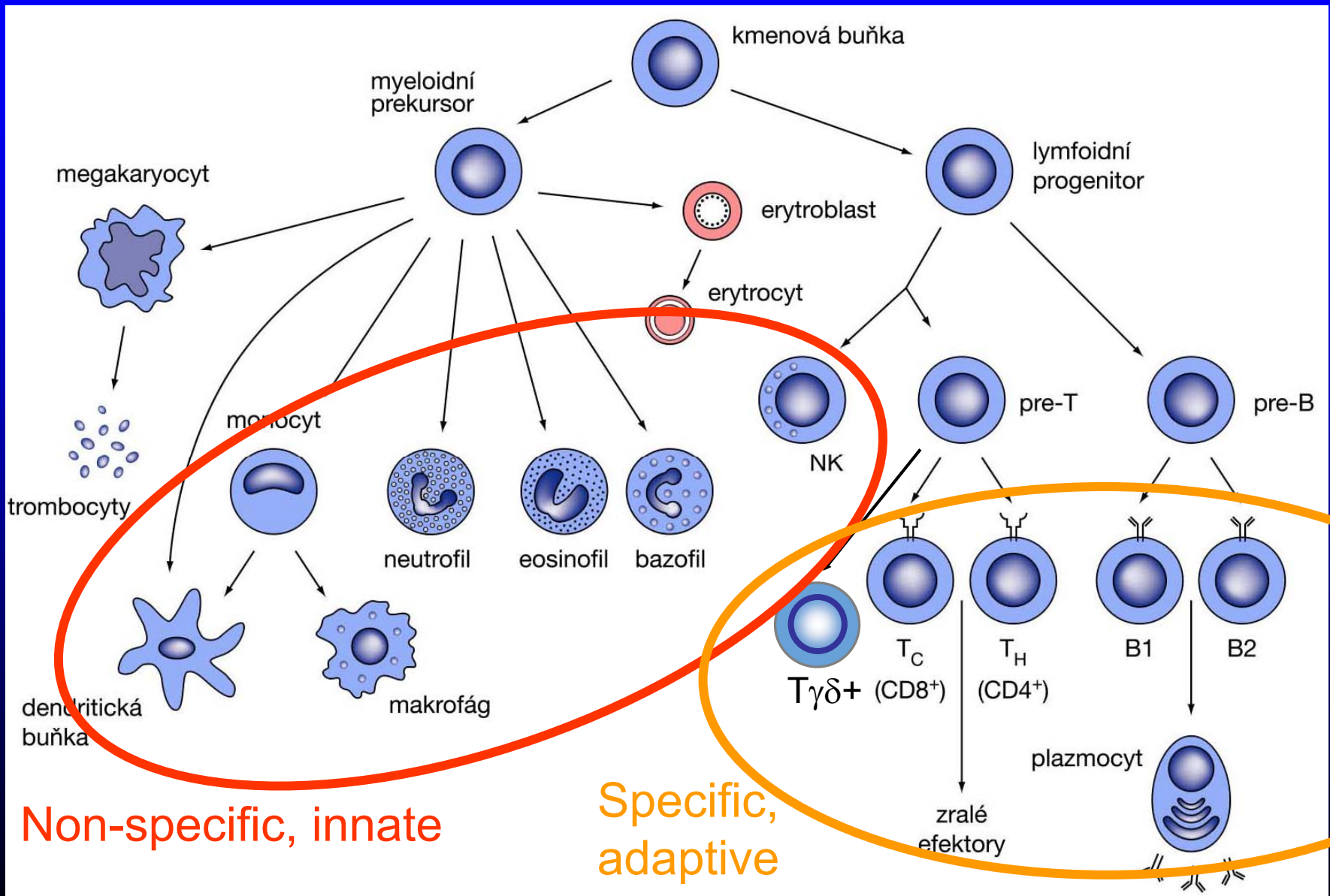
Specific (adaptive) immunity

Immunology, 3rd year

Contents

- Specific immunity: Basics
  Immunoglobulins and T cell receptor
  B and T development
  T cell function
  Innate-like lymphocytes
  Examples: B and T cell function

Characters and cast



Components of immunity

	innate	adaptive
cellular	neutrophils monocytes-macrophages, DC, NK cells	T lymphocytes
humoral	complement acute phase proteins (CRP,MBL..)	antibodies (B lymphocytes)

Differences between innate and adaptive immunity

	innate	adaptive
phylogenetic	older	younger
reaction/speed	minutes	hours-days
immun. memory	no	yes
Ag receptor	shared structures indirect –opsonines; all cells identically equipped	Ig, TCR, diverse repertoire, clones

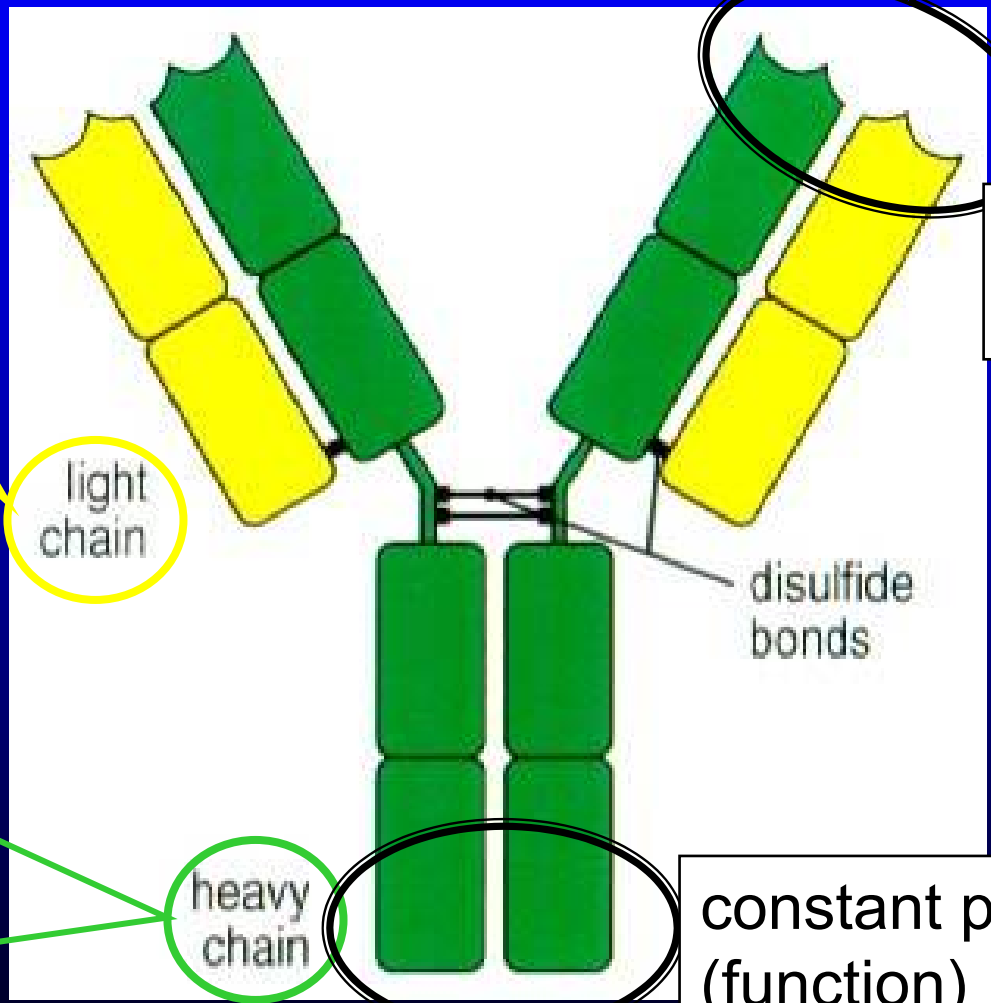
- types of antibodies: why and when they are important
- molecular basis of immune memory
- what can I learn from serology in infants
- how do I find out which lymphocytes are (mono)clonal
- what are CD3 etc.? which other CDs do I need to memorize
- how do the antibodies improve in the nodes
- weapons of the immune killers
- what happens to T and B lymphocytes during EBV infection
- why is *Haemophilus influenzae* dangerous to native American kids?
- …

Contents

Antibody (immunoglobulin) structure

κ
λ

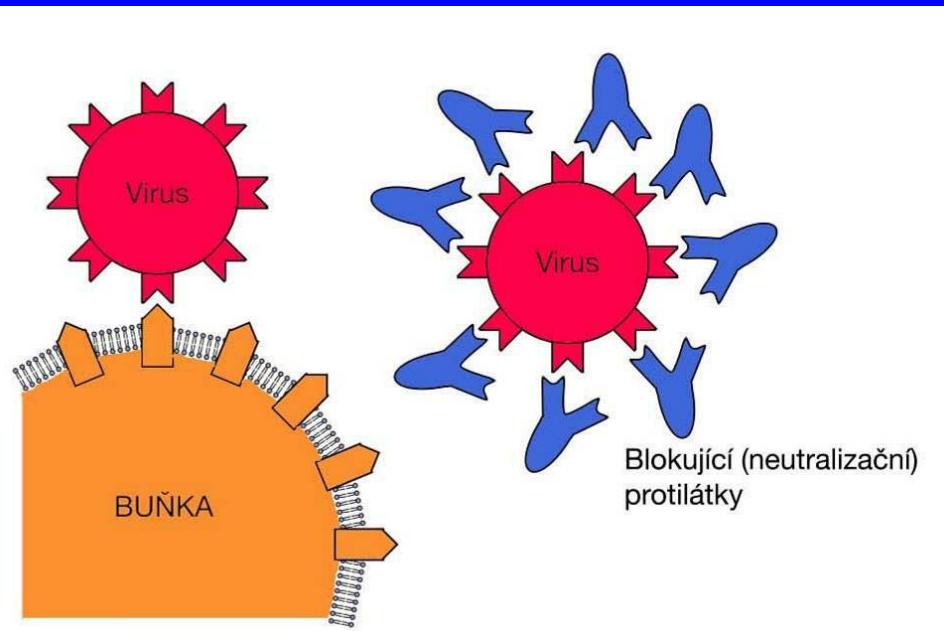
α, γ, δ, ε, μ

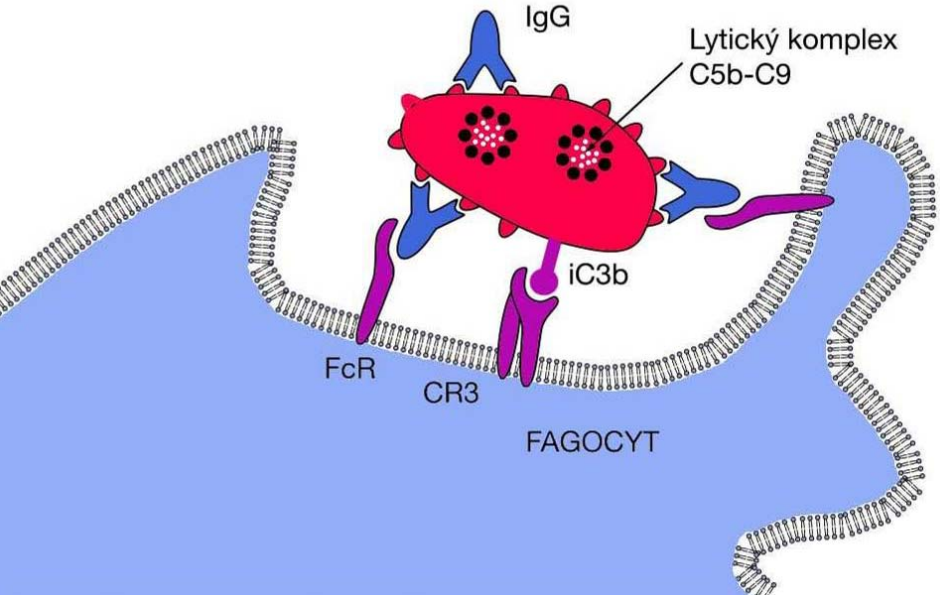


variable part (Ag binding)

constant part (function)

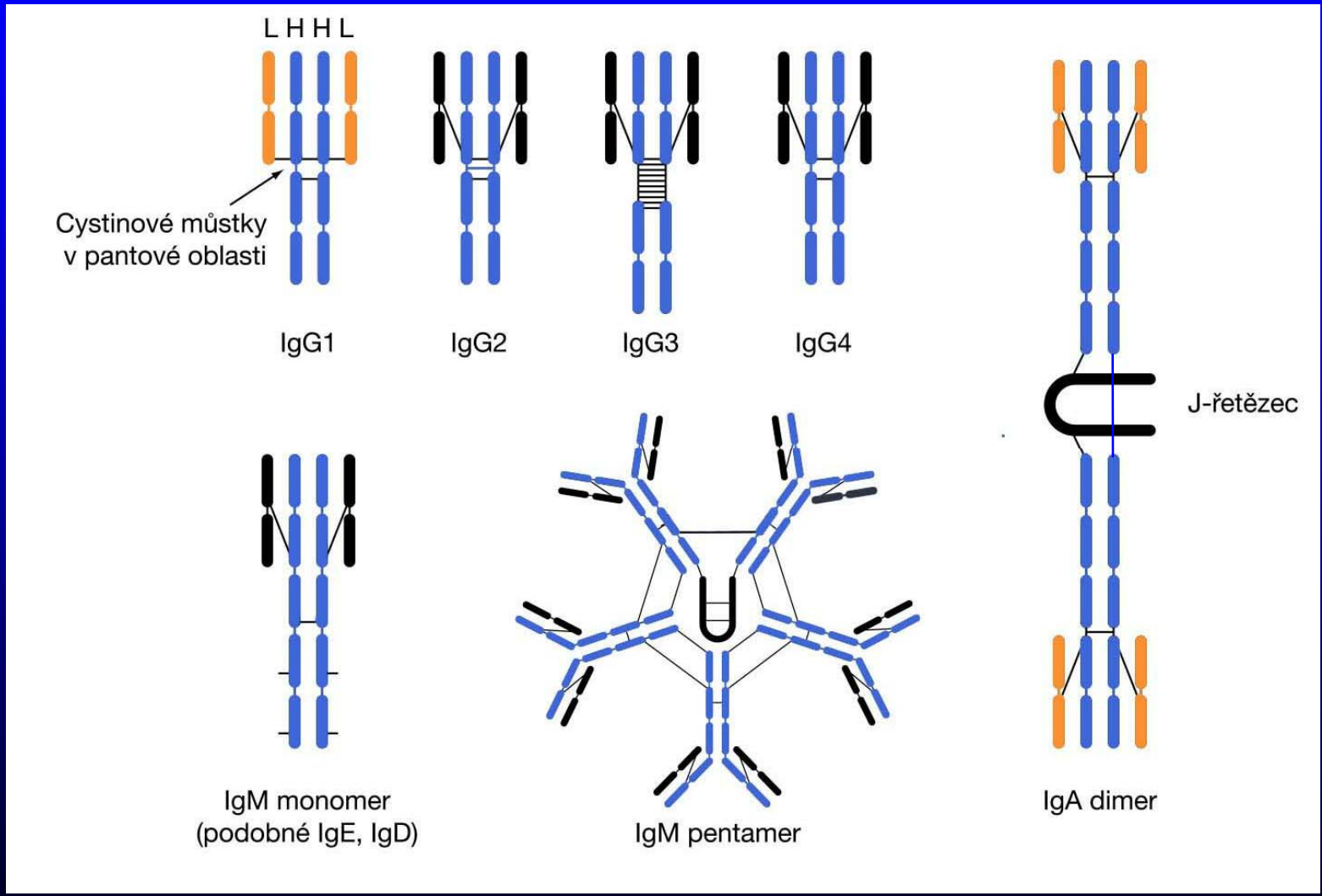
Antibody functions





- neutralizing
  IgG, IgA
- opsonization
  IgG
- complement activation
  IgM, IgG3 >G1>G2,IgA
- sensitizing for NK cell killing (ADCC), or for granulocyte activation
  IgG
- mast cell sensitizing
  IgE

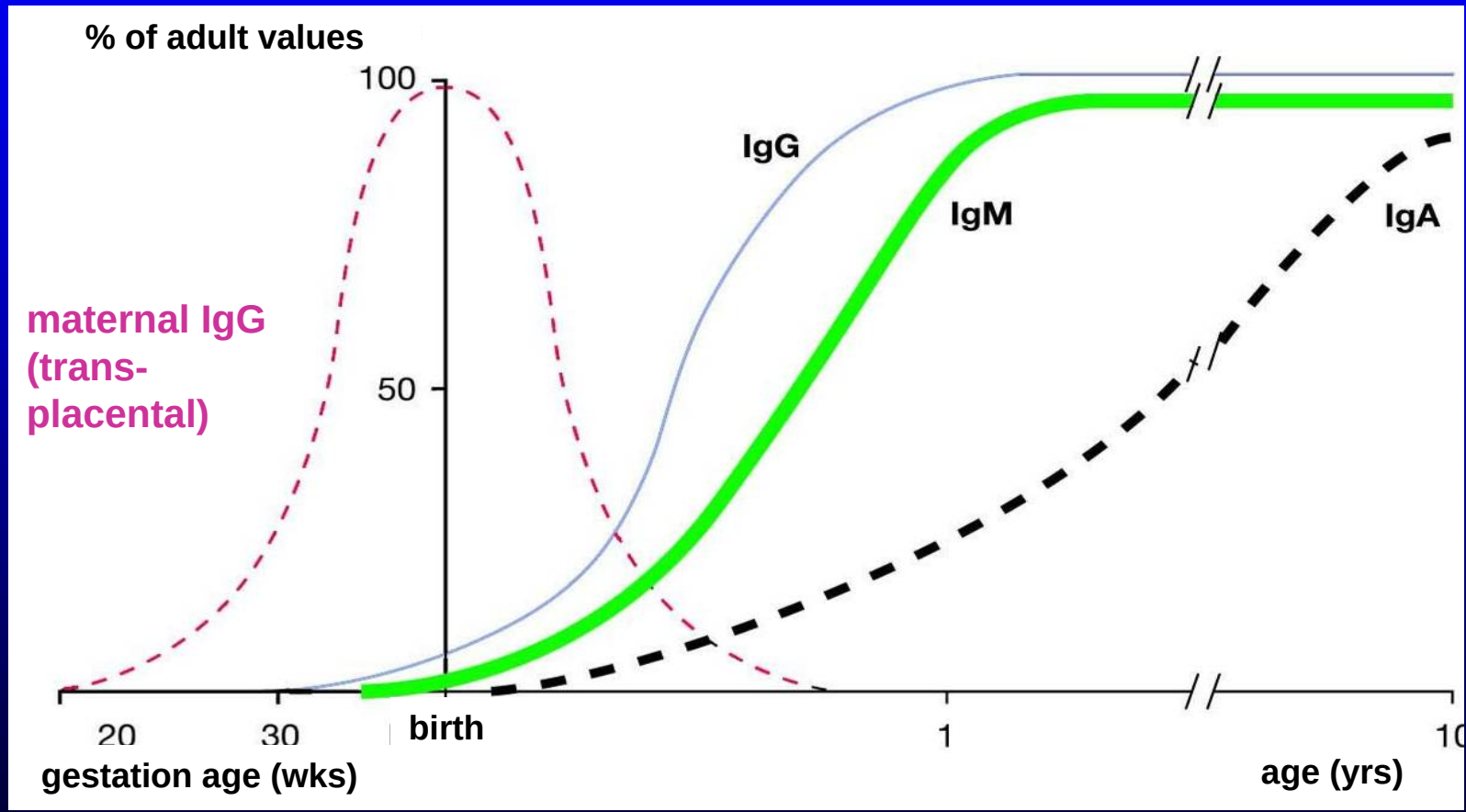
Isotypes


L H H L
Cystinové můstky
v pantové oblasti
IgG1
IgG2
IgG3
IgG4
J-řetězec
IgM monomer
(podobné IgE, IgD)
IgM pentamer
IgA dimer

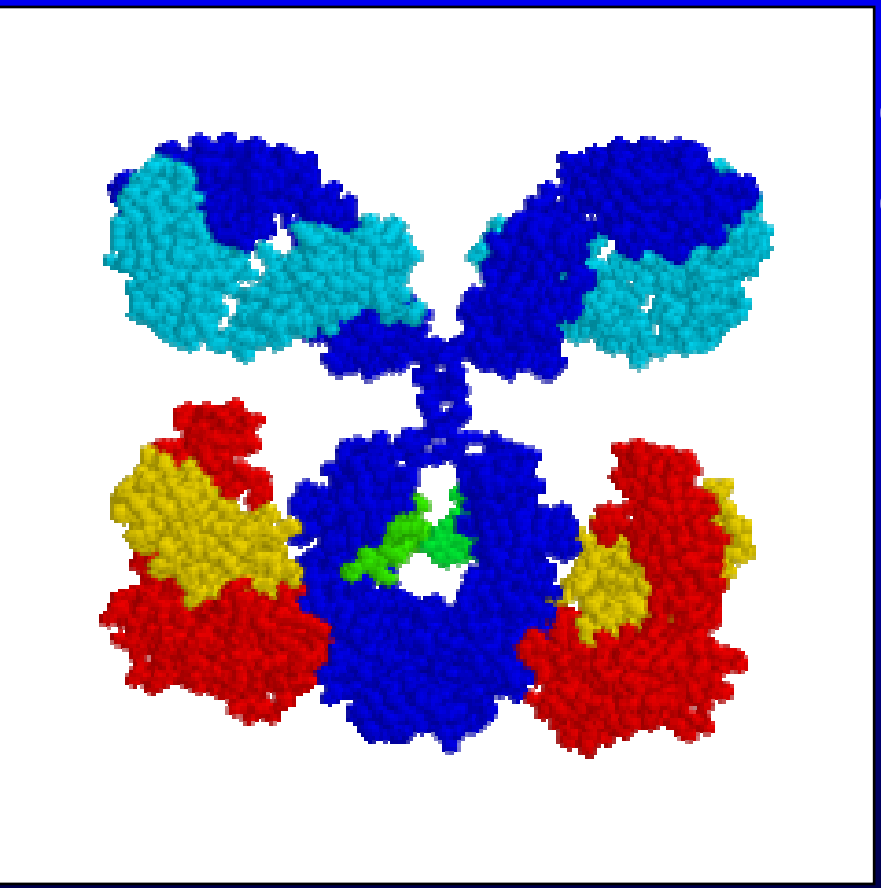
Ig isotypes, facts

Iso type	Mol mass (kDa)	Serum conc (g/l)	Localization	T (1/2)biol (days)	Function
IgG	155	8-18	serum, intersticial fluid	21	opsonization; neutralization; crosses placenta; secondaryí response
IgA	160-350	0.9-3.5	serum, mucosae, tears, saliva	6	mucosal defense, opsonization
IgM	900	0.9-2.5	serum, B-cell surface	6	complement activation; primary response; Ag receptor
IgD	180	0.1	serum, B-cell surface	3	Ag receptor
IgE	190	3x10-4	serum, intersticial fluid	2	anti-parasite defense

Ig after birth, physiological infants



FcRn: neonatal FcR

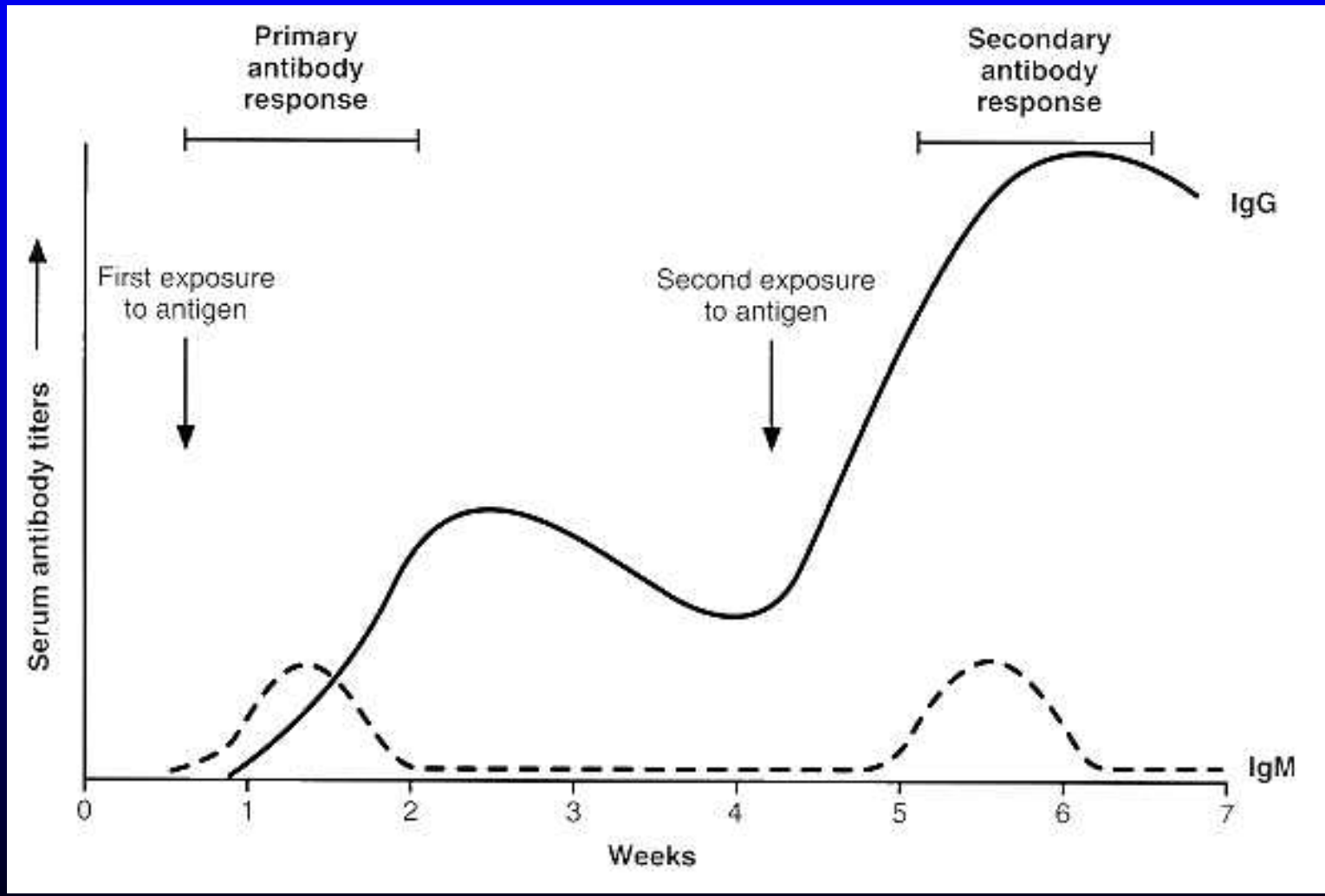


- Beta-2-microglobulin
- FcRn

transport across placenta

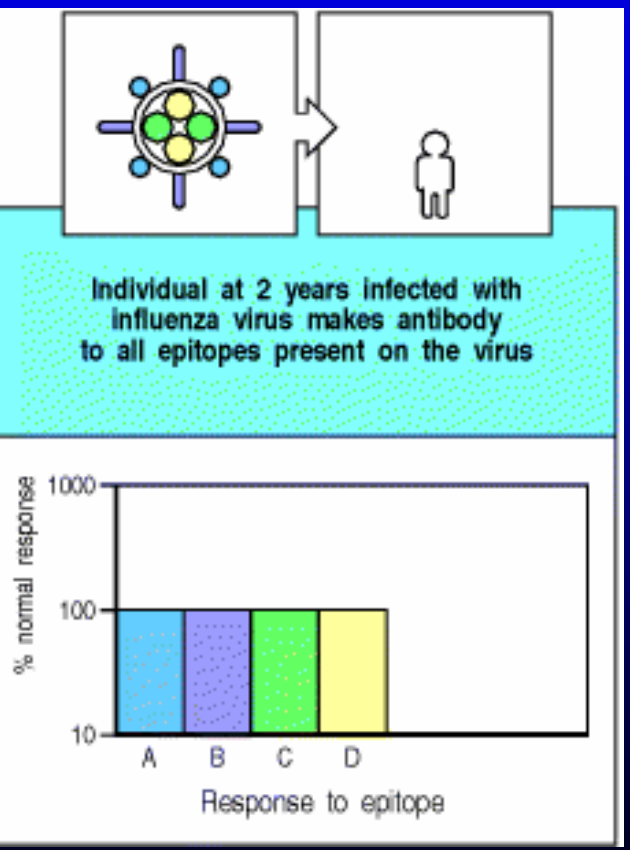
extends $T_{1/2}$

Antibody response

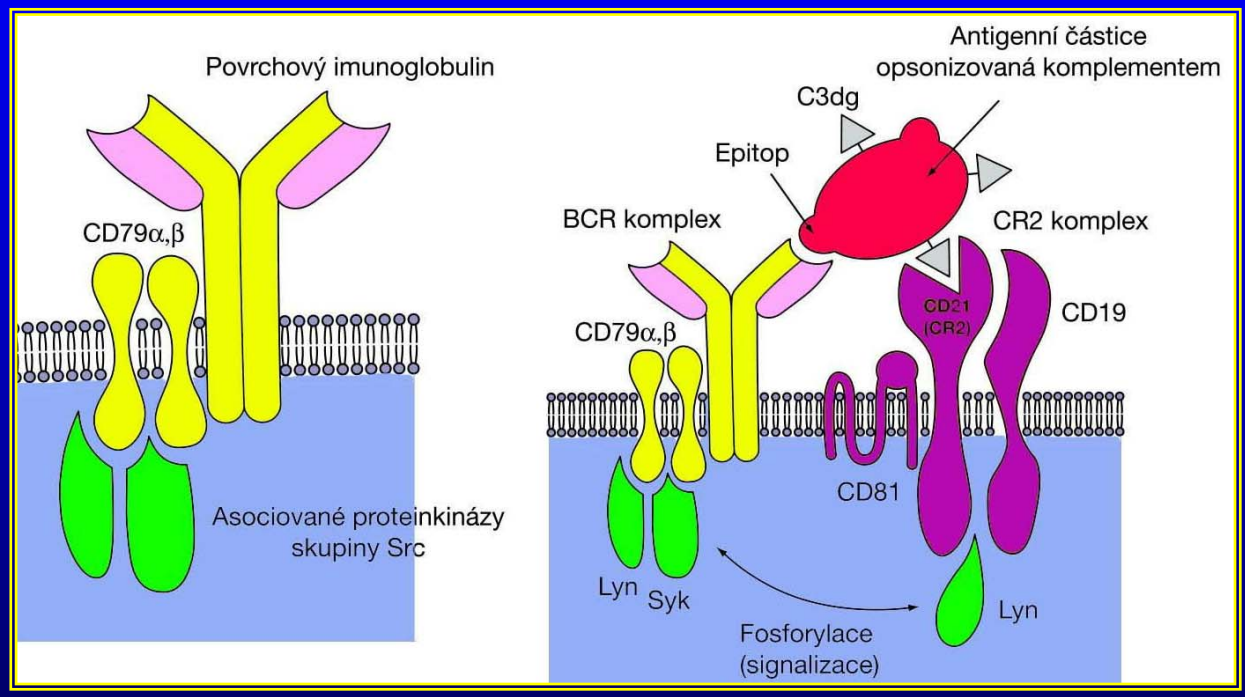


Primary antigenic sin

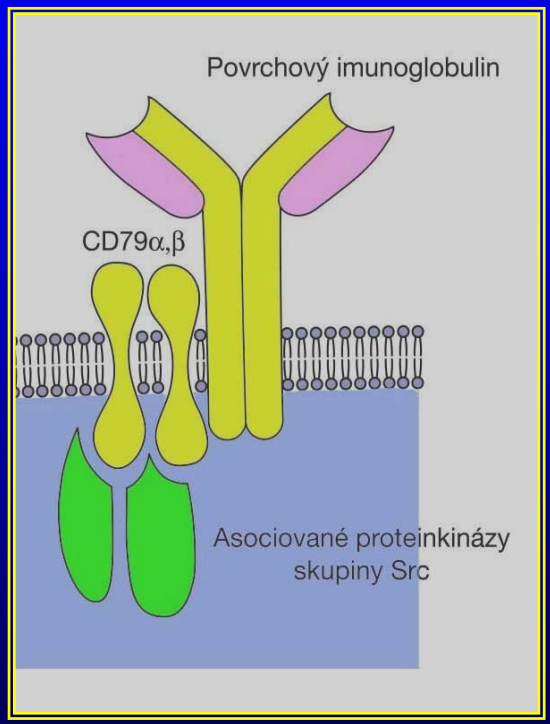
ABCD

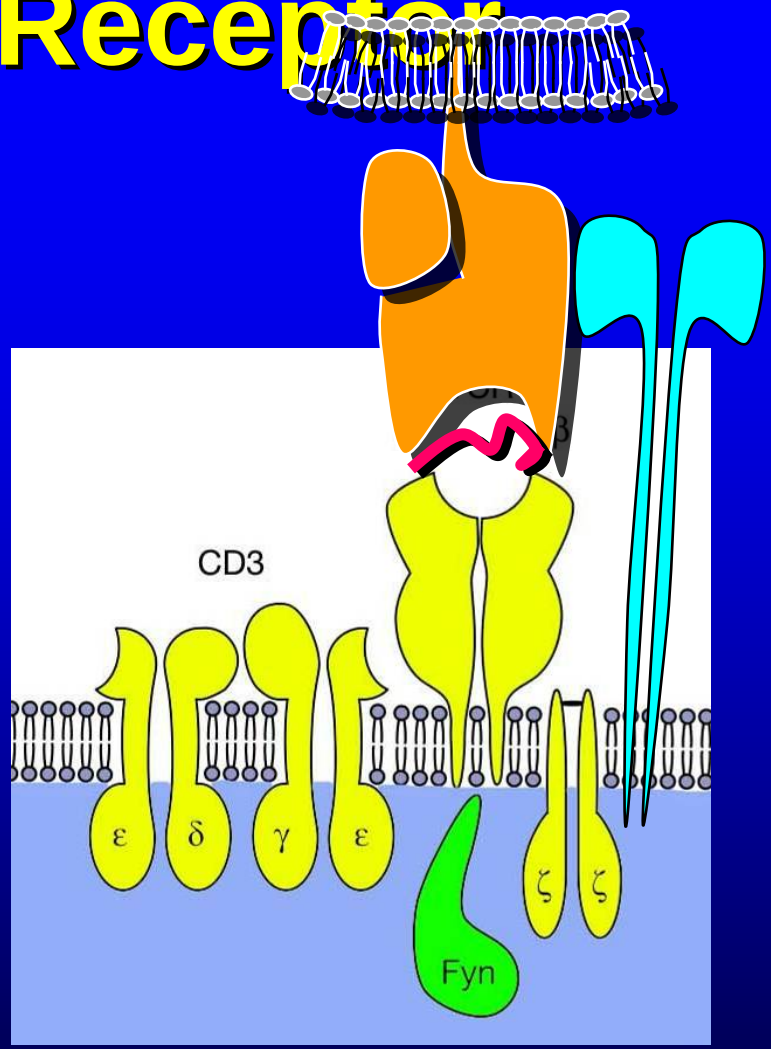


B cell receptor

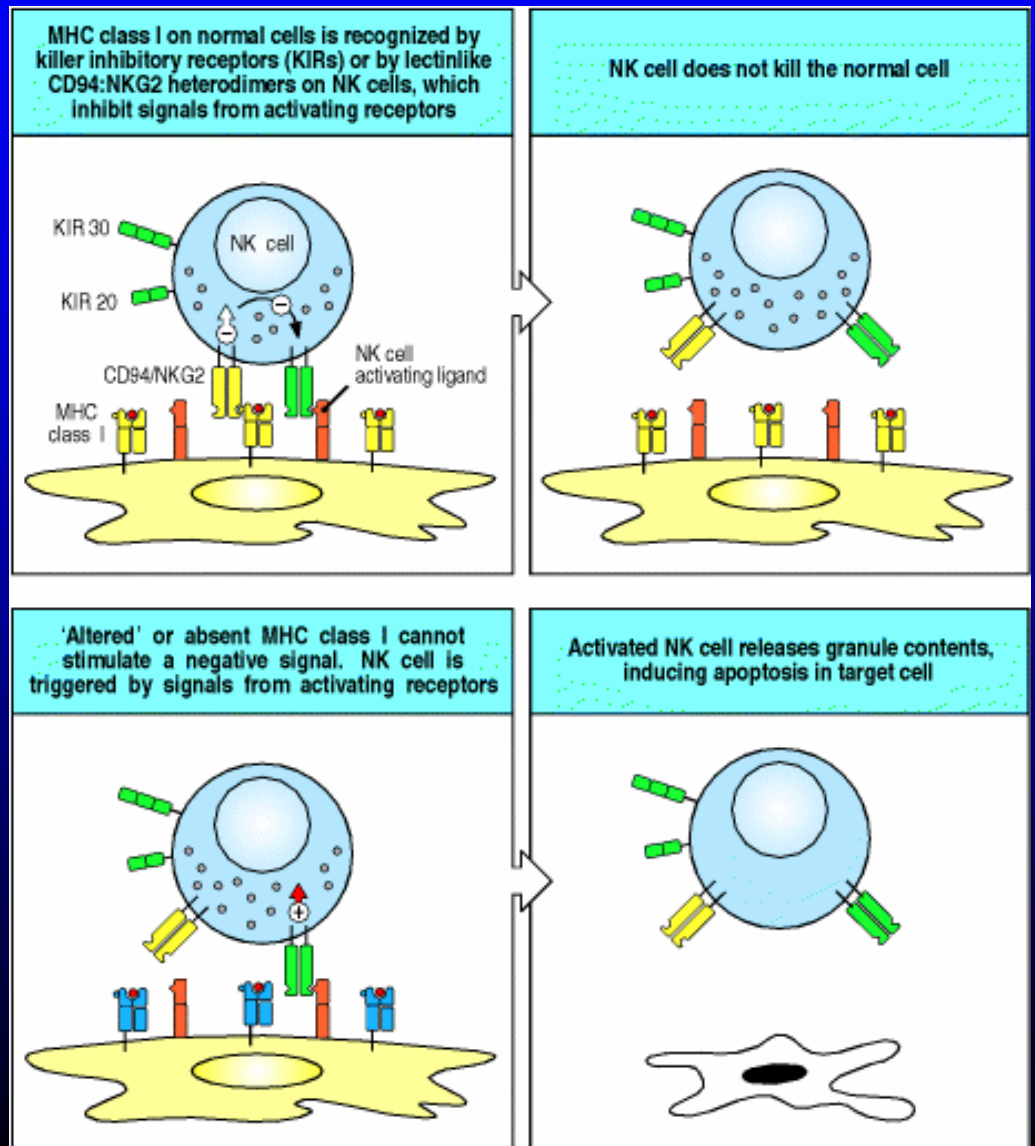


T Cell Receptor





NK cells: no specific antigen receptor



CD nomenclature

CD	Alternative Name	HLDA Section	Ligand/ receptor/ substrate/ associated molecule	Description and Function	MW (kDa)
CD1a	R4	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related to thymic T-cell development	49/-
CD1b	R1	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related to thymic T-cell development	45/-
CD1c	M241, R7	T		Non-peptide antigen presenting molecules; involved in lymphocyte activation; related	43/-
CD8β	Lyt3	T		Co-receptor molecule; binds to MHC class I.	
CD9	p24, DRAP-1, MRP-1	Platelet	CD63, CD81,CD82	Modulates cell adhesion and migration; triggers platelet activation; expressed on eosinophils and basophils.	-/24,26
CD10	CALLA, NEP, gp100	B		Zinc Metalloprotease; neutral endopeptidase; regulator of B-cell growth and proliferation by hydrolysis of peptides with proliferative/anti-proliferative effects.	100/-
CD11a	LFA-1a	Adhesion	ICAM-1,2,3	Intracellular adhesion and co-stimulation; binds to ICAM-1, ICAM-2, ICAM-3;	170/

CD3 = T lineage

CD4 = T helpers*

CD8 = cytotoxic T*

CD19 = B lineage

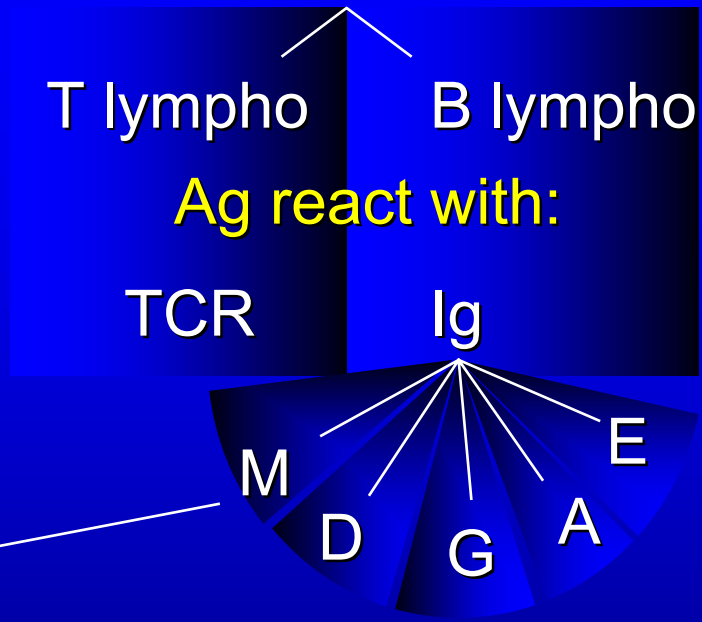
CD10 = immature lymphoid cells*

CD34 = progenitors*

**also other cells*

CD40/CD40L

Adaptive immunity:



[structure, function]

IgM: first isotype after primary infection

IgG: main isotype of long-lasting defense, crosses placenta

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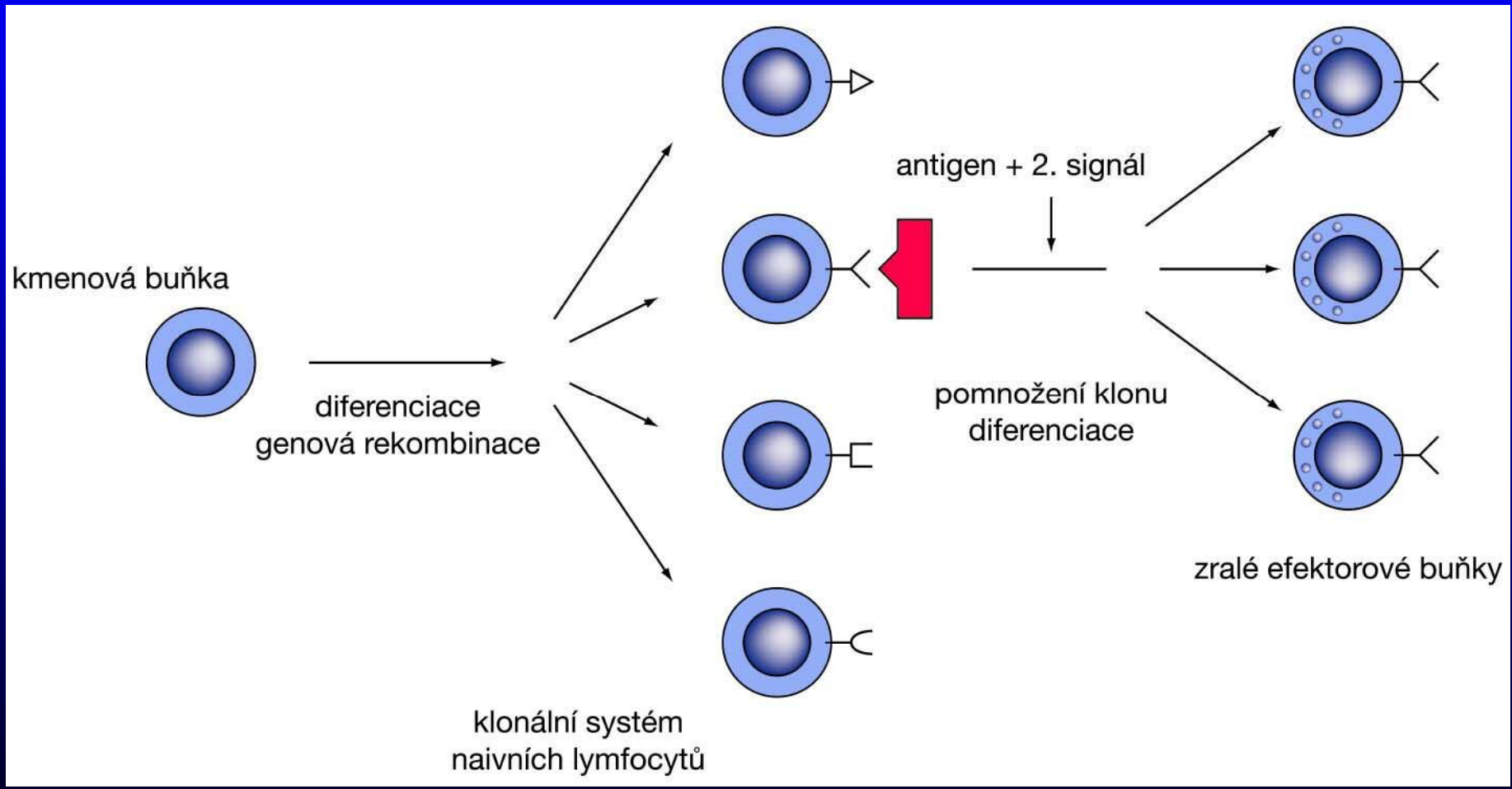
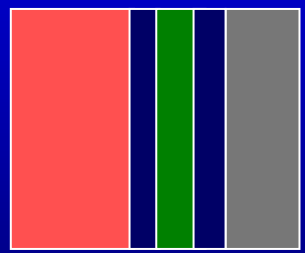
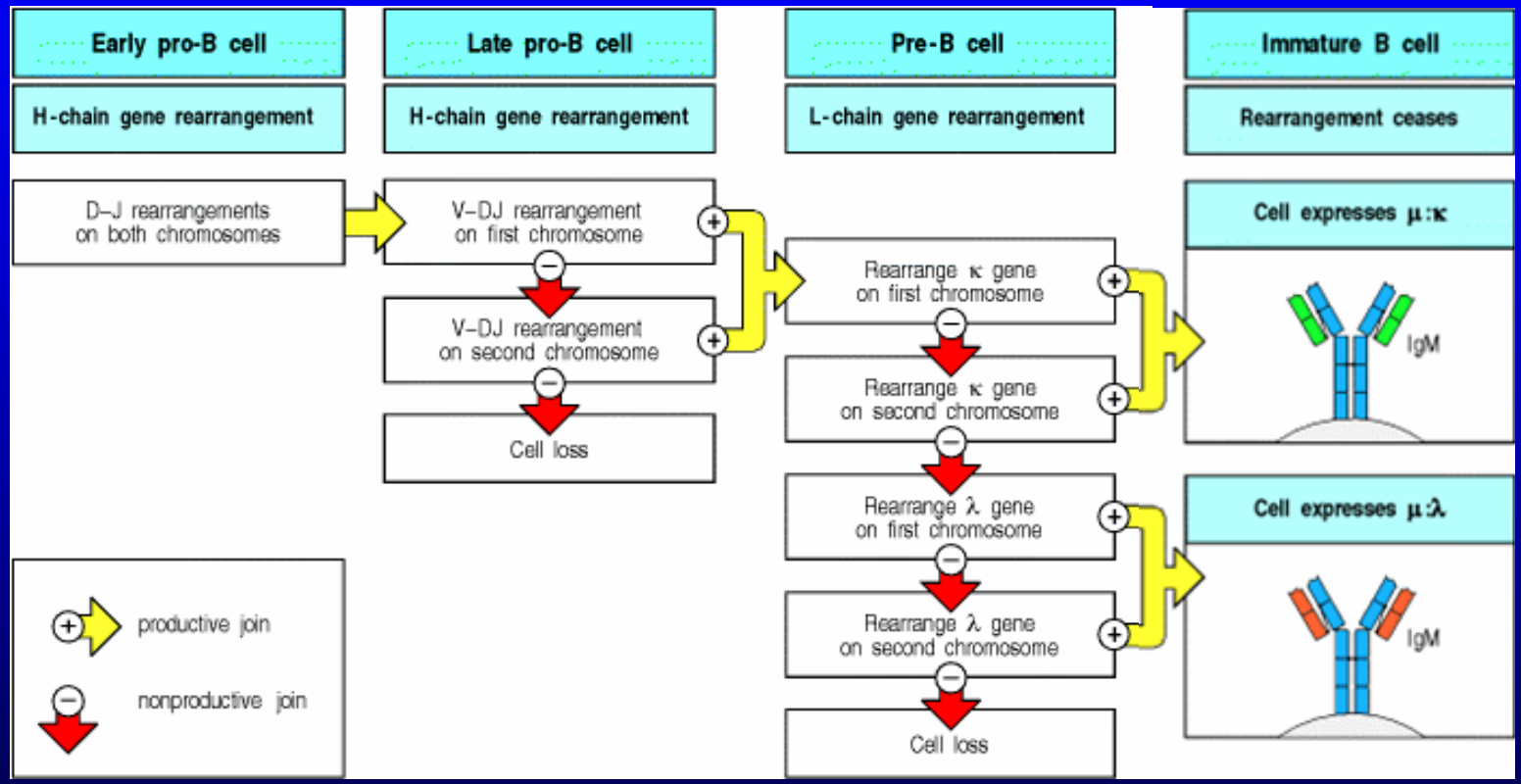
Antigen specifity - clonal theory



Immunoreceptor gene rearrangement



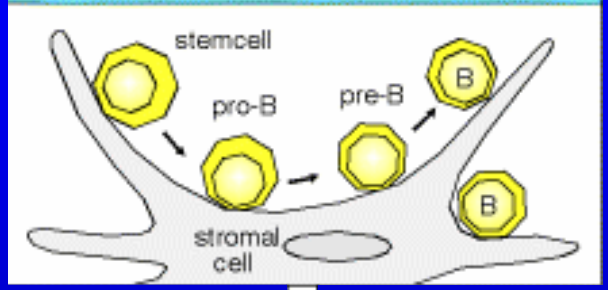
Genes for various chains..



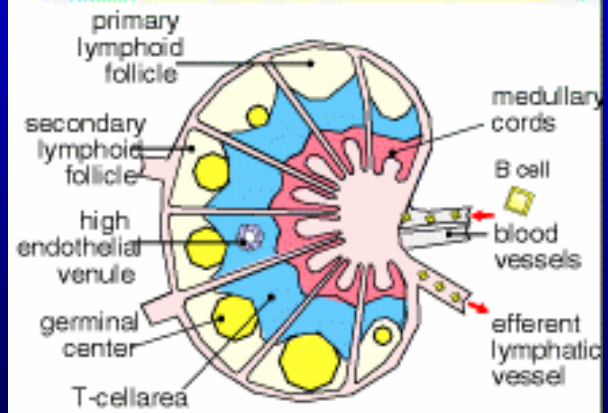
Allelic exclusion

B lymphocytes - development

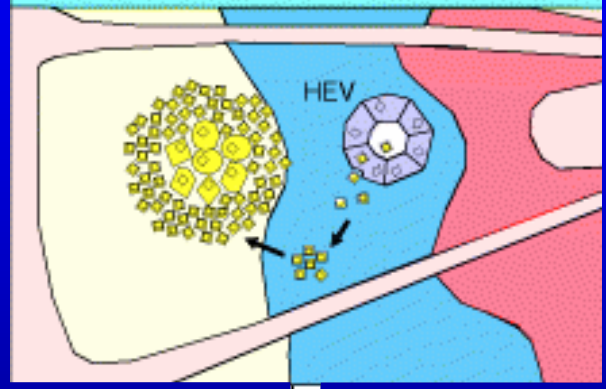
B cells develop in the bone marrow



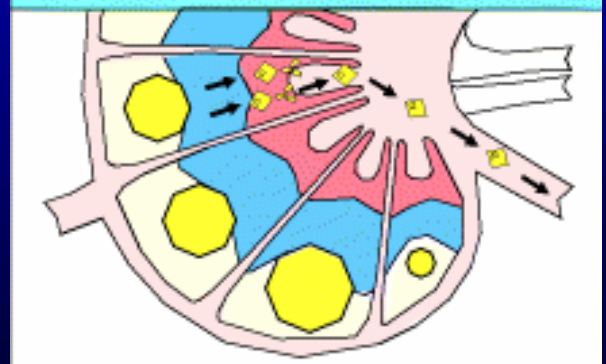
Mature B cells travel to the lymph node via the bloodstream and leave via the efferent lymph



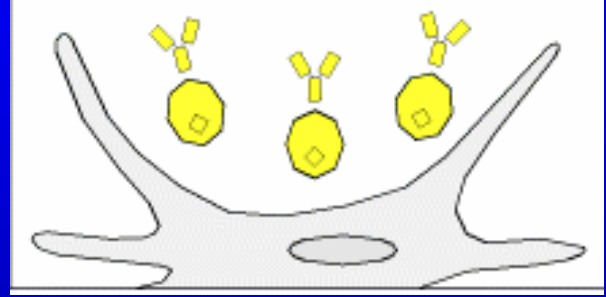
B cells that encounter antigen form primary foci from which proliferating cells migrate to the primary follicle forming a secondary follicle with a germinal center



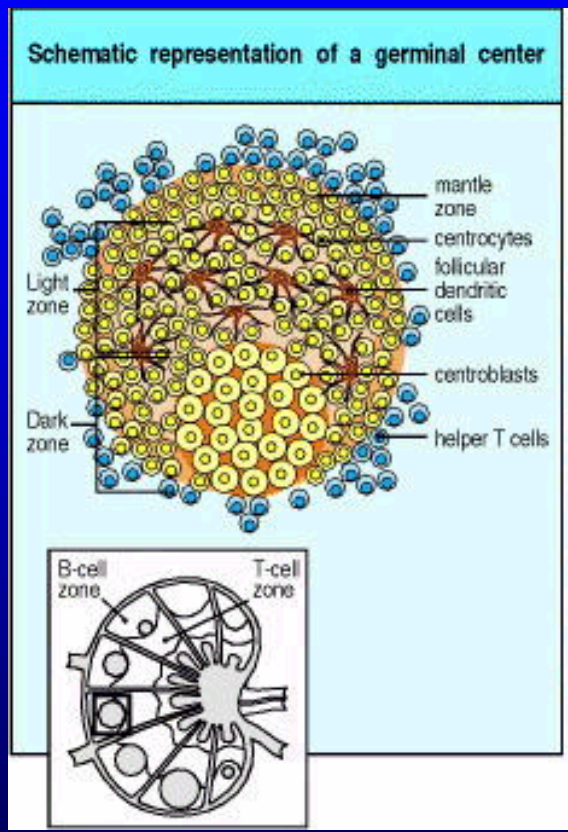
Plasmacells migrate to the medullary cords or leave via the efferent lymphatics

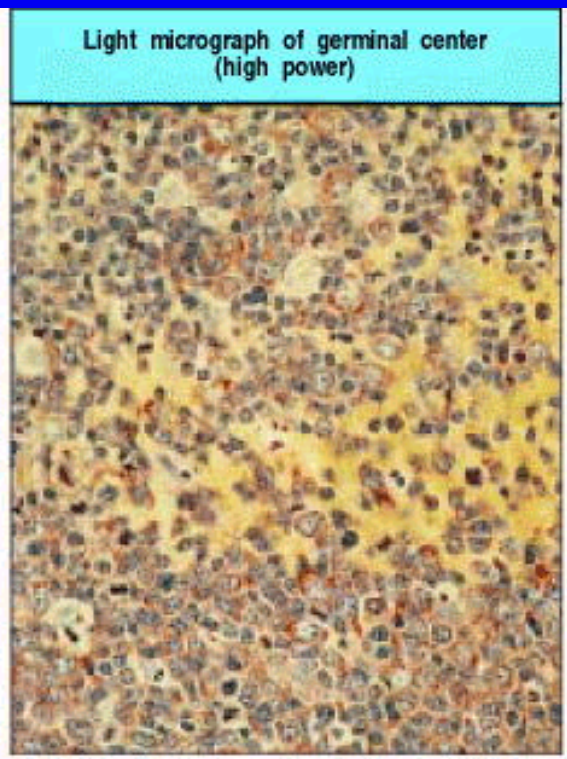


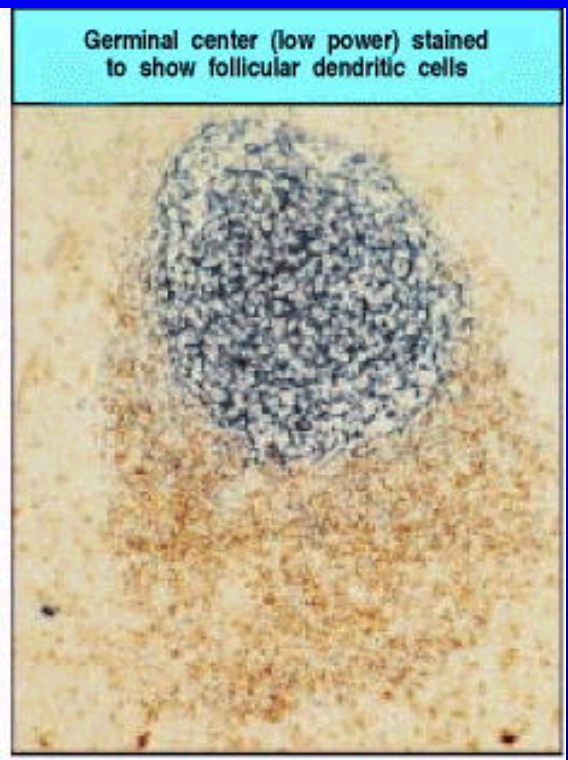
Plasmacells migrate to the bone marrow



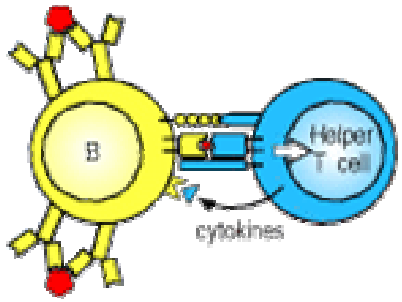
Germinal center close-up





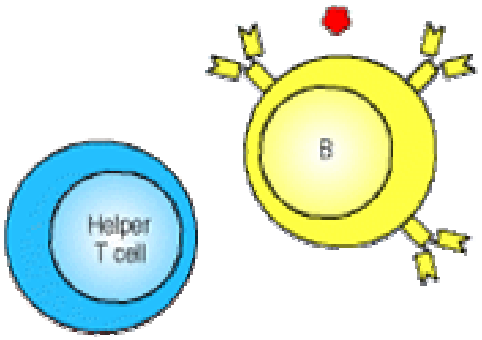


Activated B cell



Somatic hypermutation of immunoglobulin V regions in rapidly proliferating GC B cells

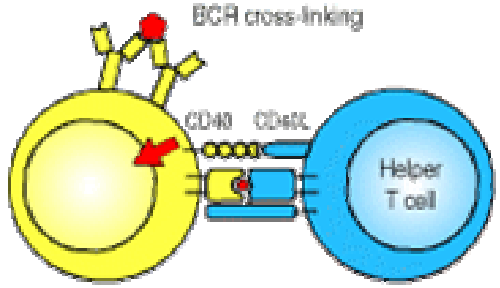
GC B cell with low-affinity surface immunoglobulin



BCR is not cross-linked and B cell cannot present Ag to T cell

B cell dies by apoptosis

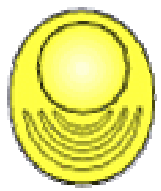
GC B cell with high-affinity surface immunoglobulin



T-cell help and BCR cross-linking sustain B cell proliferation and maturation

Memory B cell

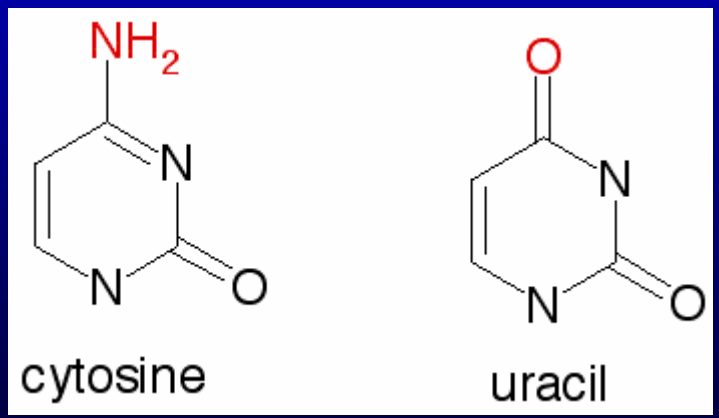
Plasma cell

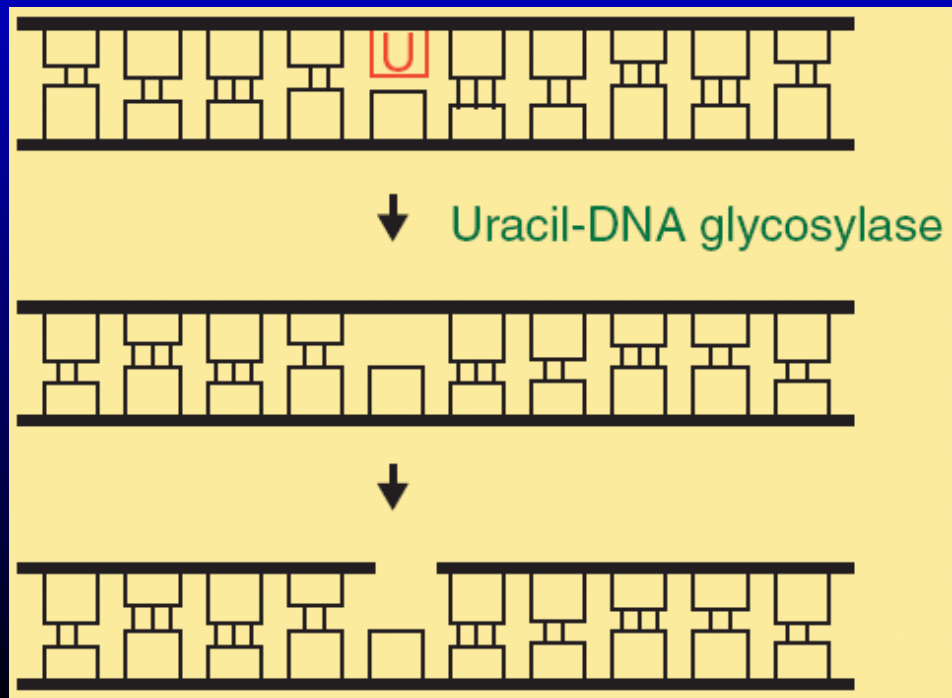


Somatic hypermutation

mutation in variable loci Ig genes
in germinal centers
together with isotype switch

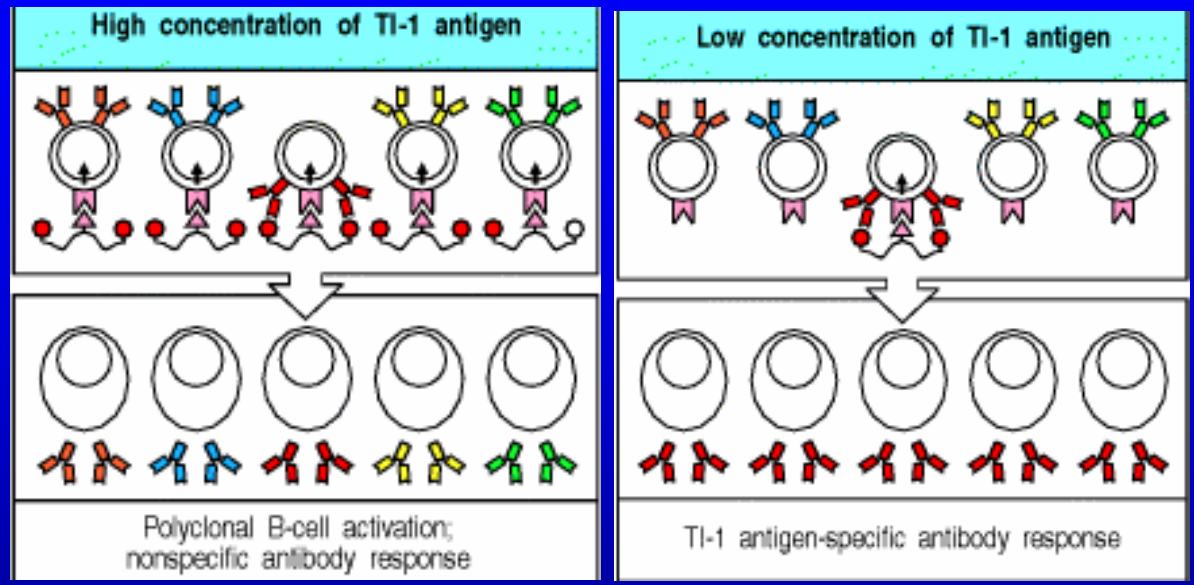
AID (aktivation induced deaminase)





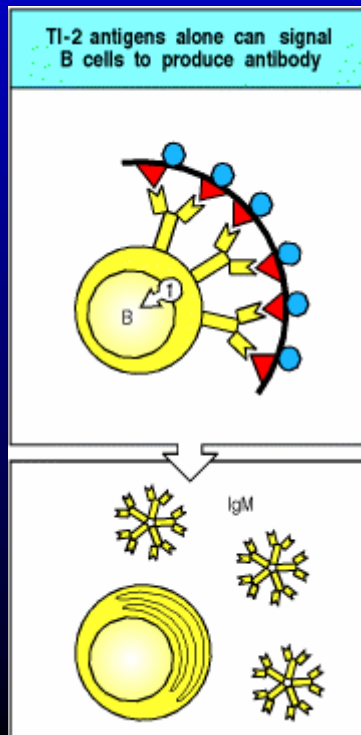
Thymus-independent (TI) antigens

Type 1: mitogenic potential (e.g.: *lipopolysacharide*)

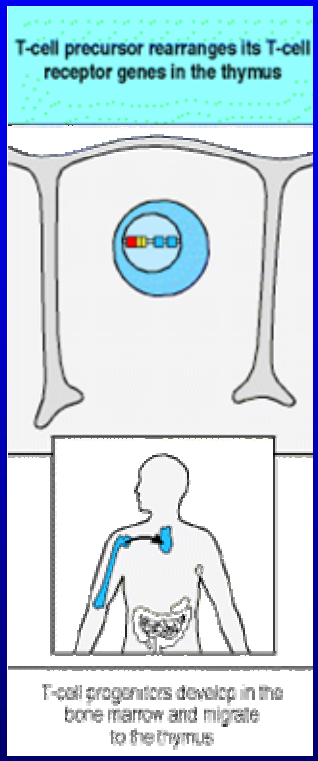


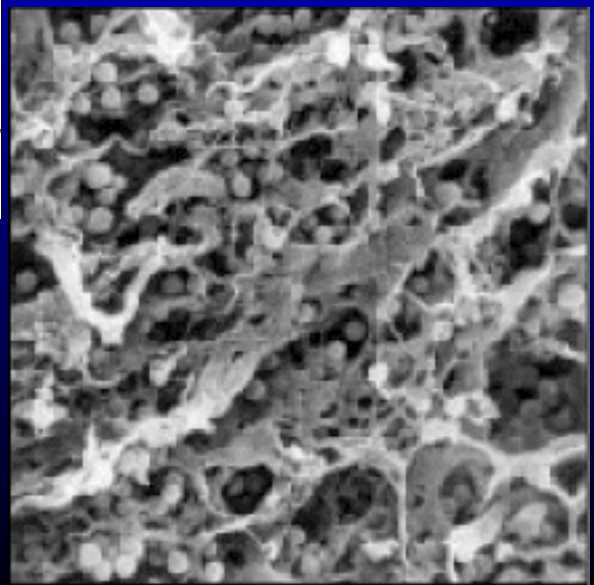
Type 2: - repetitive structures (often polysaccharides)

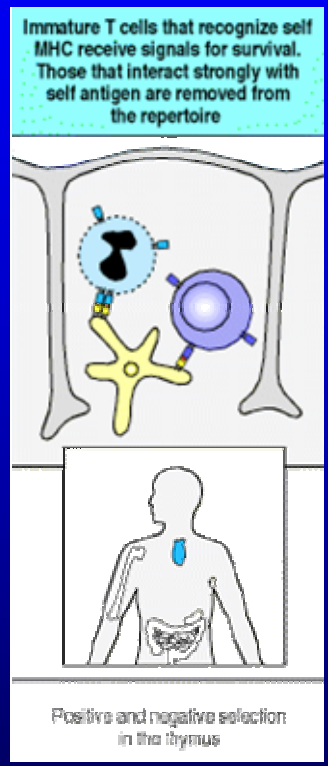
- no help: IgM only
- mostly created by B1 cells or by marginal zones
- children under 2 yrs: weak response

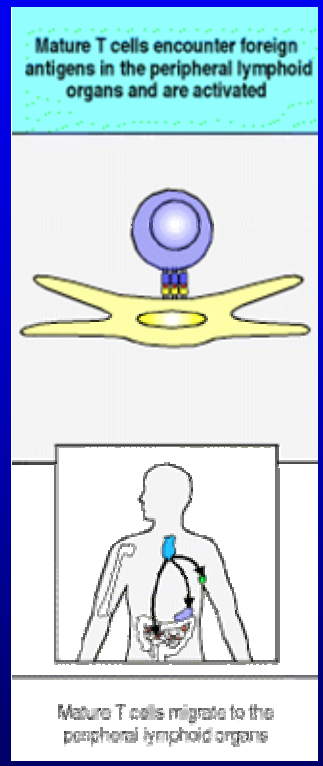


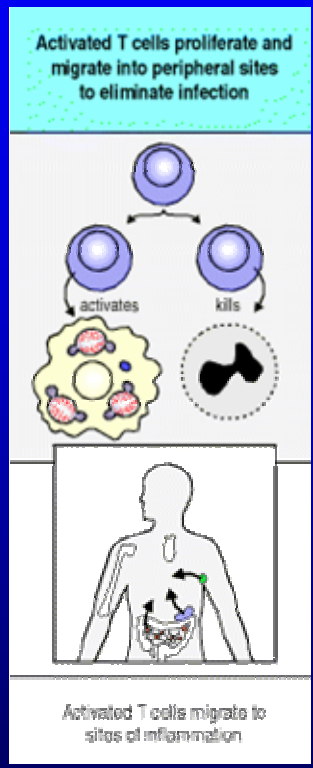
T cell development











T lymphocyte subpopulations

CD 8 - Tc, cytotoxic lymphocytes

CD4 - Th - helpers, Treg- regulatory
[attacked by HIV]

Normal frequency in blood: CD4/CD8 cca 2

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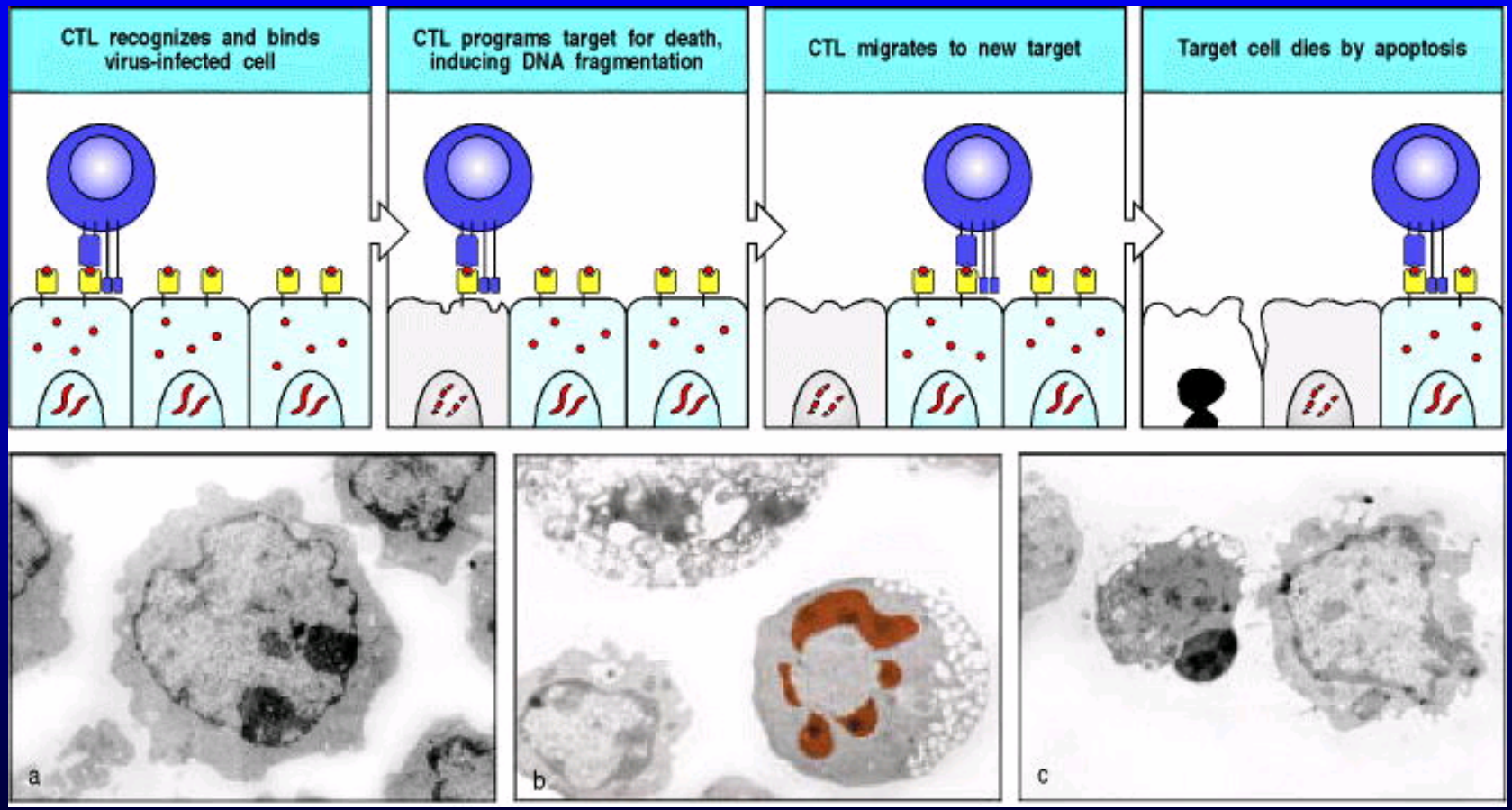
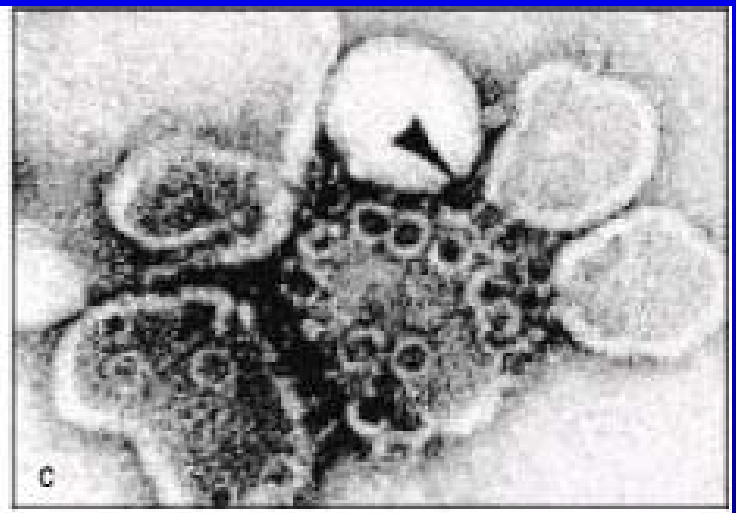
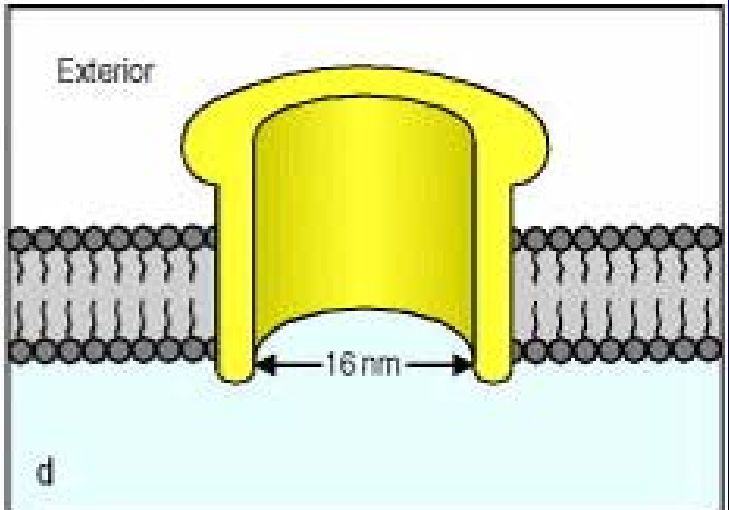
Cytotoxic T lymphocyte



NK a Tc cells: granules

perforin





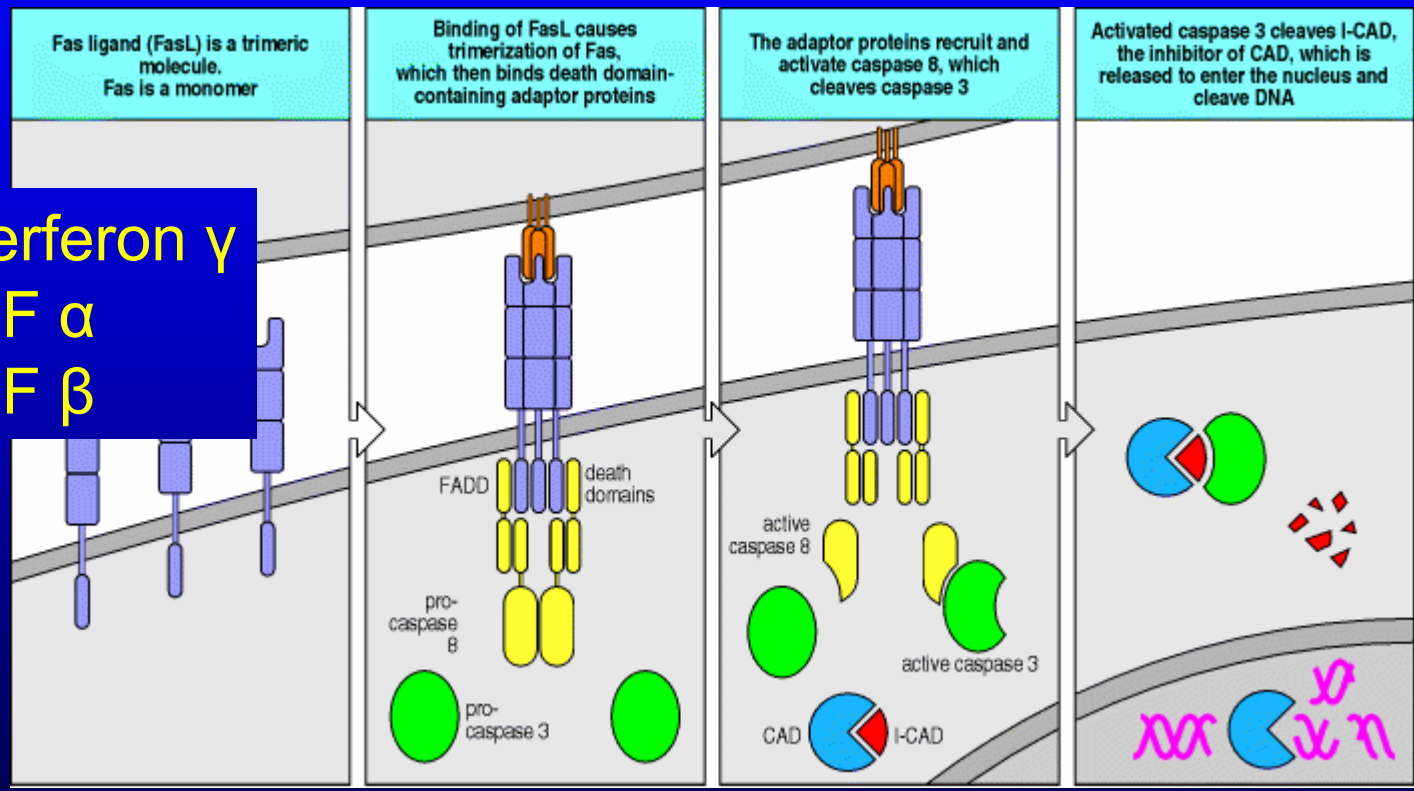
granzymes
granulysin

Cytotoxic T lymphocyte: other mechanisms

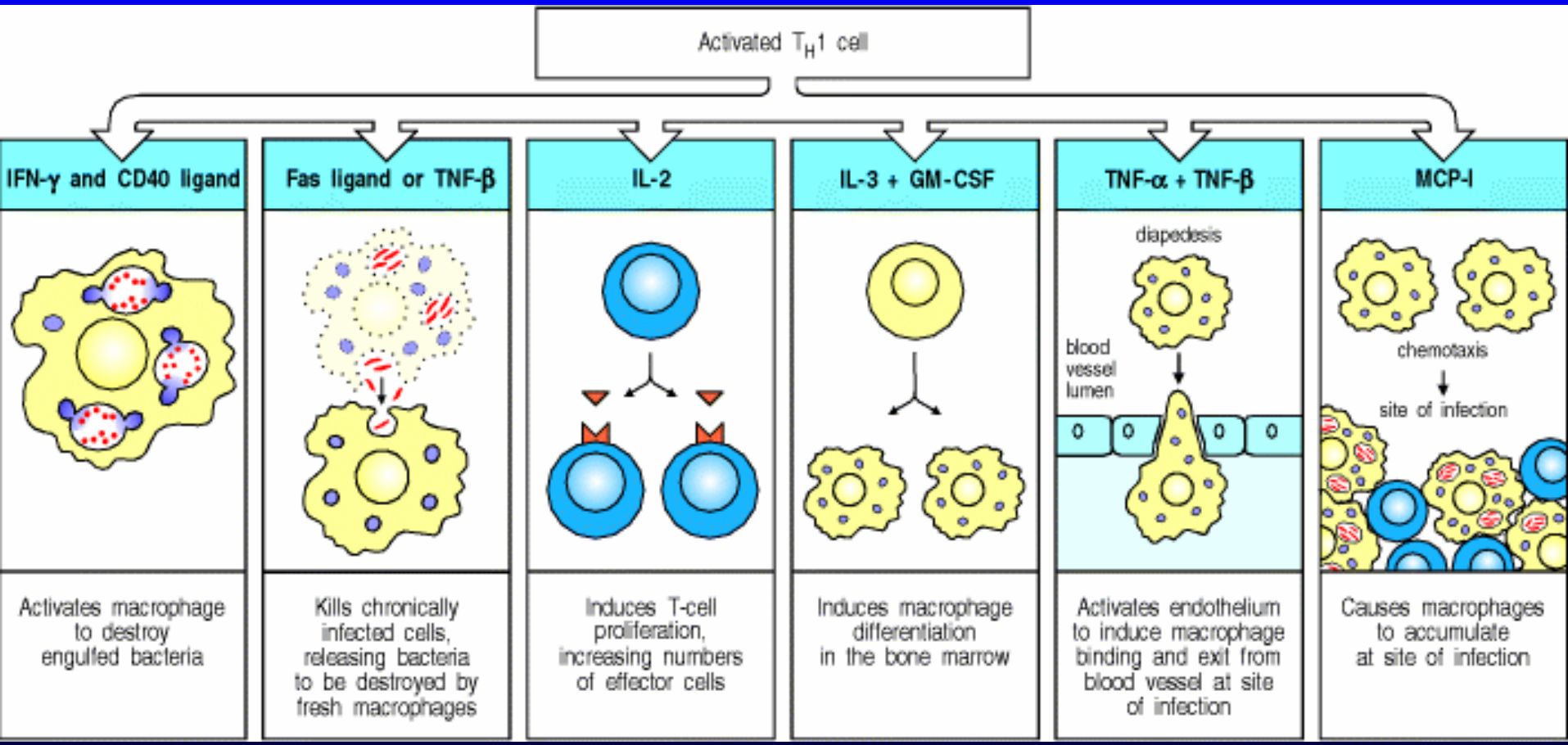
Fas ligand

cytokines

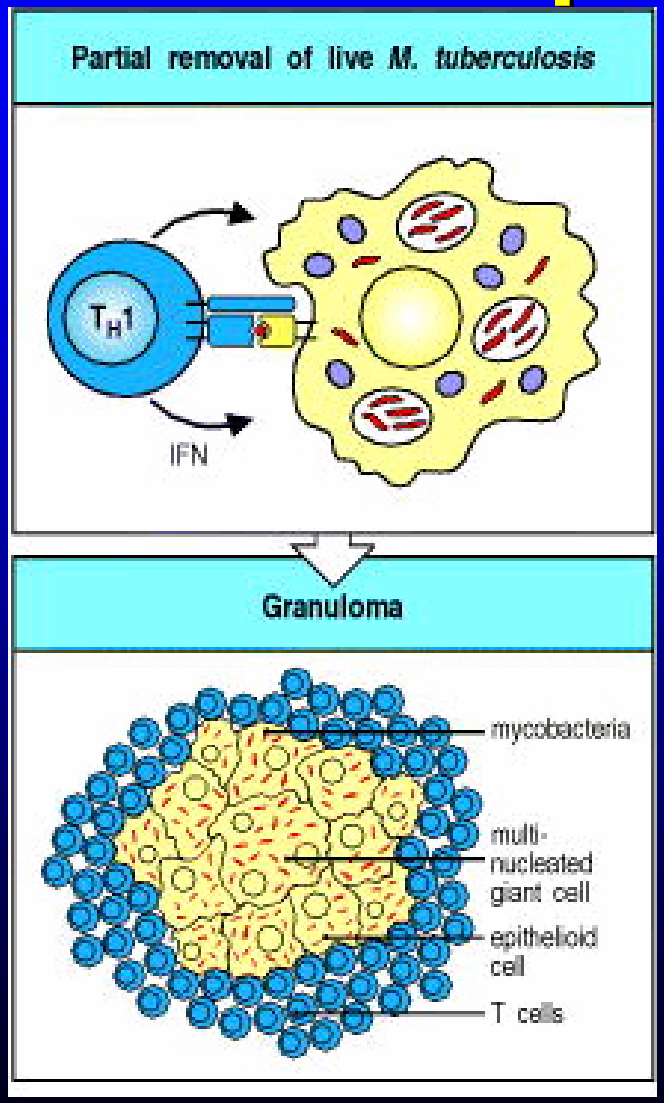
interferon γ
TNF α
TNF β

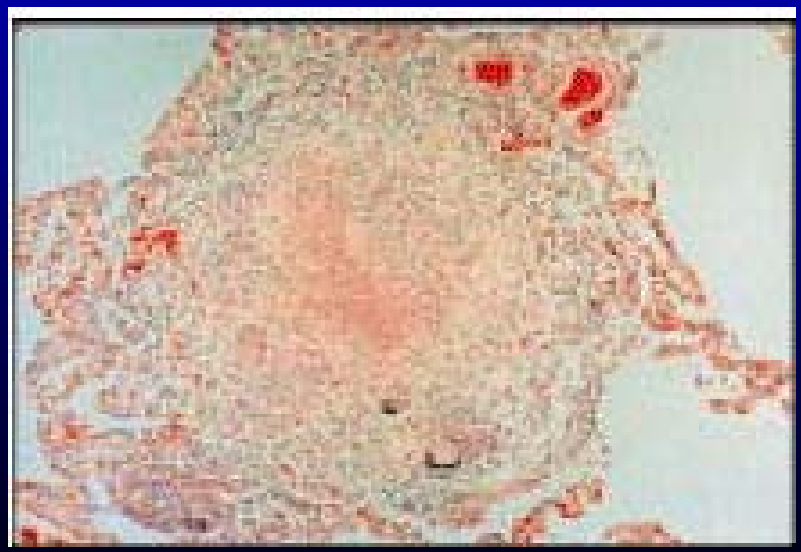


Th cells as effector

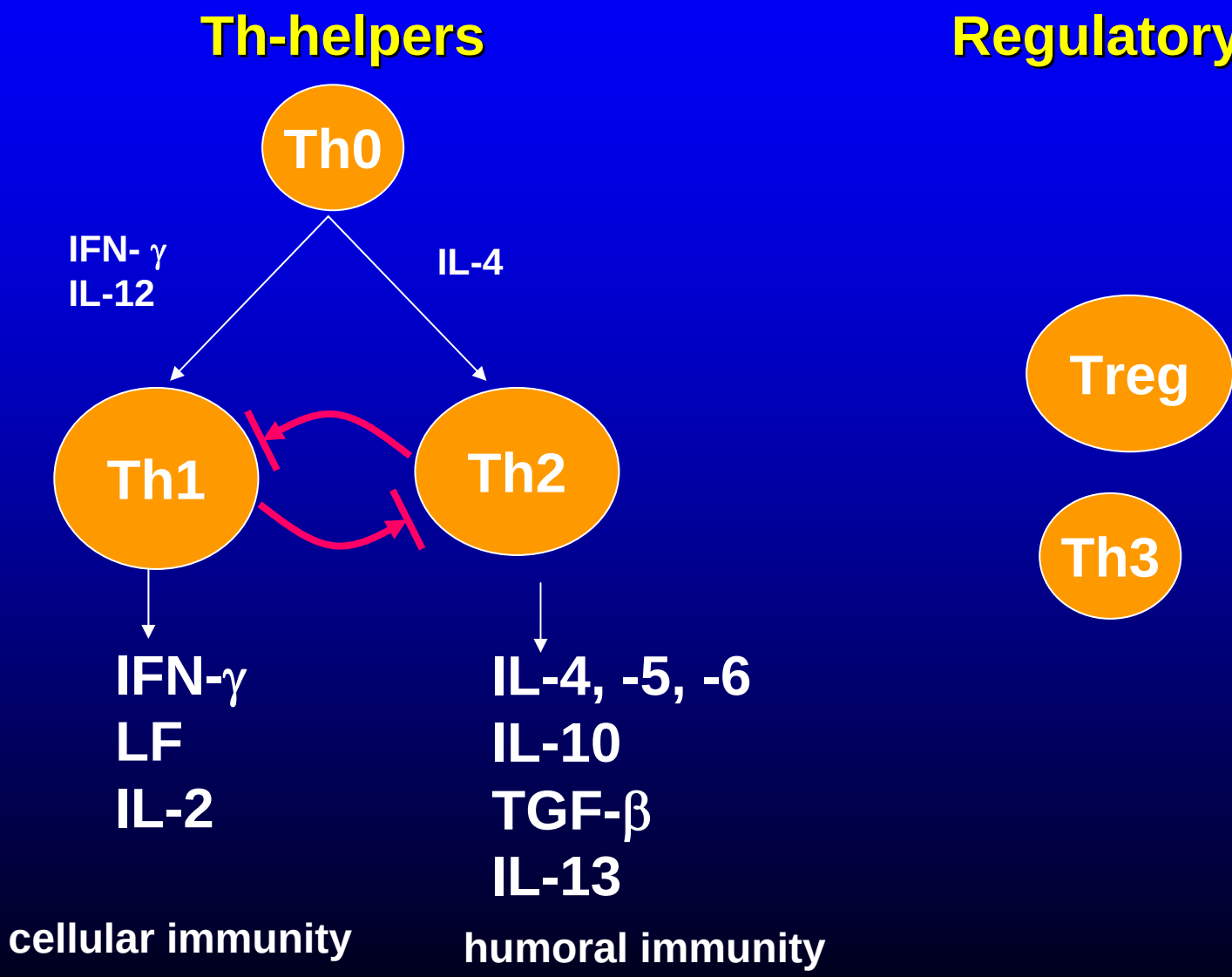


If macrophages cannot eat it..



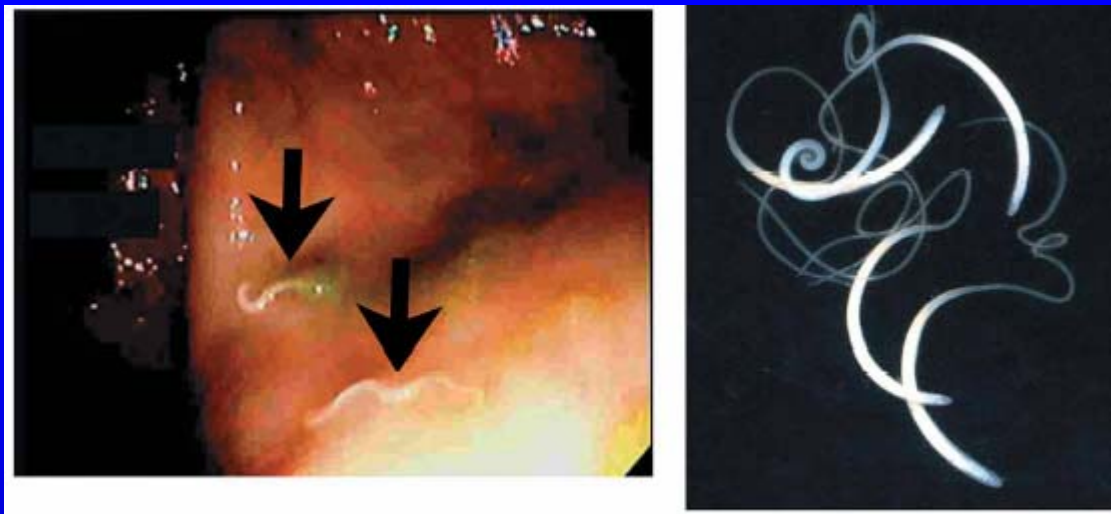


Regulatory role of CD4+ cells



Allergy:

possible role of T[reg] cells



An adult *Trichuris suis* worm (right) in the colon of a patient (left) can cause dysentery and mental retardation. It may also protect against asthma.

Courtesy: Anita van den Biggelaar

Children in Lambaréné, Gabon, play in a pool where they probably get infected with schistosomes. The village has negligible rates of asthma, even as tested by responses to dust-mite allergens (inset).

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Innate-like lymphocytes

limited repertoir
specific function and localization
mostly autonomous

- Tγδ
- B1
- NKT

- Diversity stems from rearrangements of genes
- All lymphocytes arise from bone marrow precursors
- Autoreactive lymphocytes die
- Non-productive and areactive lymphocytes die

- Somatic hypermutation of B lymphocytes leads to the selection of the best Ig
- Main T lymphocyte subsets are Th (CD4+) and Tc (CD8+)
- Th comprise of Th1 and Th2, related are Th3 and Tr1 with regulatory function

Contents

- Specific immunity: Basics
- Immunoglobulins and T cell receptor
- B and T development
- T cell function
- Innate-like lymphocytes
- Examples: B and T cell function

B and T lymphocyte disorders

- lymphopenia:

decreased production

- inborn errors (T, B, T and B)
- malnutrition
- TB and other infections

increased destruction

- steroids, radiation, chemotherapy
- AIDS (T)

losses (gut, chylothorax,..) (T and B)

B and T lymphocyte disorders

- lymphocytosis:

normal absolute counts vary throughout age
virus infections
other infections (mycoplasma, syphilis, ..)
dif. dg.: clonal proliferations (incl. leukemias)

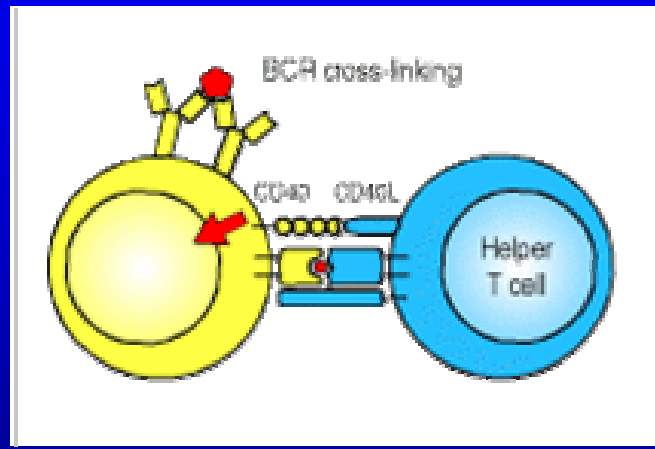
B and T lymphocyte disorders

- functional defects:

antibody deficiency
IgA

hereditary mutation CD40/CD40L

polymorphism of V(D)J in some ethnic groups



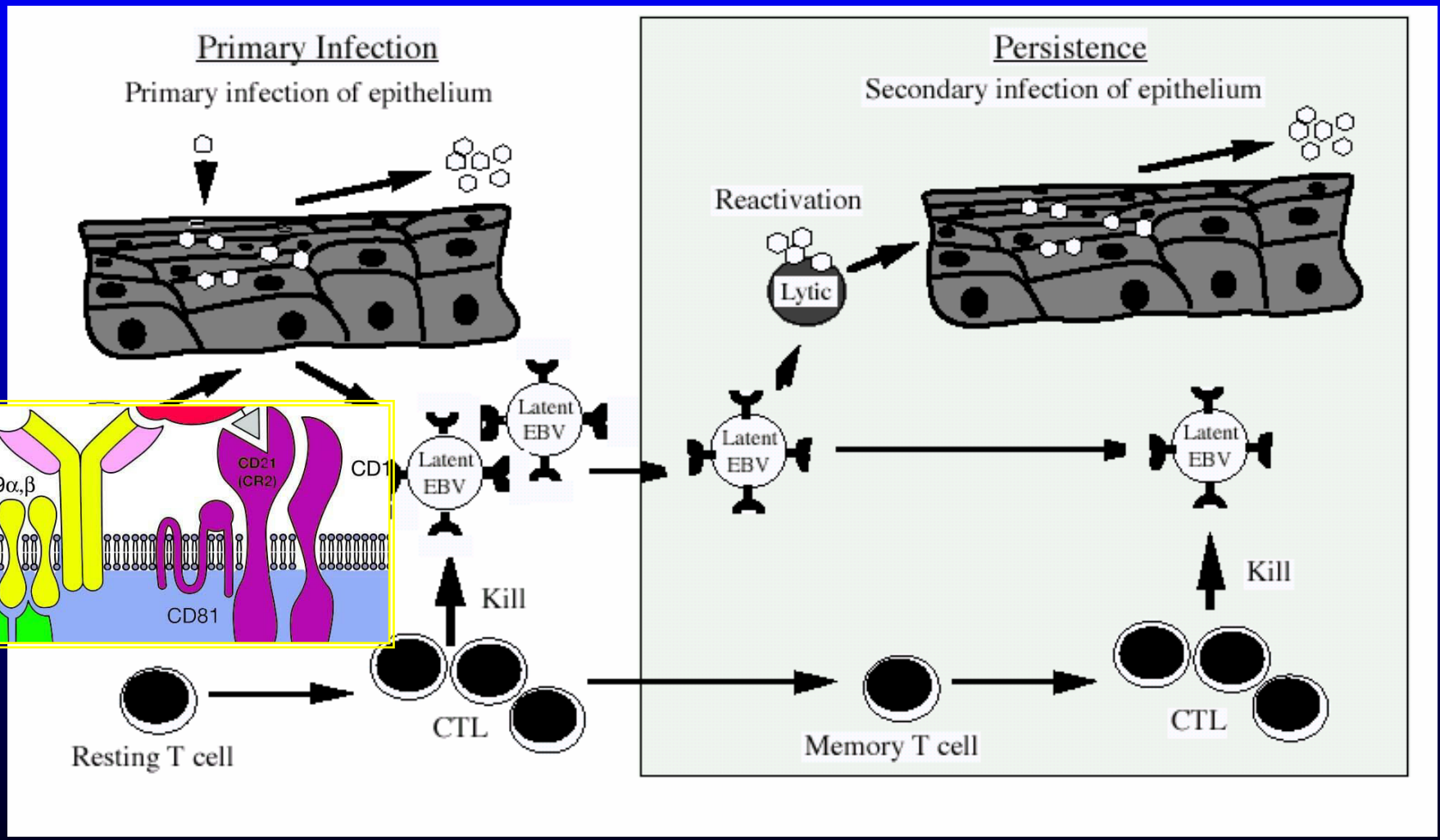
EBV, Epstein-Barr virus

- 95% world population

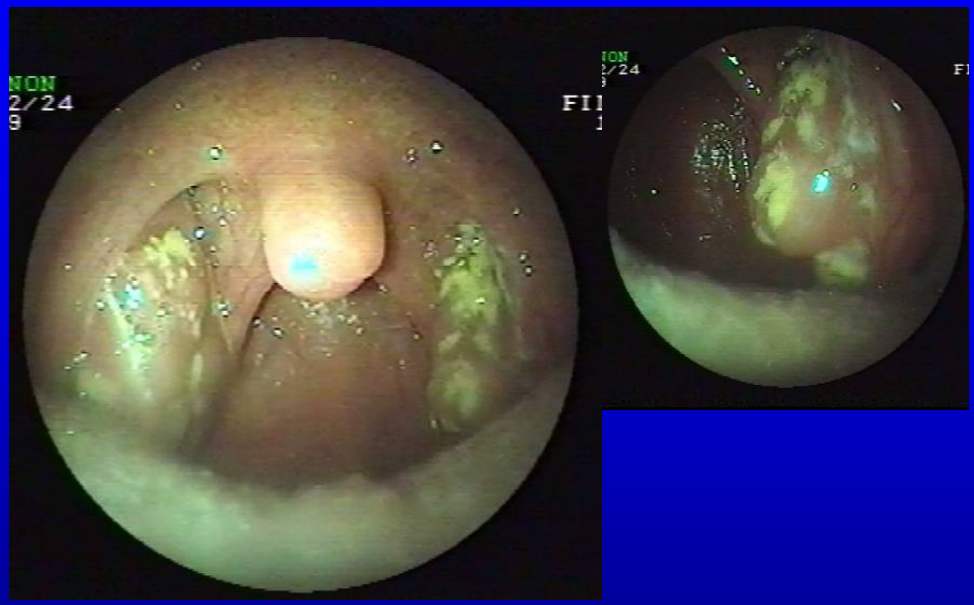
- Primoinfection:

- infants, preschool kids: mostly asymptomatic or indistinguishable from other infections
- adolescence (rarely at different age): inf. mononucleosis

Life cycle, EBV



Infectious mononucleosis: clinics



+fever

splenomegaly up to 50% patients
hepatomegaly (10%)
elevated transaminases, LDH
petechiae na patře
eye-lid oedemas
exanthemas (up to 15%)
(typically no stomachache)

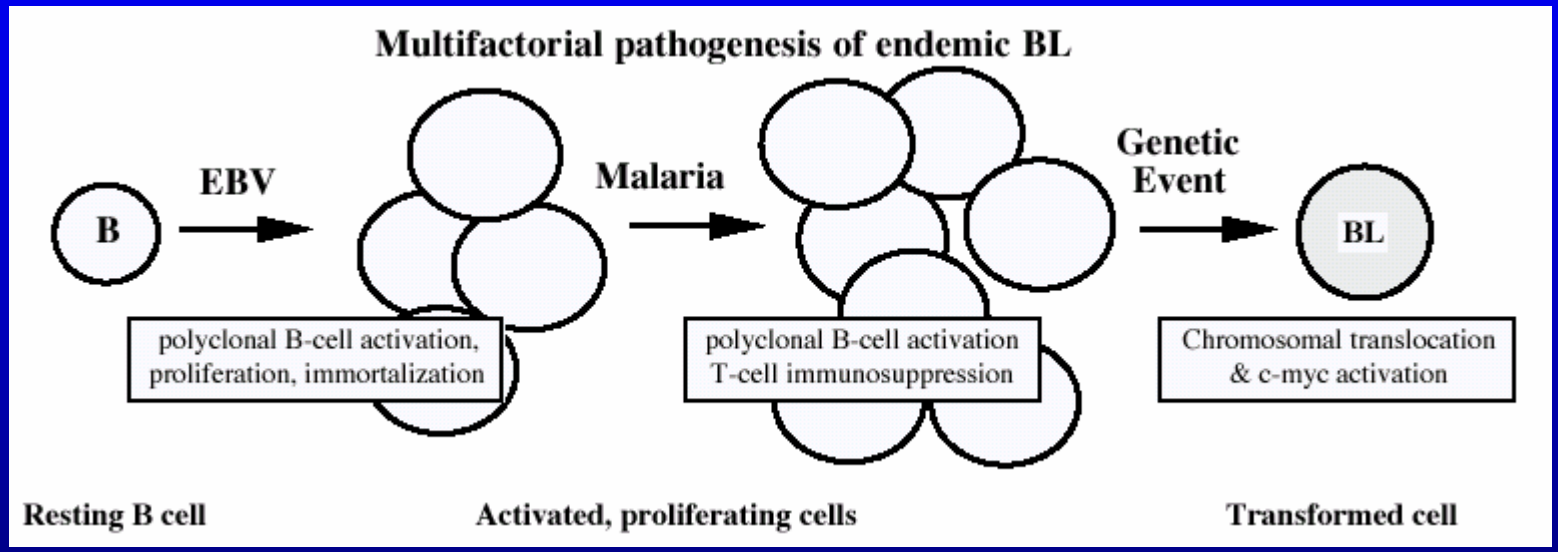
Severe EBV complications

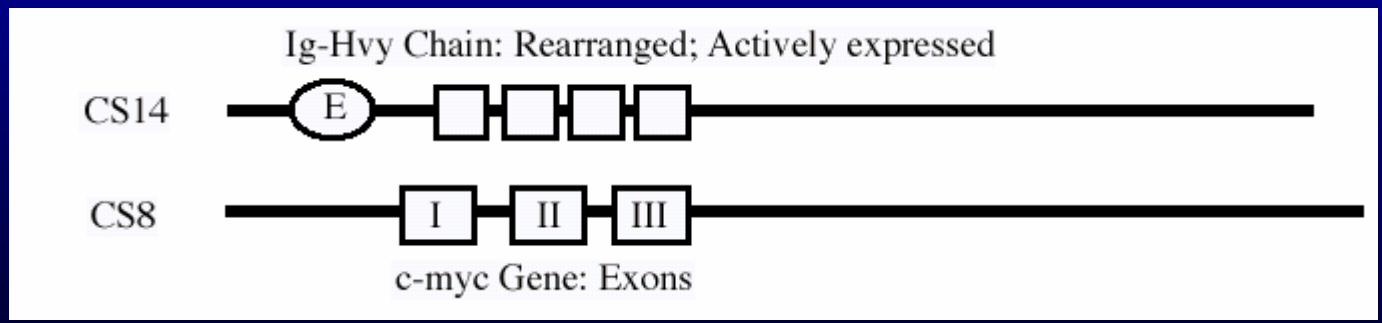
Severe lymphoproliferations

virus-associated hemophagocytic syndrome
familiar hemofagocytic lymfohistiocytosis
X-linked lymphoproliferation

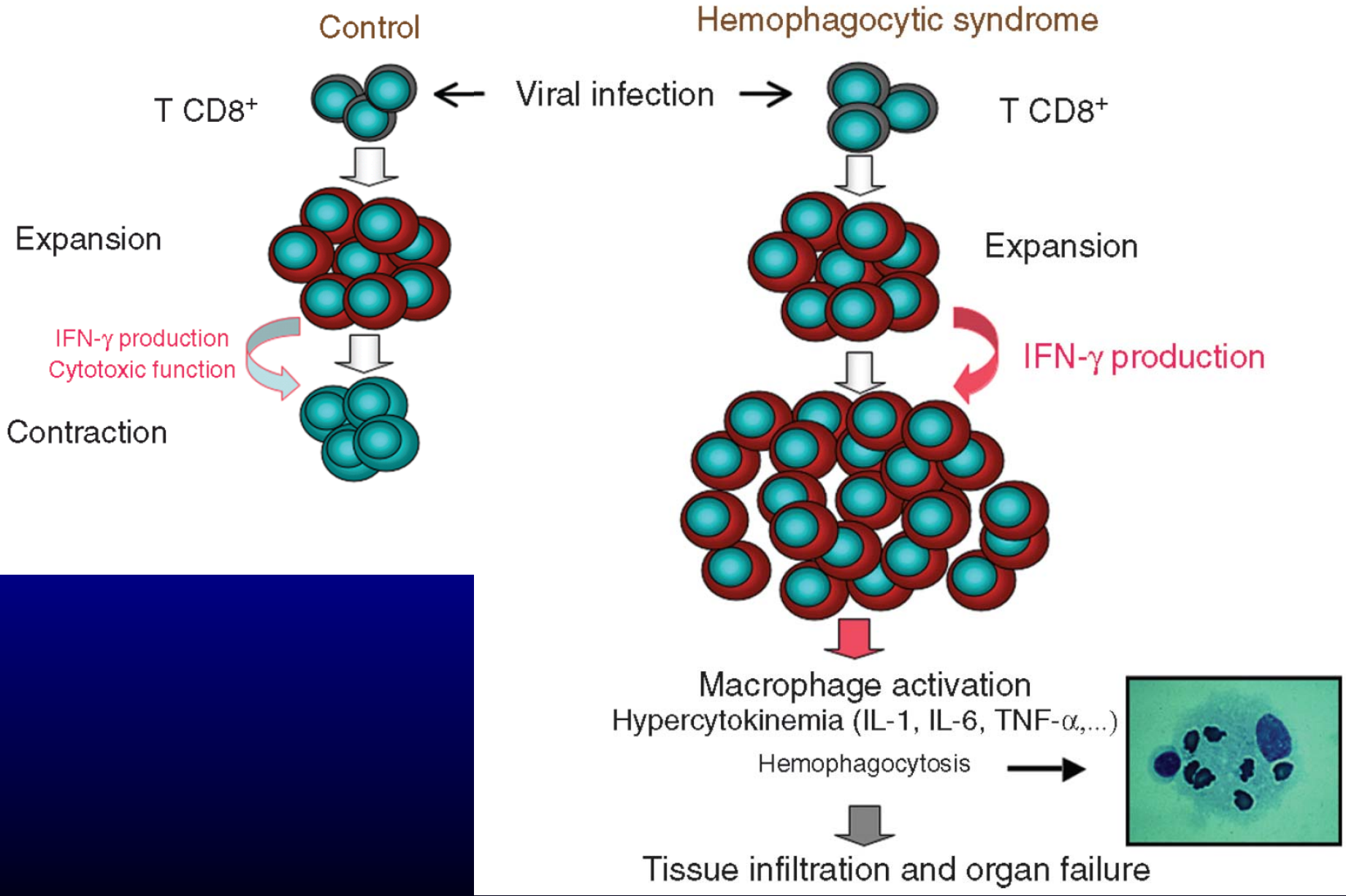
malignities: nasofaryngeal carcinoma
endemic Burkitt lymphoma
other malignancies (Hodgkin, ...)

Burkitt lymphoma





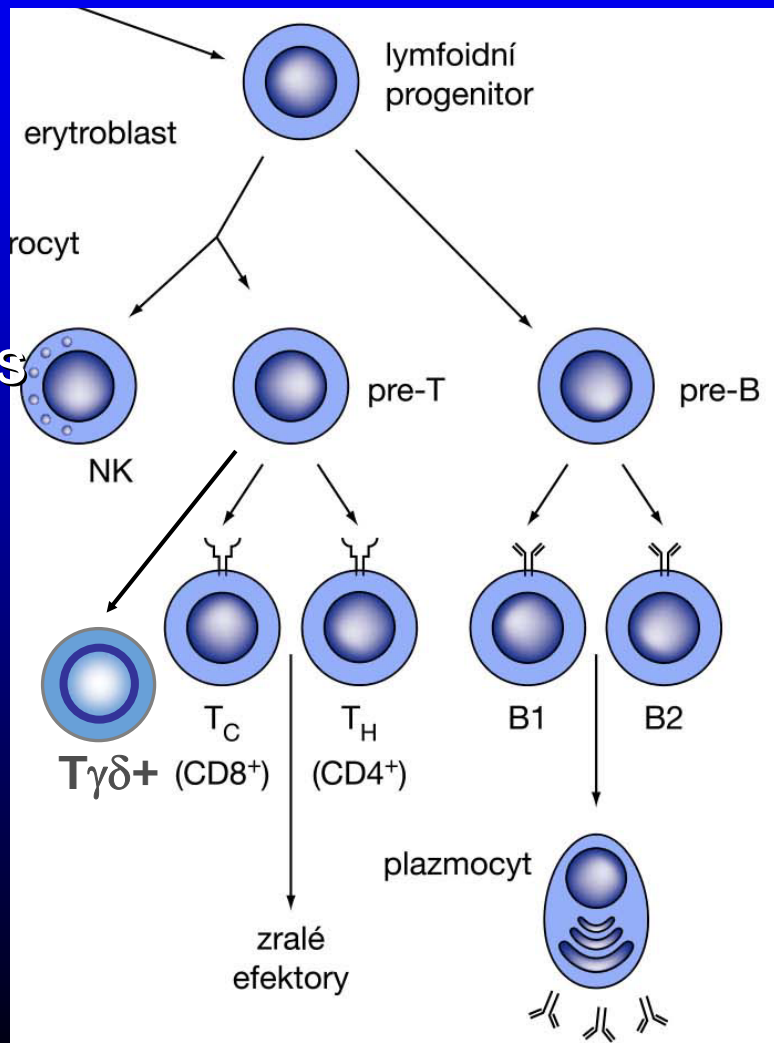
perforin deficiency



Imunodeficiencies: not just losses

Autoimmune lymphoproliferative syndrome

hyper-Ig
splenomegaly
lymphadenopathy
autoimmunity
increased CD3+TCRαβ+CD4-CD8- cells
risk of lymphomas



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ORIGINAL ARTICLE

Autoimmune Lymphoproliferative Syndrome with Somatic *Fas* Mutations

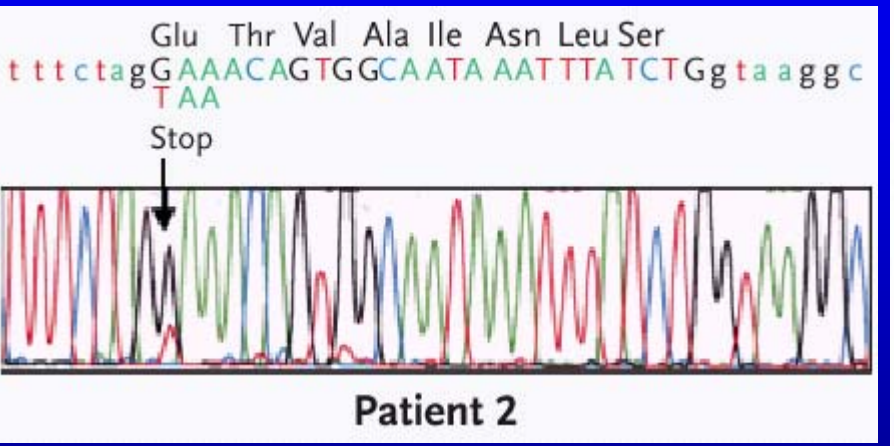
Eliska Holzelova, M.D., Cédric Vonarbourg, M.S., Marie-Claude Stolzenberg, Ph.D., Peter D. Arkwright, M.D., Françoise Selz, B.S., Anne-Marie Prieur, M.D., Stéphane Blanche, M.D., Jirina Bartunkova, M.D., Etienne Vilmer, M.D., Alain Fischer, M.D., Ph.D., Françoise Le Deist, M.D., Ph.D.,

Genetic causes of ALPS

Table. Categorization of ALPS Cases According to Underlying Gene Defects.*

ALPS Type	Defective Gene	Protein	Percent of ALPS Cases
Ia	*TNFRSF6*	Fas, major transmembrane receptor for apoptosis in lymphocytes	74
Ib	*TNFSF6*	Fas ligand	<1
IIa	*CASP10*	Caspase 10, intracellular apoptosis-pathway protease	Approximately 2
IIb	*CASP8*	Caspase 8, intracellular apoptosis-pathway protease	<1
III†	Unknown	Unknown	24

ALPS3: the clue



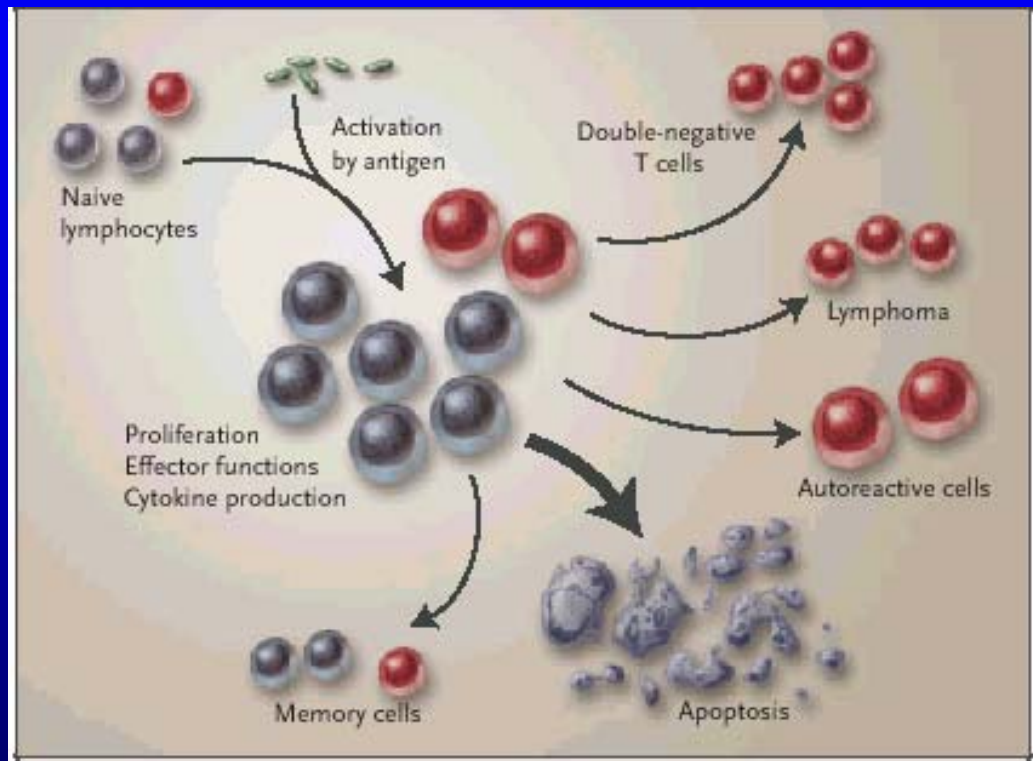


Figure. Survival Advantage and Effects of Lymphocytes with Somatic *Fas* Mutations.

Normal lymphocyte homeostasis depends on maintaining a balance between the expansion of naive cells and their elimination by apoptosis, with a small minority of the cells that are generated after stimulation persisting as memory lymphocytes. Somatic mutations in a fraction of naive cells (brown) lead to their persistence as double-negative T cells, premalignant cells, and autoreactive cells that can mediate autoimmune responses.