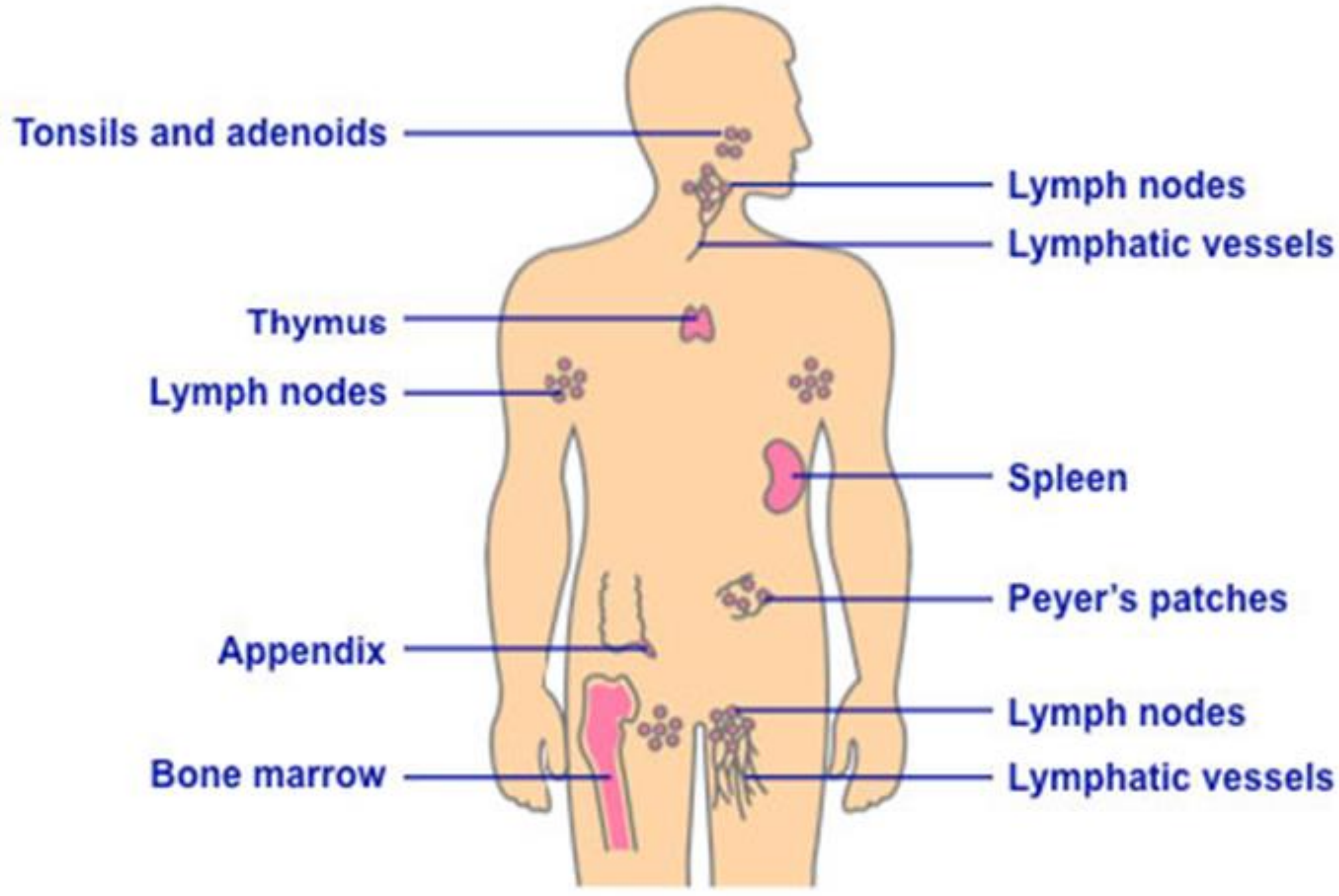
Poruchy imunity

Imunodeficity
Hypersensitivita
Alergie
Autoimunita

Orgány imunitního systému



Fyziologické použití imunitního systému

imunitní systém (nespecifická a specifická imunita)

genetika (MHC aj. lokusy)

invaze a rekognice cizorodého

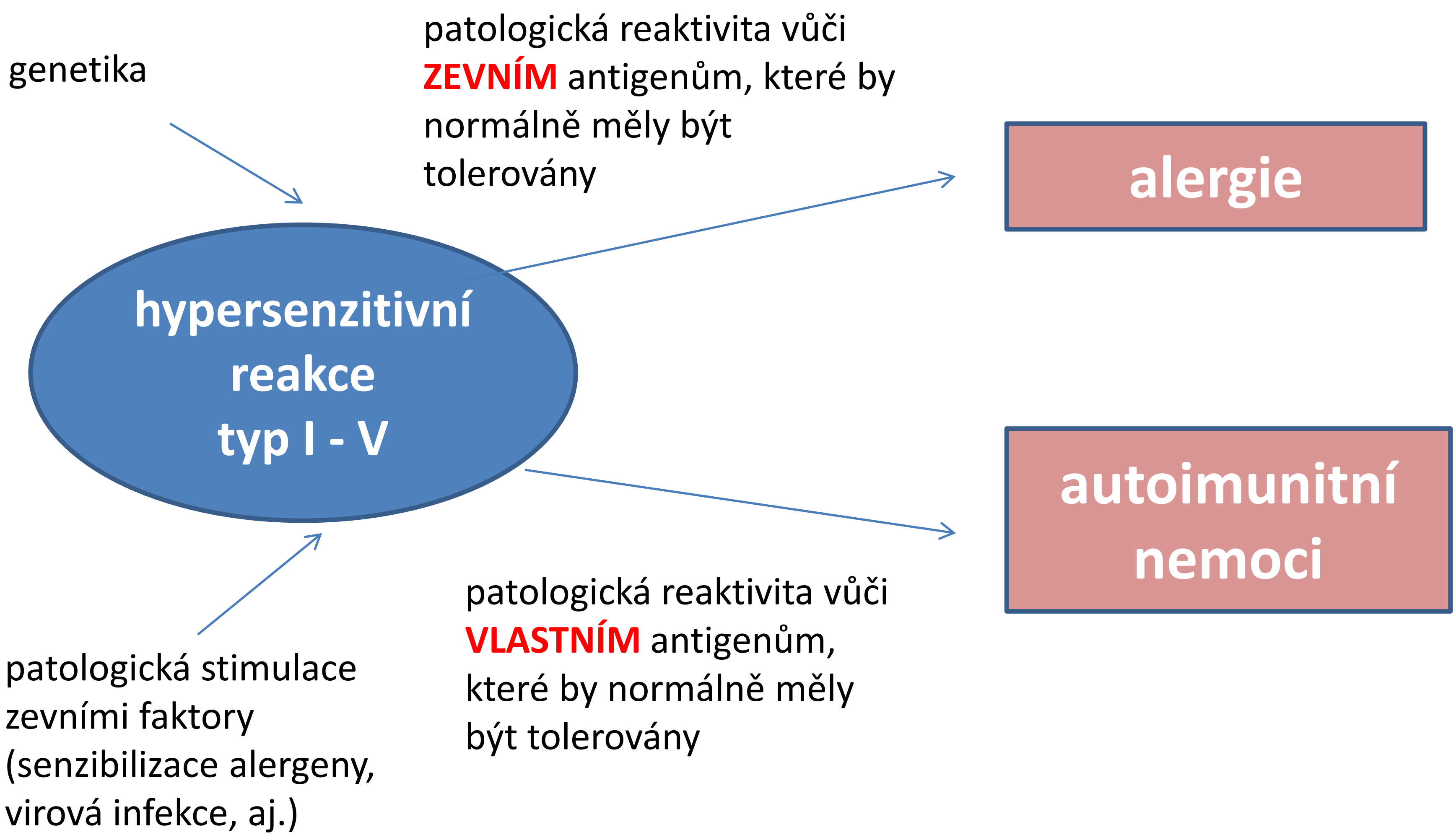
bakterie
viry
paraziti
plísně
toxiny
nádorové buňky
cizorodé buňky a tkáně (vč. transplantace)

stimulace zevními faktory během vývoje imunitního systému (tj. prodělané infekce, (ne)hygiena, ATB, vakcinace aj.)

účelná imunitní reakce

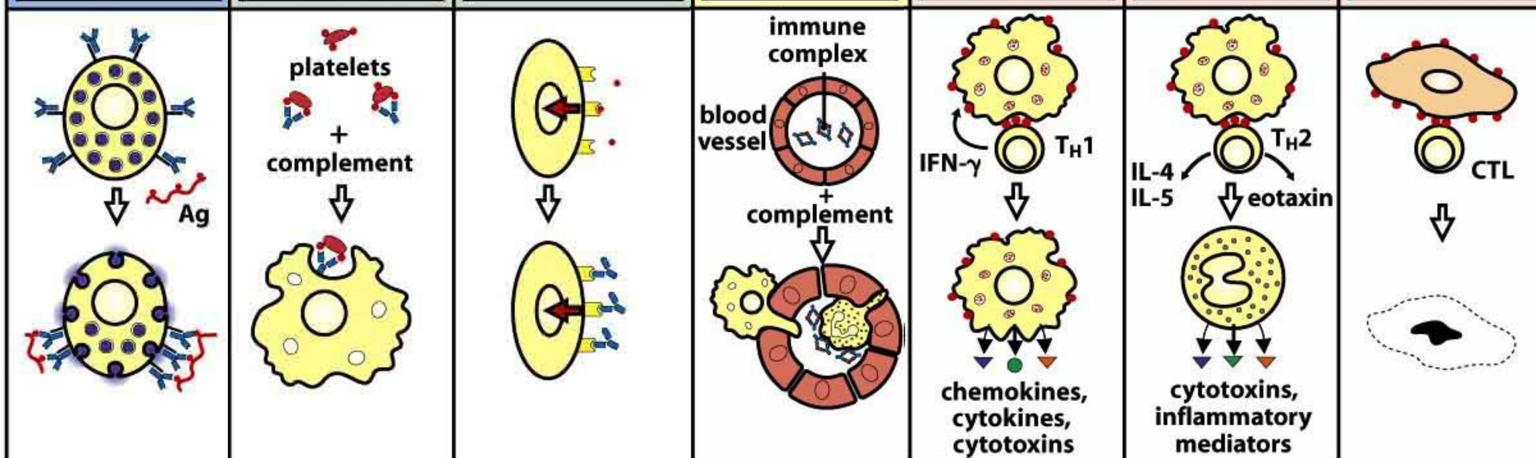
obnovení původního stavu

Patologická aktivita imunitního systému



Hypersenzitivní reakce (Coombs & Gell)

	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity

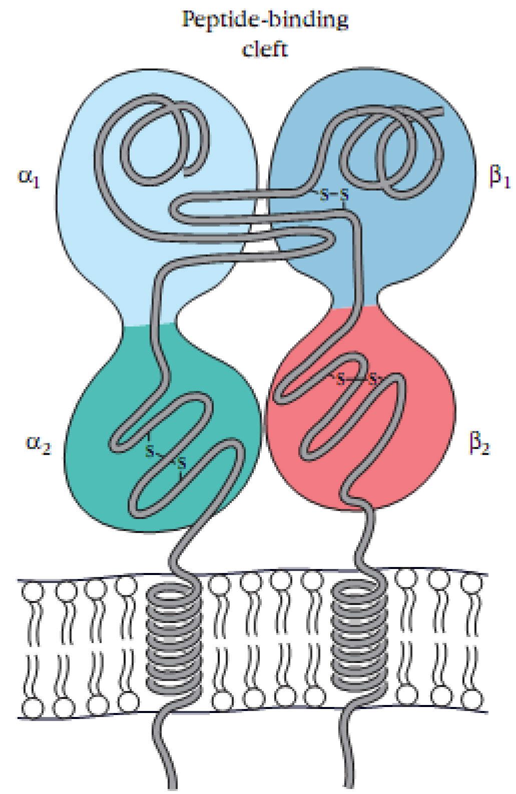


	Type I	Type II		Type III	Type IV		
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g. penicillin)	Chronic urticaria (antibody against FCεRIα)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Graft rejection

Figure 13-1 Immunobiology, 7ed.

Klasifikace poruch imunity

- imunodeficity
  - problém nespecifické (fagocytóza, komplement) nebo specifické imunity (T či B lymfocyty, protilátky)
    - primární, vrozené *(detailněji viz Imunologie)*
      - genetika
    - sekundární, získané
      - nemoci GIT (malabsorpce), ledvin (nefrotický sy), kostní dřeně (aplasie, leukemie), výživy (kachexie), nádory, infekce (AIDS), ….
- hypersenzitivní reakce - výhradně záležitost specifické (adaptivní) imunity!!!
  - alergie *(mechanizmus viz Resp. systém - astma bronchiale)*
  - autoimunitní nemoci

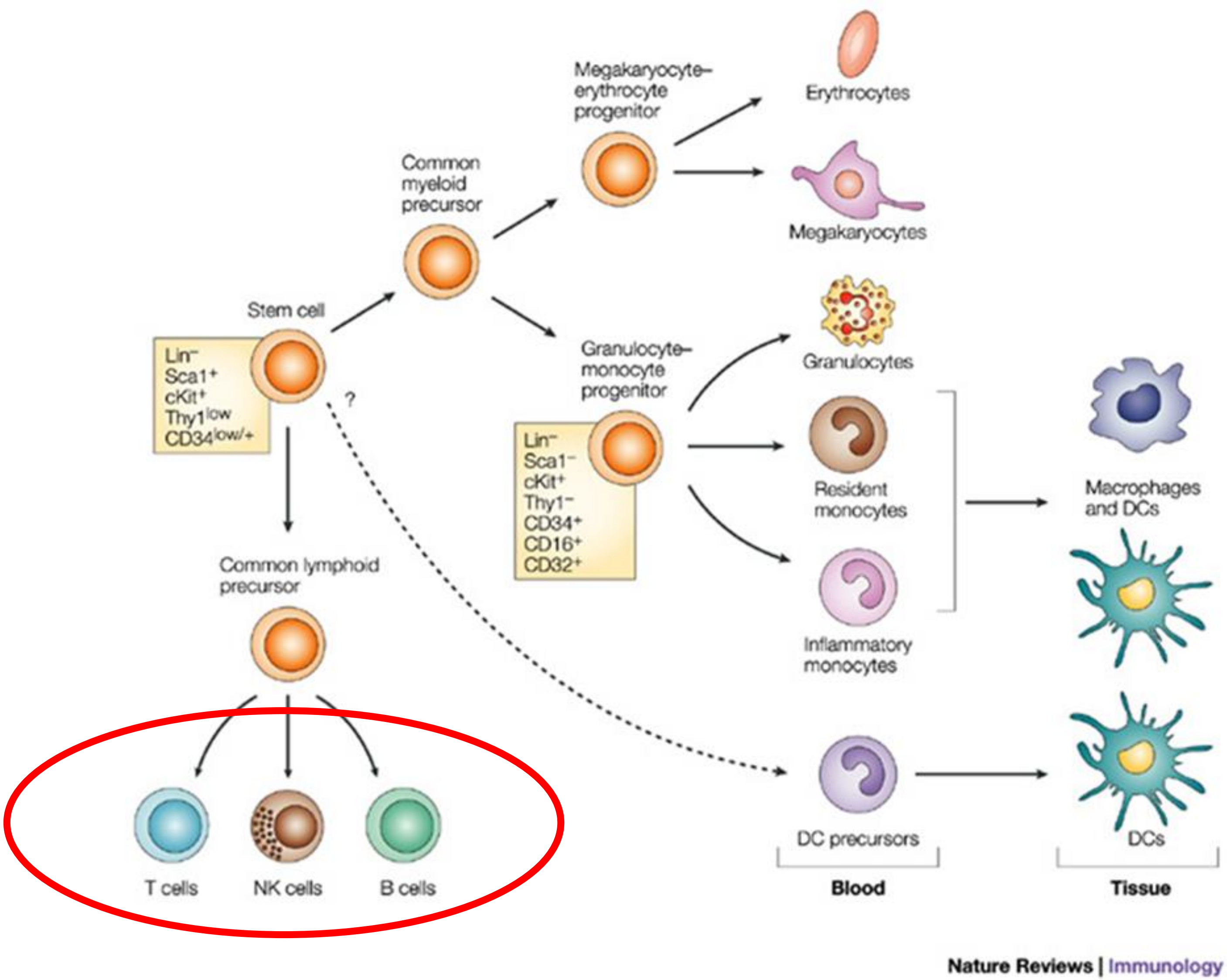


PRINCIPY IMUNITNÍ TOLERANCE (AUTOTOLERANCE)

Imunitní tolerance vs. autoimunita a autoimunitní nemoci

- autoimunita = imunitní reaktivita proti vlastním antigenům („self“ antigeny)
  - původní představa
    - autoimunita = nežádoucí fenomén („horror autotoxicus“, Paul Ehrlich)
  - ale ve skutečnosti běžný (nicméně klinicky němý) fenomén
    - prokazatelná existence autoreaktivních klonů T-lymfocytů
  - musí být tudíž **zaručena tolerance vlastních nepoškozených buněk** (self tolerance) **na více úrovních**
    - centrální
    - periferní
- autoimunitní choroby
  - detekovatelné morfologické a funkční poškození

Autoimunita je záležitostí adaptivní (specifické) imunity!!!



Molekulární mechanizmy centrální imunotolerance

- B &T lymfocyty mají původ v kostní dřeni
- pozitivní a negativní selekce upravuje jejich repertoár
  - **B** lymf. maturují a jsou selektovány v „**b**one marrow“
  - **T** lymf. maturují a jsou selektovány v **t**hymu
- tudíž většina autoreaktevních lymfocytů je centrálně odstraněna (**apoptóza**) nebo je anergická

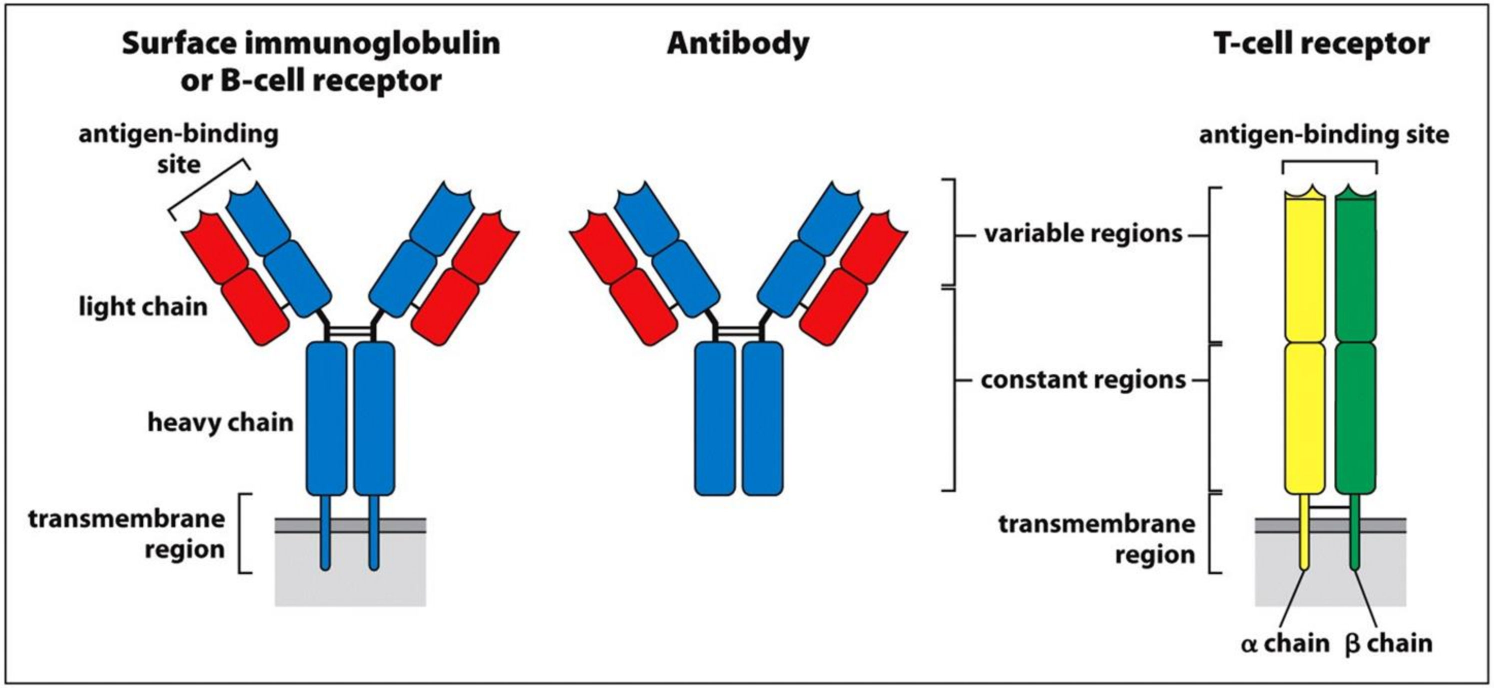
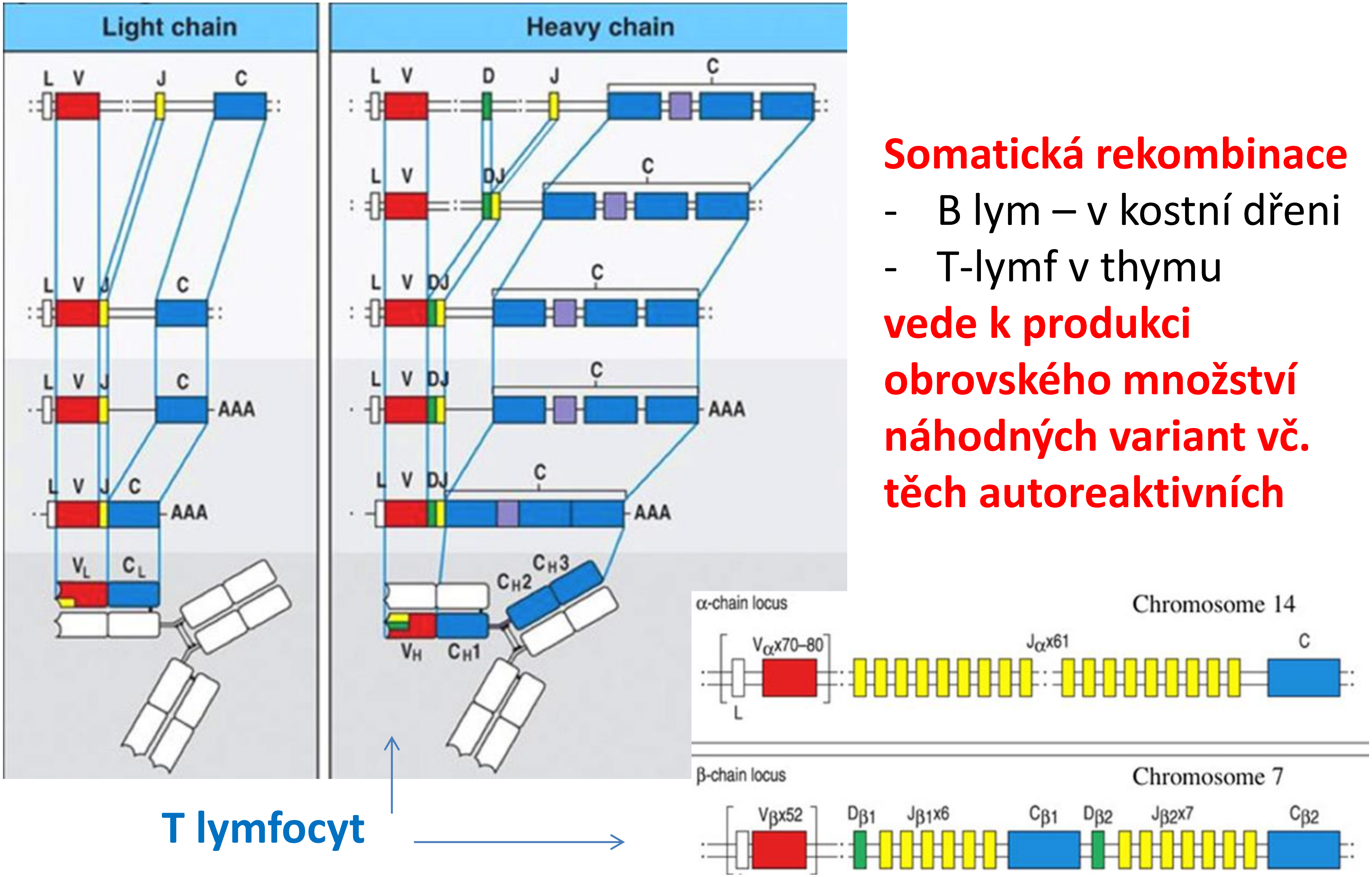


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

Jak se dosahuje diverzity receptorů lymfocytů (B a T)



T lymfocyt

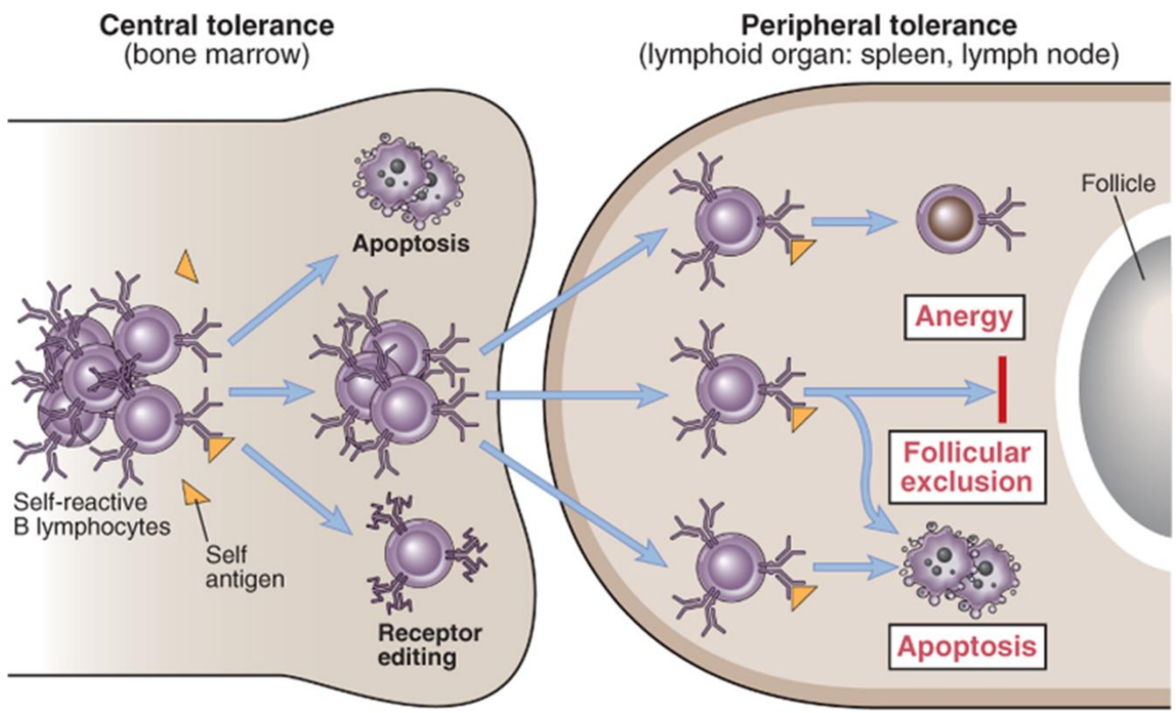
Somatická rekombinace

- B lym – v kostní dřeni
- T-lymf v thymu

vede k produkci obrovského množství náhodných variant vč. těch autoreaktivních

Centrální a periferní tolerance B lymfocytů

- možnosti v případě autoreaktivity
  - apoptóza
  - receptor editing
- protože stimulace B lymfocytů periferně vyžaduje spolupráci T lymf., jejich tolerance musí být kontrolována důsledněji



Thymus

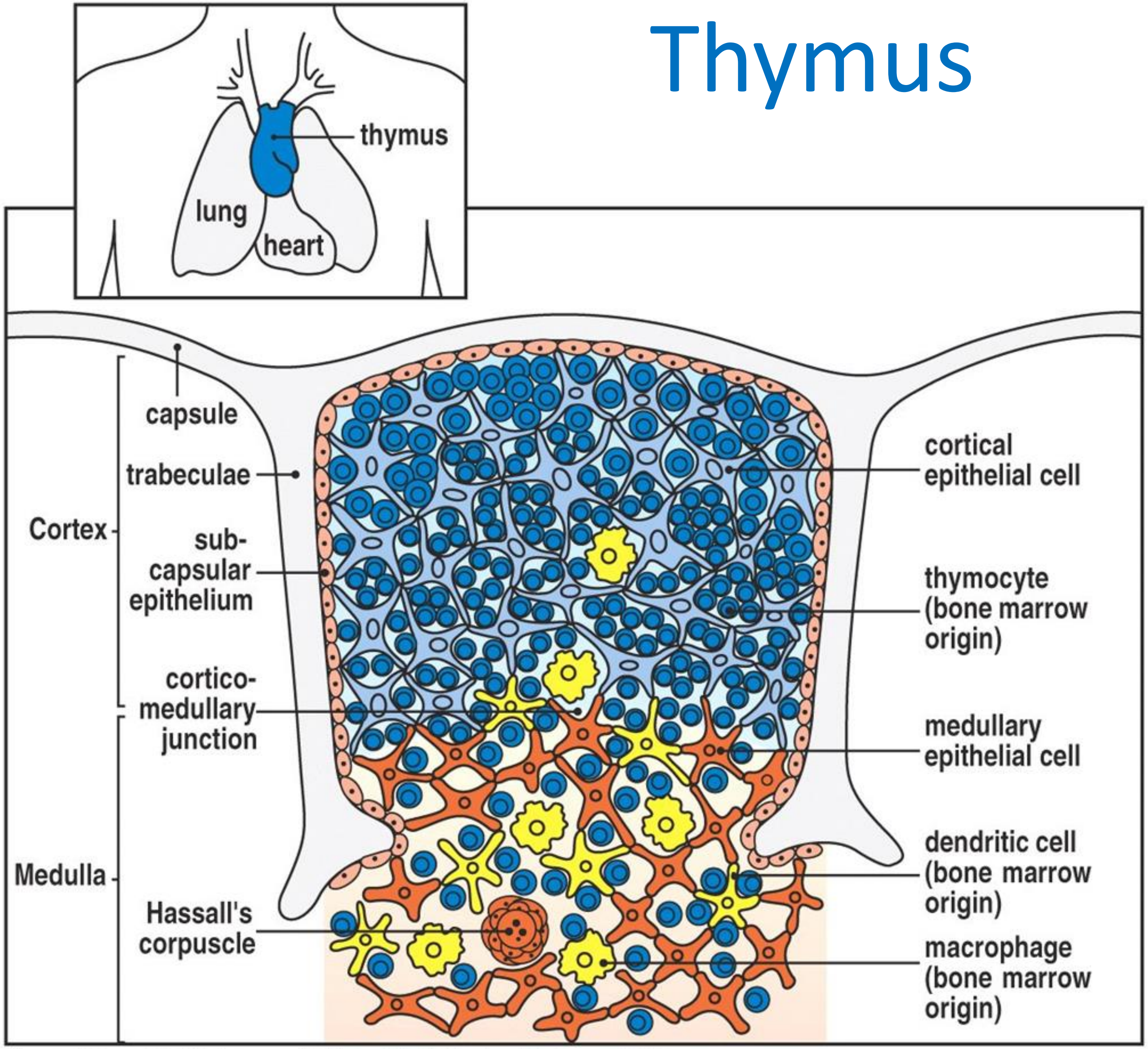


Figure 7-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

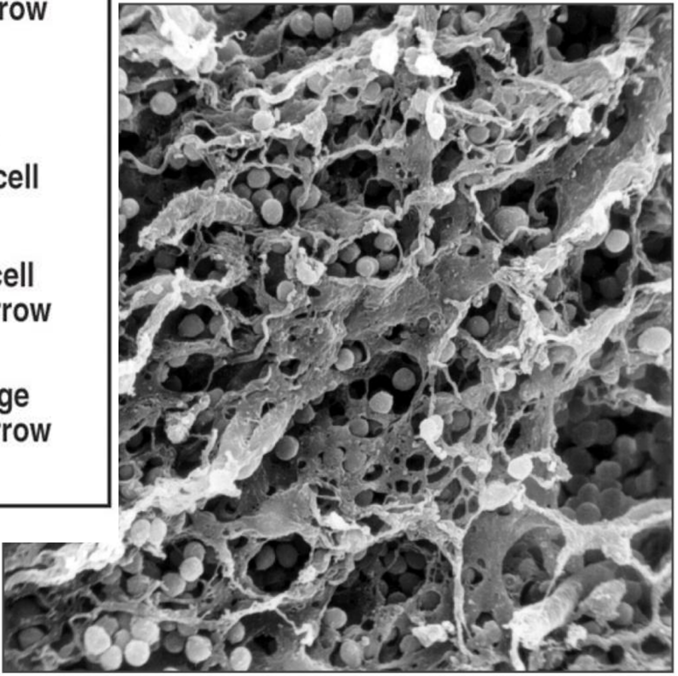


Figure 7-9 Immunobiology, 6/e. (© Garland Science 2005)

Centrální tolerance T lymfocytů – thymus

diferenciace a zároveň **selekce**

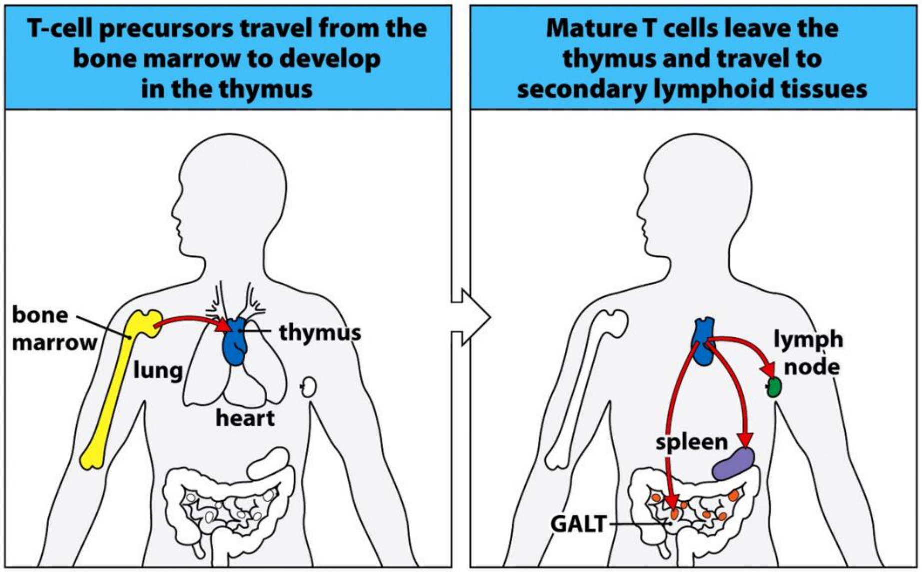


Figure 7.1 The Immune System, 3ed. (© Garland Science 2009)

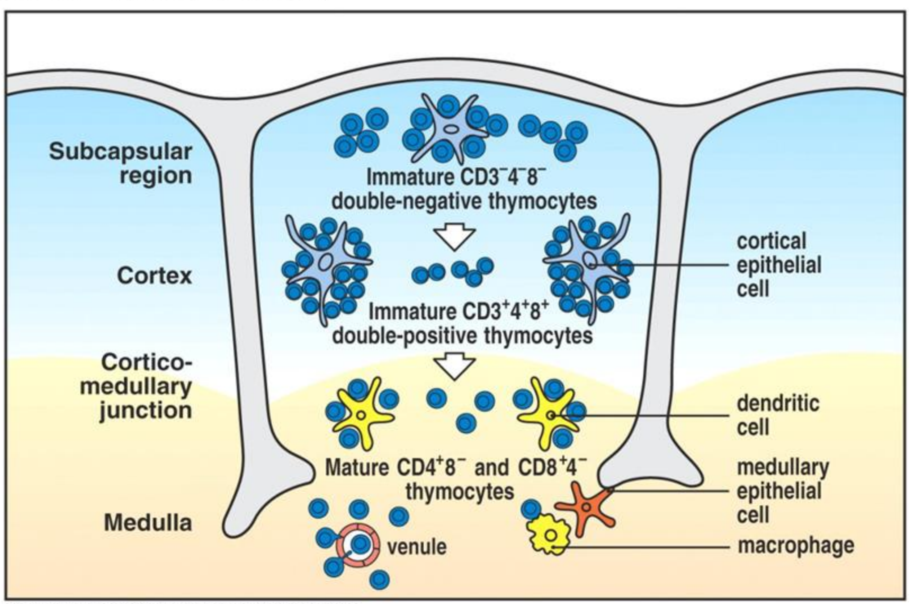


Figure 7-14 Immunobiology, 6/e. (© Garland Science 2005)

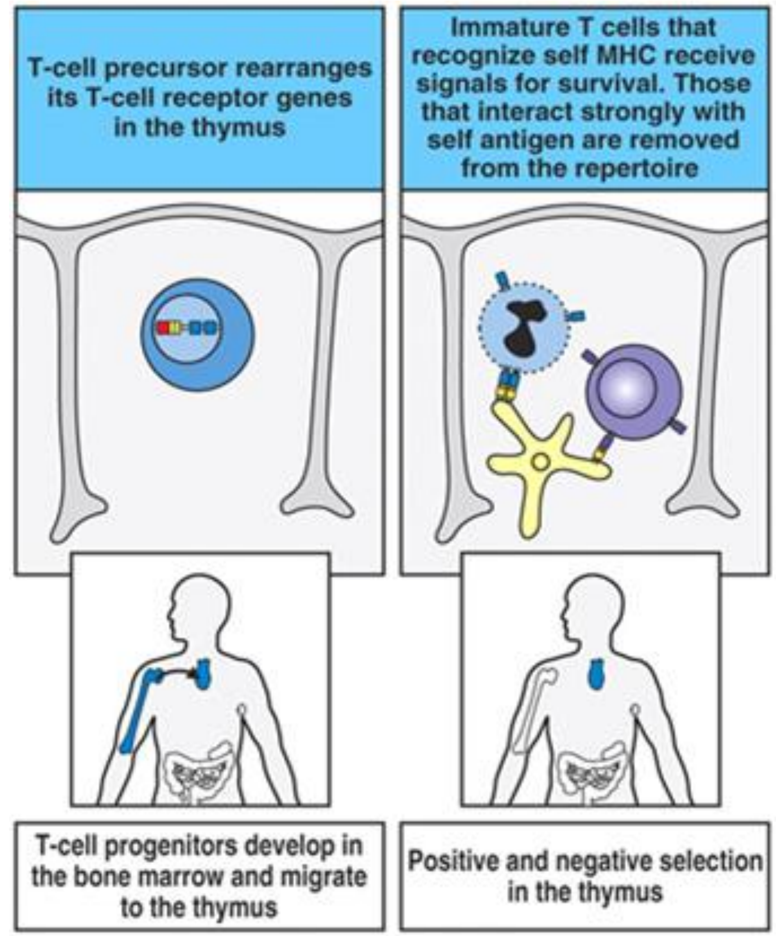
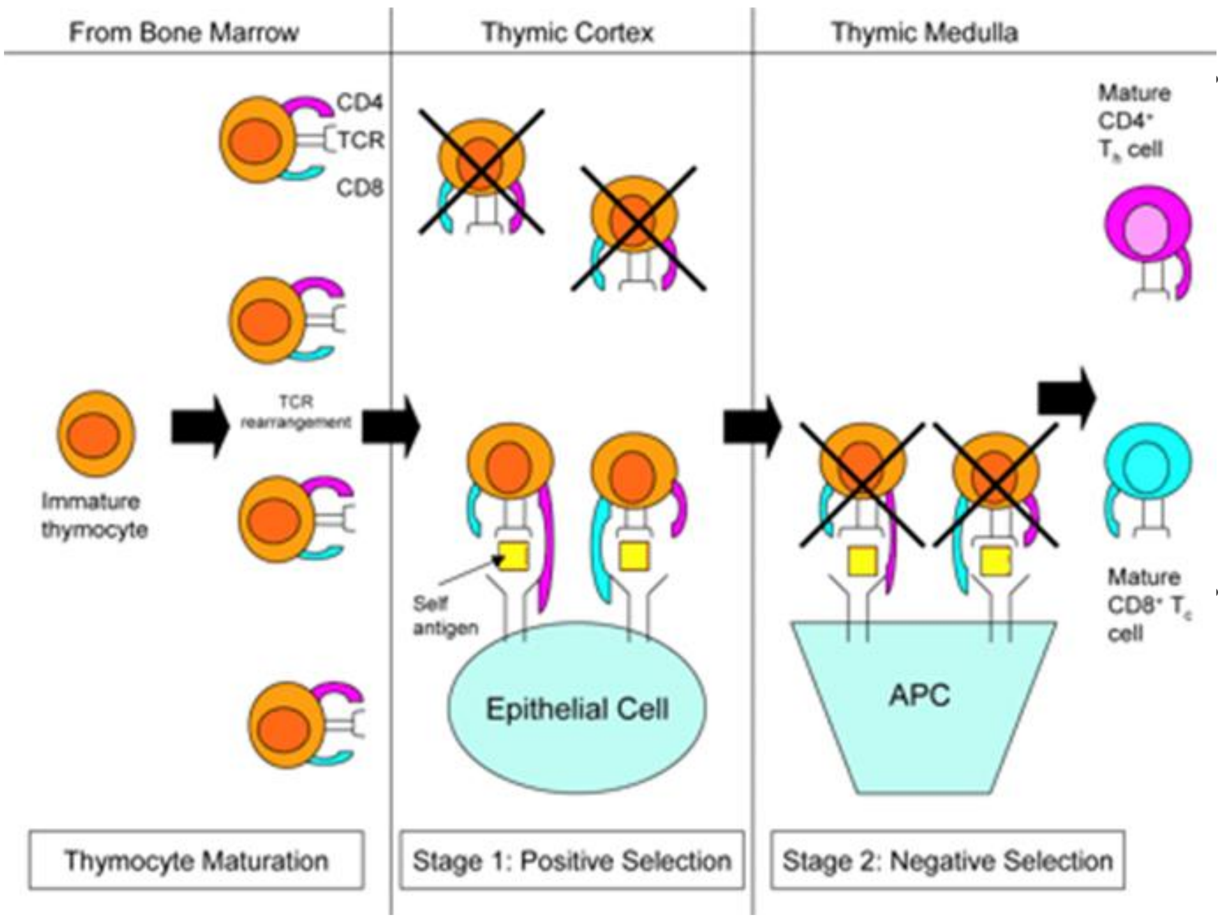


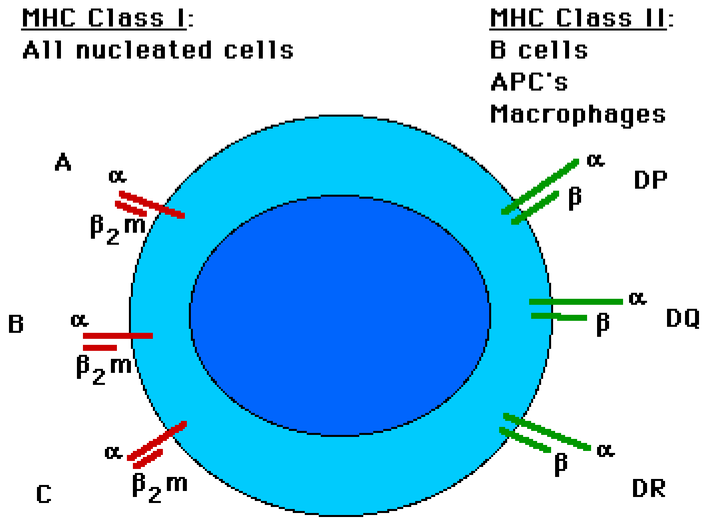
Figure 7-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

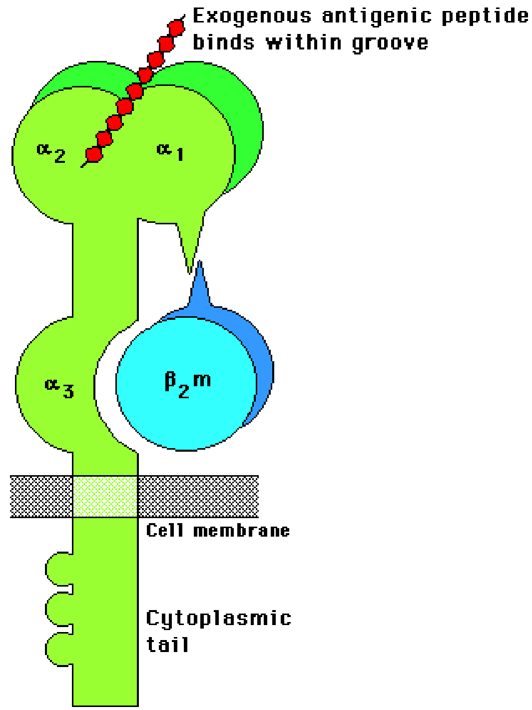
Princip of centrální tolerance – maturace thymocytů

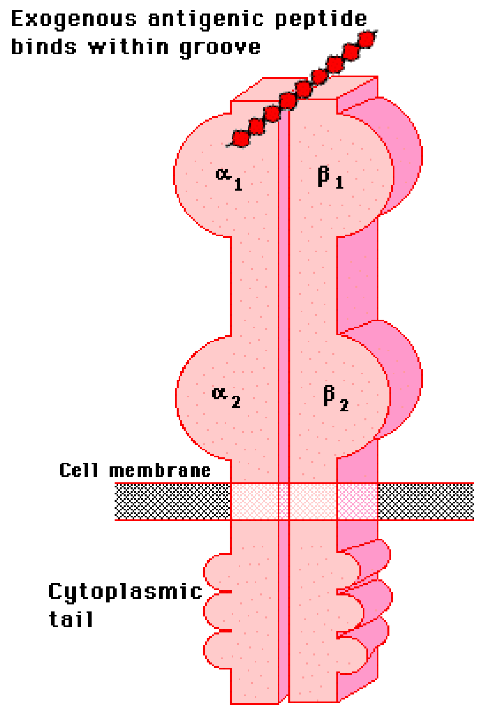


- immature thymocytes from the bone marrow **undergo T-cell receptor (TCR) rearrangement**
- stage 1: once immature CD4+8+ thymocytes enter the thymus they undergo **MHC restriction**, whereby only CD4+8+ thymocytes that interact with MHC-presented antigen on epithelial cells receive a positive survival signal
  - those that do not interact are deleted by **apoptosis.**
- stage 2: this stage involves the **negative selection** of thymocytes that survive stage 1. Thymocytes with too strong an association for self-MHC and self-antigens are deleted by apoptosis, allowing the remaining thymocytes to mature into CD4+ T-helper (Th) cells or CD8+ cytotoxic (Tc) cells

Role MHC v selekci T lymfocytů







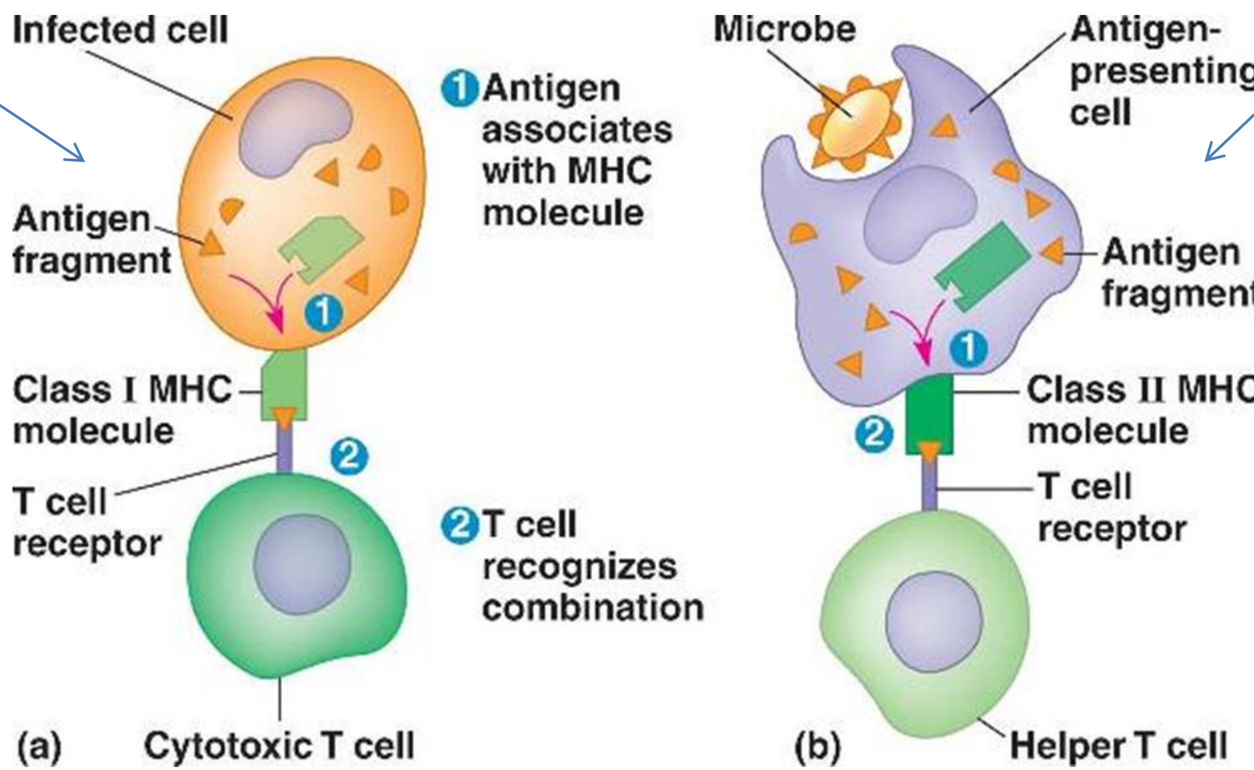
Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

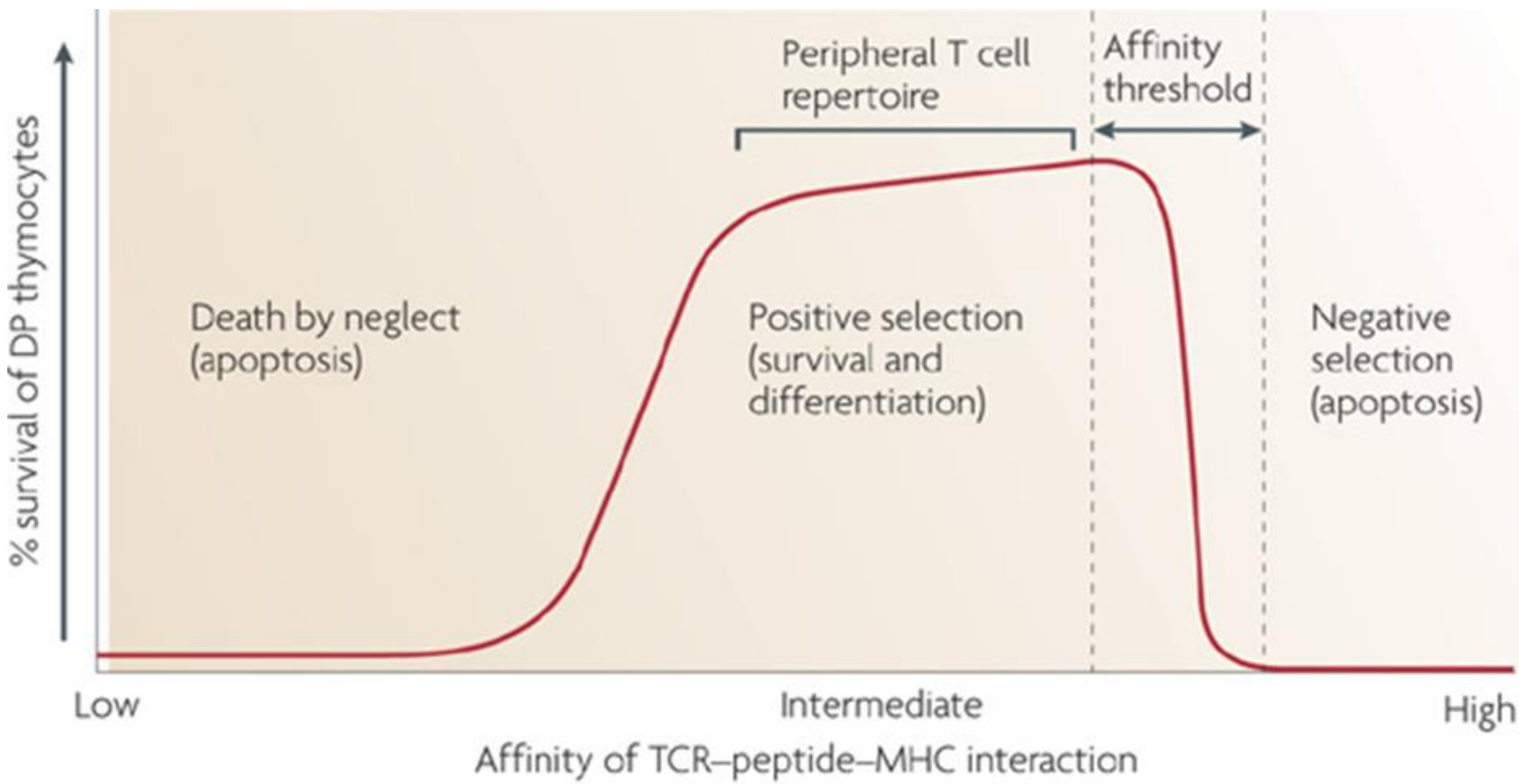
Peptide generation & loading on MHC

z cytoplazmy (např. virové)
proteazom (+IFNγ)
kratší délky

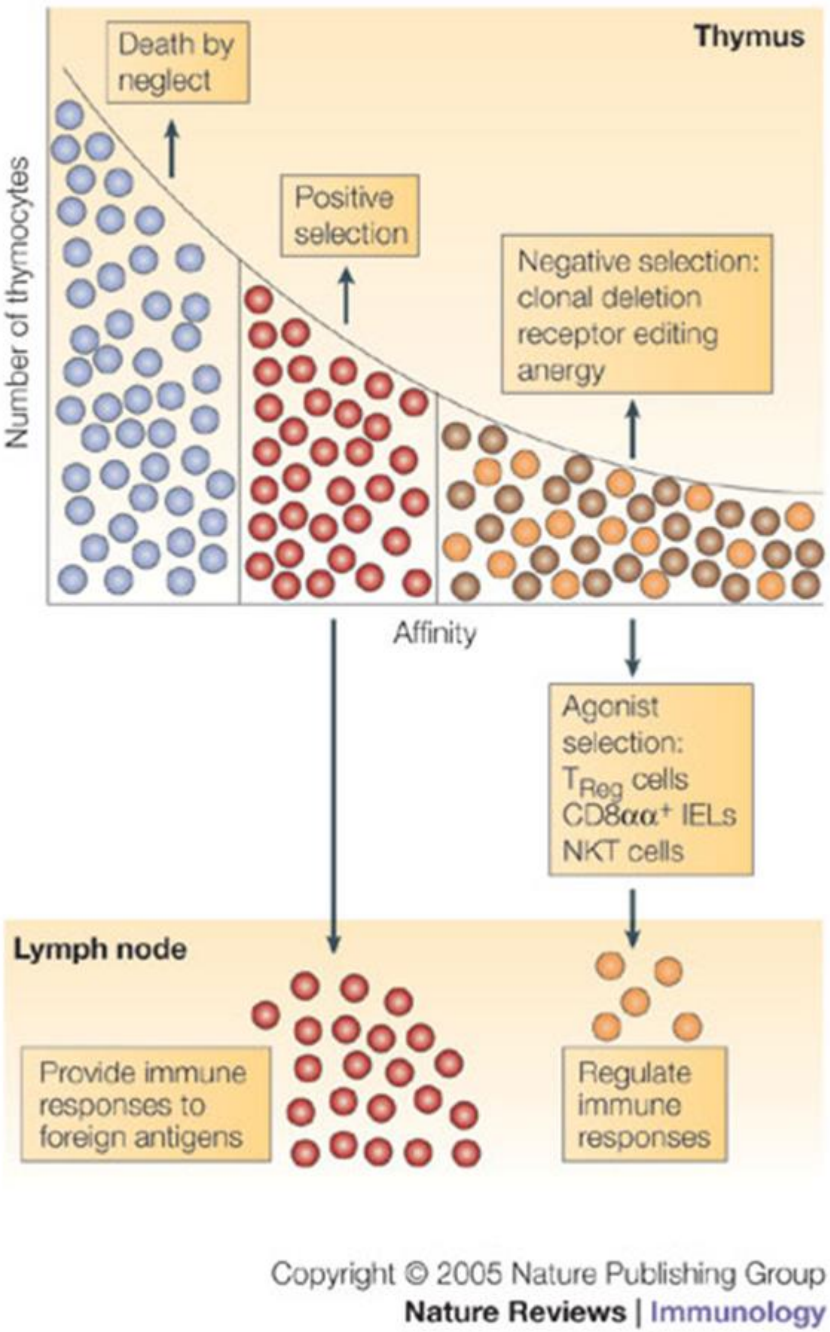
z ednozomu (např. extracelulární fagocytované)
lyzozomální proteázy
delší délky



Selekce T lymfocytů v thymu je podmíněna **afinitou** jejich TCR k antigenům/ peptidům MHC II



Nature Reviews | Immunology



Quantitative perspective

The affinity of the T-cell receptor (TCR) for self-peptide–MHC ligands is the crucial parameter that drives developmental outcome in the thymus.

- Progenitors that have no affinity or very low affinity **die by neglect**. This is thought to be the fate of most thymocytes.
- If the TCR has a low affinity for self-peptide–MHC, then the progenitor survives and differentiates, a process that is known as **positive selection**.
- If the progenitor has a high affinity for self-peptide–MHC, then several outcomes are possible.
  - First, the progenitor can be selected against, a process that is known as **negative selection**. The main mechanism of negative selection is clonal deletion, but receptor editing and anergy have also been described.
  - Second, there seem to be mechanisms that select for high-affinity self-reactive cells and result in differentiation into a **'regulatory'-cell phenotype.** It is not known what determines whether a T cell is tolerized by negative selection or is selected to become a regulatory T cell.
  - (IEL, intestinal epithelial lymphocyte; NKT cell, natural killer T cell; T_{Reg} cell, $CD4^{+}CD25^{+}$ regulatory T cell).

Thymus opouštějí kompetentní ale „naivní“ T lymfocyty, které ale musí být aktivovány v periferii

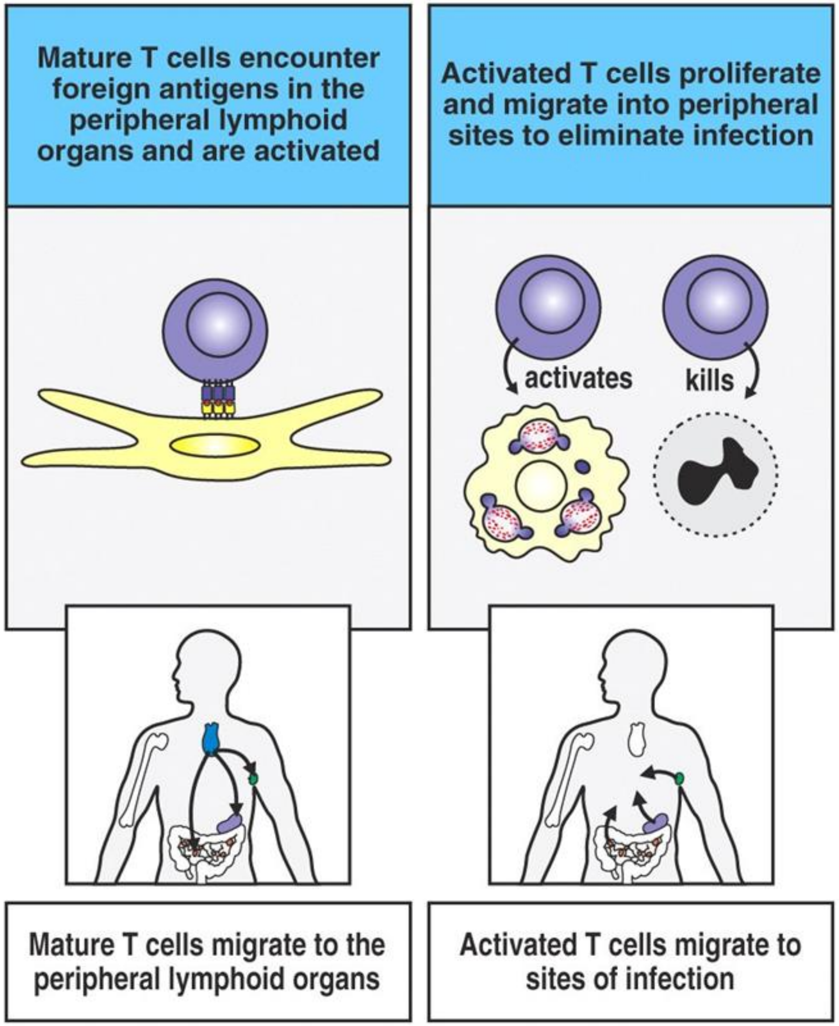


Figure 7-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Normální aktivace T lymfocytů

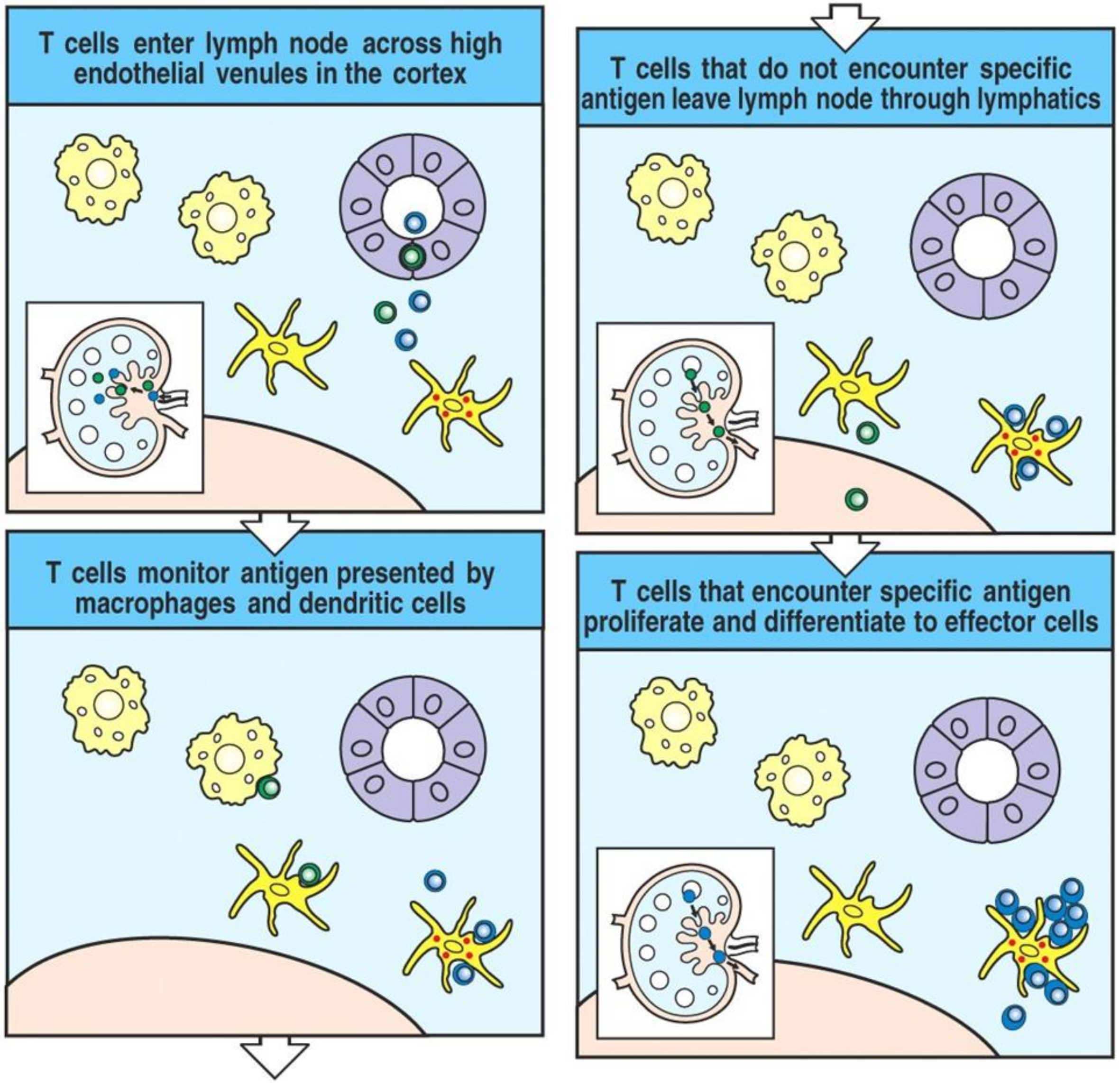
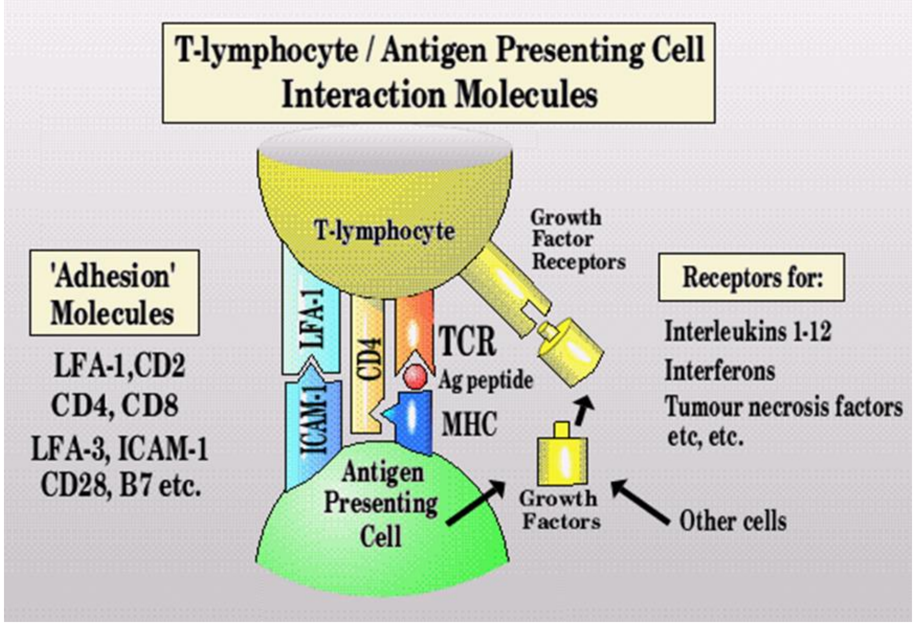


Figure 8-4 Immunobiology, 6/e. (© Garland Science 2005)

- An important part of determining which signalling molecules are present is the **local environment** within the architecture of the immune system = i.e. the inflammatory environment shapes the activation of both T cells and APCs
- Infections tend to cause inflammation and the release of inflammatory cytokine molecules like interferon-gamma, and find their way into the immune system via the lymph system to the lymph-nodes. Therefore the **lymph-node** is specialized for presenting *foreign* antigens to generate immune responses.

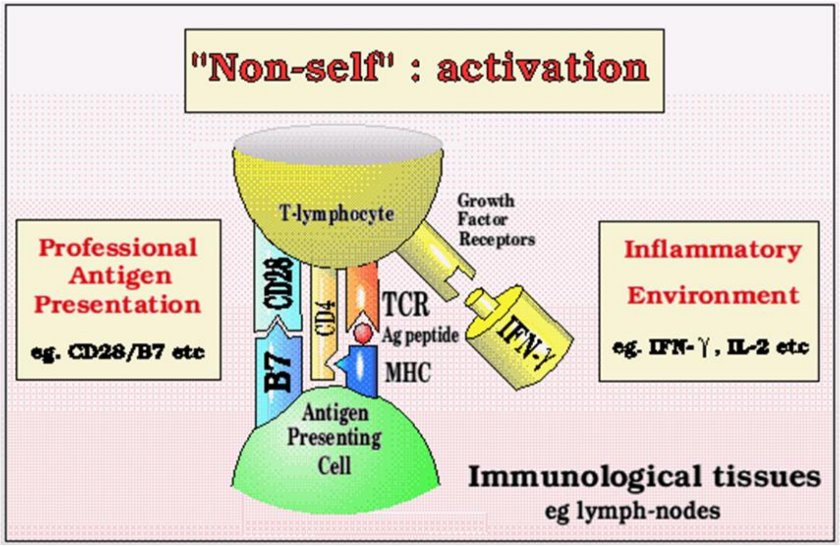
Normální aktivace Th lymfocytů

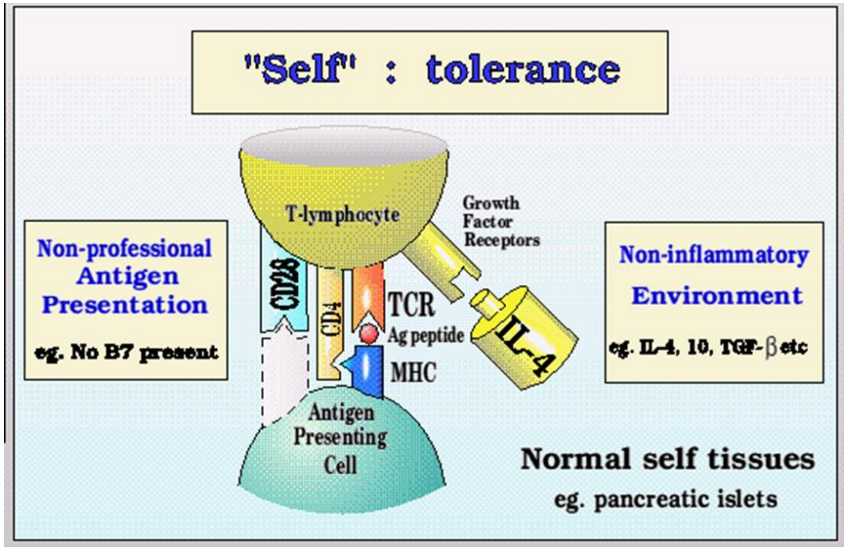


- T-lymphocytes express **a CD4, a receptor for the MHC-class II molecule**
- antigens from the infectious organism or foreign tissue are processed into peptides by **APCs** (B cells, Mac, and DCs) and these peptides that bind to the MHC-II molecules that are recognised by the T-lymphocyte using its antigen receptor
  - **MHC restriction**
- A number of other adhesion molecules and growth factors are also used to send signals between the T- lymphocyte and the APCs, and only if all the signals are correct does the T-lymphocyte become activated and aggressive
  - an aggressive response results in the multiplication of that clone of T-lymphocytes, which also develop the ability to kill all further infected cells, using a similar recognition process to that shown above

Aktivace Th lymfocytů tedy zásadně závisí na „lokálním prostředí“

- outside the immune system many of the important molecules for signaling aggression are not expressed
- In this situation, although antigen can still be recognized by the T-lymphocyte, the response is not one of aggression, but rather of tolerance
- This non-inflammatory environment can be reinforced by the presence of **anti-inflammatory cytokines like IL-4 and IL-10**, that can either be produced by healthy tissues, or by a population of T-lymphocytes that are protective and tend to yet further suppress any tendency to (self) aggression





Aktivace T lymfocytů vede k jejich proliferaci ve funkčně různorodé efektorové buňky

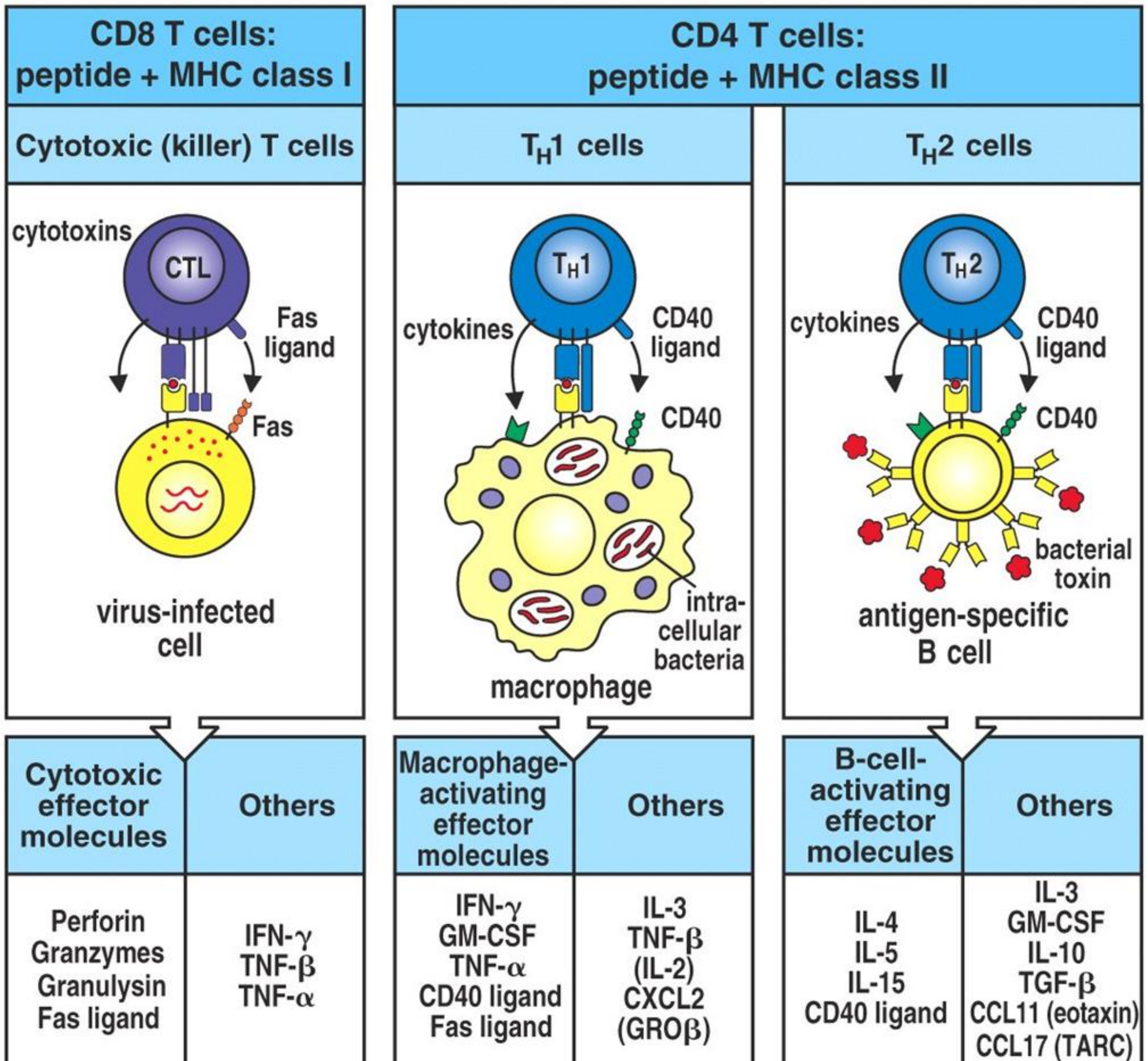


Figure 8-31 Immunobiology, 6/e. (© Garland Science 2005)

Funkce T lymf. (CD4/CD8) se liší primárně podle jejich cytokinového profilu

Cytokine	T-cell source	Effects on: B cells	Effects on: T cells	Effects on: Macrophages	Effects on: Hematopoietic cells	Effects on: Other somatic cells	Effect of gene knockout
Interleukin-2 (IL-2)	Naive, T_H1, some CD8	Stimulates growth and J-chain synthesis	Growth	–	Stimulates NK cell growth	–	↓ T-cell responses IBD
Interferon-γ (IFN-γ)	T_H1, CTL	Differentiation IgG2a synthesis (mouse)	Inhibits T_H2 cell growth	Activation, ↑ MHC class I and class II	Activates NK cells	Antiviral ↑ MHC class I and class II	Susceptible to mycobacteria, some viruses
Lymphotoxin (LT, TNF-β)	T_H1, some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen

Figure 8-32 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Cytokine	T-cell source	Effects on: B cells	Effects on: T cells	Effects on: Macrophages	Effects on: Hematopoietic cells	Effects on: Other somatic cells	Effect of gene knockout
Interleukin-4 (IL-4)	T_H2	Activation, growth IgG1, IgE ↑ MHC class II induction	Growth, survival	Inhibits macrophage activation	↑ Growth of mast cells	–	No T_H2
Interleukin-5 (IL-5)	T_H2	Mouse: Differentiation IgA synthesis	–	–	↑ Eosinophil growth and differentiation	–	Reduced eosinophilia
Interleukin-10 (IL-10)	T_H2, (human: some T_H1)	↑ MHC class II	Inhibits T_H1	Inhibits cytokine release	Co-stimulates mast cell growth	–	IBD

Figure 8-32 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Funkce T lymf. (CD4/CD8) se liší primárně podle jejich cytokinového profilu

Cytokine	T-cell source	Effects on					Effect of gene knockout
		B cells	T cells	Macrophages	Hematopoietic cells	Other somatic cells	
Interleukin-3 (IL-3)	T_H1, T_H2, some CTL	–	–	–	Growth factor for progenitor hematopoietic cells (multi-CSF)	–	–
Tumor necrosis factor-α (TNF-α)	T_H1, some T_H2, some CTL	–	–	Activates, induces NO production	–	Activates microvascular endothelium	Resistance to Gram –ve sepsis
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T_H1, some T_H2, some CTL	Differentiation	Inhibits growth ?	Activation Differentiation to dendritic cells	↑ Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	–	–
Transforming growth factor-β (TGF-β)	CD4 T cells	Inhibits growth IgA switch factor	Inhibits growth, promotes survival	Inhibits activation	Activates neutrophils	Inhibits/ stimulates cell growth	Death at ~10 weeks

Figure 8-32 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Molekulární mechanizmy **periferní** autotolerance

- **NEZBYTNÁ, CENTRÁLNÍ BY SAMA O SOBĚ NESTAČILA!!!**
  - it is not possible to express all self-antigens in thymus and ensure the elimination of entire pool of auto-aggressive T lymphocytes
- (1) very low number of self-reactive lymphocytes (surviving the clonal deletion) escape the central mechanisms and leave the thymus
  - autoreactive B & T lymphocytes are normally present in healthy individuals
    - but in order **to be activated they need many other signals, mainly from the innate immune cells**
      - usually in the presence of infection or tissue damage
- (2) intentional survival of autoreactive T cell differentiated into natural peripheral Treg to boost immune tolerance
  - CD4+CD25+ (about 5-10% of CD4 cells)
  - their development and maintenance is highly dependent on co-stimulation and IL-2
  - Treg express CD25, TNFa receptor, CTLA-4, and Foxp3
  - act in tissues to control inflammation via direct effects on effector T cells or DCs
  - suppression is contact and also cytokine dependent (TGF-b/ IL-10)

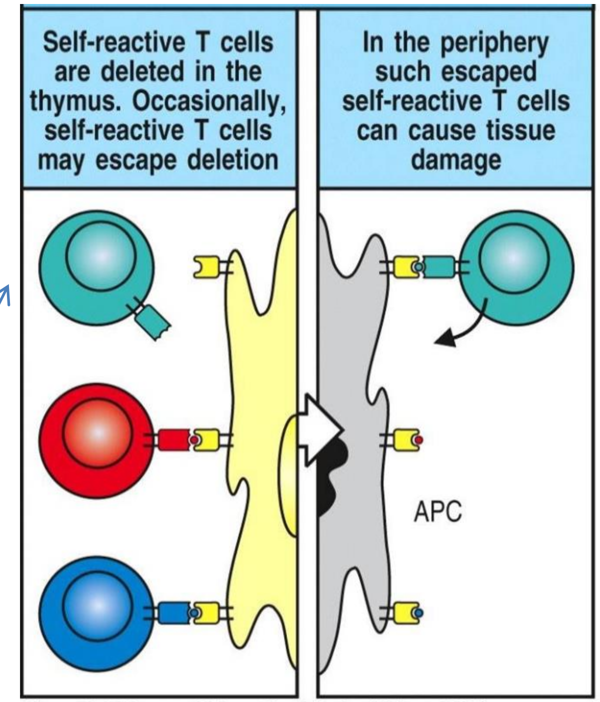
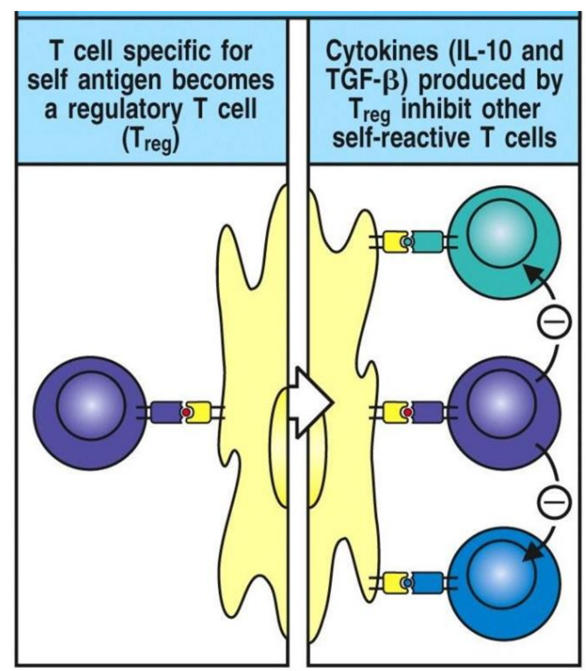
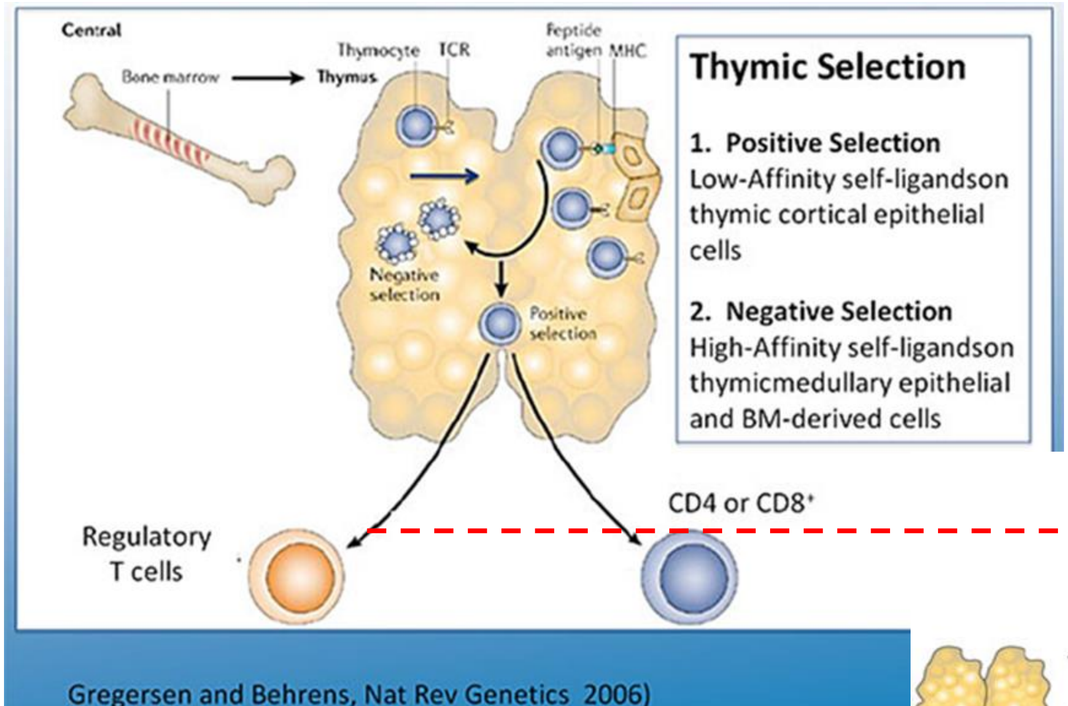
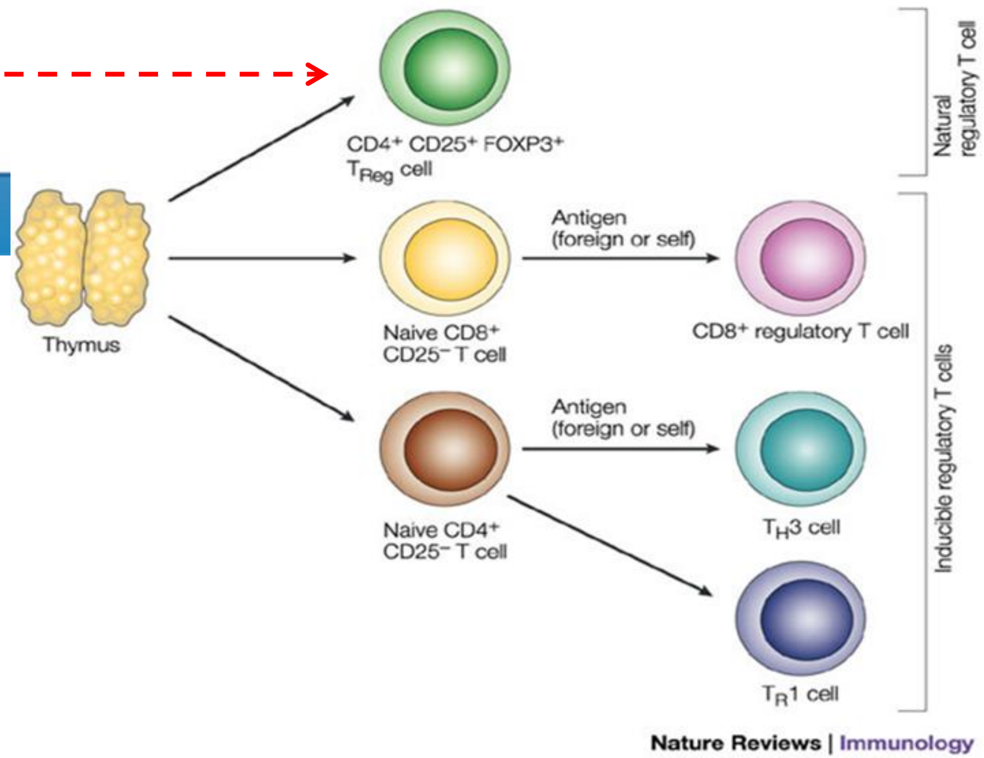


Figure 13-14 Immunobiology, 6/e. (© Garland Science 2005)



Existují ještě další (CD25⁻) subpopulace supresorových Treg lymfocytů které jsou **inducibilní**





Shrnutí mechanizmů autotolerance

Layers of self-tolerance		
Type of tolerance	**Mechanism**	**Site of action**
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (eg, thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T_H2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal exhaustion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

Figure 13-16 Immunobiology, 6/e.

AKTIVAČNÍ A EFEKTOROVÉ MECHANIZMY AUTOIMUNITY

Molecular mechanisms of abnormal B or T cell activation, i.e. autoimmunity

- (1) **genetically** determined failure of central or peripheral self-tolerance
- (2) mechanisms related to **infection**
  - production of proinflammatory/costimulatory signals
  - cross-reactivity (molecular and viral mimicry)
  - polyclonal B cell activation by viruses and bacteria
- (3) release of **sequestered antigen** (several sites of „immune privilege“)
- (4) **haptens** becoming immunogenic
- (5) inappropriately high, **abnormal MHC expression**

Molecular mechanisms of abnormal B or T cell activation, i.e. autoimmunity

- (1) **genetically** determined failure of central or peripheral self-tolerance
  - strong or nearly monogenic determination
    - mutated AIRE (APS 1) = insufficient expression of tissue-specific antigens in v thymus
    - mutated FoxP3 (IPEX) = impaired differentiation of Treg
    - mutated Fas = defects of apoptosis (a thus negative selection)
  - moderate to weak genetic predisposition

Příklad (1): APS 1 – geneticky podmíněné selhání negativní selekce v thymu

- autoimunní polyglandulární syndrom typu 1 (APS1)
- autozomálně recesivní
- defective autoimmune regulator – AIRE (AutoImmune Regulator) gene (chromosom 21q22.3)
  - AIRE protein - transcription factor exprimován v lymfoidních orgánech
- role v indukci imunitní tolerance
  - kontroluje expresi důležitých „self-antigenů“, zejm. těch, které jsou jinak exprimovány jen v endokrinních žlázách, na úrovni epiteliálních buněk thymu

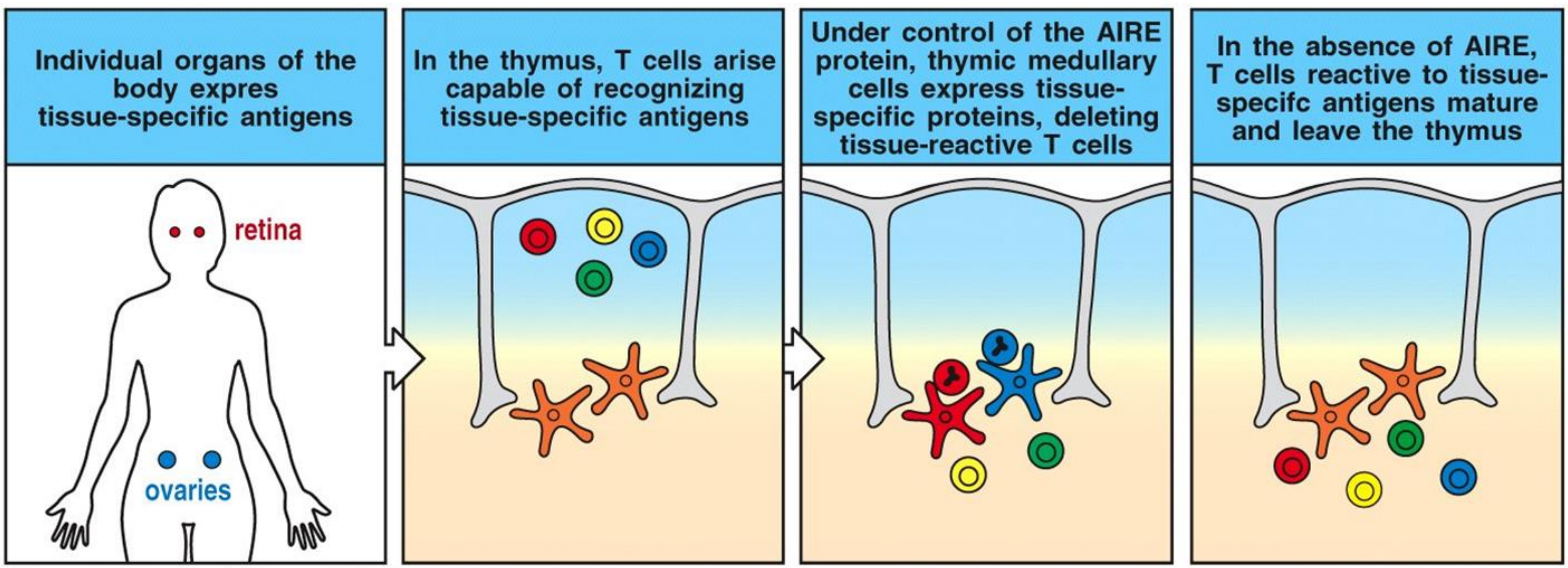
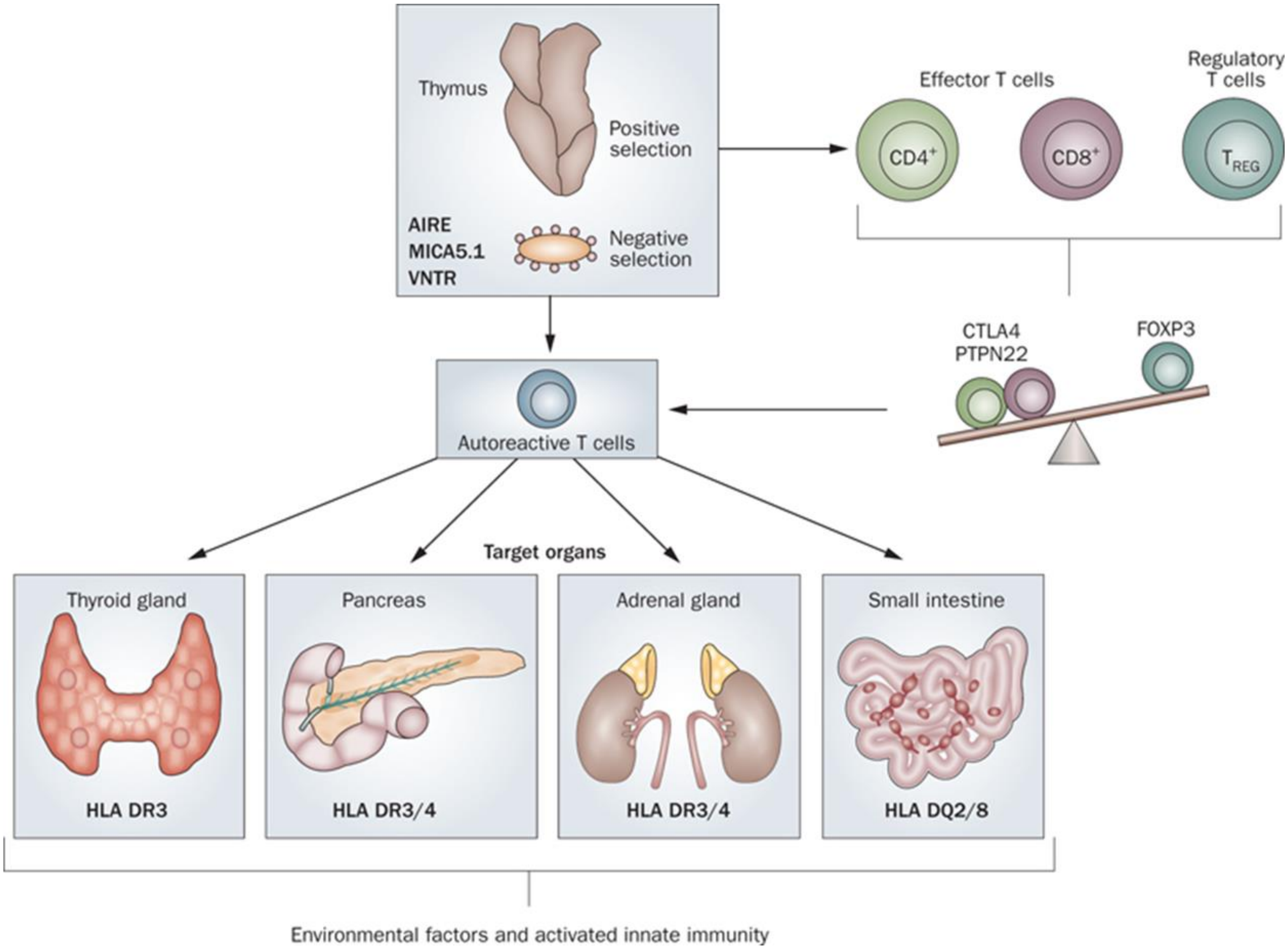


Figure 13-9 Immunobiology, 6/e. (© Garland Science 2005)

Endokrinopatie u APS 1



Genetické predispozice k autoimunitním nemocem

- silná (často monogenní)
  - skupina autoimunitních polyglandulárních syndromů
    - defekt AIRE = APS 1 (syn. APECED (autoimunní polyendokrinopatie – candidiasis - ektodermální dystrofie), Whitakerův syndrom)
      - M. Addison, + hypoparathyreoidismus, další
    - heterogenní genetický defekt = APS 2 (Schmidtův syndrom)
      - M. Addison, hypothyreoidismus, T1DM
    - defekt FoxP3 = IPEX (immune dysfunction, polyendocrinopathy, and enteropathy, X-linked)
- polygenní
  - MHC alely →
  - jiné geny

Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Figure 13-20 Immunobiology, 6/e. (© Garland Science 2005)

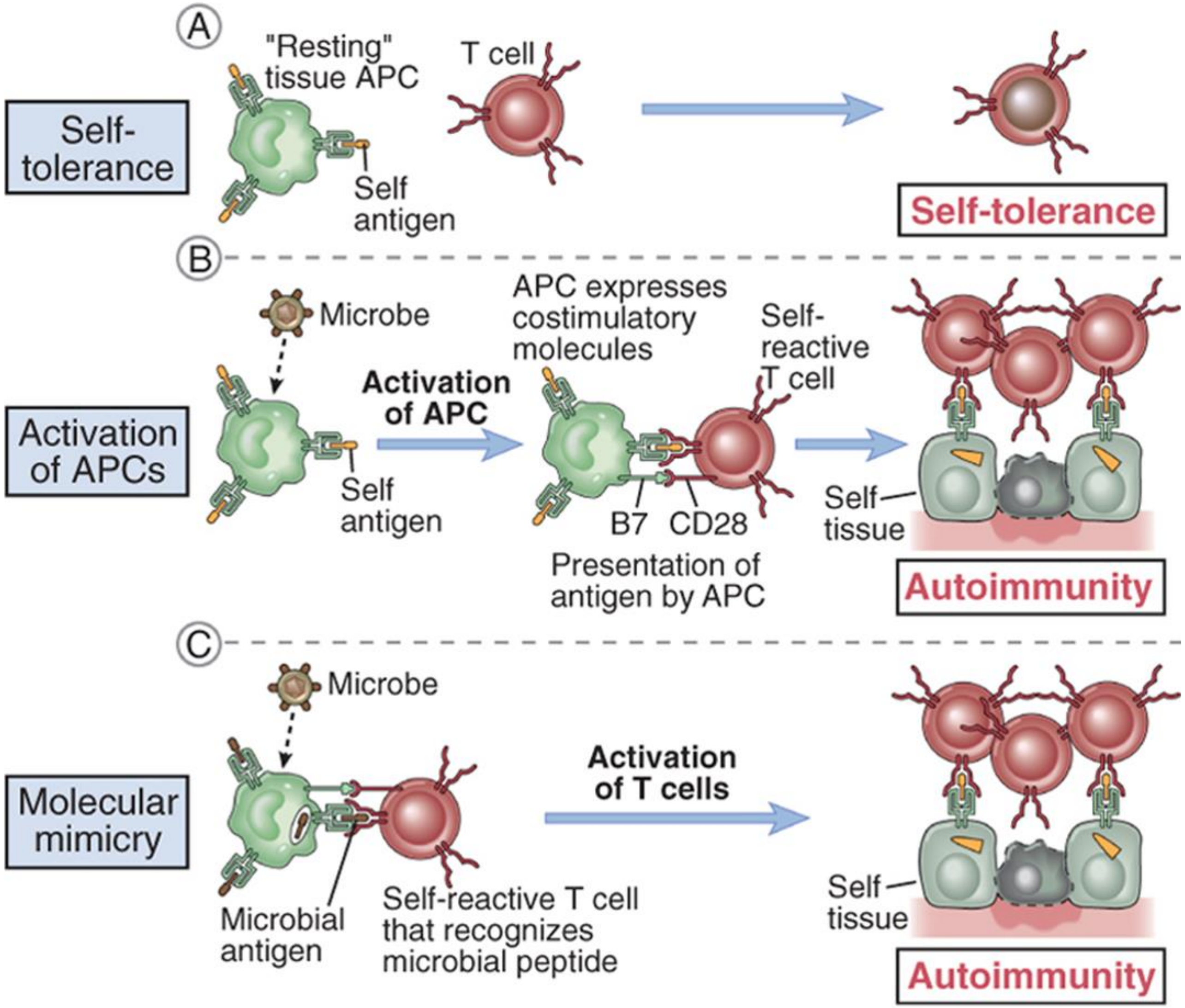
Příklady non-MHC genetických variant asociovaných s rizikem autoimunitních nemocí

Gene	Phenotype of mutant or knockout mouse	Mechanism of failure of tolerance	Human disease?
AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	SLE
CTLA-4	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in $CD4^+$ T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
Fas/FasL	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature $CD4^+$ T cells	Autoimmune lymphoproliferative syndrome (ALPS)
FoxP3	Multi-organ lymphocytic infiltrates, wasting	Deficiency of regulatory T cells	IPEX
IL-2; IL-2Rα/β	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival or function of regulatory T cells	None known
SHP-1	Multiple autoantibodies	Failure of negative regulation of B cells	None known
PTPN22	Increased lymphocyte proliferation, antibody production	Reduced inhibition by tyrosine phosphatase?	PTPN22 polymorphisms are associated with several autoimmune diseases

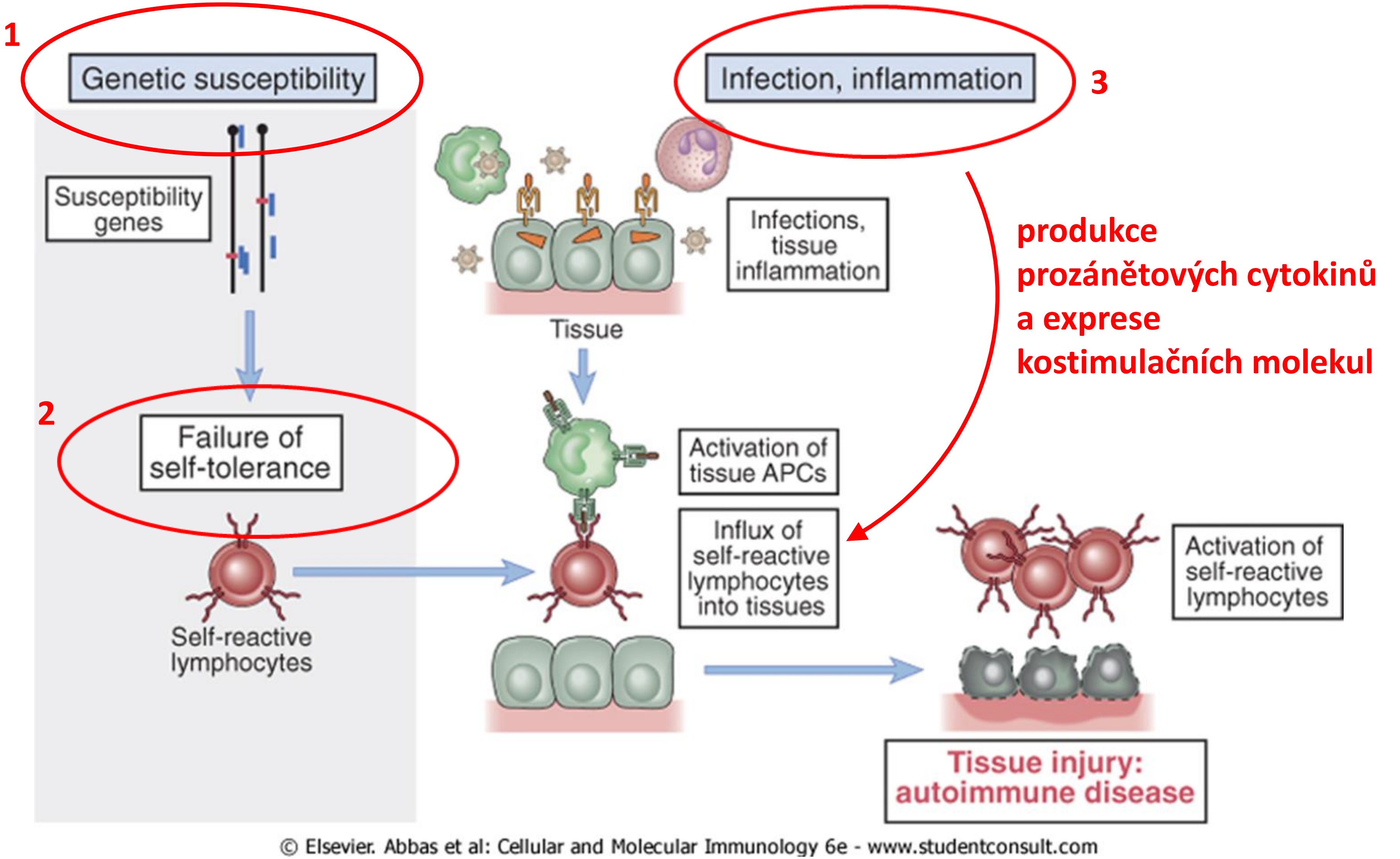
Molecular mechanisms of abnormal B or T cell activation, i.e. autoimmunity

- (1) **genetically** determined failure of central or peripheral self-tolerance
  - strong or nearly monogenic determination
    - mutated AIRE (APS 1) = insufficient expression of tissue-specific antigens in v thymus
    - mutated FoxP3 (IPEX) = impaired differentiation of Treg
    - mutated Fas = defects of apoptosis (a thus negative selection)
  - moderate to weak genetic predisposition
- (2) mechanisms related to **infection**
  - production of proinflammatory/costimulatory signals
  - cross-reactivity (molecular and viral mimicry)
    - viral and non-viral peptides can mimic self-peptides and induce autoimmunity
  - polyclonal B cell activation by viruses and bacteria
    - typical for some bacteria and viruses (e.g. G- bacteria, CMV, EBV) inducing nonspecific polyclonal activation of B-lymphocytes (expressing IgM) in absence of Th-ly („by-pass oeffect“)
    - if B cells reactive to self-peptides are activated, autoimmunity can occur

Příklad (2): Role infekcí v rozvoji autoimunity



Taken together - the most common postulated mechanism of autoimmunity



Molekulární mimikry

- sequential or structural identity or similarity of microbe with host tissue
  - auto-aggressive reaction is mediated by the same effector mechanisms used for host defense against pathogen
  - however, often in the terrain of genetic predisposition
    - mainly MHC II alleles
    - but also MHC I – e.g. HLA B27

Associations of infection with immune-mediated tissue damage		
Infection	**HLA association**	**Consequence**
Group A *Streptococcus*	?	Rheumatic fever (carditis, polyarthritis)
Chlamydia trachomatis	HLA-B27	Reiter's syndrome (arthritis)
Shigella flexneri, *Salmonella typhimurium*, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Campylobacter jejuni*	HLA-B27	Reactive arthritis
Borrelia burgdorferi	HLA-DR2, DR4	Chronic arthritis in Lyme disease
Coxsackie A virus, Coxsackie B virus, echoviruses, rubella	HLA-DQ2, HLA-DQ8 DR4	IDDM

Figure 11-30 The Immune System, 2/e (© Garland Science 2005)

TABLE 20-3 MOLECULAR MIMICRY BETWEEN PROTEINS OF INFECTIOUS ORGANISMS AND HUMAN HOST PROTEINS

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

†Each number indicates the position in the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from MBA Oldstone, 1987, *Cell* **50**:819.

Revmatická horečka jako příklad mol. mimikry

- Etiology: Streptococci group A (angina, pharyngitis)
- Pathogenesis: Ab X-react w/ connective tissue in susceptible individuals→ autoimmune reaction (2- 3 wks) → inflammation (T cells, macrophages) → heart, skin, brain & joints
- Acute RF – acute inflammation
  - heart – pancarditis
  - skin – erythema marginatum
  - CNS – chorea minor (Sydenham)
  - migrating polyarthritis
- Chronic RF
  - deformities of heart valves
    - most commonly mitral stenosis

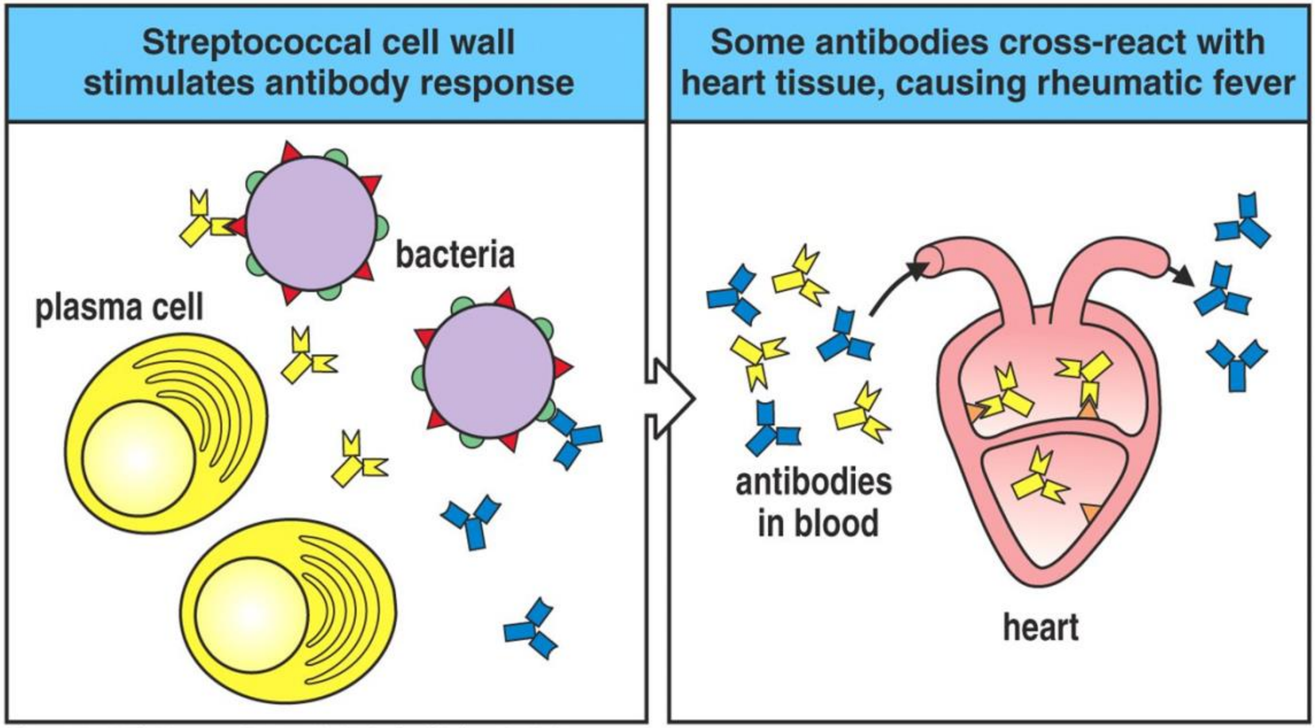


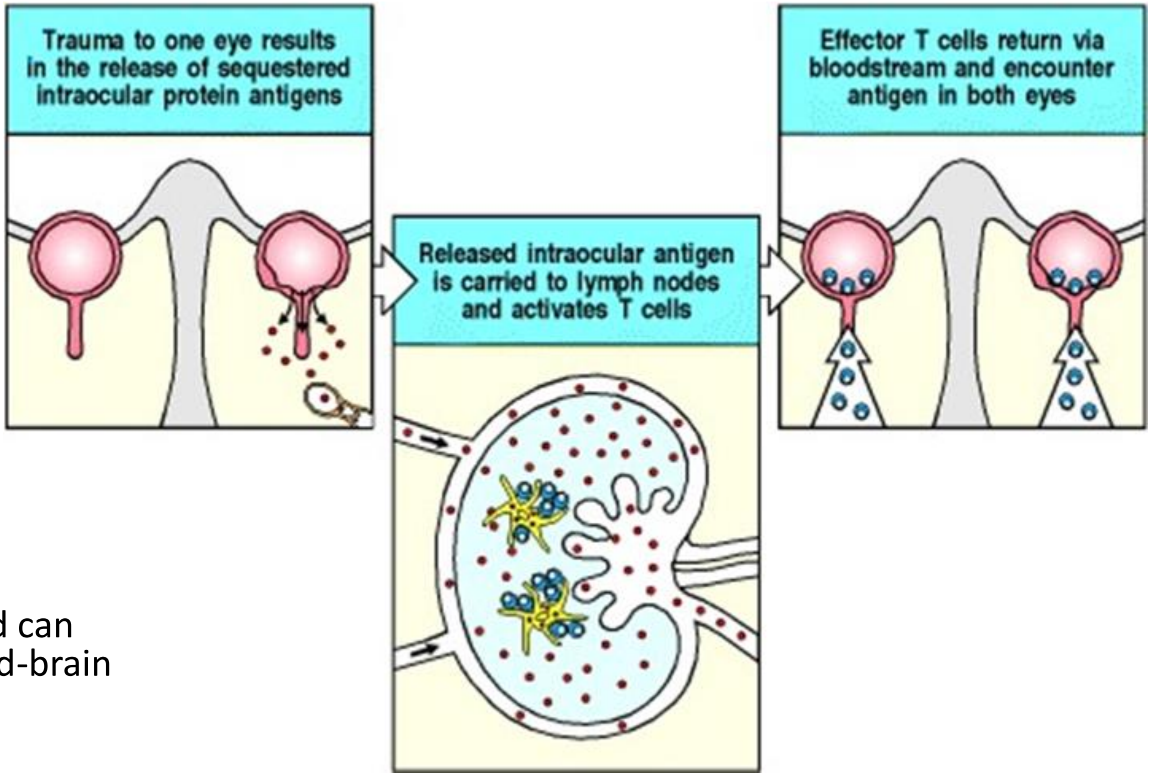
Figure 11-29 The Immune System, 2/e (© Garland Science 2005)

Molecular mechanisms of abnormal B or T cell activation, i.e. autoimmunity

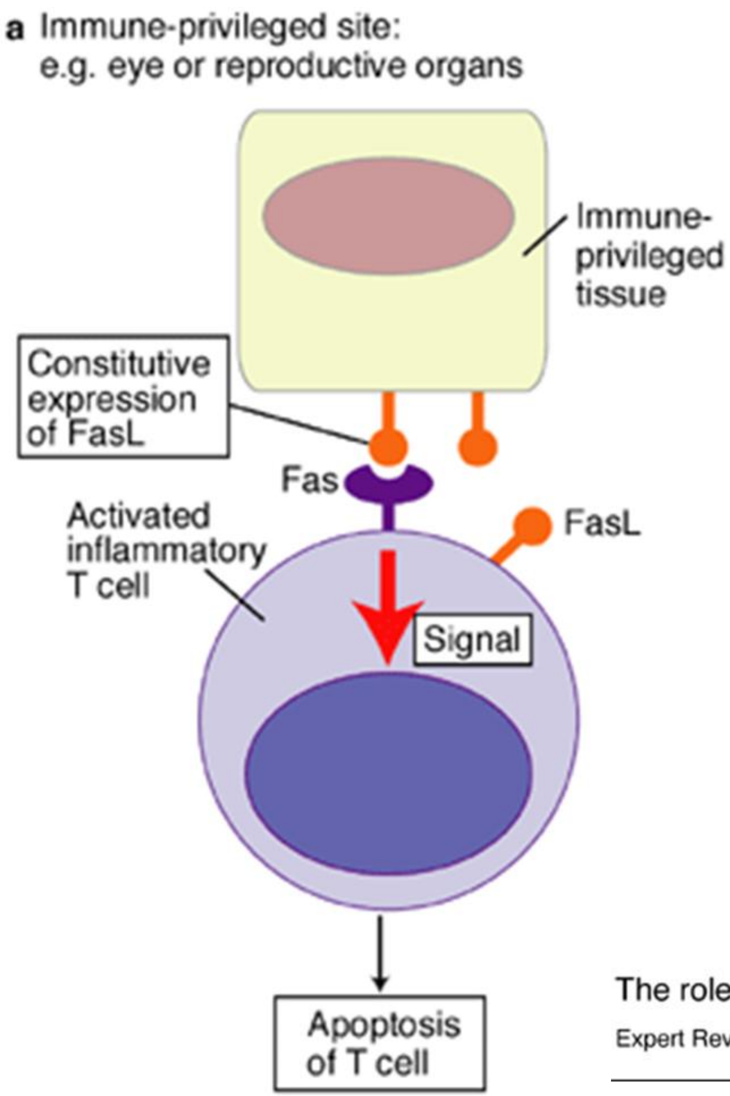
- (1) **genetically** determined failure of central or peripheral self-tolerance
  - strong or nearly monogenic determination
    - mutated AIRE (APS 1) = insufficient expression of tissue-specific antigens in v thymus
    - mutated FoxP3 (IPEX) = impaired differentiation of Treg
    - mutated Fas = defects of apoptosis (a thus negative selection)
  - moderate to weak genetic predisposition
- (2) mechanisms related to **infection**
  - cross-reactivity (molecular and viral mimicry)
    - viral and non-viral peptides can mimic self-peptides and induce autoimmunity
  - polyclonal B cell activation by viruses and bacteria
    - typical for some bacteria and viruses (e.g. G- bacteria, CMV, EBV) inducing nonspecific polyclonal activation of B-lymphocytes (expressing IgM) in absence of Th-ly („by-pass oeffect“)
    - if B cells reactive to self-peptides are activated, autoimmunity can occur
- (3) release of **sequestered antigen** (several sites of „immune privilege“)
  - eye, testes , brain, uterus, …

Příklad (3): Ztráta „imunitní privilegovanosti“

- the original idea of „requested antigens“
  - auto-antigens separated from auto-reactive T-lymphocytes by anatomical barriers
- nowadays more of a functional concept of „immune priviledge“
  - anatomic factors
  - absence of lymphatics
  - absence of APCs
  - low expression of MHC I antigens
  - high concentration of anti-inflammatory cytokines
  - high expression of FasL → high activity of apoptosis of T lymph
  - etc.
- examples
  - eye → sympathetic ophthalmia
    - against lens proteins (crystallin)
  - testes → anti-sperm & orchitis
  - brain (BBB) → antibodies in blood can attack myelin basic Protein if blood-brain barrier is breached
  - uterus (placenta) → abortion
  - hair follicles → alopecia



FasL expression may play a role in "immune privilege"



The role of Fas ligand (FasL) in immune privilege

Expert Reviews in Molecular Medicine©2001 Cambridge University Press

- FasL expression in brain, eye, placenta, and reproductive organs is believed to contribute to immunological privilege
- Aberrant FasL expression may also be an adaptation of tumors to evade immune surveillance

Molecular mechanisms of abnormal B or T cell activation, i.e. autoimmunity

- (1) **genetically** determined failure of central or peripheral self-tolerance
  - strong or nearly monogenic determination
    - mutated AIRE (APS 1) = insufficient expression of tissue-specific antigens in v thymus
    - mutated FoxP3 (IPEX) = impaired differentiation of Treg
    - mutated Fas = defects of apoptosis (a thus negative selection)
  - moderate to weak genetic predisposition (see further)
- (2) mechanisms related to **infection**
  - cross-reactivity (molecular and viral mimicry)
    - viral and non-viral peptides can mimic self-peptides and induce autoimmunity
  - polyclonal B cell activation by viruses and bacteria
    - typical for some bacteria and viruses (e.g. G- bacteria, CMV, EBV) inducing nonspecific polyclonal activation of B-lymphocytes (expressing IgM) in absence of Th-ly („by-pass oeffect“)
    - if B cells reactive to self-peptides are activated, autoimmunity can occur
- (3) release of **sequestered antigen** (several sites of „immune privilege“)
  - eye, testes , brain, uterus, …
- (4) **haptens** becoming immunogenic
- (5) inappropriately high, **abnormal MHC expression**
  - e.g. type I diabetes: pancreatic β cells might express abnormally high levels of MHC I and MHC II upon the pathologic stimulation
    - MHC II – APC only! this may hypersensitize TH cells to β cell peptides

Příklad (5): abnormální exprese antigenů MHC II. třídy v neimunitních bb.

- MHC II antigens are normally expressed only on certain cells!!!
- due to pathologic activation by pro-inflammatory cytokines (IFNγ) this can change (MHC II are expressed together with tissue-specific Ag)
- auto-reactive T lymphocytes become activated
- examples
  - pancreas
    - β cells normally low MHC I expression, no MHC II
    - β cells in T1DM – high expression of MHC I and II
      - upon stimulation by infection?
  - similarly thyroid gland in autoimmune thyroiditis (Hashimoto)

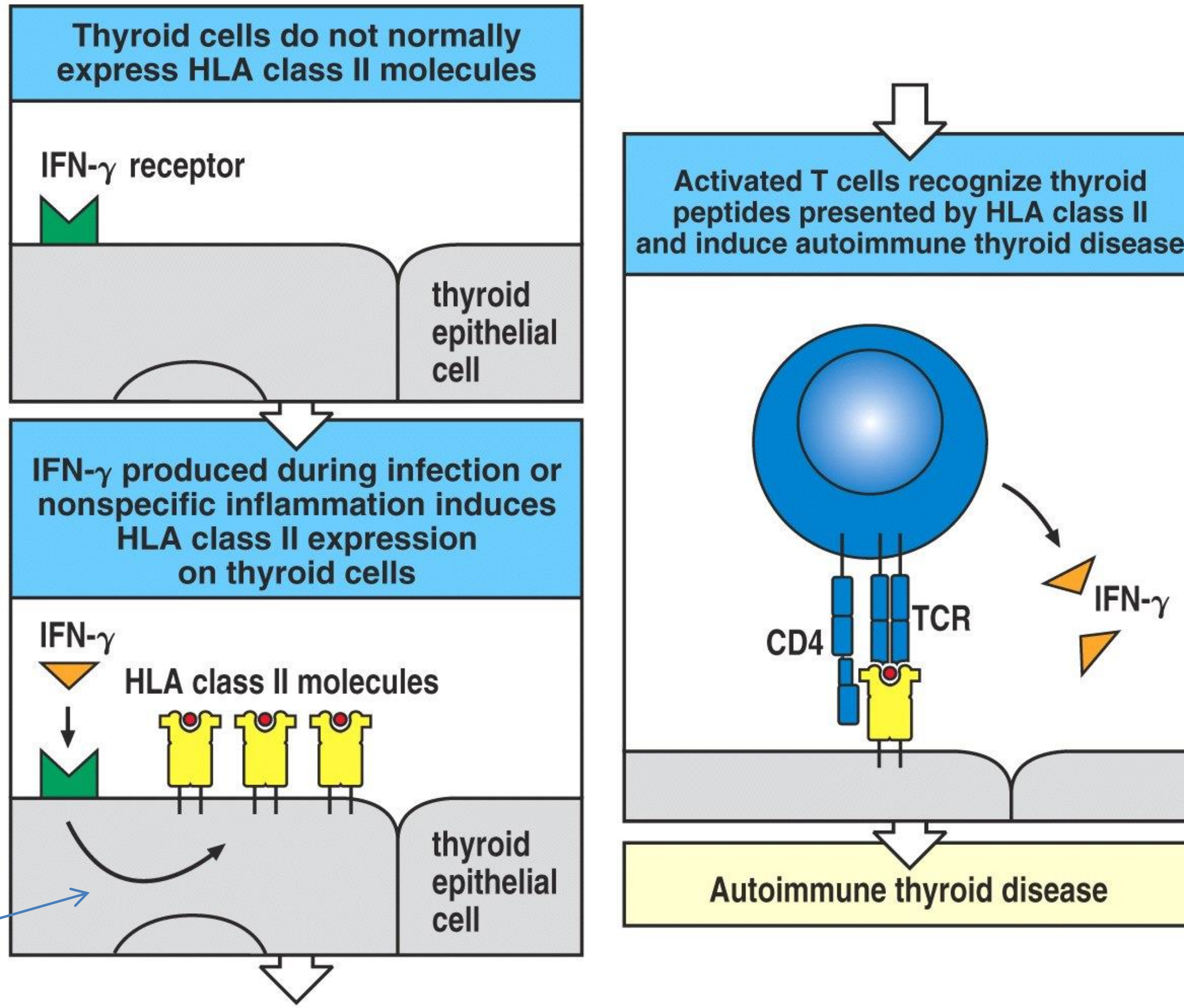
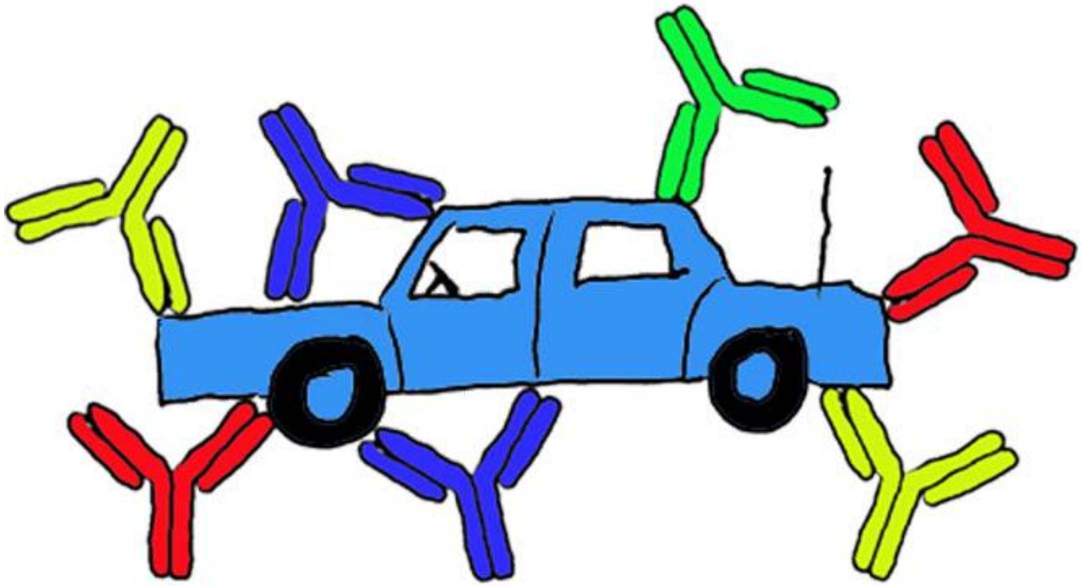


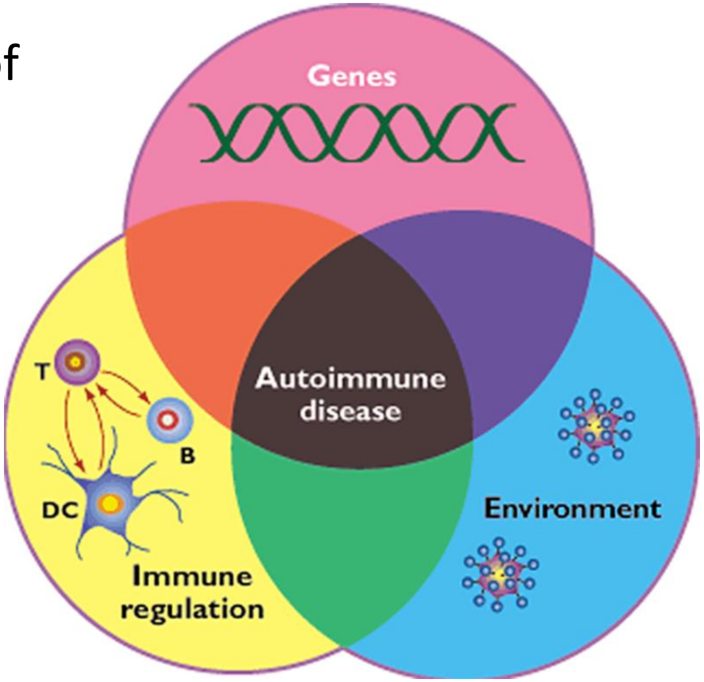
Figure 11-32 The Immune System, 2/e (© Garland Science 2005)



AUTOIMUNITA A PRINCIPY ETIOPATOGENEZE AUTOIMUNITNÍCH NEMOCÍ

Autoimunitní nemoci (AN)

- postihují cca 3 - 5% populace
- results from a failure or **breakdown of** the mechanisms normally responsible for maintaining **self-tolerance** in B cells, T cells, or both
  - nicméně patologická autoimunitní odpověď je obvykle cílena na **omezené množství autoantigenů**, která vede k poškození tkání, je velmi specifická, většina imunitní tolerance zůstává zachována
- major factors that contribute to the development of autoimmunity are
  - **genetic** susceptibility
  - **environmental** triggers
    - such as infections , vitamin levels (vit. D), nutrition?, …



- AN may be either
  - **systemic**
  - **organ specific**
- various effector mechanisms are responsible for tissue injury in different autoimmune diseases
  - (A) cell-mediated (hypersensitive reaction type IV)
  - (B) antibody-mediated (hypersensitivity type II, III, V)
- **epitope spreading** (progression and exacerbation of the disease):
  - autoimmune reactions initiated against one self-antigen that injure tissues may result in the release and alterations of other tissue antigens, activation of lymphocytes specific for these other antigens

Systémové vs. orgánově specifické AN

Organ-specific autoimmune diseases	Systemic autoimmune diseases
Type I diabetes mellitus	Rheumatoid arthritis
Goodpasture's syndrome	Scleroderma
Multiple sclerosis	Systemic lupus erythematosus Primary Sjögren's syndrome Polymyositis
Graves' disease Hashimoto's thyroiditis Autoimmune pernicious anemia Autoimmune Addison's disease Vitiligo Myasthenia gravis	

Figure 13-1 Immunobiology, 6/e. (© Garland Science 2005)

(A) Příklady buněčných (T-lymfocyty zprostředkovaných) AN

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Type I (insulin-dependent) diabetes mellitus	Islet cell antigens (insulin, glutamic acid decarboxylase, others)	Yes; specificity of T cells not established	NOD mouse, BB rat, transgenic mouse models
Rheumatoid arthritis	Unknown antigen in joint synovium	Yes; specificity of T cells and role of antibody not established	Collagen-induced arthritis, others
Multiple sclerosis, experimental autoimmune encephalomyelitis	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE induced by immunization with CNS myelin antigens; TCR transgenic models
Inflammatory bowel disease (Crohn's, ulcerative colitis)	Unknown	Yes	Colitis induced by depletion of regulatory T cells, knockout of IL-10
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barre syndrome	Induced by immunization with peripheral nerve myelin antigens
Autoimmune myocarditis	Myocardial proteins	Yes (post-viral myocarditis); specificity of T cells not established	Induced by immunization with myosin or infection by Coxsackie virus

(B) Příklady AN zprostředkovaných tkáňově specifickými protilátkami

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

AN podle typu převažující hypersensitivní reakce – typ II, III a IV

Autoimmune disease	Autoantigen	Consequence
Antibody against cell-surface or matrix antigens (type II)		
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes anemia
Autoimmune thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Non-collagenous domain of basement membrane collagen type IV	Glomerulonephritis, pulmonary hemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens. Antibodies cross-react with cardiac muscle	Arthritis, myocarditis, late scarring of heart valves
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

Figure 11-1 part 1 of 3 The Immune System, 2/e (© Garland Science 2005)

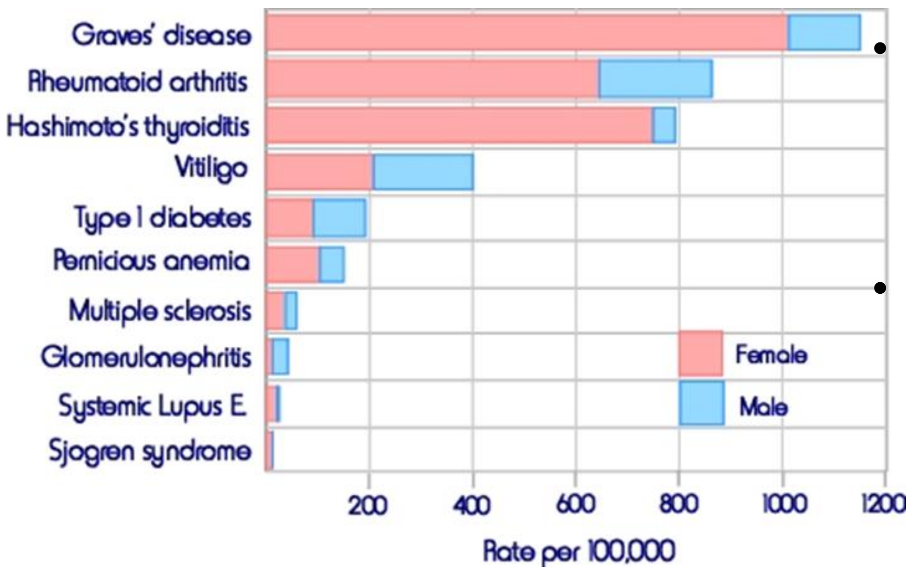
Autoimmune disease	Autoantigen	Consequence
Immune-complex disease (type III)		
Subacute bacterial endocarditis	Bacterial antigen	Glomerulonephritis
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes (with or without hepatitis C antigens)	Systemic vasculitis
Systemic lupus erythematosus	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, arthritis

Figure 11-1 part 2 of 3 The Immune System, 2/e (© Garland Science 2005)

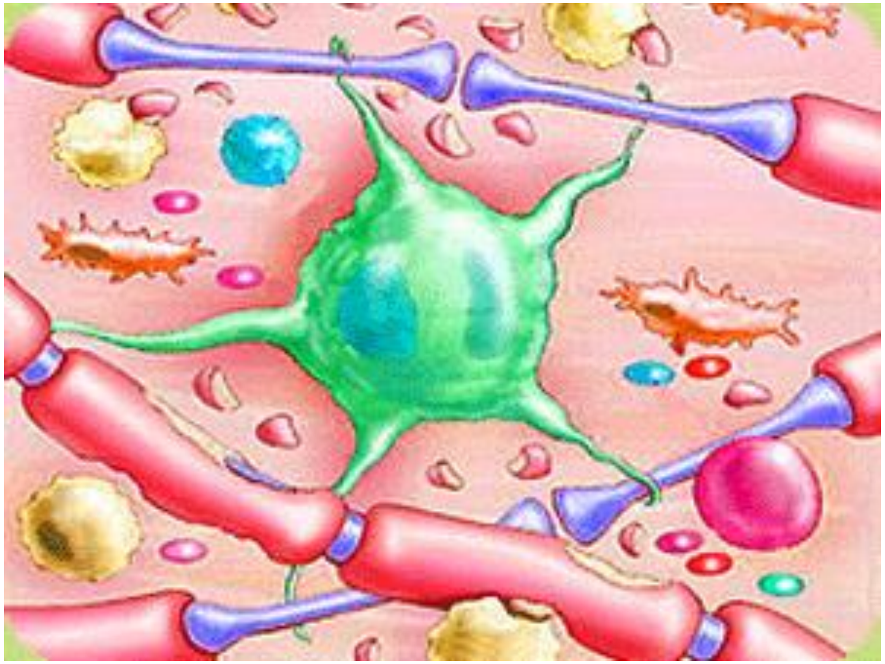
Autoimmune disease	Autoantigen	Consequence
T cell-mediated disease (type IV)		
Insulin-dependent diabetes mellitus	Pancreatic β-cell antigen	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Multiple sclerosis	Myelin basic protein, proteolipid protein	Brain degeneration. Paralysis
Celiac disease	Gluten modified by tissue transglutaminase	Malabsorption of nutrients Atrophy of intestinal villi

Figure 11-1 part 3 of 3 The Immune System, 2/e (© Garland Science 2005)

Prevalence a pohlavně specifické rozdíly



- Sex-based differences in AD can be traced to sex hormones
  - sex hormones circulate throughout the body and alter immune response by influencing gene expression
  - (in general) estrogen can trigger autoimmunity and testosterone can protect against it
- Gender-difference in immune response
  - ♀ produce a higher titer of antibodies and mount more vigorous immune responses than ♂
  - ♀ have a slightly higher cortisol secretion than ♂
  - ♀ have higher levels or CD4+ T-cells and serum IgM
- Pregnancy
  - during this, ♀ mount more of a TH2-like response
  - the change in hormones creates an anti-inflammatory environment (high cortisol levels)
  - diseases enhanced by TH2-like responses are exaggerated
  - diseases that involve TH1 inflammatory responses are suppressed
- Fetal cells can persist in the mother's blood or the mother's cells may appear in the fetus (microchimerism)
  - this can result in autoimmunity if the fetal cells mount an immune response in the mother's body (or vice versa)



PŘÍKLADY NĚKTERÝCH SYSTÉMOVÝCH AN (SLE A REVMATOIDNÍ ARTRITIDA)

Systémový lupus erythematoides (SLE)

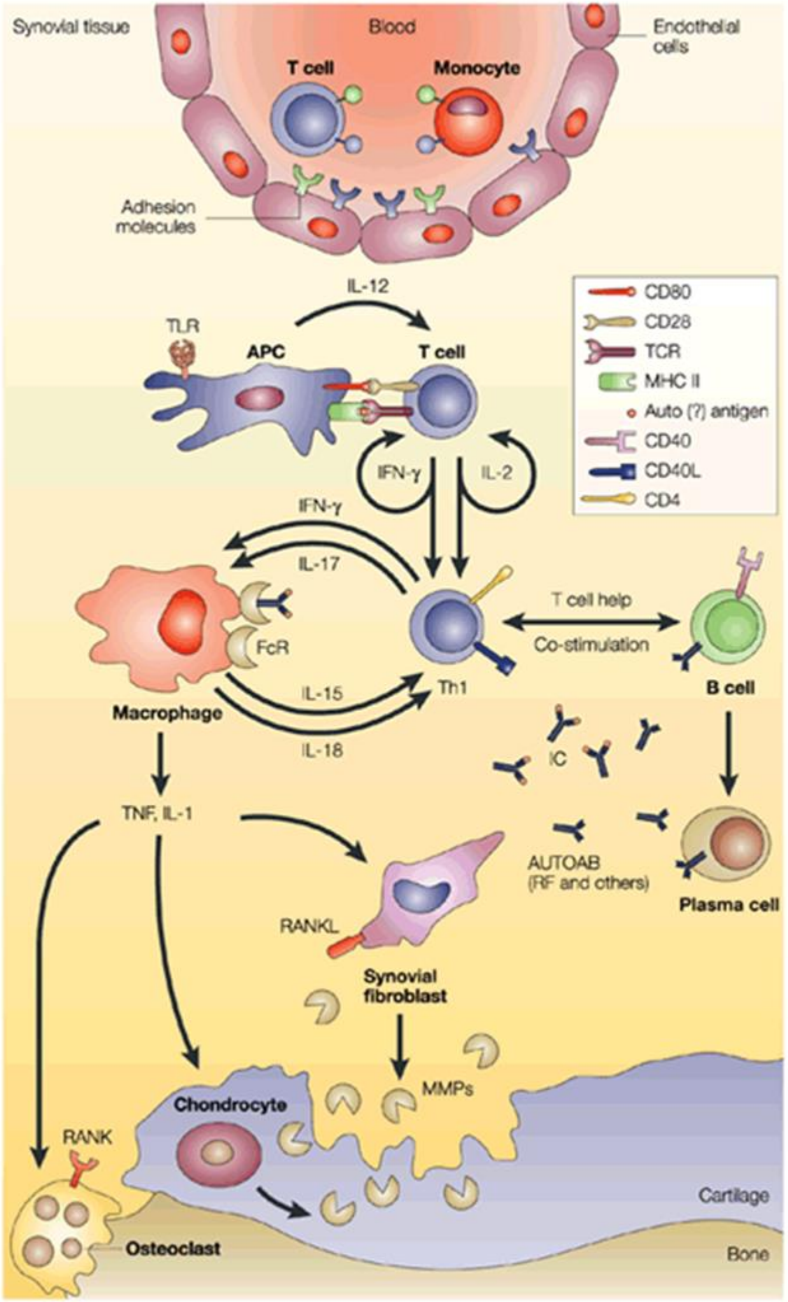
- affected organs
  - skin (butterfly rash)
  - vessels (vasculitis)
  - kidneys (lupus nephritis)
  - joints (arthritis)
  - CNS (encephalopathy)
- Immune mechanism
  - abnormal activation of DNA specific B cells by engagement of their TLR9 (binding of CpG motifs) and DNA receptors by antigens released from apoptotic cells
  - production of Ab against nuclear components
    - dsDNA (double stranded)
    - RNA-protein complexes
    - histones
  - complexes are formed (e.g. anti-dsDNS-DNA) and deposited in predilection sites (e.g. glomerulus, synovia, vessel wall) or in sites of death cells releasing DNA and DAMPs
    - this explains rash after sun exposure (UV-induced apoptosis of keratinocytes)
- very variable clinical course
  - 80% patients survive 10 yrs after diagnosis

Revmatoidní artritida (RA)

- Demographics
  - affects 1-2% of worldwide population
  - patients are 75% women between 40-60 years of age
- RA mostly damages joints, but it can also affect the heart, kidneys and eyes
- Molecular mechanism
  - T-cell mediated AD, however Ab are Also produced
    - Rheumatoid Factor (Rf): IgM antibodies to Fc fragment of IgG
  - HLA-DR4 association (MHC II)
- Mechanism of Tissue Damage
  - Invasion of T lymphocytes in the synovia and pro-inflammatory cytokine production
  - immune cells accumulate in the joints (bones, cartilage, surrounding tissue) and cause chronic inflammation. The inflammation causes destruction and scarring of the joints. Later the joints deform and lose their structure

Molecular mechanism operating in RA

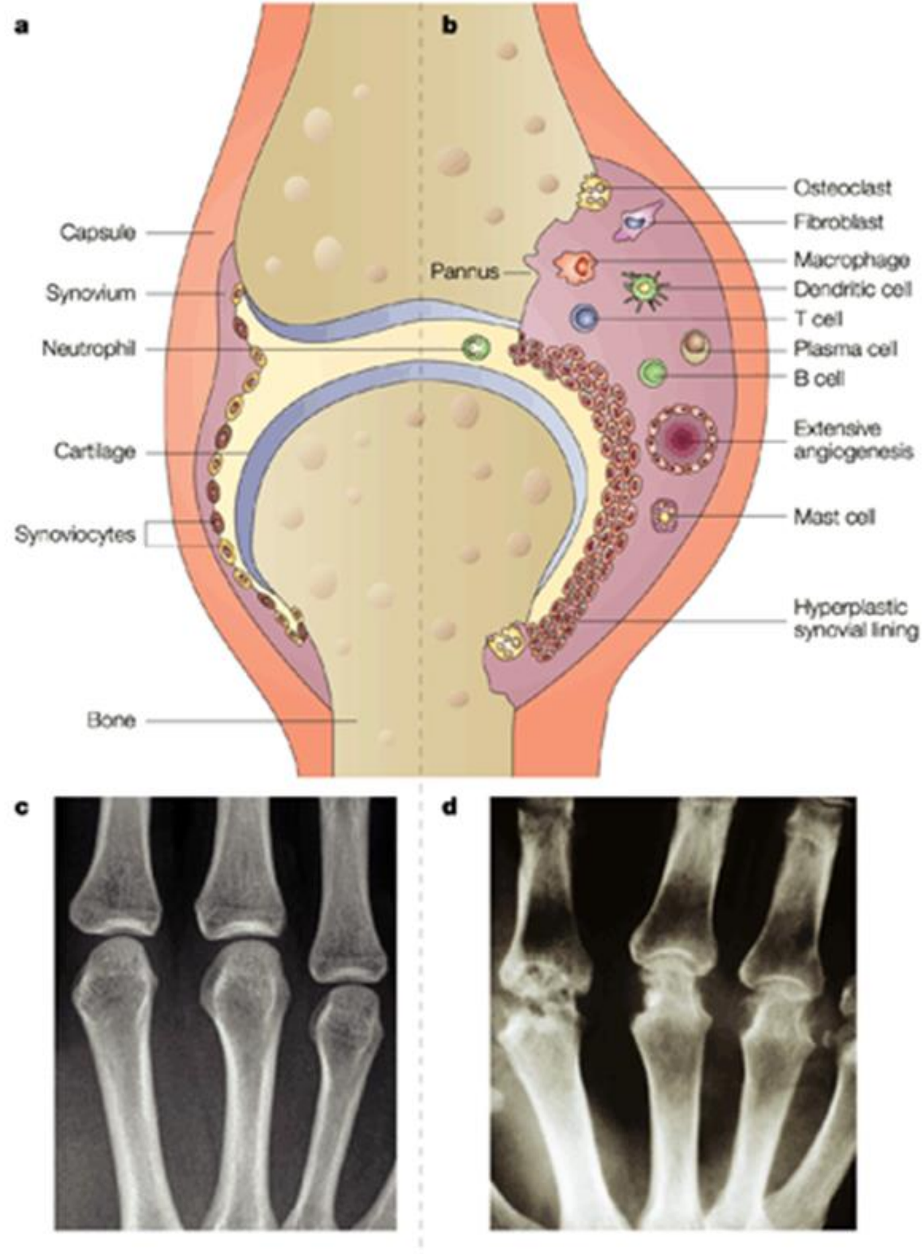
T cells (primarily CD4$^+$ memory cells) invading the synovial membrane produce IL-2 and IFN-gamma. Through cell–cell contact and through cytokines (produced also by APCs, such as IFN-gamma, TNFa IL-17) these T cells activate monocytes, macrophages and synovial fibroblasts. They then overproduce pro-inflammatory cytokines, mainly TNF-, IL-1 and IL-6 causing chronic inflammation. These cytokines also activate a variety of genes characteristic of inflammatory responses, including genes coding for various cytokines and matrix metalloproteinases (MMPs) involved in tissue degradation. TNF- and IL-1 also induce RANK expression on macrophages which, when interfering with RANKL on stromal cells or T cells, differentiate into osteoclasts that resorb and destroy bone. in addition, chondrocytes also become activated, leading to the release of MMPs



Nature Reviews | Drug Discovery

Inflammatory response of the synovial membrane ('synovitis')

Transendothelial influx and/or local activation of a variety of mononuclear cells, such as T cells, B cells, plasma cells, dendritic cells, macrophages, mast cells, as well as by new vessel formation. The lymphoid infiltrate can be diffuse or, commonly, form lymphoid-follicle-like structures. The lining layer becomes hyperplastic (it can have a thickness of >20 cells) and the synovial membrane expands and forms villi. However, in addition, the hallmark of RA is bone destruction . The destructive portion of the synovial membrane is termed 'pannus', and the destructive cellular element is the osteoclast; destruction mostly starts at the cartilage–bone–synovial membrane junction. Polymorphonuclear leukocytes are found in high numbers in the joint fluid, enzymes, together with enzymes secreted by synoviocytes and chondrocytes, lead to cartilage degradation.



Nature Reviews | Drug Discovery

PŘÍKLADY AN V GIT (CELIAKIE A NESPECIFICKÉ STŘEVNÍ ZÁNĚTY)

GIT je lokalizací mnoha běžných AN

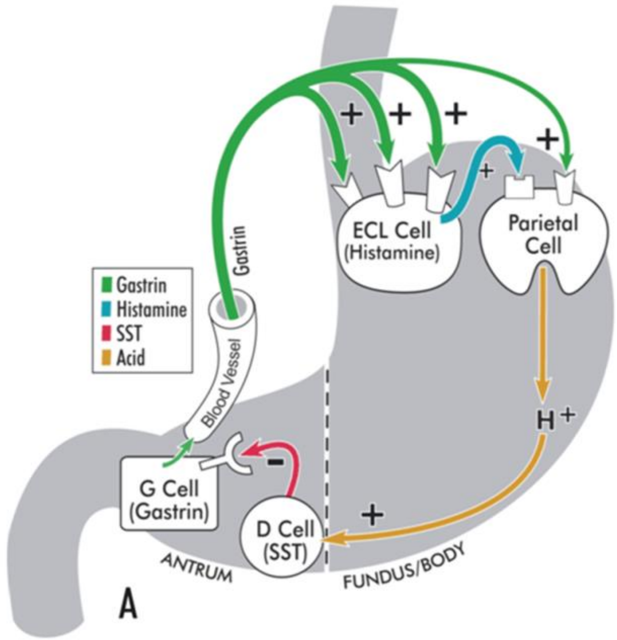
- autoimmune
  - salivary glands
    - Sjögren syndrome
  - stomach
    - atrophic gastritis
  - intestine
    - celiac disease
    - inflammatory bowel disease
      - Crohn's disease
      - ulcerative colitis
  - liver
    - primary sclerosing cholangitis
    - primary biliary cirrhosis
    - autoimmune hepatitis
  - pancreas
    - autoimmune pancreatitis

- allergy
  - food allergy (e.g. milk or dairy products)
    - more precisely particular proteins
    - difference from lactose intolerance due to enzyme disorder (lactase deficiency)
      - extremely frequent – mainly due to the fact that lifetime ability to digest milk (i.e. lactose) is considered a normal state
      - however, most mammals and part of human population loses the activity of lactase after weaning
      - the lifetime activity could be considered exceptional – persistence of lactase
        - » genetic polymorphism (geographical distribution is evidently a consequence of genetic selection) in promoter of gene for lactase
          - highest prevalence of lactase persistence in Europe in Swedes a Danes (~90 %)
          - Czech population ~ 70 %
          - lowest in Turks (~ 20 %)
          - outside Europe high fervency of persistence e.g. in desert nomadic populations in North Africa
            - the reason for selection of persistence haplotype in northwest Europe could be the richer source of calcium in low vit. D generation climate
      - manifestation
        - » intestinal discomfort after fresh milk intake (not after diary fermented products such as cheese or yogurt)
        - » diarrhea, flatulence, abdominal pain

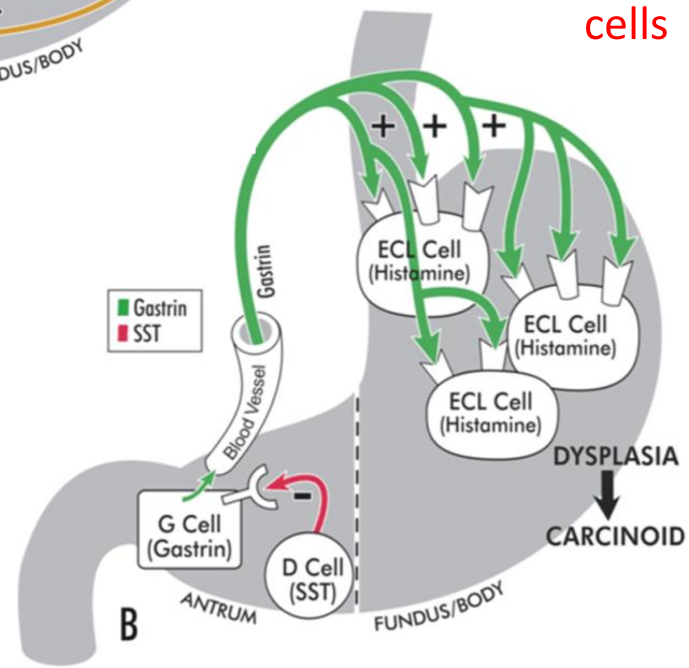
Atrofická gastritida

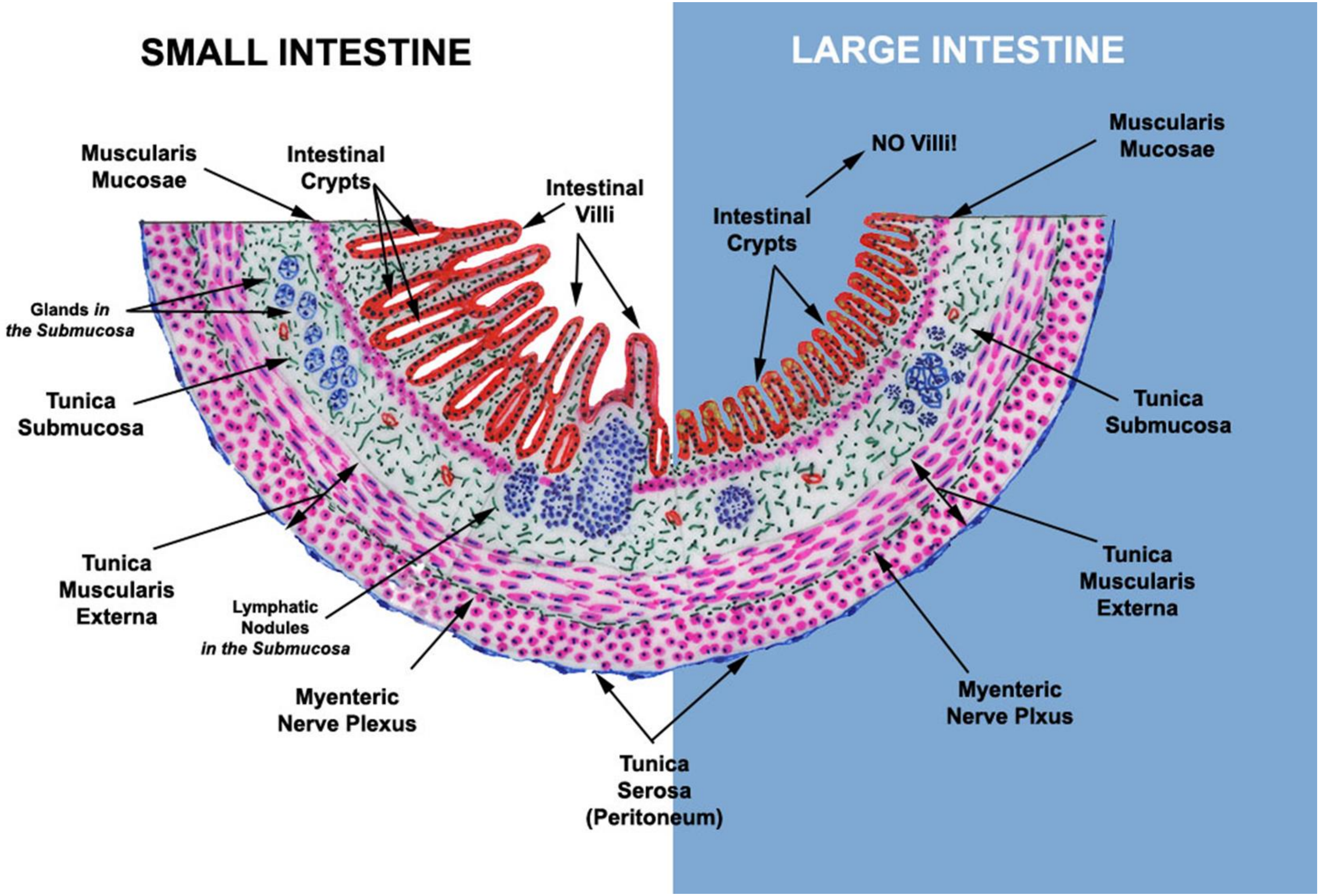
- destruction of mainly parietal cells by cytotoxic lymphocytes
    - compensatory ↑ gastrin
- antibodies against
    - intrinsic factor (IF) and complexes IF/B12
    - Na/K-ATPase
    - carbonic anhydrase
    - gastrin receptor
- consequences
    - achlorhydria leading to sideropenic anaemia
    - later megaloblastic (pernicious) anaemia
    - precancerosis

normally

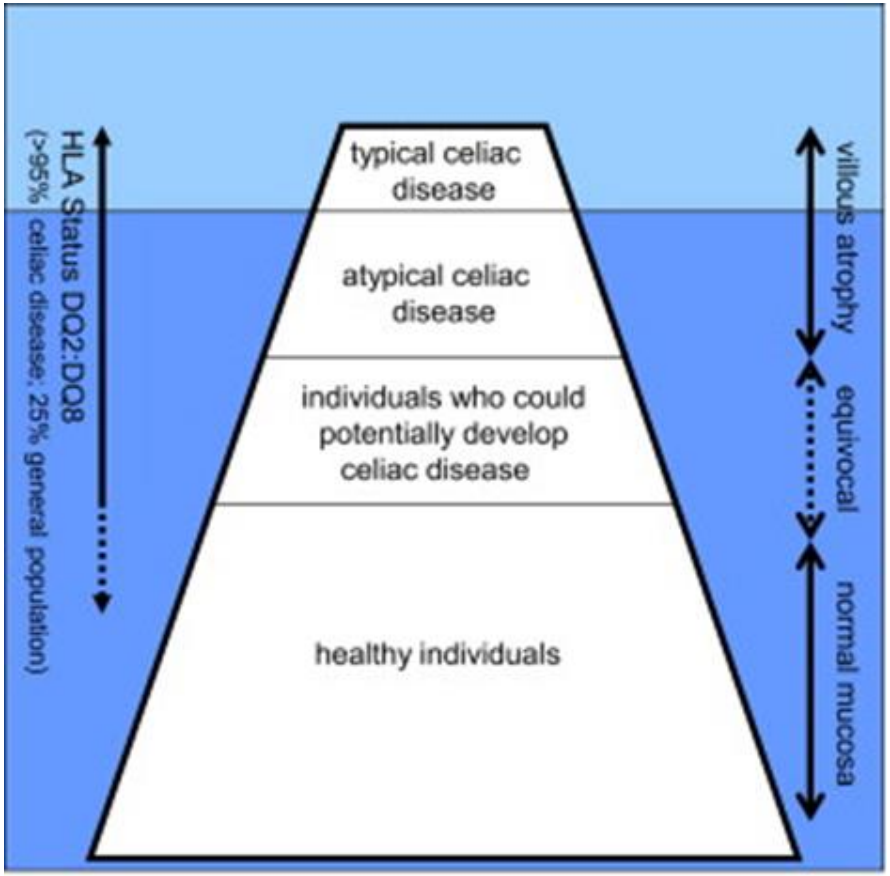


absence of parietal cells




SMALL INTESTINE
LARGE INTESTINE
Muscularis Mucosae
Intestinal Crypts
Intestinal Villi
Glands *in the Submucosa*
Tunica Submucosa
Tunica Muscularis Externa
Lymphatic Nodules *in the Submucosa*
Myenteric Nerve Plexus
Tunica Serosa (Peritoneum)
NO Villi!
Muscularis Mucosae
Intestinal Crypts
Tunica Submucosa
Tunica Muscularis Externa
Myenteric Nerve Plxus

Celiakie



HLA = Human Leukocyte antigen.

- synonyms: celiac sprue, gluten-sensitive enteropathy, gluten intolerance
- T-cell mediated autoimmune reaction against intestinal mucosa (mainly duodenum and jejunum) initiated by gluten and its products (gliadins)
- prevalence ~1% of populations
  - but commonly underdiagnosed
- manifestation:
  - often starts in child after the stop of breast feeding when flour is introduced (though latency of many years)
  - but anytime in life
- symptoms are very variable!!!
  - typical
  - untypical

Patofyziologie celiakie

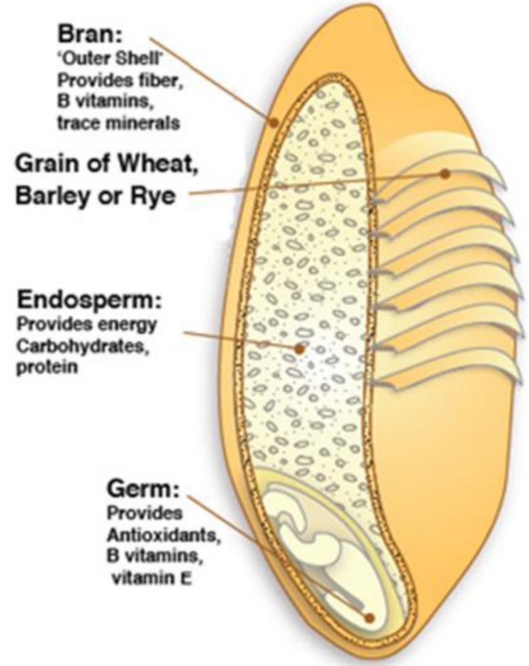
- etiology
  - gen. predisposition –
    - variants of MHC II genes
      - DQ2 and DQ8 haplotypes
      - celiac d. often associated with other autoimmunities, e.g. T1DM
    - other non-HLA alleles
  - external factors
    - gluten in diet
      - gluten consist of two component (= peptides) gliadin and glutenin polypeptides
        - » i.e. a heterogeneous mixture of gliadins (prolamines) and glutenins
      - relatively resisitant to digestion by GIT enzymes, and allow immunogenic peptides to reach mucosal surfaces
    - infection by adenoviruses

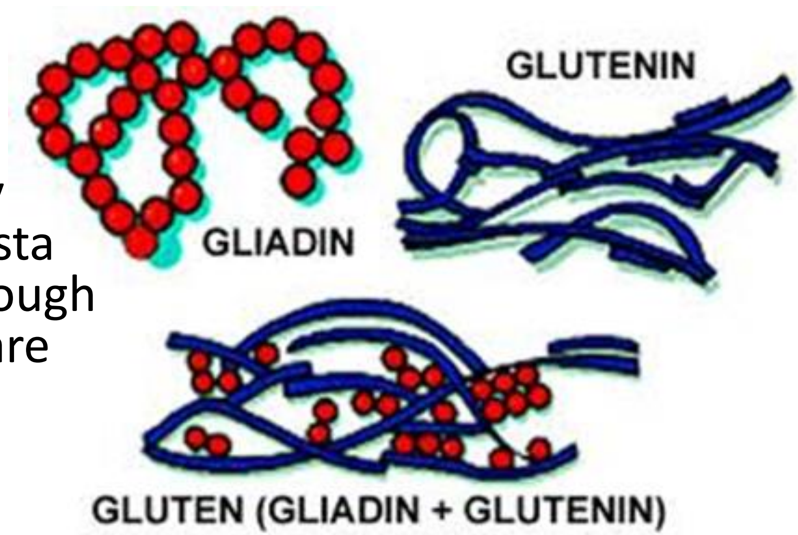
      molecular mimicry

      damage of intestinal barrier

Co je gluten?

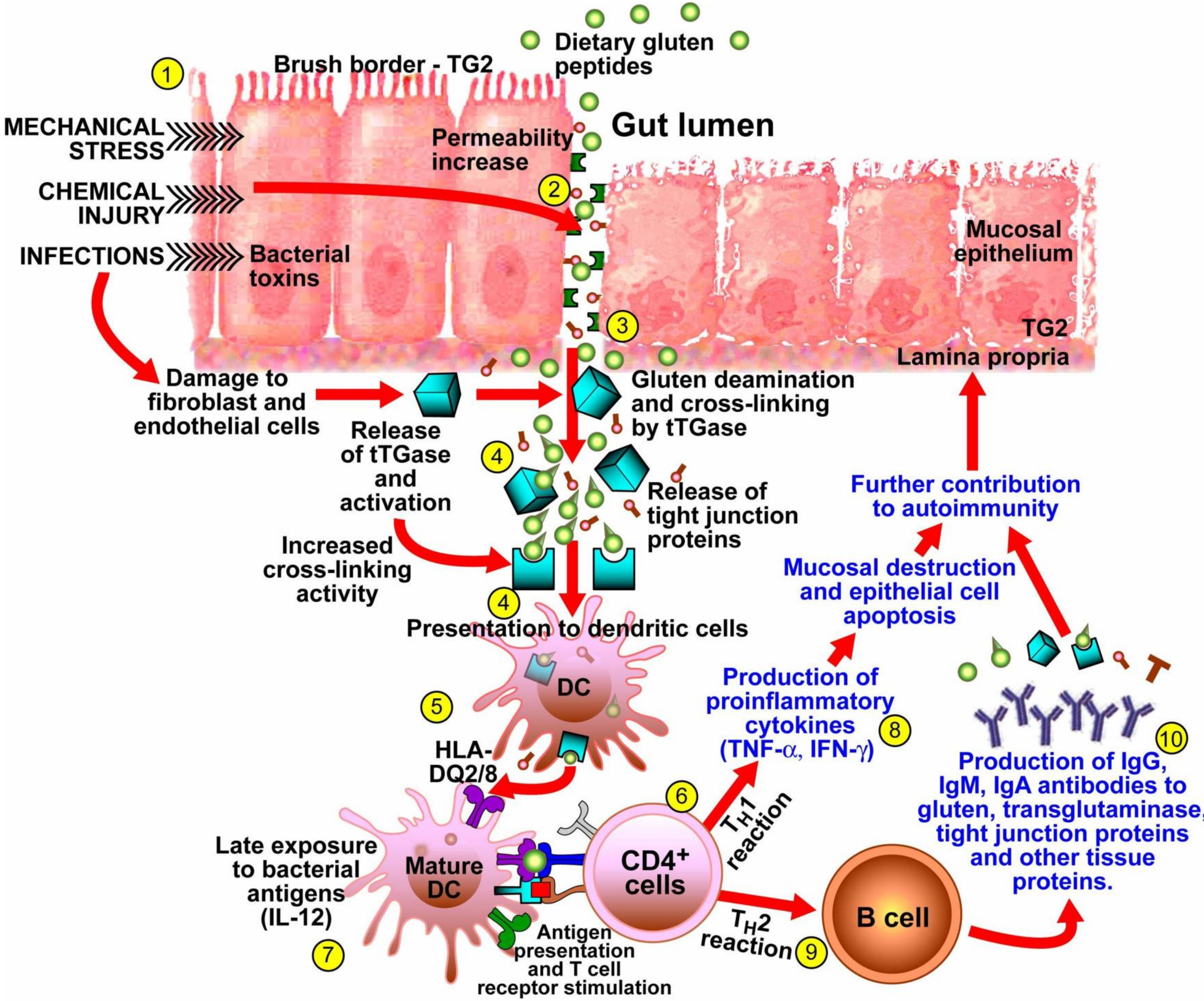
- gluten (= proteins) is a part of endosperm of cereals (especially wheat)
  - “gluten” is a term applied specifically to the combination of the prolamin proteins (called gliadins) and the glutelin proteins (called glutenins) that are found in wheat
- gluten is found in the following grains:
  - wheat, barley, bulgur, rye, spelt, oats (possibly, the proportion of individuals with gluten sensitivity that are also sensitive to the storage proteins in oats is likely less than 1%), kamut, triticale, semolina, pumpernickel, farro
- gluten is not found in the following grains:
  - rice (all varieties), buckwheat, teff, amaranth, quinoa, corn, hominy, millet
- gluten adds elasticity to dough (makes bakery products chewy, pizza dough stretchy, and pasta noodles elastic so that they can be pulled through the pasta press without breaking when they are made
  - thus, getting a desirable texture in gluten free baked goods can be difficult





Patoyziologie celiakie

- pathogenesis
- **HLA-DQ2 and HLA-DQ8** prefer to bind peptides with negative charges, but gluten peptides are usually devoid of these
  - **enzyme transglutaminase** 2 (TG2) can modify gluten peptides, either by introducing negative charges through deamination or through crosslinking gliadin peptides with each other or the TG2 enzyme itself
  - TG2 is usually expressed intracellularly in an inactive form and is released when inflammation or other stressors damage the cell
    - thus under normal circumstances gluten proteins are unaltered and cannot bind to HLA-DQ
    - if TG2 is present and native gluten peptides are presented to CD4+ cells, IFNy is released and an inflammatory response occurs
    - this in turn leads to more damage and release of TG2, and this loop leads to the damage caused by celiac disease
  - HLA-DQ8 usually binds to peptides that are not proline rich, and thus several deamination steps are required before the gluten peptide becomes immunogenic
    - this limits the risk of developing celiac disease in individuals that are only HLA-DQ8+
- activated gluten-specific CD4+ T helper 1 (Th1) cells secrete high levels of pro-inflammatory cytokines (e.g. IFN)gamma and IL-21 that promote the activation of **intraepithelial cytotoxic CD8+ T** lymphocytes
- Th2 response – via B cells – leads to production of **antibodies** against gliadin, reticulin and transglutaminase

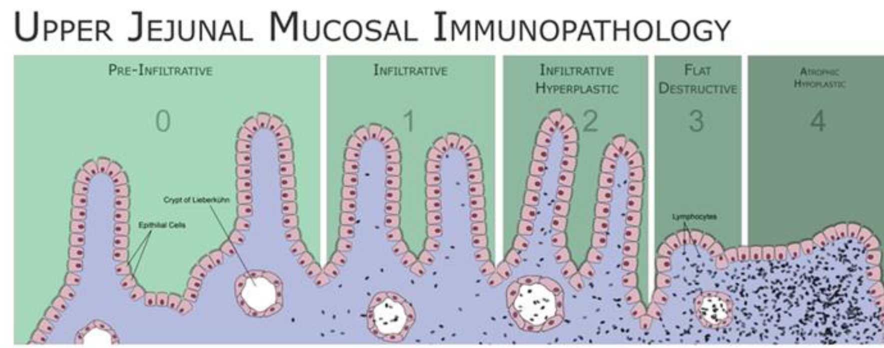


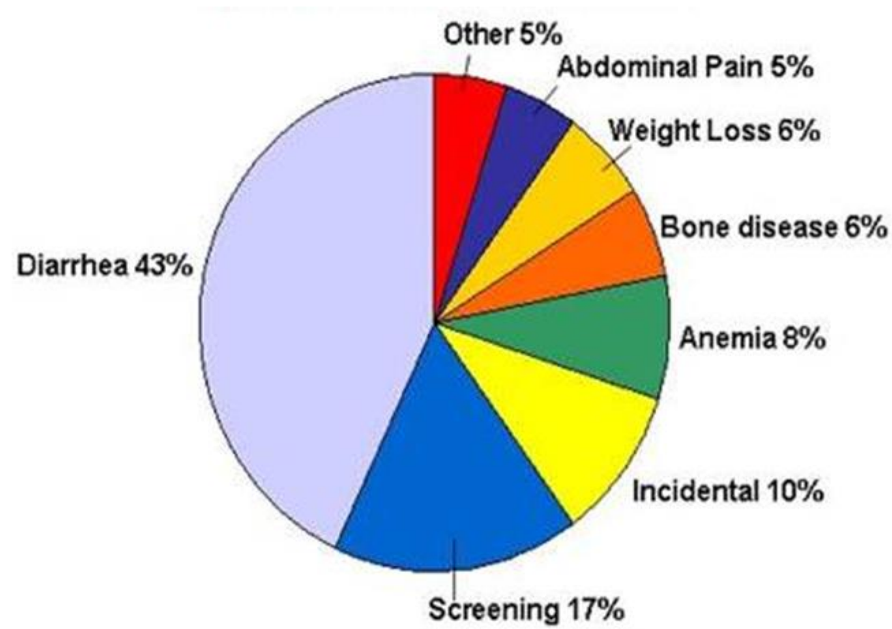
Depiction of the intestinal mucosa with emphasis on the factors involved in the development of celiac disease in individuals with HLA-DQ2/DQ8 positive

Manifestace celiakie

- consequences of auto-aggressive inflammation **- villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis** (typical markers for celiac disease)

- clinical course & symptoms
  - diarrhea
  - abdominal pain
  - bloating
  - malabsorption of main nutrients, vitamins, trace elements
    - hypo-/malnutrition or weight loss
  - non-gastrointestinal manifestation
    - children: short stature, anemia, neurological symptoms
    - adults: dermatitis herpetiformis, anaemia, reduced bone density, infertility, irritable bowel syndrome, dyspepsia, esophageal reflux, neurological symptoms
  - in 20-40 years risk of intest. lymphoma (50%) or carcinoma (10%)

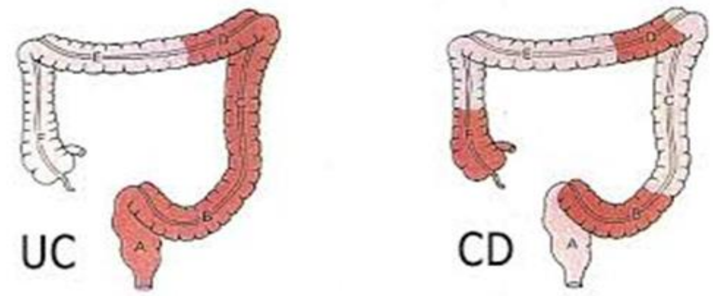


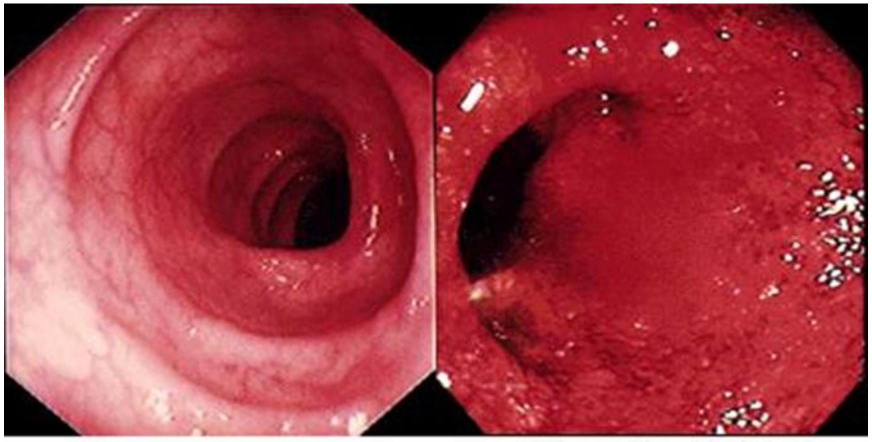


"Maybe she's gluten intolerant."

Inflammatory bowel diseases (IBD)

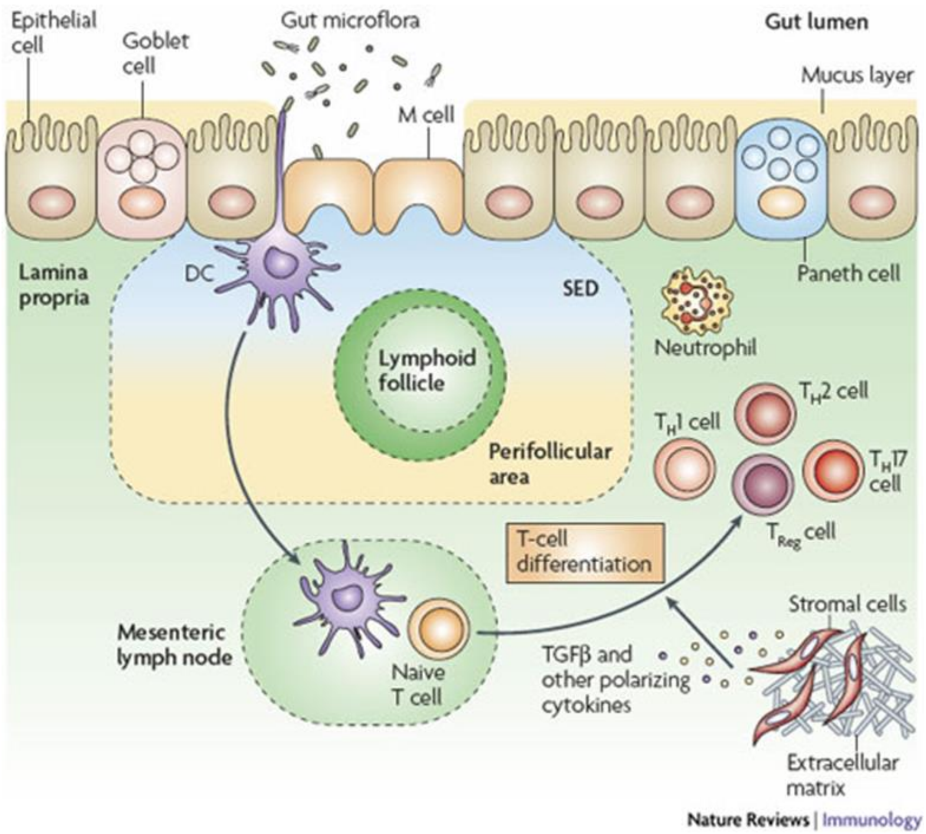
- both **Crohn's disease** (CD) and **ulcerative colitis** (UV) exhibit certain similar features
  - manifestation in young adults
  - clinical course
    - intermittent flares (exacerbations) followed by remissions
  - genetic predisposition
    - though different genes in CD and UC
  - abnormal reactivity of innate immune system to intestinal microbiota (bacteria)
  - abnormal lymphocyte activity and subsequent cytokine spectrum
    - predominance of Th1/Th17 in CD
    - atypical Th2 in UC
- localization
  - m. Crohn – any segment of GIT, transmural, granulomatous inflammation
  - ulcerative colitis – only rectum and colon, inflammation confined to mucosa





Healthy Colon　　Ulcerative Colon

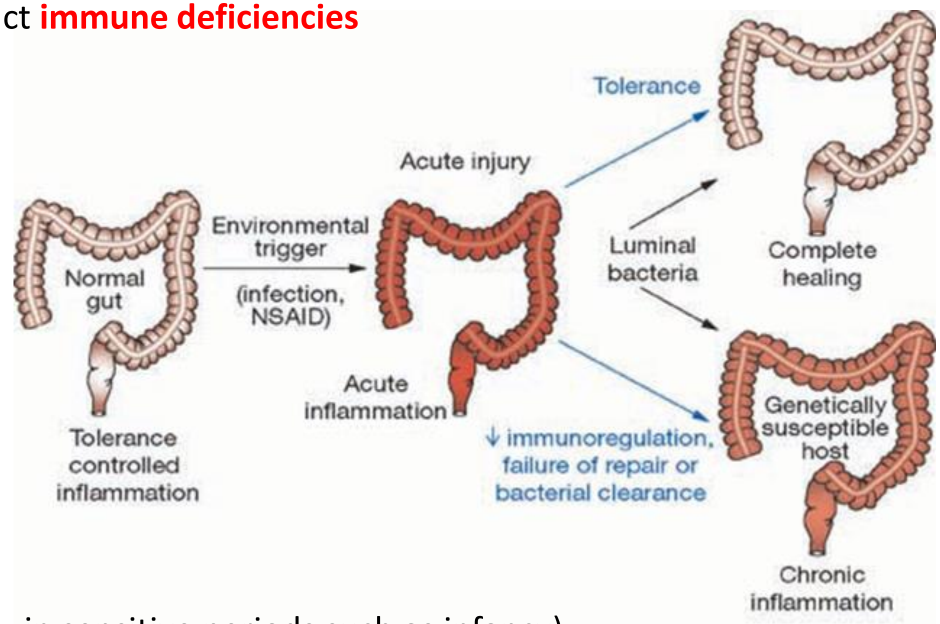
Imunitní systém střeva



- Unique with respect to its close apposition to intraluminal bacteria, which are separated from the underlying lamina propria by only a single layer of epithelial cells
- The epithelial-cell layer is comprised of absorptive and secretory cells, goblet cells (formation of the protective mucus layer) and Paneth cells.
- Immune Microfold cells (M cells) and dendritic cells (DCs) sample intestinal luminal contents
  - under normal conditions, the innate immune cells in the intestinal mucosa are largely tolerogenic, in order to prevent inflammatory responses to beneficial commensal bacteria in the gut
  - macrophages and dendritic cells have a key role in this regard. Intestinal macrophages are involved in phagocytosis of pathogens and removal of cell debris. Unlike most macrophages, intestinal macrophages do not produce pro-inflammatory cytokines in response to phagocytic activities
    - due to downregulation in the expression of certain cell surface receptors, like CD14 (which reduces ability to response to lipopolysaccharide) and several of the TLRs
  - CD103+ DCs in the gut are able to induce the formation of regulatory T cells, which are one of the cell types involved in the adaptive component of tolerance
  - the anti-inflammatory environment of the intestinal mucosa is promoted by the presence of cytokines such as IL-10 and TGFb which are associated with many anti-inflammatory functions
- The presence of either pathogenic bacteria or disruption of the epithelial-cell barrier results in activation and migration of DCs to the mesenteric lymph nodes, where they activate naive T cells, which then undergo differentiation under the influence of factors released by DCs and other stromal elements.

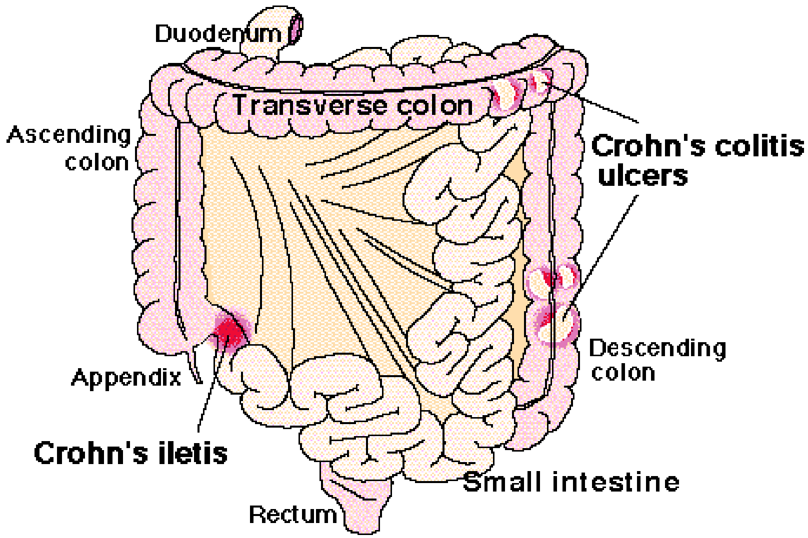
Etiologie nespecifických střevních zánětů

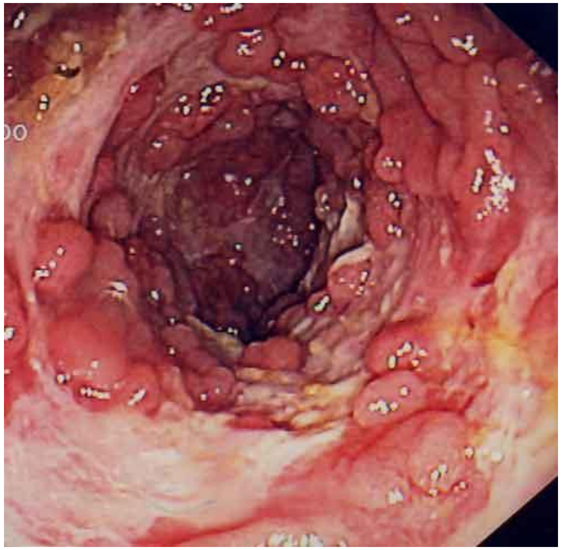
- genetic factors cases abnormal immune reactivity of **innate immune system**
  - CD
    - mutation causing altered expression of **pattern-recognition receptors** (PRRs), e.g. Toll-like receptors (UC) or NOD2 and abnormal activity of **autophagy** → bacterial invasion and defective bacterial clearance → low production of pro-inflammatory cytokines → granulomatous lesions
  - UC
    - primary defects in intestinal barrier (tight junctions) → excessive production of pro-inflammatory cytokines (TNFa) → inflammatory infiltration of mucosa by leucocytes
  - abnormal adaptive immune response is likely secondary
    - therefore some propose CD and UC are in fact **immune deficiencies**
- environmental factors
  - incidence rises in Europe and N. America
  - the same is now evident on southern hemisphere and in Asia
- microbial factors
  - gut microflora is very complex
    - Bacteroidestes
    - Firmicutes
    - Actionobacteria
    - Preoteobacteria
  - modified by plethora of factors
    - way delivery (vaginal vs. CS), use of ATB (esp. in sensitive periods such as infancy), quality and quantity of food, food additives, xenobiotics, drugs etc.



Crohnova choroba

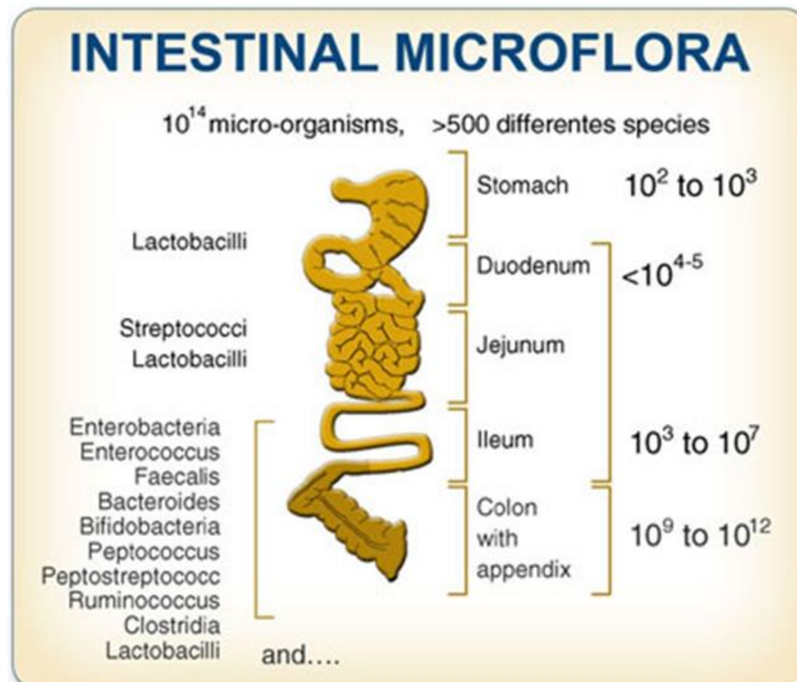
- = ileitis terminalis, enteritis regionalis
- chronic, relapsing, systemic inflammatory disease of
  - commonly small intestine
    - but can affect any part of GIT beginning with oral cavity to anus
    - manifestation typically between 3. to 6. decade, more often women
  - extraintestinal manifestations
    - arthritis
    - uveitis
    - pyoderma gangrenosum and erythema nodosum
- manifestation & clinical course
  - periods of exacerbations (stomach pain, diarrhea, fever, seizures, blood in stools (enterororhagia)/remissions
- histopathology
  - granulomatous type of inflammation affects all layers of intest. wall
  - ulcerations and bleeding
  - penetrated ulcers create fistulas (often perirectal)
  - affected areas interspersed by unaffected

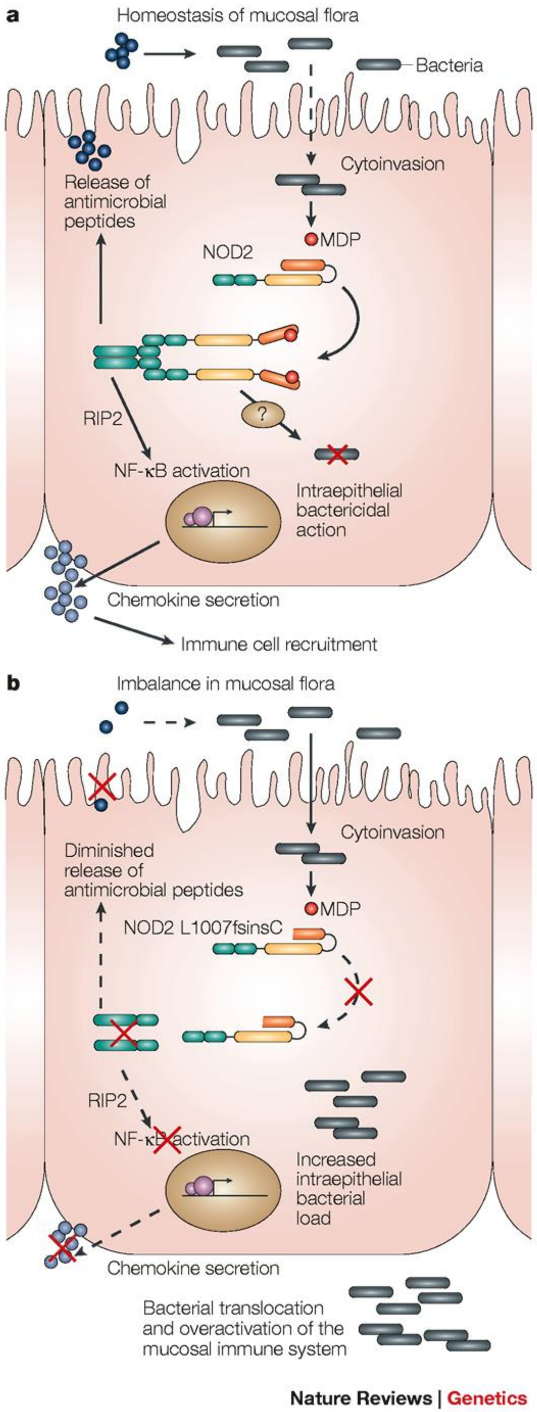




Etiopatogeneze CD

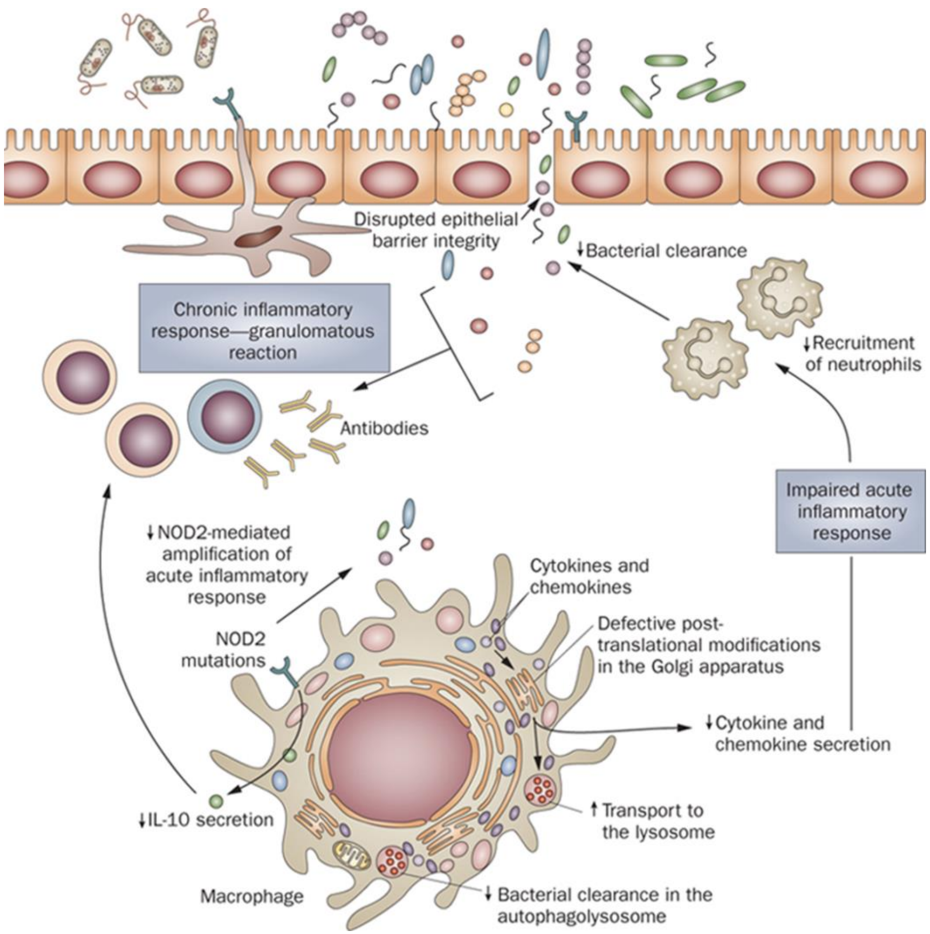
- multifactorial
  - genetic factors (= predisposition) lead to abnormal immune response of intest. mucosa to natural commensal bacterial antigens (>500 bact. strains, aerobes and anaerobes)
    - normally opposed by production of defensins
    - GWAS
      - mutation in gene for CARD15
      - autophagy protein ATG16L1
      - many other loci
  - triggering environmental factors nor known (infection?) = sterile animals protected
    - lipopolysaccharide, peptidoglycan, flagellin, …
    - suspects Mycobacteria, Listeria and Yersinia (the latter two unconfirmed)





- reaction to intraluminal bacteria – normally “controlled inflammation”
- intracellular recognition of components of bacterial wall (pathogen-associated molecular patterns, PAMPs), e.g. muramyl-dipeptide (MDP) by NOD2 (product of CARD15 gene) lead to oligomerization and activation of NFk-B
    - secretion of chemokines and defensins by Paneth cells
- variants of NOD2 associated with Crohn’s d. lead to deficient epithelial response, loss of barrier function and increased exposition to intest. microflora
    - impaired secretion of chemokines and defensins
    - altered expression of pattern-recognition receptors (PRRs), e.g. Toll-like receptors
    - production of inflammatory cytokines
    - activation of dendritic cells and production of Ig and activation of Th1 lymph.

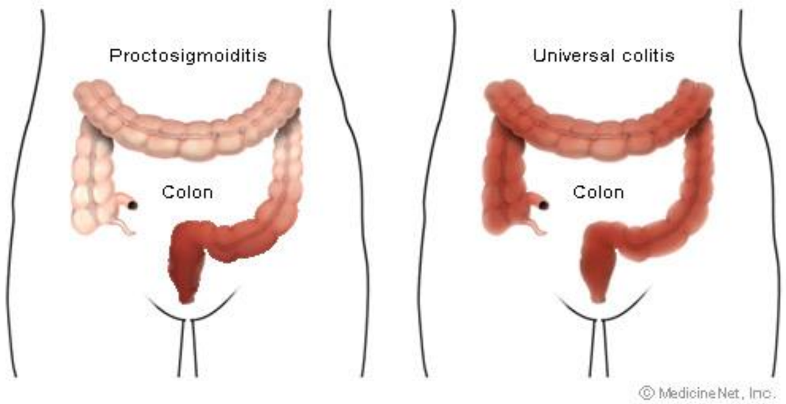
Defective bacterial clearance in CD

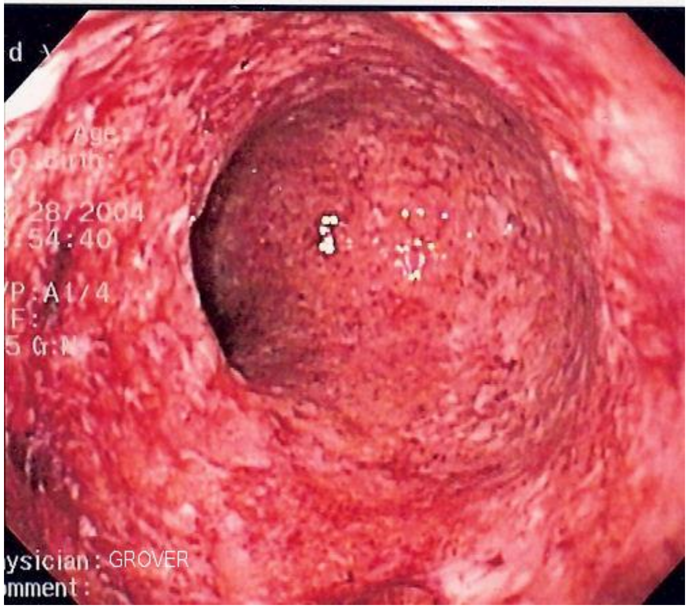


- Defective post-translational modifications in macrophages direct cytokines and chemokines to the lysosome, thus reducing secretion and leading to decreased neutrophil recruitment and persistence of bacteria in the intestinal mucosa. Vesicle transport defects also lead to reduced bacterial clearance in the autophagolysosome. Impaired epithelial barrier integrity contributes to increased bacterial load, thereby exacerbating the adaptive immune response. Mutations in the NOD2 receptor reduce the acute inflammatory response to bacteria and amplify the chronic inflammatory response by inhibiting the transcription of IL-10

Ulcerativní kolitida

- two peak incidence between 20 – 40. na after 50 years of age
- typically Caucasian race, north-south gradient
- inflammation limited to mucosa
  - starts at the bottom of Lieberkuhn's crypts (infiltration by immune cells)
    - mainly rectum and sigmoideum
  - hyperemia, abscesses and ulcerations, bleeding, pseudopolyps, event. strictures
  - high activity of TNFa (→ treatment with anti-TNFa antibodies)
- clinical course
  - periodical = exacerbations x remissions (diarrhea, bleeding, abdominal pain, fever)
  - extraintestinal manifestations (5 – 15%):
    - polyarthritis, osteoporosis, uveitis, cholangitis
  - chronic anemia, strictures, hemorrhoids
  - carcinoma
- in severe form indication for colectomy





Imunologie v kostce