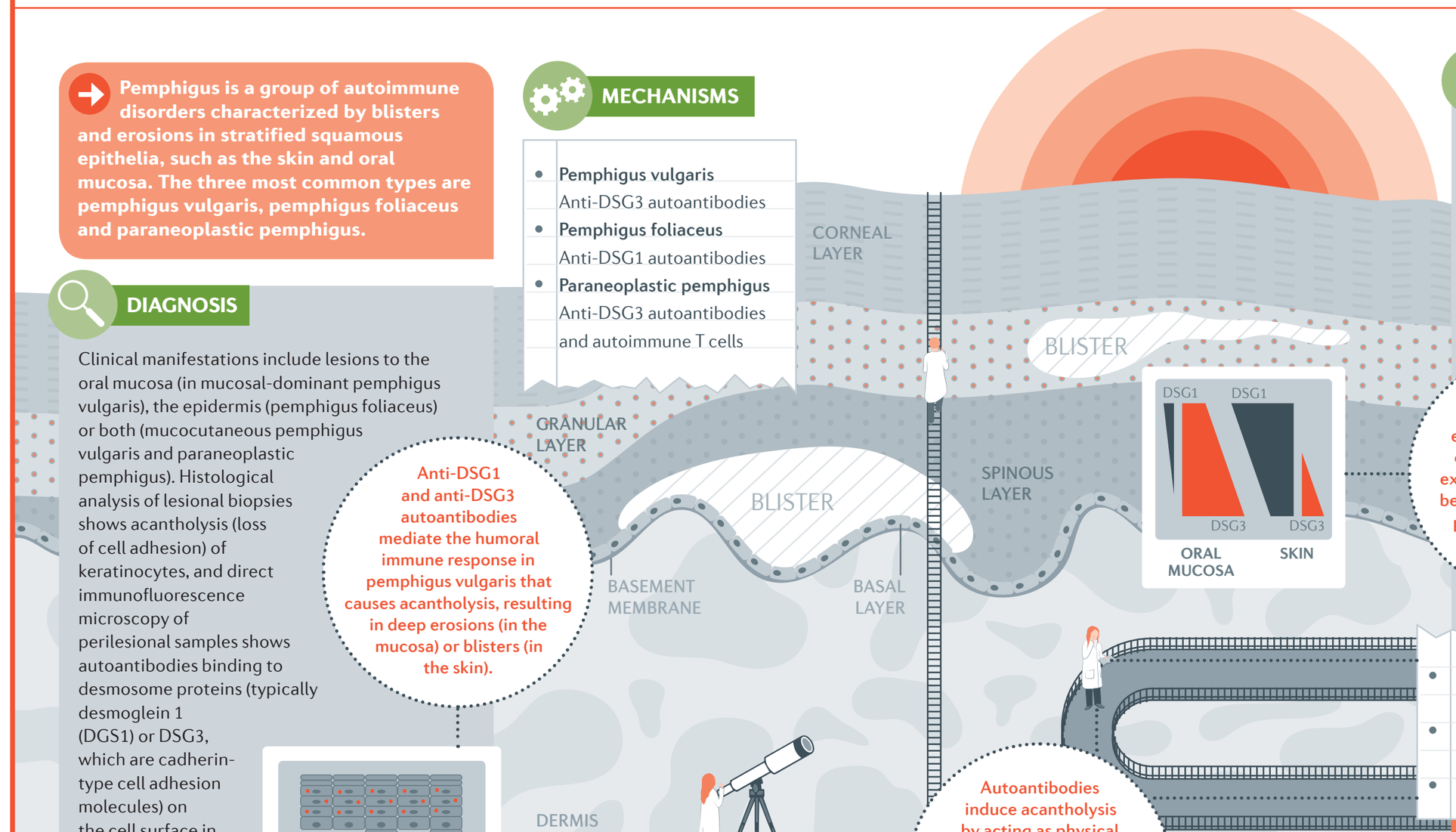
Clinical manifestations include lesions to the oral mucosa (in mucosal-dominant pemphigus vulgaris), the epidermis (pemphigus foliaceus) or both (mucocutaneous pemphigus vulgaris and paraneoplastic pemphigus). Histological analysis of lesional biopsies shows acantholysis (loss of cell adhesion) of keratinocytes, and direct immunofluorescence microscopy of perilesional samples shows autoantibodies binding to desmosome proteins (typically desmoglein 1 (DGS1) or DSG3, which are cadherin-type cell adhesion molecules) on the cell surface in a characteristic honeycomb pattern. Serological tests can be used to identify and quantify specific autoantibodies.



Some alleles of the HLA locus have been associated with an increased susceptibility to pemphigus.

MECHANISMS

- **Pemphigus vulgaris**
  Anti-DSG3 autoantibodies
- **Pemphigus foliaceus**
  Anti-DSG1 autoantibodies
- **Paraneoplastic pemphigus**
  Anti-DSG3 autoantibodies and autoimmune T cells



Anti-DSG1 and anti-DSG3 autoantibodies mediate the humoral immune response in pemphigus vulgaris that causes acantholysis, resulting in deep erosions (in the mucosa) or blisters (in the skin).

The tissue-specific expression patterns of desmogleins can explain the correlation between autoantibody profiles and clinical phenotypes.

Autoantibodies induce acantholysis by acting as physical obstacles to intercellular adhesion (steric hindrance) or by promoting desmoglein degradation and interfering with desmosome assembly.

EPIDEMIOLOGY

Global prevalence varies according to the subtypes: pemphigus vulgaris is most common in Europe, the United States and Japan, whereas pemphigus foliaceus is most frequently observed in South America and North Africa. Incidence of pemphigus vulgaris ranges from <1 to 50 cases per million individuals in different populations. Only ~300 cases of paraneoplastic pemphigus have been reported.

QUALITY OF LIFE

Pemphigus is associated with substantial morbidity and mortality and has detrimental effects on quality of life owing to its unpredictable, variable and potentially life-threatening course. Possible comorbidities are other autoimmune diseases (such as thyroid diseases and rheumatoid arthritis) and corticosteroid-related adverse outcomes.

MANAGEMENT

Treatment aims at improving symptoms by reducing the levels of circulating autoantibodies, by directly targeting the autoantibodies or by general immunosuppression. Systemic corticosteroids are the first-line therapy, owing to their rapid efficacy. Adjunctive therapies include steroid-sparing agents and biological agents, such as rituximab, a monoclonal anti-CD20 antibody that targets B cells. Intravenous immunoglobulin therapy has the advantage that it is not immunosuppressive, although it carries other risks, such as thrombotic complications. Plasmapheresis and immunoadsorption can be effective in cases of treatment-refractory pemphigus.

OUTLOOK

Pemphigus is a well-characterized human autoimmune disease. Animal models and samples from patients are useful biological tools to investigate the mechanisms of antigen-specific tolerance and epithelial cell adhesion, which in turn can lead to novel strategies for adjunctive therapy in pemphigus. Current approaches include the generation of chimeric autoantibody receptor T cells, which specifically recognize and kill B cells that produce autoantibodies, and the development of novel anti-B cell monoclonal antibodies.

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