WHY DO AUTOIMMUNE DISEASES HAPPEN?

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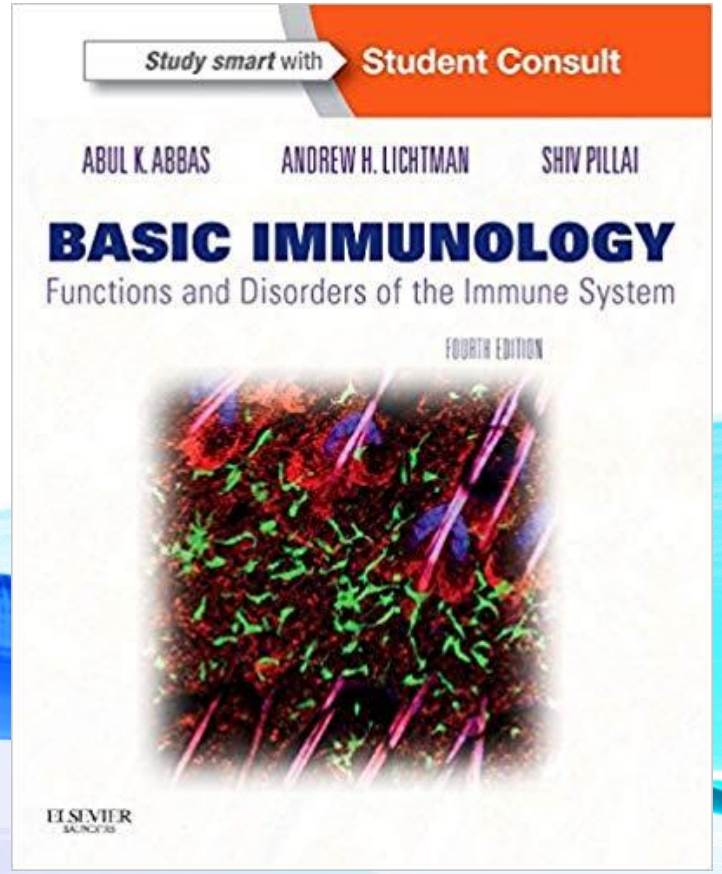
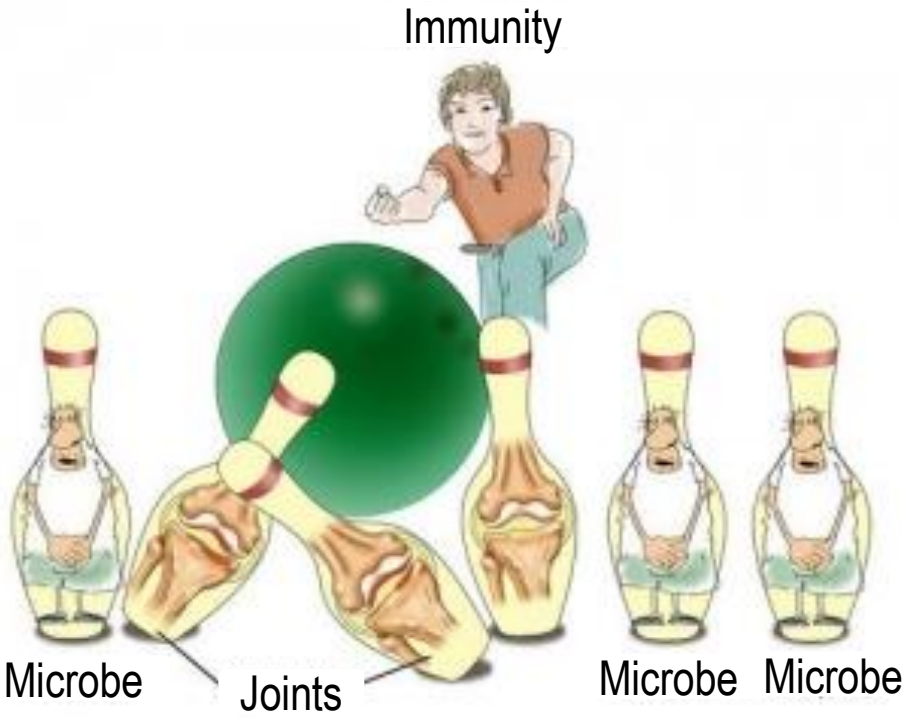


WHAT IS AUTOIMMUNITY?

- Impaired tolerance to self antigens, which leads to the activation of autoreactive T and / or B lymphocytes and the development of autoimmune pathologies
  - Multifactorial process.



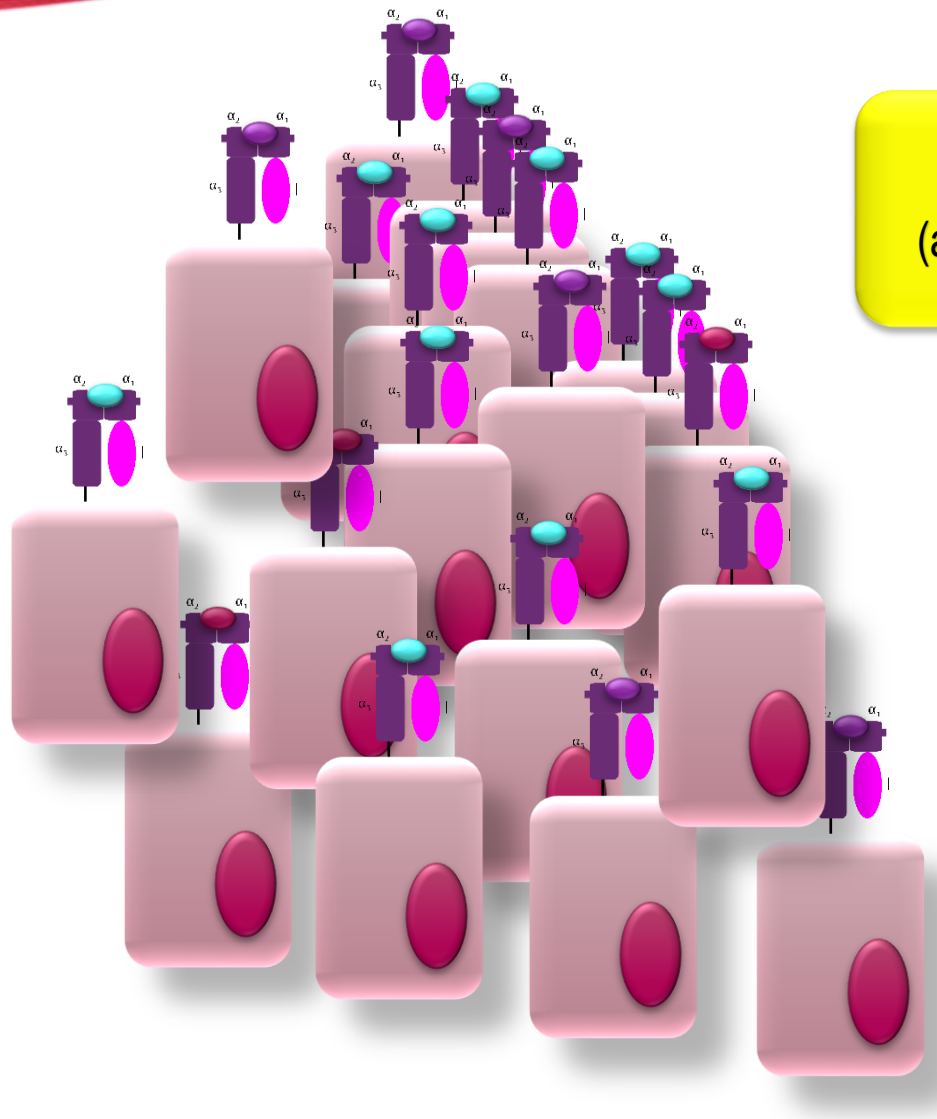
IMMUNOLOGICAL TOLERANCE

- State of unresponsiveness of the immune system to particular antigens.
  - It arises as a result of a special “acquaintance” of lymphocytes with these antigens and the selection and survival only those lymphocytes that are tolerant to self-antigens.

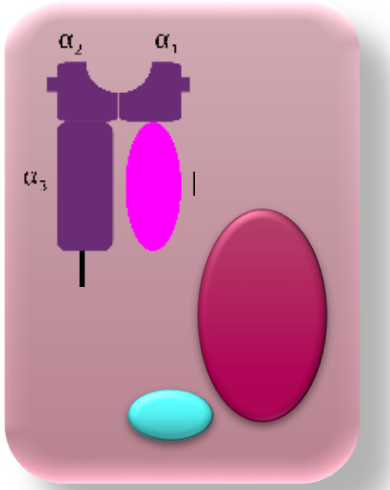
WHAT SHOULD LYMPHOCYTES RECOGNIZE?

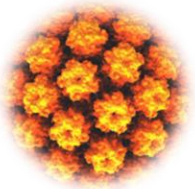
- Molecules of the main histocompatibility complex
- Antigen

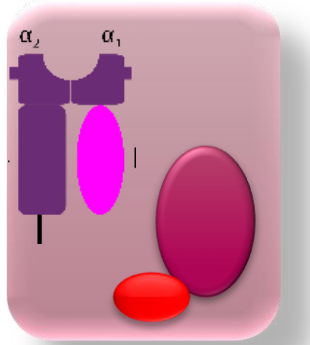
MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)



MHC class I
(all nucleated cells)

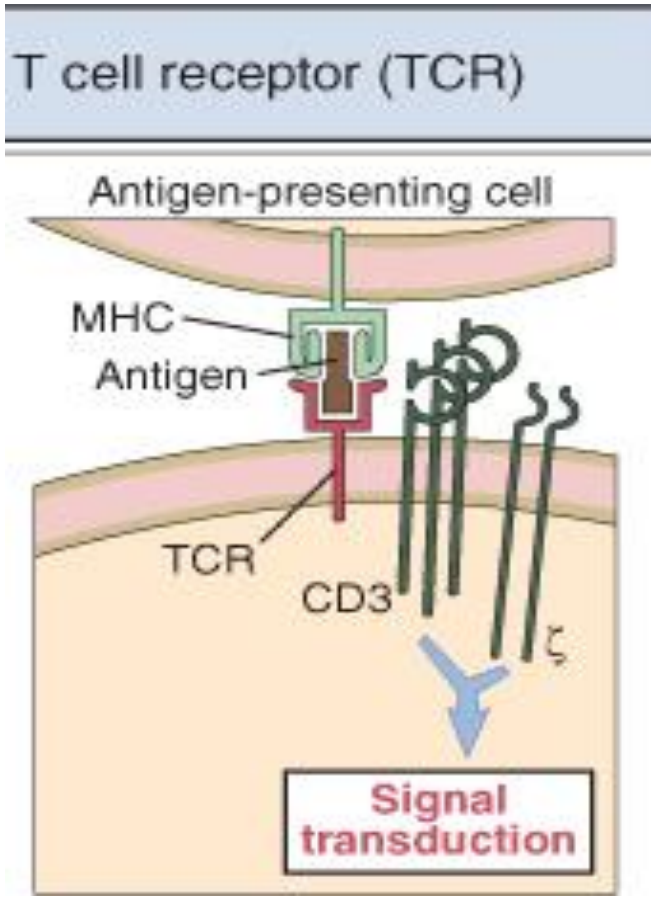




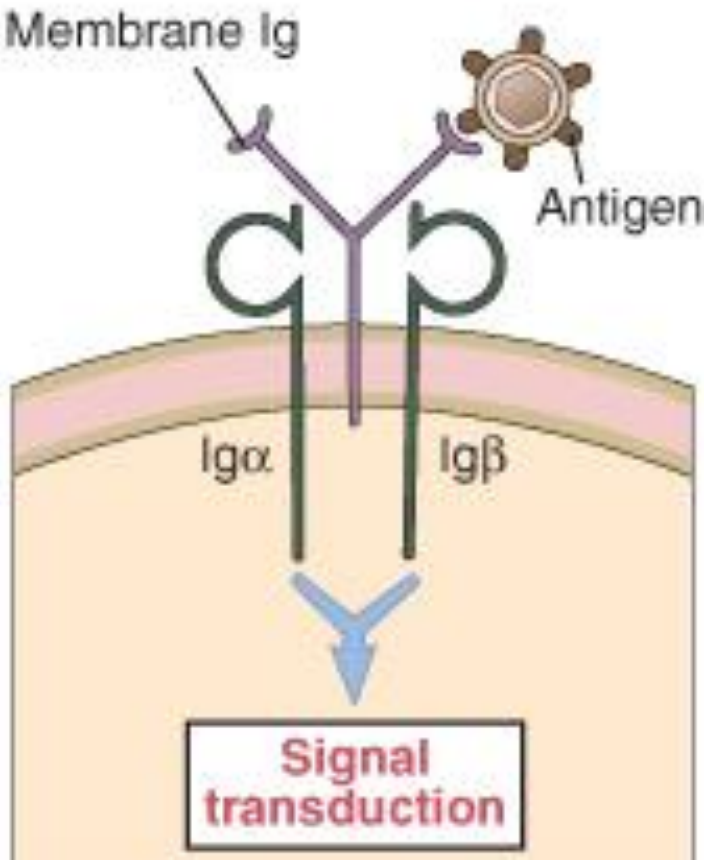


LYMPHOCYTE RECEPTORS

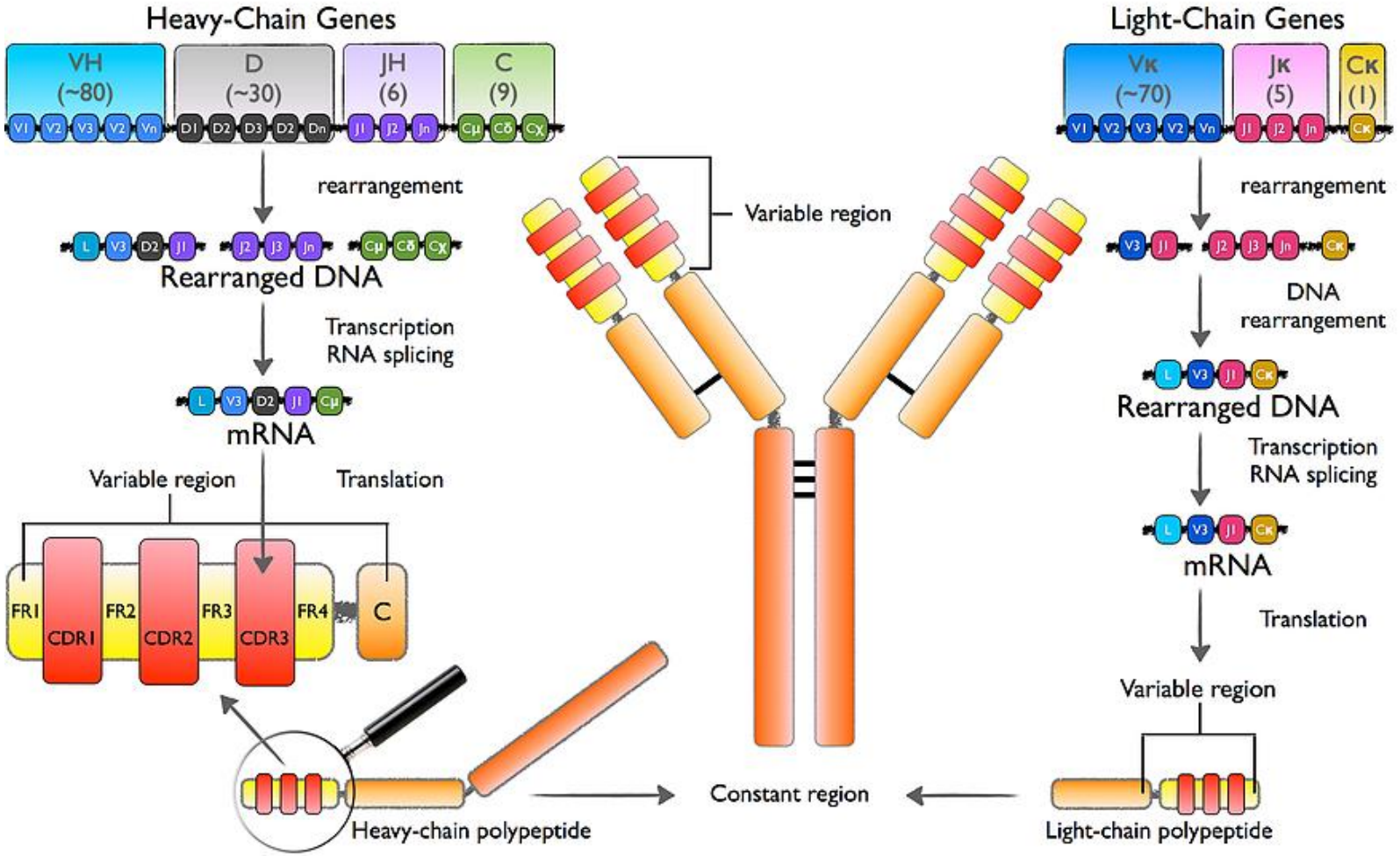
T-lymphocyte



B-lymphocyte



HOW IS THE DIVERSITY OF LYMPHOCYTE RECEPTORS FORMED?



LYMPHOCYTE SELECTION

- All lymphocytes are originated from the bone marrow.
- Maturation and differentiation of lymphocytes occurs in the bone marrow (B lymphocytes) and thymus (T lymphocytes)
- Huge variety of lymphocyte receptors
- Lymphocyte selection:
  - Positive: only lymphocytes that recognize self-MHC survive
  - Negative: removal of lymphocytes that are activated by the recognition of self-peptides.

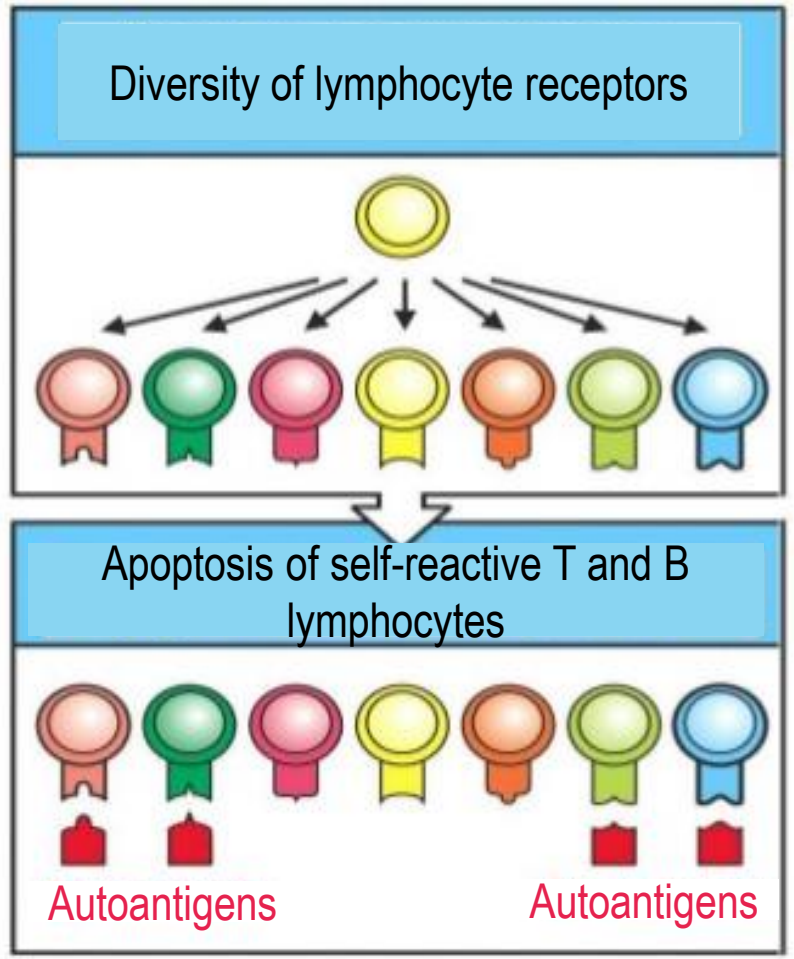


Figure 1-14 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

TOLERANCE

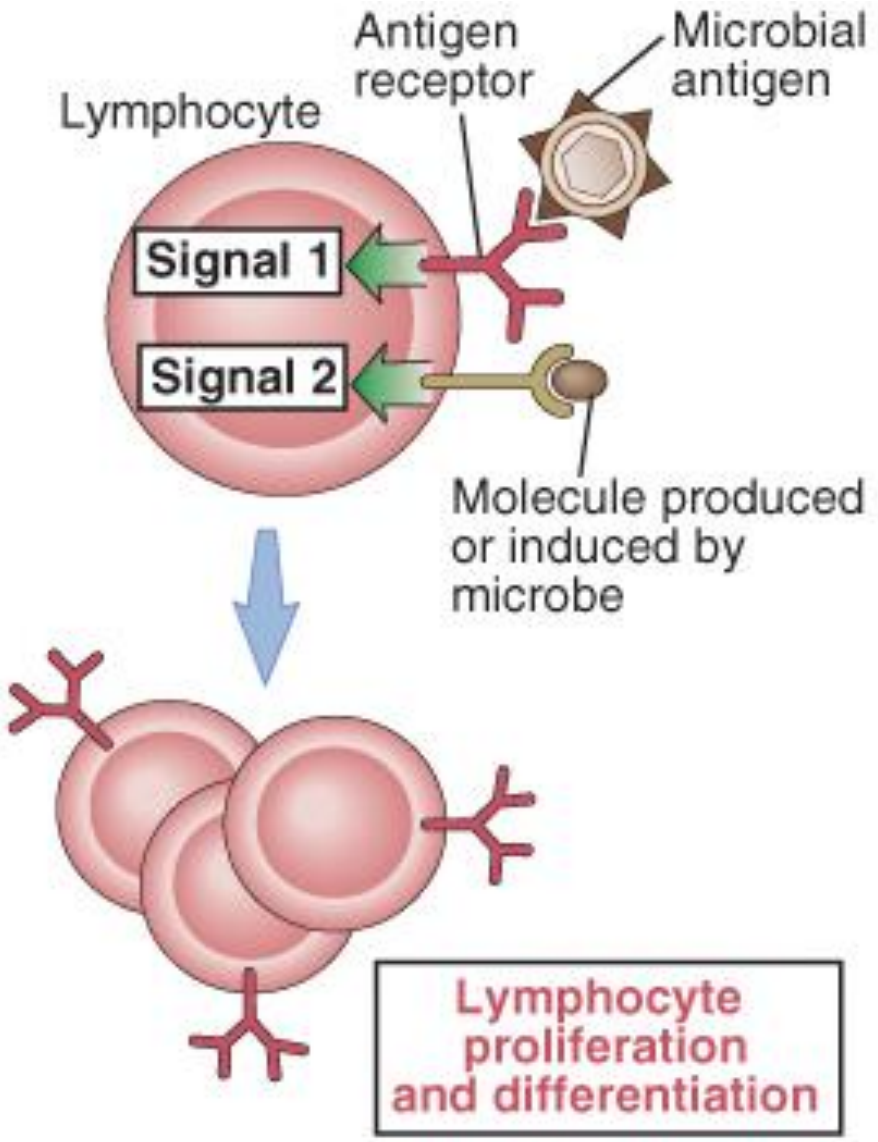
Central

- Lymphocyte selection during their formation and maturation
  - Not all of the autoantigens can be presented in the central immune system organs
- Development of T-regulatory cell (suppressors), which also recognize autoantigens

Peripheral

- Absence of second signal (co-stimulation) after antigen recognition

LYMPHOCYTES, ANTIGEN RECOGNITION



Second signal (co-stimulation)

- Microbial proteins
- Microbe-induced derivates of natural immune cells (macrophages) (B7, cytokines)
- Complement component C3d, attached to the microbe
- T-cell cytokine for B-lymphocyte.

TOLERANCE

Central

- Lymphocyte selection during their formation and maturation
  - Not all of the autoantigens can be presented in the central immune system organs
- Development of T-regulatory cell (suppressors), which also recognize autoantigens

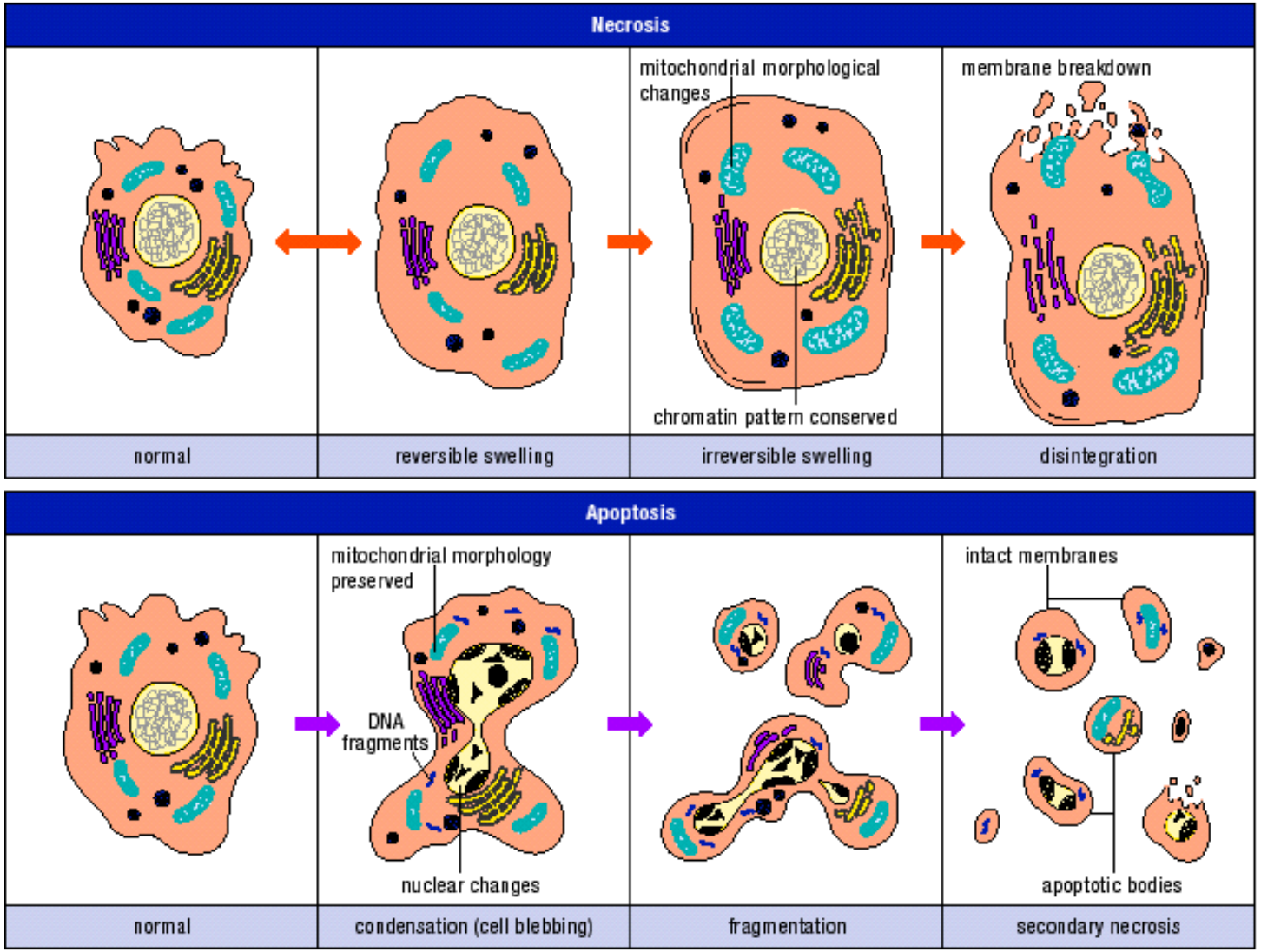
Peripheral

- Absence of second signal (co-stimulation) after antigen recognition - anergy
- The action of T-regulatory cells suppressing lymphocytes in the tissues
- Apoptosis of lymphocyte which recognize self-antigens in tissue – caspase activation
- Physiological separation of autoantigens from lymphocytes:
  - Follicles, testicles, eyes, placenta and fetus, brain.

AUTOIMMUNITY MECHANISMS (1)

- Overexpression of certain autoantigens
  - Violation of the apoptosis mechanism

APOPTOSIS VS. NECROSIS

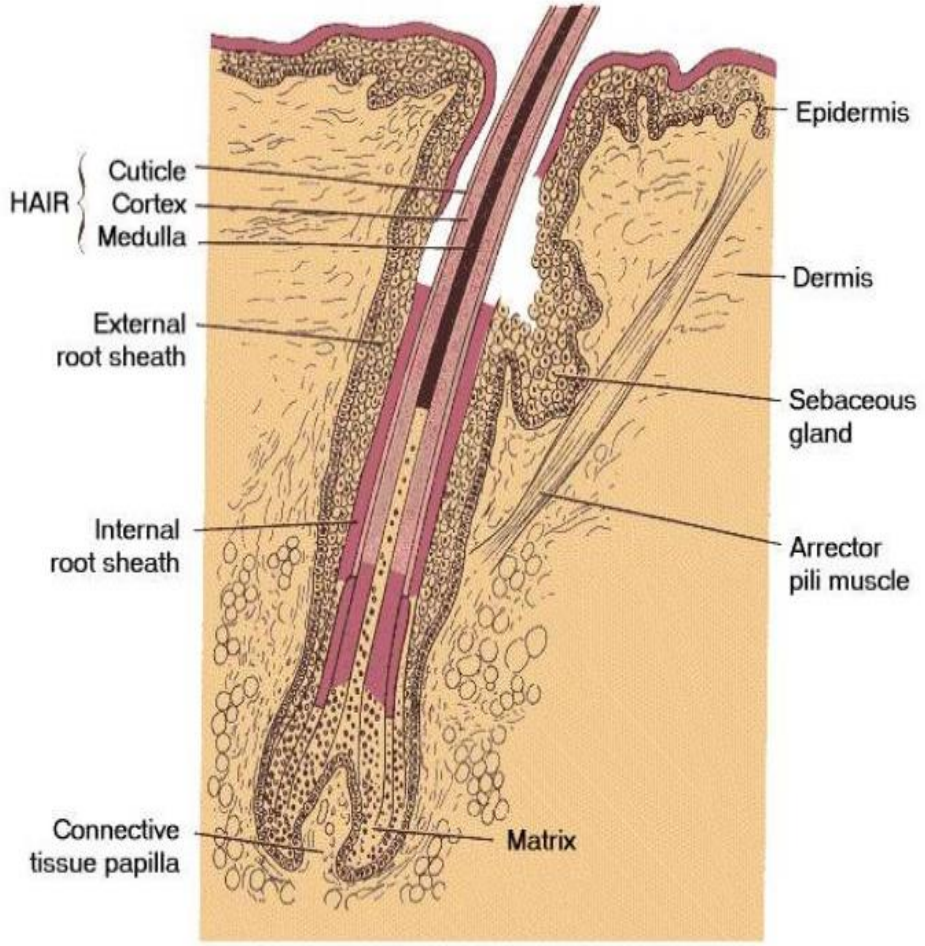


AUTOIMMUNITY MECHANISMS(1)

- Overexpression of certain autoantigens
  - Defect of the apoptosis mechanism
  - Defect of the removal of apoptosis products
- Expression of “hidden” self-antigens or antigens from “immune-privileged” organs (follicles, testicles, eyes, etc.)
  - Injuries and infections
  - Expression of secondary "hidden" auto-antigens due to inflammation.

FOLLICLE IS AN IMMUNO-PRIVILEGED ORGAN

- Follicle cells do not express MHC molecules.
- Reduced number of antigen-presenting cells (APC)
- Increased number of molecules that induce tolerance (IL-10, TGFβ)
- Defect of this “privilege” may be a mechanism for the alopecia areata development.



AUTOIMMUNITY MECHANISMS (2)

- Defect of the central tolerance mechanisms
  - Autoimmune polyendocrinopathy syndrome, candidiasis and ectodermal dystrophy - hypoparathyroidism, hypoadrenocorticism, hypothyroidism, hypogonadism, vitiligo, alopecia areata, hepatitis
    - Defect of self-antigens presentation for negative selection of T-lymphocytes in the thymus
  - Thymoma-associated autoimmune diseases – paraneoplastic pemphigus, myasthenia gravis, erythema multiforme.

AUTOIMMUNITY MECHANISMS (3)

- Molecular mimicry - identical short sequences of amino acids in molecules of foreign and self-proteins - similar epitopes
  - Rheumatism - antibodies to Streptococcus group A cross-react with autoantigens of the heart, skin, joints and brain - polyarthritis, etc.
  - Fogo Selvagem (FS) – endemic pemphigus foliaceous
    - Possible cross-reaction with saliva antigens of flies.

PREDISPOSING AND TRIGGERING FACTORS

- Immunological imbalance
  - Decreased T-regulatory lymphocyte activity
  - Increased T-helper activity 17
- Genetic predisposition
- Age, gender, diet, lifestyle
- Infections, chemical exposure, tumors, UV light exposure.

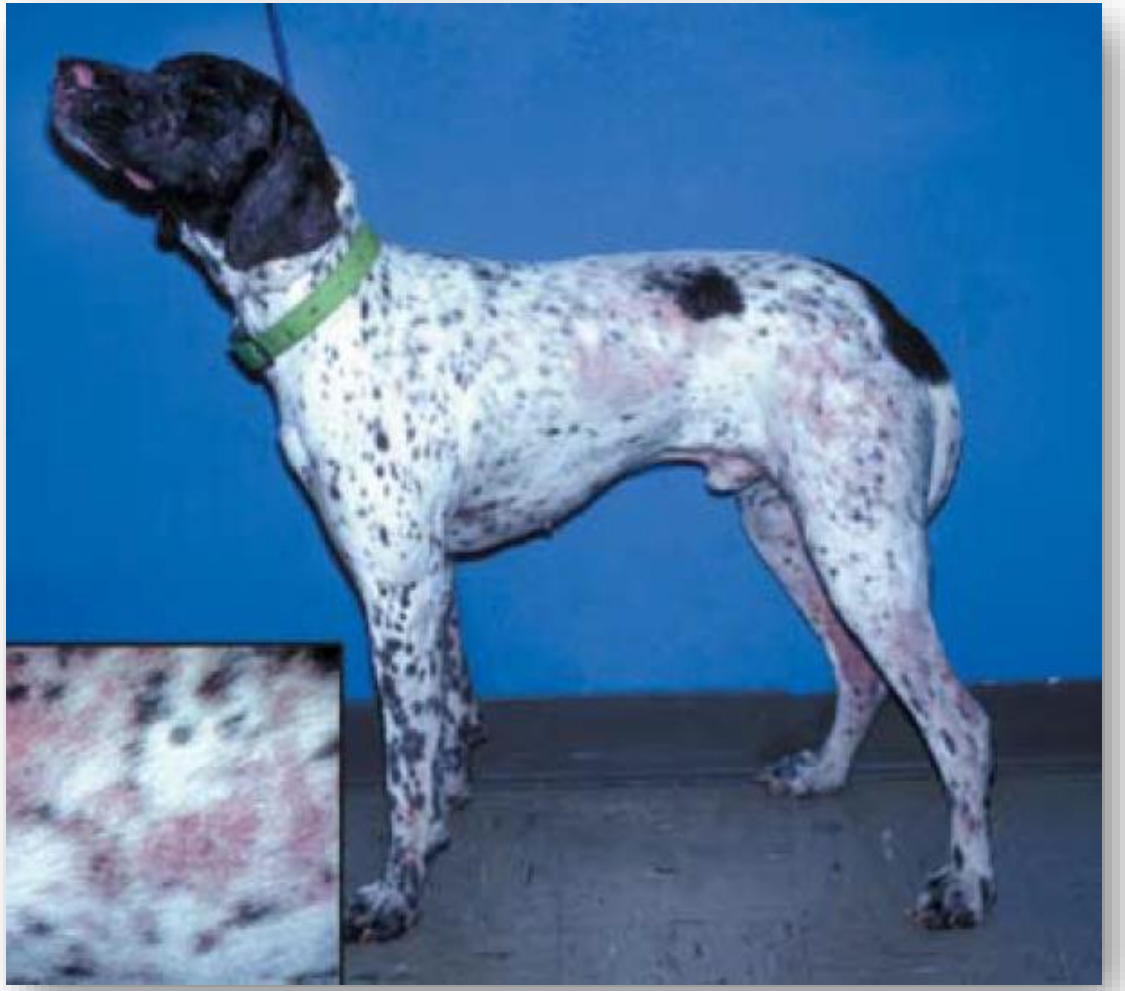
GENETIC PREDISPOSITION

- Most often - the pathology of MHC genes
- Examples:
  - Collie and sheltie – vesicular lupus erythematosus
  - Collie and sheltie – familiar dermatomyositis
  - Akita Inu – uderomatological syndrome
  - German pointers – exfoliative cutaneous lupus erythematosus.

Veterinary Dermatology 2005, **16**, 239–252

Clinical, histopathological and immunological characteristics of exfoliative cutaneous lupus erythematosus in 25 German short-haired pointers

SHARON L. BRYDEN*, STEPHEN D. WHITE‡, STANLEY M. DUNSTON†, AMANDA K. BURROWS* and THIERRY OLIVRY†



GENETIC PREDISPOSITION

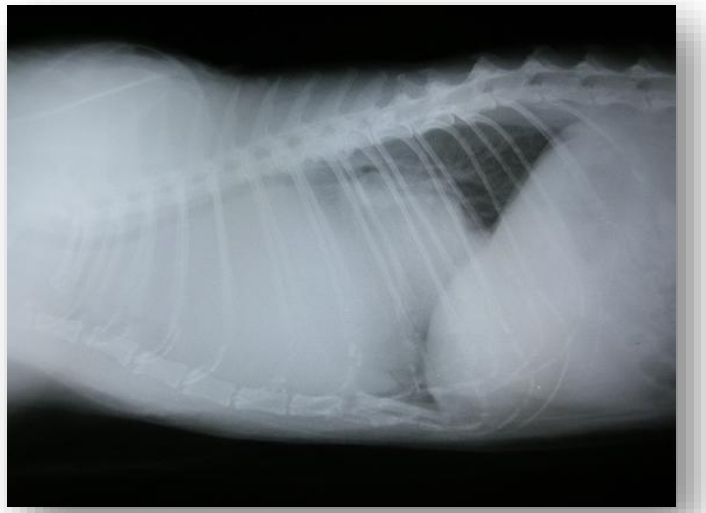
- Most often - the pathology of MHC genes
- Shar Pei, German Shepherds
  - IgA deficiency - susceptibility to infections and autoimmune diseases
- American Cocker Spaniels
  - Autoimmune cytopenia (anemia, thrombocytopenia)
- Nova Scotia Duck Tolling Retriever
  - Multisystem autoimmune pathology - defect of T-lymphocyte activation
- Golden Retriever (?), Hovawart and Giant Schnauzers
  - Lymphocytic thyroiditis - hypothyroidism.

AGE

- Most autoimmune pathologies affect middle aged and older patients
- Increased immunoglobulin levels
- Decreased cellular immunity
- Reducing the percentage of T-helper cells, including T-regulatory cells.

TUMORS AS TRIGGERS AUTOIMMUNITY

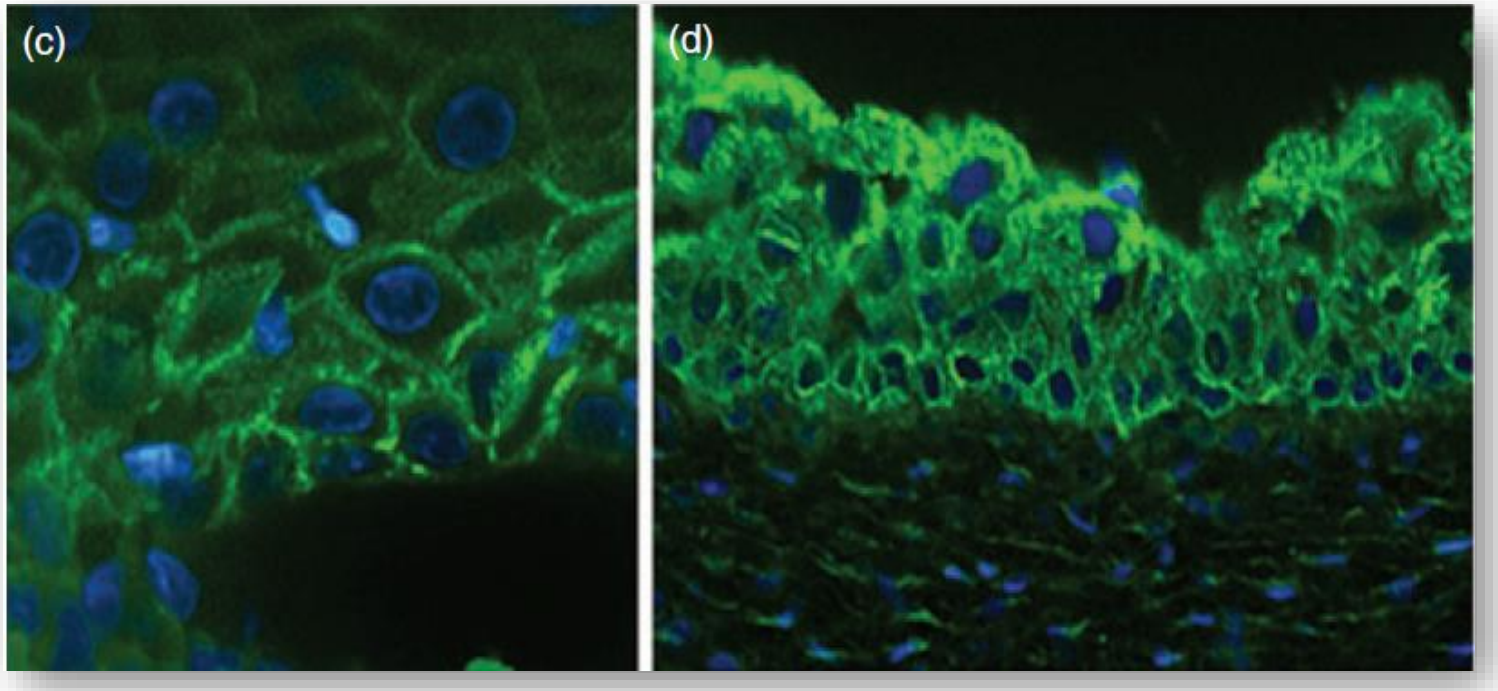
- Cytopenia in tumors
- Thymoma-associated exfoliative dermatitis
- Paraneoplastic pemphigus.

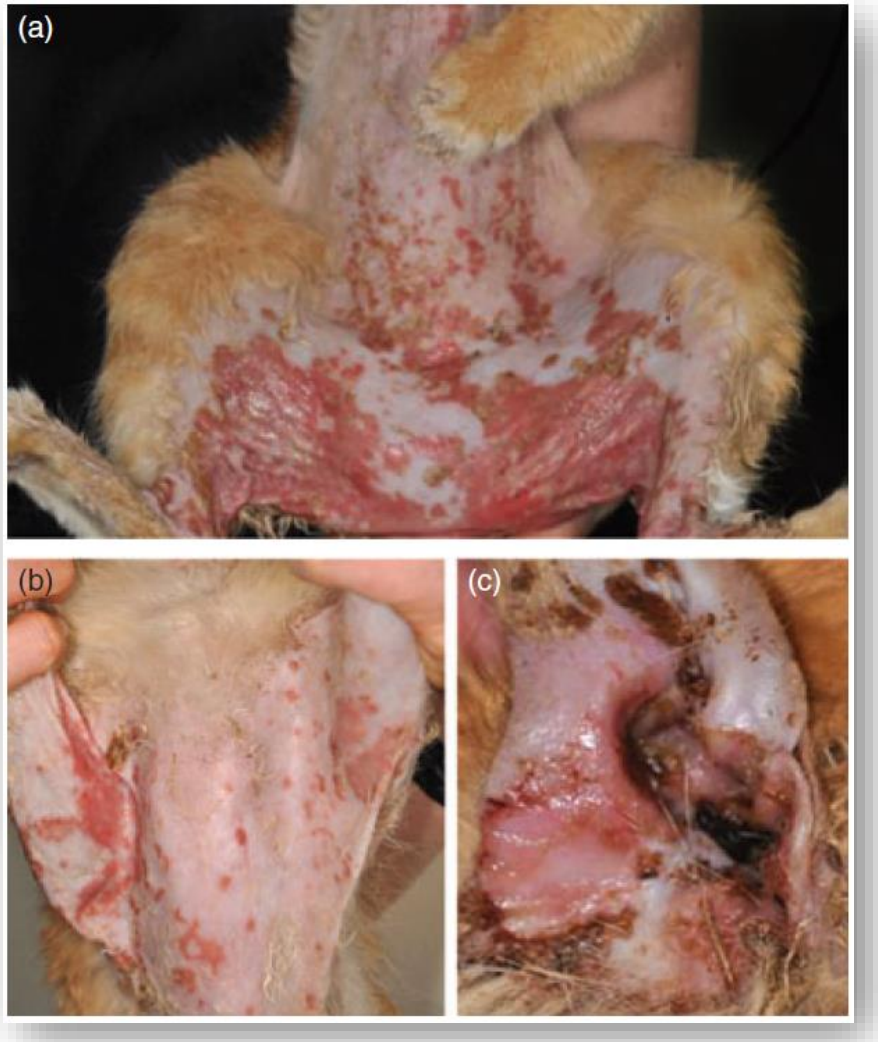


Vet Dermatol 2013; **24**: 646–e164 DOI: 10.1111/vde.12086

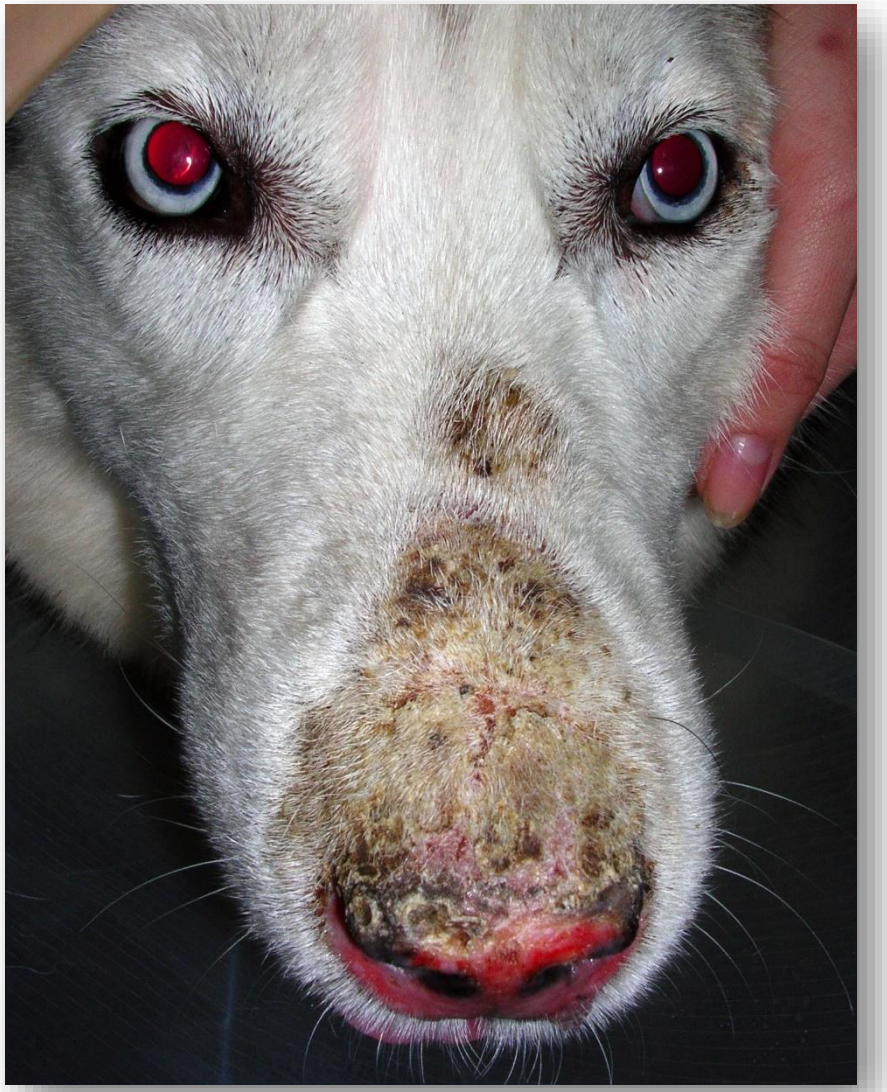
Putative paraneoplastic pemphigus and myasthenia gravis in a cat with a lymphocytic thymoma

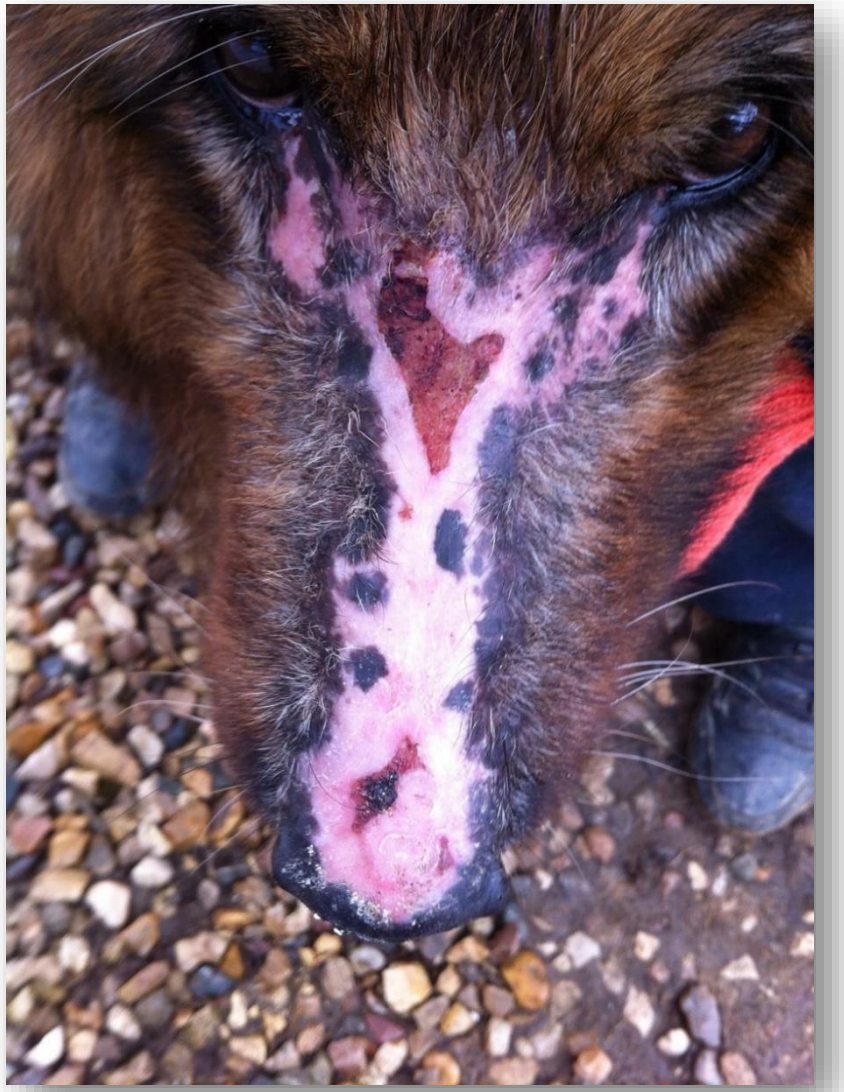
Peter B. Hill*, Phil Brain†, David Collins†, Steve Fearnside† and Thierry Olivry‡





UV LIGHT EXPOSURE



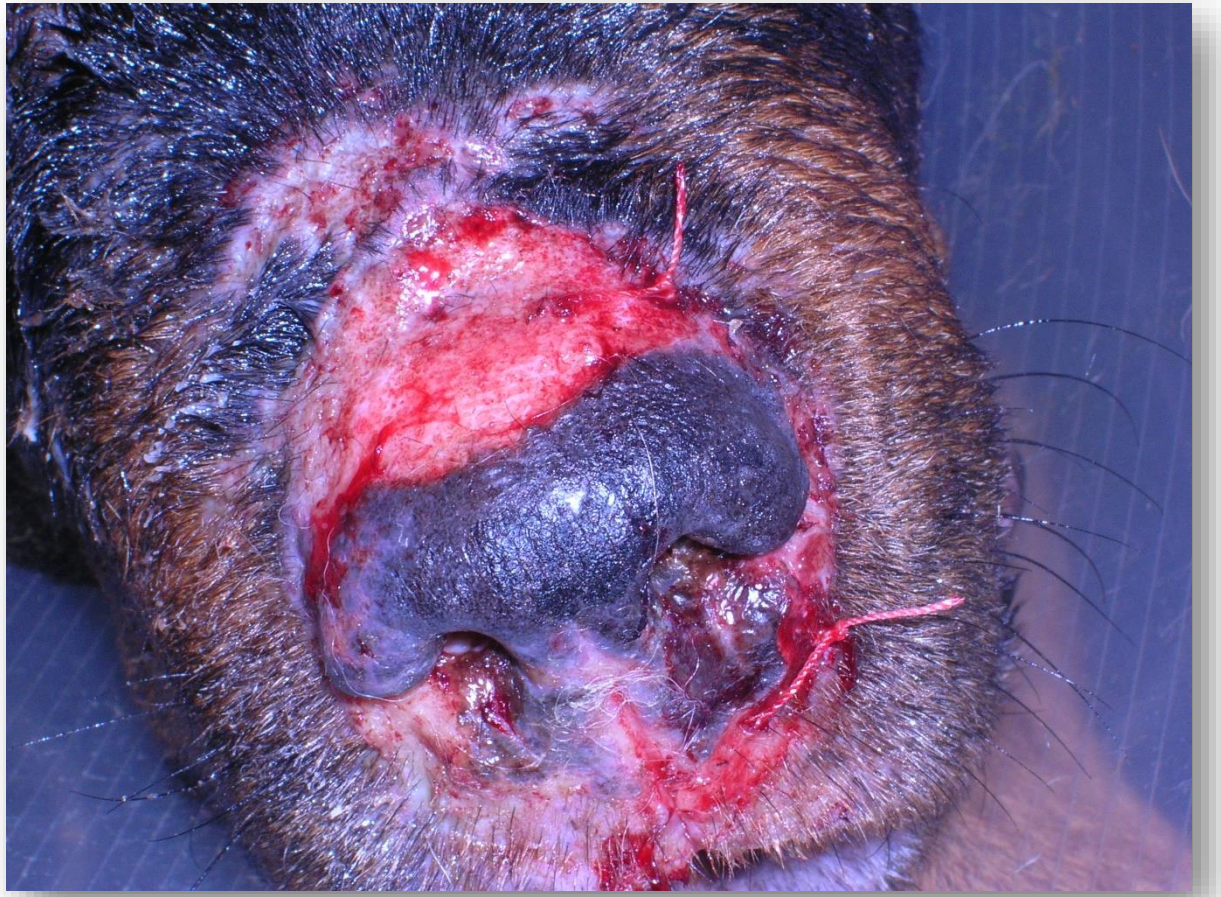


DRUG-INDUCED REACTIONS

- Drug-induced pemphigus foliaceus:
  - Promeris Duo
  - Certifect
  - Vectra 3D.

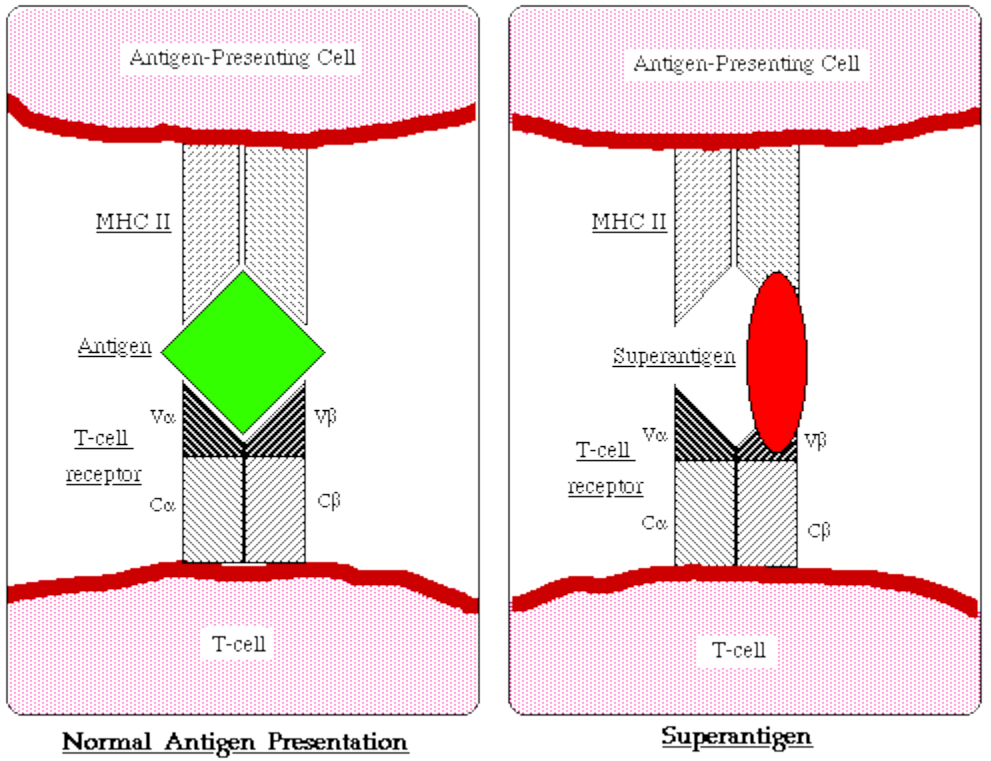
DRUG-INDUCED REACTIONS

- Drug-induced or triggered vasculopathies.

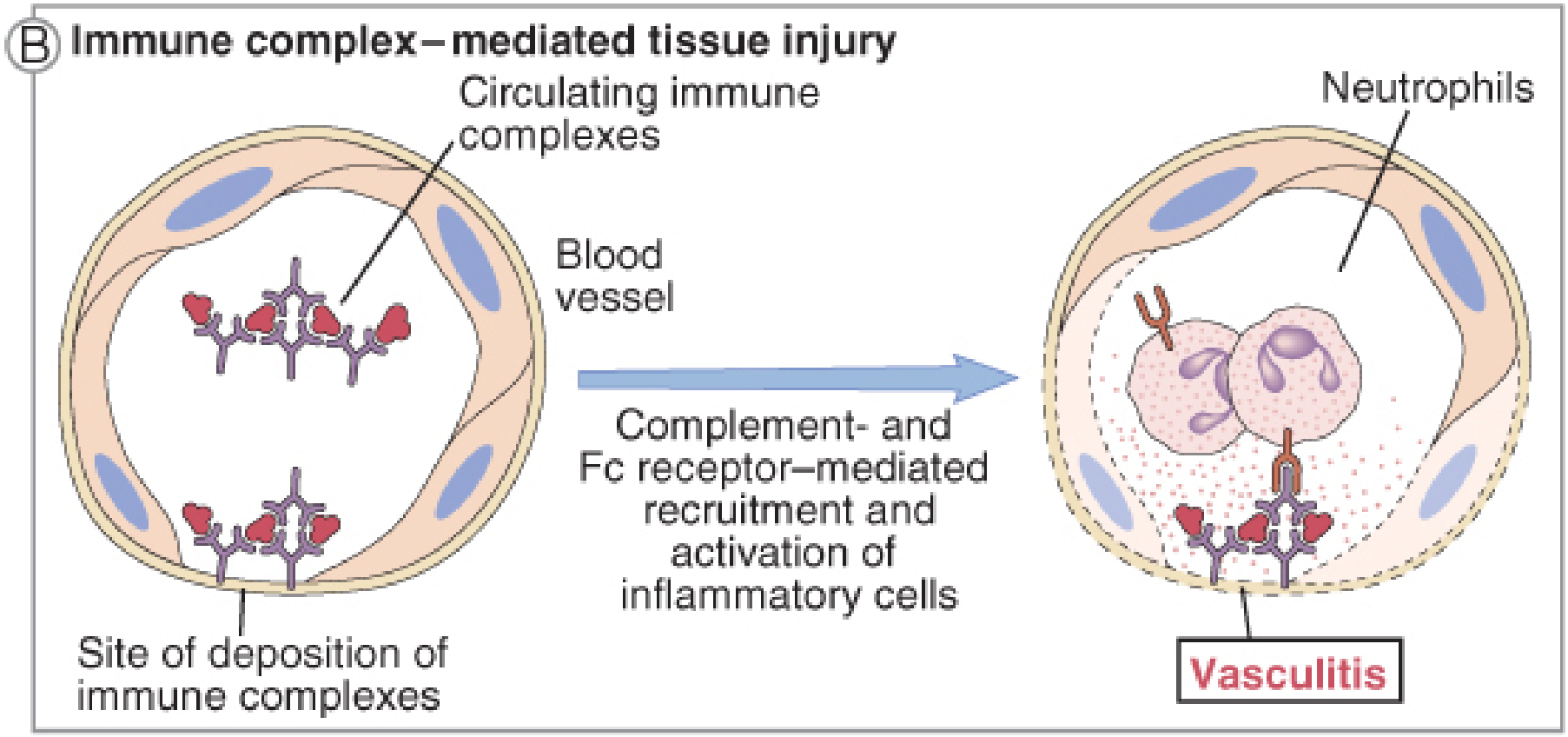


INFECTIONS AS TRIGGERS OF AUTOIMMUNITY(1)

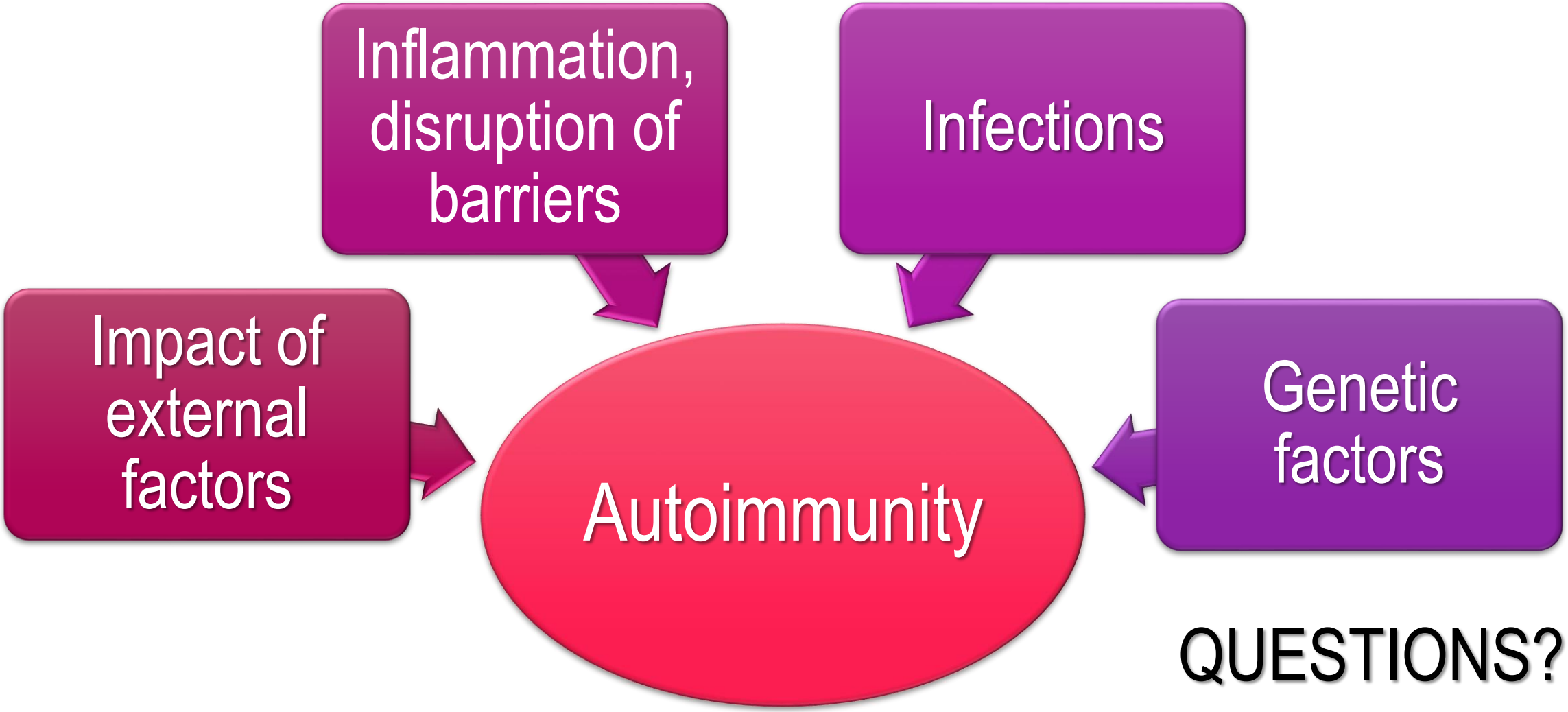
- Viral infections
  - May cause polyclonal B-lymphocyte activation
  - Polyclonal hypergammaglobulinemia and peripheral lymphadenopathy.
- Bacterial infections
  - Superantigens



INFECTIONS AS TRIGGERS OF AUTOIMMUNITY(2)



CAUSES OF AUTOIMMUNITY



QUESTIONS?