Pathogenesis of autoimmune diseases

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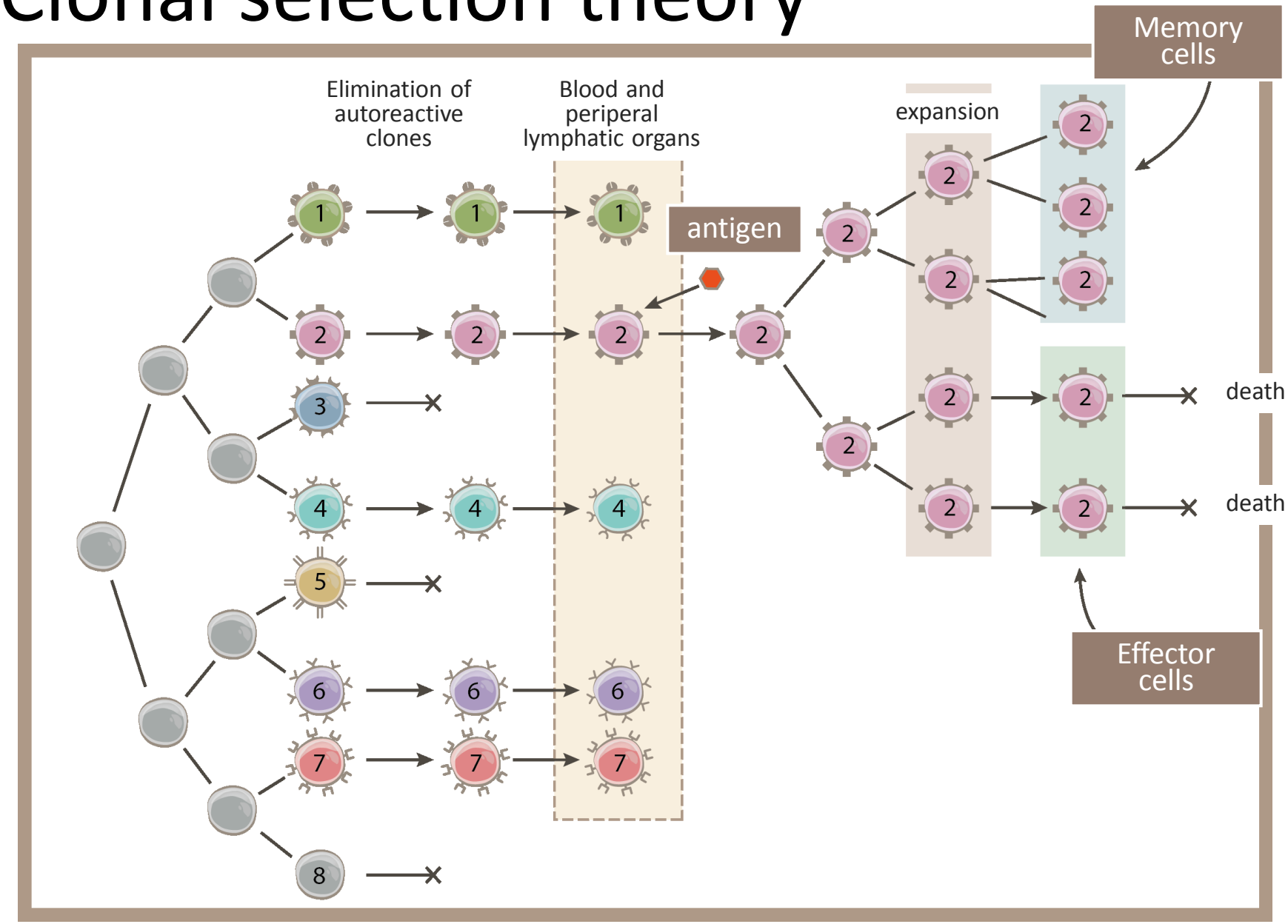
Immmune tolerance

Clonal selection theory - Forbidden clones F.M. Burnet, 1957

- During (mainly fetal) development immunocompetent cells of the immune system develop. Each cell is characterized by its own antigen specific receptor. Each cell reacts only with one concrete specific antigen.
- After exposure to autoantigen during fetal life autoreactive clones are eliminated („**forbidden clones**“).
- If a concrete cell recognizes its specific antigen, it is stimulated, proliferates and forms a clone = clonal selection.
- After repeated divisions the cell becomes a terminally differentiated cell, that does not proliferate and after some time dies.
- The cells of the clone that do not differentiate into the terminal stage become a memory cells which will quickly react after the second exposure to the antigen.

Clonal selection theory



Immune tolerance

- Central
- Peripheral

Central immune tolerance
= clonal deletion

- Negative selection during the thymic education proces.

- Deletion of autoreactive B-lymphocytes in the bone marrow

Development of lymphocytes in the thymus

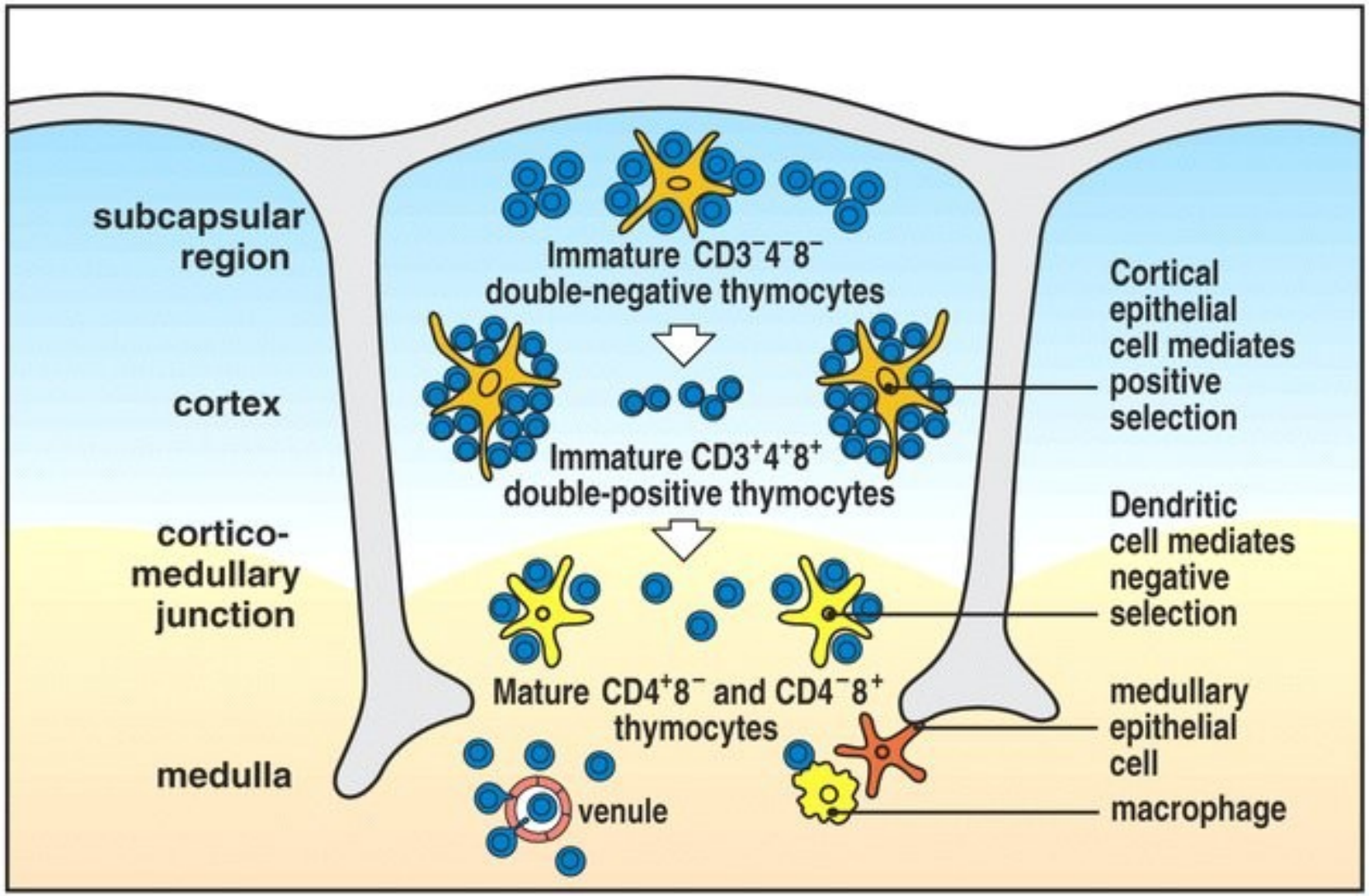


Figure 5-13 The Immune System, 2/e (© Garland Science 2005)

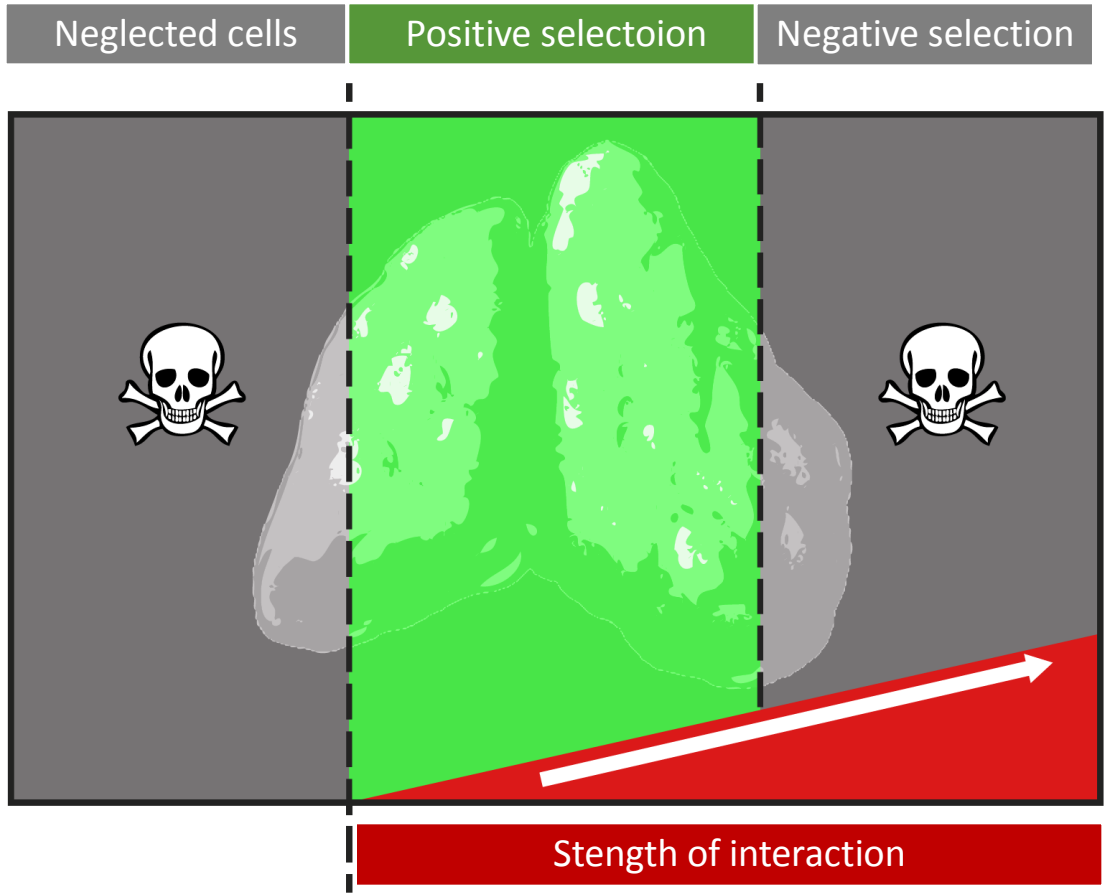
Thymic education

- Positive selection: survival of cells reacting with low affinity to HLA antigens expressed on antigen-presenting cells in the thymus. Only those cells that recognize HLA antigen of the concrete person survive. The non-reacting cells die by neglect.
- Negative selection – those thymocytes that react with high affinity with complexes of HLA-autoantigens in thymus die by apoptosis.
- It is supposed that more than 90-95% of thymocytes die during these processes.

Negative selection during thymic education

- Negative selection – in the subcortical and mainly medullary areas of the thymus. Thymic epithelial cells in the subcortical and medullary areas of the thymus express a variety of somatic antigens on their HLA.
- This expression is controlled by the gene AIRE. Apoptosis is induced in the thymocytes with high affinity with complexes of HLA-autoantigen.
- It is estimated that during the processes of positive and negative selection up to 98% of the thymocytes are eliminated.

Strength of interaction between TCR and HLA-(antigen) complexes determines the fate of thymocytes



Cell death

AIRE gene deficiency

- Results is a rare disease APECED (Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy)
- Autoimune manifestations: autoimmune polyendokrinopathy (most importantly hypoparathyroidism, Addison's disease), autoimmune hepatitis, vitiligo, alopecia....
- Mucocutaneous kandidiasis is caused by autoantibodies against IL-17.

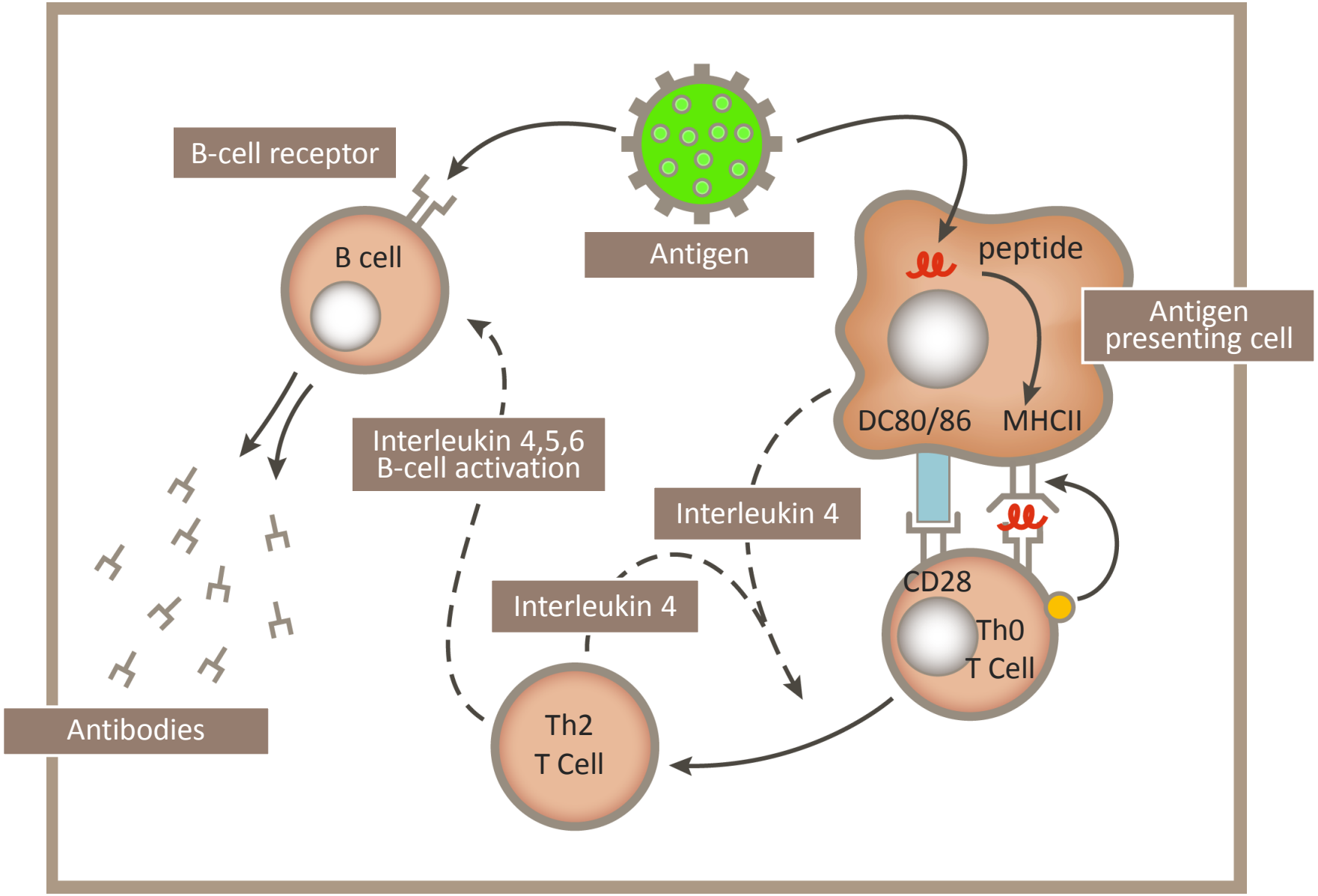
Innate defects of apoptosis

- A number of genes may be affected.
- The most frequent disease – autoimmune lymphoproliferative syndrome (ALPS).
- Lymphadenopathy, hepatosplenomegaly, autoimmune anaemia, thrombocytopenia, other autoimmune diseases.
- A significant increase of CD4-CD8-T-lymphocyte in the blood.

Immune tolerance

- Peripheral:
  - Clonal deletion - elimination of autoreactive cells by apoptosis
  - Clonal anergy - costimulatory signals are lacking
  - Clonal ignorance - to low concentration of antigen does not stimulate immune response
  - Suppression - autoreactivity is blocked by regulatory cells

Activation of immune system by antigen



T_{reg} lymphocytes

- Thymic development, but can be induced also in periphery.
- FOX-P3 is a crucial transcription factor
- In flow cytometry CD4+CD25+ (FOX-P3+)
- Involved in tolerance of autoantigens
- Direct effect on other T cells by CTLA-4 molecule and also by soluble or membrane bound TGF-β.
- Suppress function of antigen-presenting cells.
- However also involved in „autotoleration“ of tumor cells
- Comprise approximately 5-10% of peripheral CD4+ lymphocytes.

FOX-P3 transcription factor deficiency

- Results is a serious rare disease - IPEX syndrome (Immune by the dysregulation, Polyendocrinopathy, Enteropathy, X-linked)
- Severe autoimmune enteritis, diabetes mellitus, eczema, hypothyroidism...
- The gene is on X-chromosome.
- Lethal if haematopoietic cells are not transplanted.

Genetic aspects of autoimmune diseases

- The accumulation of autoimmune diseases in families.
- Inbred strains of animals which develop a defined autoimmune disease.
- Association of autoimmune diseases with HLA antigens.
- The significance of various polymorphism of cytokine/ cytokine receptors and other regulatory genes.
- Failure of apoptosis leads to autoimmune diseases.
- Majority of autoimmune diseases are more frequent in women.

Environmental factors in the development of autoimmune diseases

- Infection
  - "Bystander" effect in the ongoing inflammation.
  - Molecular mimicry.
  - Polyclonal stimulation.
- Abnormal response to the physiological flora (IBD).
- Effect of UV light on the development and exacerbation of SLE
- The effect of stress is considered
- Several autoimmune diseases are more frequent in vaious geographical areas (the north-south gradient in multiple cerebrospinal sclerosis)
- Increased intake of iodine is associated with more frequent occurrence of Hashiomoto thyroiditis.

Development of autoimmune disease after pregnancy

- Suspected are hormonal changes after delivery and the termination of "immunosuppression" present during pregnancy.

Frequency of autimmune diseases
(Mackay IR, BMJ 2000; 321: 93-96)

- It is estimated that approximately 5% (other estimations > 10%) of the population suffer from any autoimune disease.
- Autoimmune impairment of the thyroid gland: approximately 3% of females.
- Rheumatoid arthritis: 1% of the population.
- Primary Sjogren's syndrome: 0.6-3% of women.
- SLE: 0,12% of the population.
- Multiple sclerosis: 0.1% of the population.

Autoreactitity and autoimmunity

- **Autoreactivity** is a physiological process in which the immune system recognizes its own structure and respond to them.
- It is involved during the growth, differentiation, removal of old cells.
- **Autoimmunity** is a pathological condition, if there are clinical signs we speak about an **autoimmune disease.**

Pathogenesis of Autoimmune Diseases

- Autoantibodies cause opsonization, activate the complement system, block/stimulate the receptors, may be involved in ADCC phenomenon.
- Complexes with autoantigens cause immunocomplex diseases.
- Autoreactive T-lymphocytes: cytotoxic but also Th lymphocytes are involved . The best-known example is multiple sclerosis, DM-I.
- Non-specific mechanisms: chemotaxis of leukocytes to the site of inflammation.

Autoantibodies in pathogenesis of autoimmune diseases

- The presence of various of autoantibodies in low titre can be observed quite frequently in many people not suffering from autoimmune diseases.
- This incidence increases with age.
- Quite often we encounter situation when diagnostically used autoantibodies are different from the autoantibodies of pathogenetic importance or cellular immunity plays a crucial role.
- The finding of certain autoantibodies may precede autoimmune disease by many years (antimitochondrial, anti-cyclic citrulinated peptides).
- Autoimmune disease must have clinical symptoms, the presence of autoantibodies never provides a diagnosis of a disease!

Mechanisms leading to autoimmune diseases

- Visualization of hidden antigens
- Cross-reactivity of exo - and endoantigens (molecular mimicry)
- "Bystander" activation
- Abnormal expression of HLA-II antigens
- Polyclonal stimulation of T-and B – lymphocytes
- Impaired function of regulatory T-lymphocytes.
- The formation of neoantigens (e.g. the effect of drugs, infections.

Hashimoto thyroiditis

- Autoimmune thyroiditis
- Lymphacytic infiltration of the gland
- The presence of antibodies against thyroglobulin (TG) and microsomal peroxidase (MPO).

Hashimoto thyroiditis

- Symptoms of hyperthyroidism can be observed at the beginning of the disease – perhaps as a result of release of hormones from the colloid due to the necrosis of follicular cells.
- Sometimes, it is possible to demonstrate antibodies against TSHR, but they have usually a blocking effect.
- On the contrary, in some patients with Graves - Basedow disease antibodies against TG and the MPO can be demonstrated.

Autoimmunity in Hashimoto thyroiditis

- Antibodies against thyroglobulin and microsomal peroxidase - some fix complement, i.e. they can have a cytolytic effect, in another patients complement fixation cannot be demonstrated.
- Some patients have antibodies against TSH – they have usually a blocking effect.
- Pathogenetically, T-lymphocytes are probably the most important: Cytotoxic CD8 lymphocytes, Th1 lymphocytes stimulate both CD8 lymphocytes (IL-2, IFN-gamma), macrophages Th2 lymphocytes stimulate formation of antibodies

Possible mechanisms leading to autoimmune thyroiditis

- Molecular mimicry – the triggering antigen was not documented.
- Now considered the possibility of cross-reactivity of HSP proteins.
- Bystander effect of abnormal expression of HLA-II on the cells of the thyroid gland.
- Induction of apoptosis – increased expression of FAS on thyreocytes under the influence of IL-1beta (product of Th1 cells)

Triggering factors of Hashimoto thyroiditis

- Infection – quite frequently and infection precedes the disease, however a concrete triggering microbe has never been demonstrated.
- Stress – can be documented in some patients
- Sex – ratio of women: men - 25:1
- A period after giving birth
- A large intake of iodine radiation (mainly studies after the Chernobyl disaster)