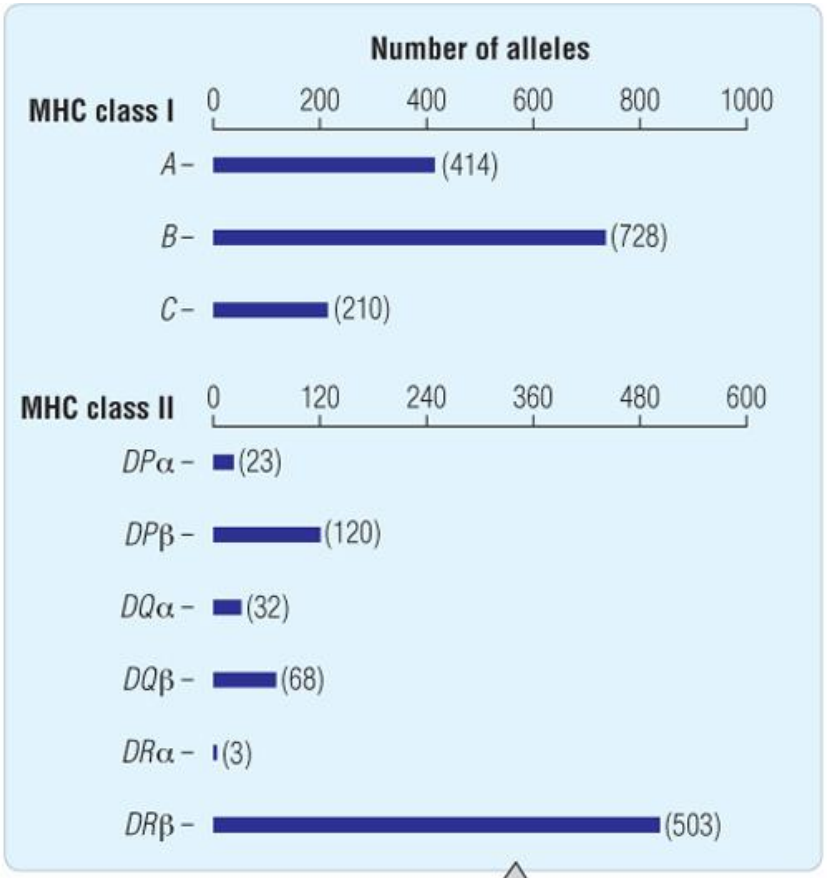
HLA antigens
(Human Leukocyte Antigens)

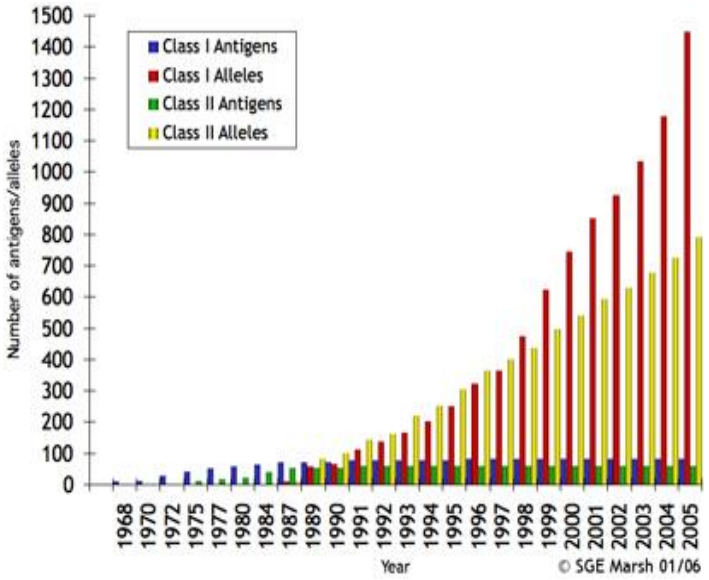
= human MHC
(Main Histocompatibility Complex)
antigens

Polymorphism of human MHC antigens



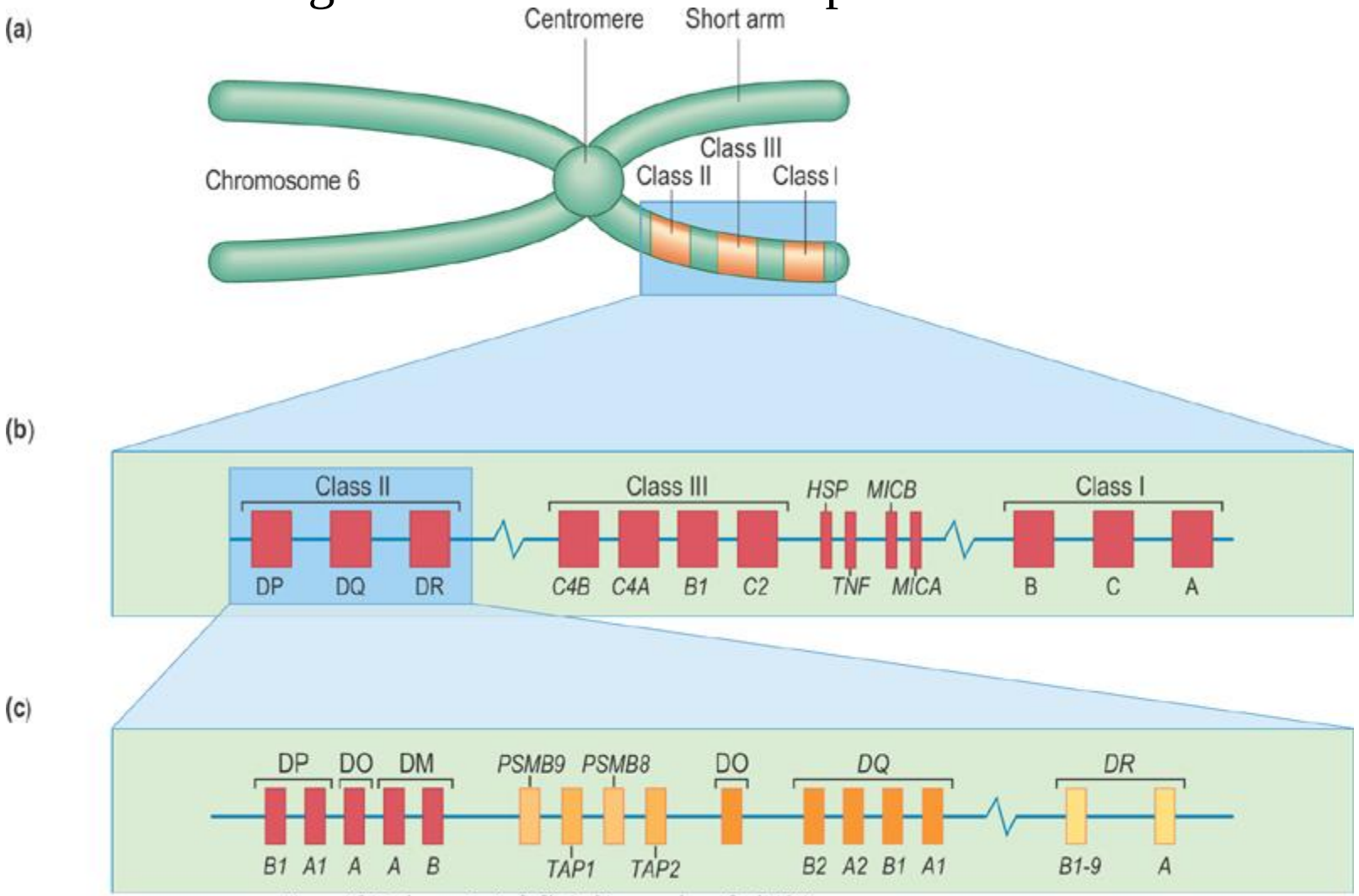
The human MHC genes (*HLA*) are extensively polymorphic (existence of multiple alleles at a locus). The length of the bars indicates the number of alleles found at each locus as of October 2005 (IMGT/HLA database). *HLA-B* and *HLA-DR*β are the most polymorphic loci shown here

Polymorphism of human MHC antigens

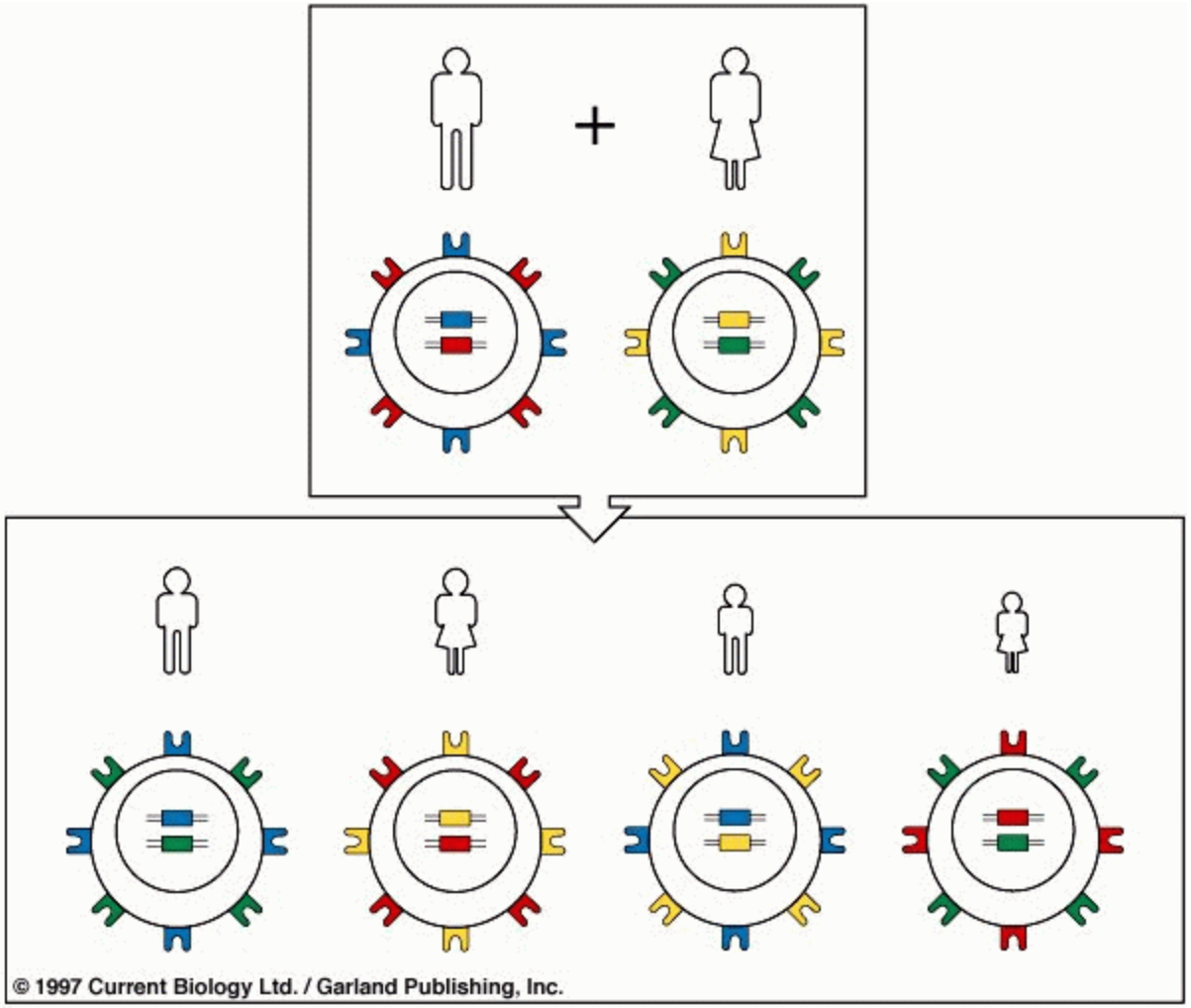


2010 Numbers of HLA Alleles	
HLA Class I Alleles	**3,411**
HLA Class II Alleles	**1,222**
HLA Alleles	**4,633**
Other non-HLA Alleles	**110**

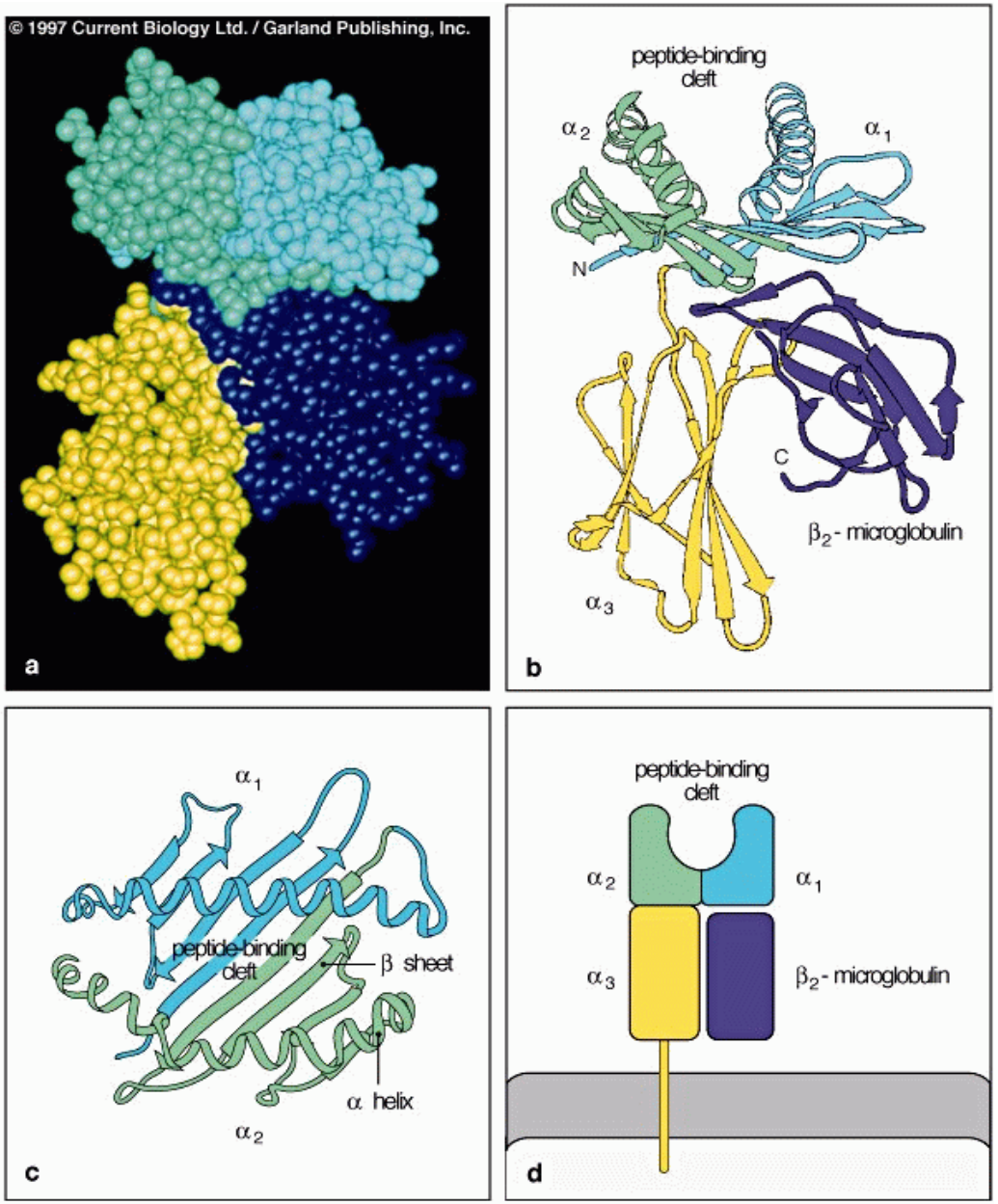
HLA genes are localized on 6p chromosome



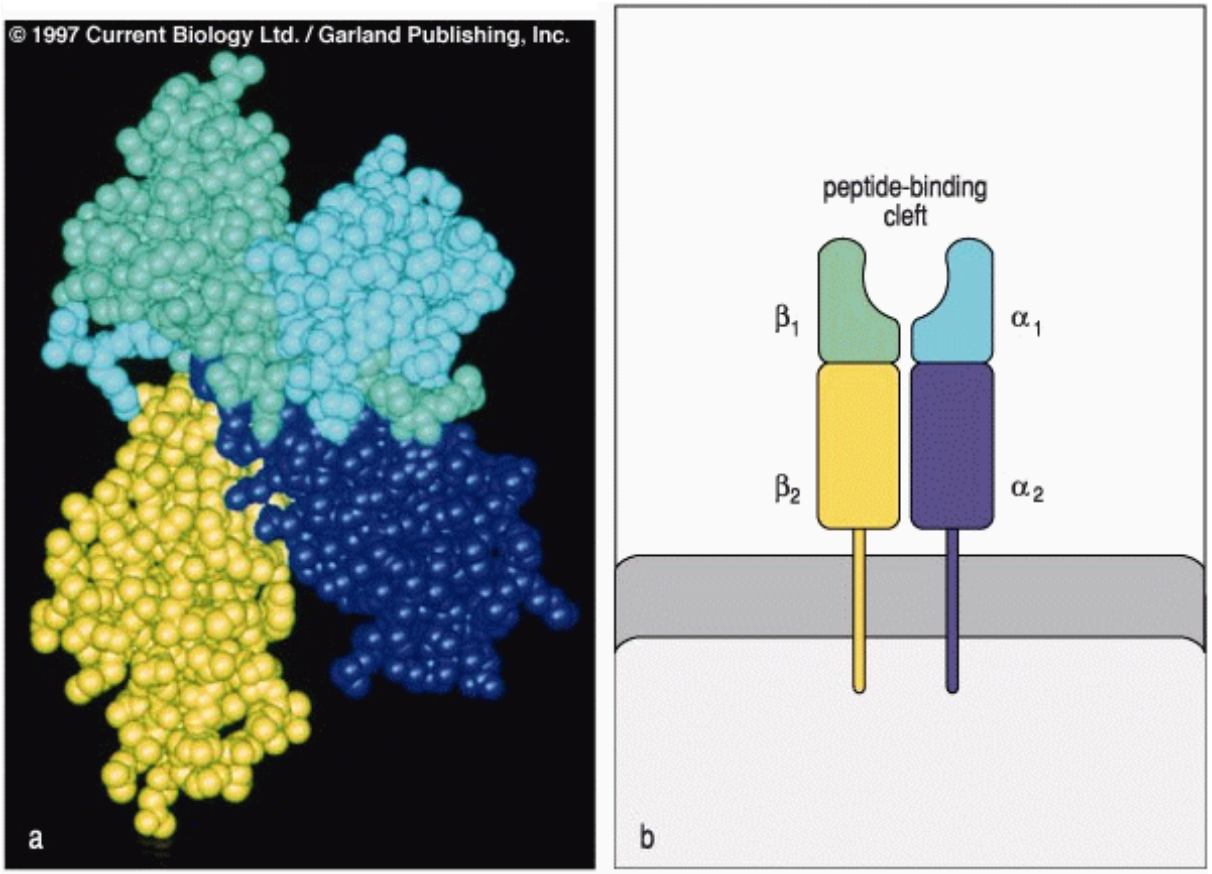
Co-dominant expression of HLA genes



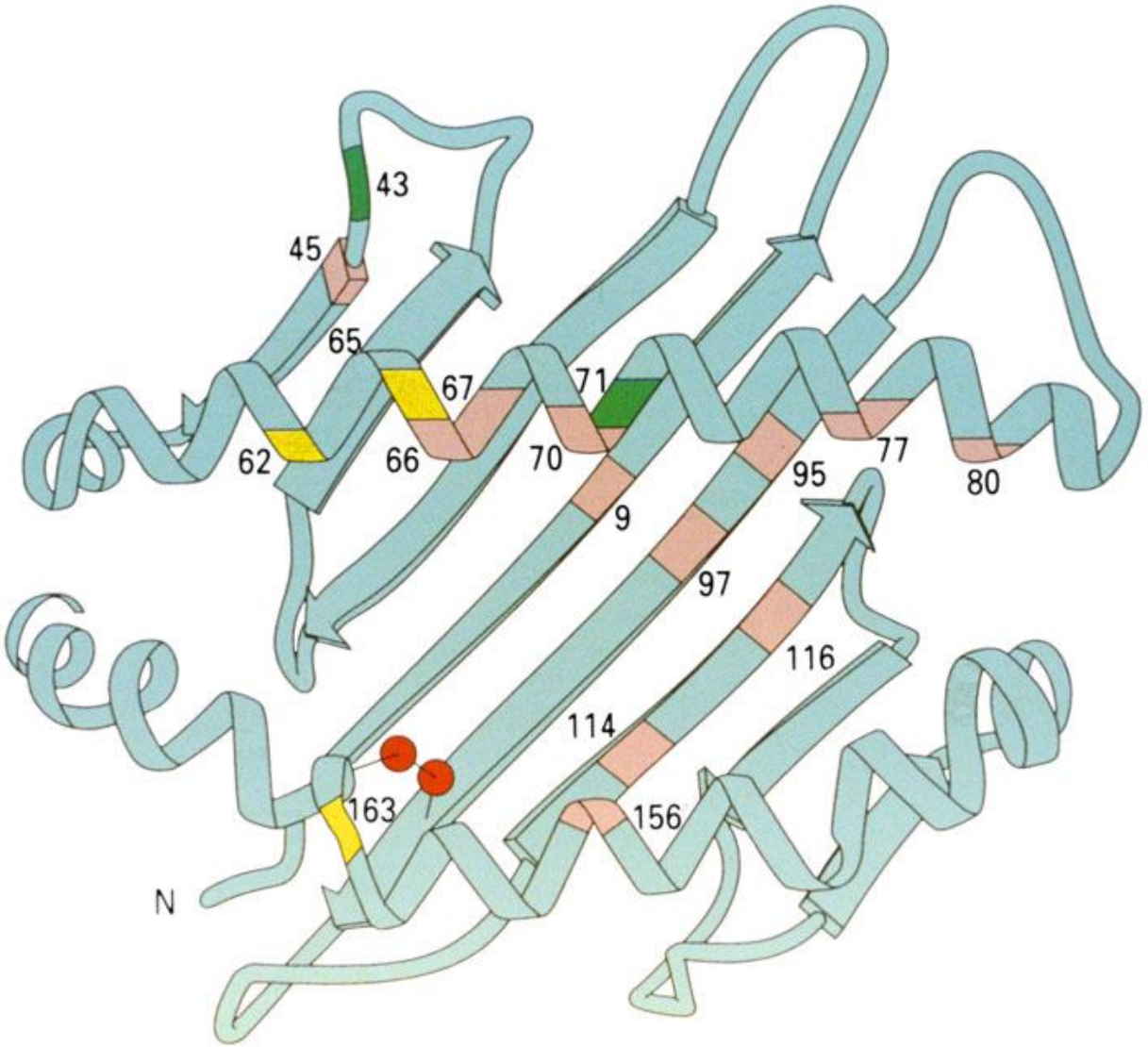
HLA-I antigens



HLA-II antigens

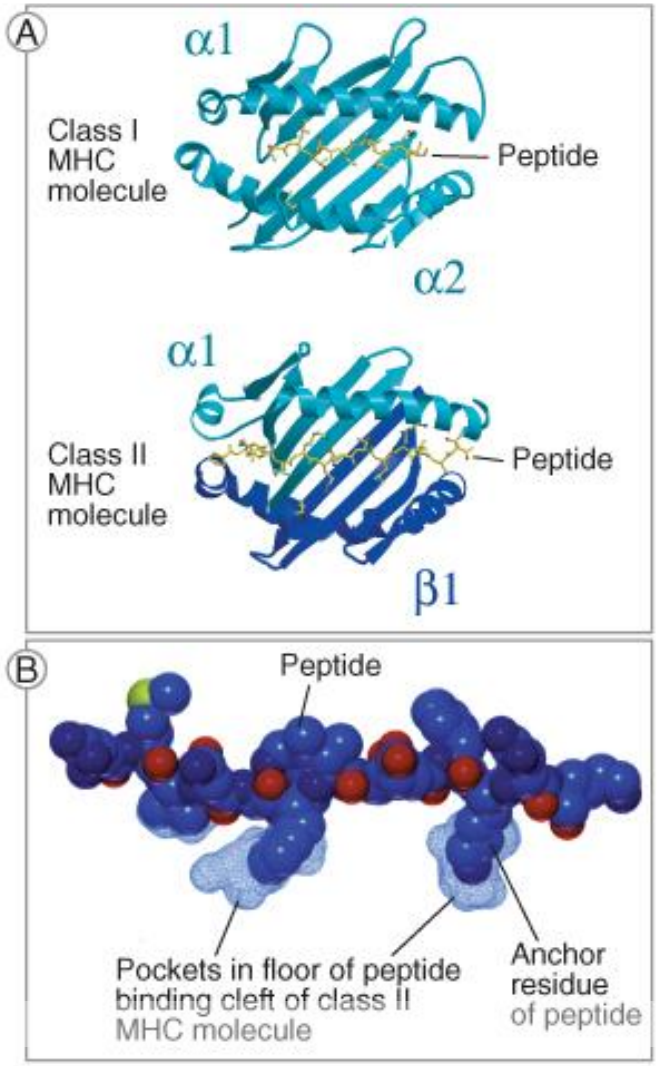


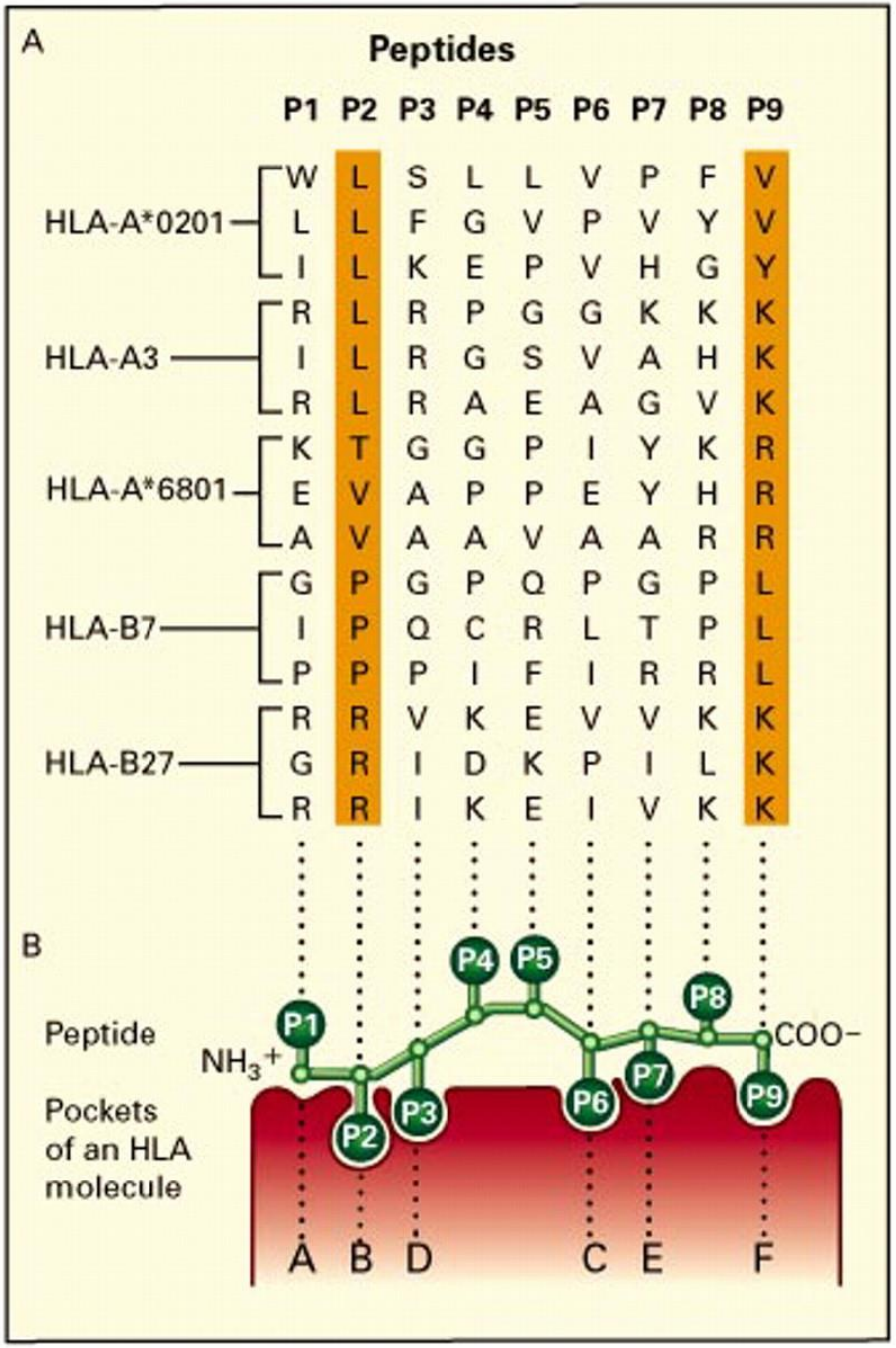
The top surface of HLA-A2



From: I. Roit et al: Slide atlas of Immunology. 3rd. edition

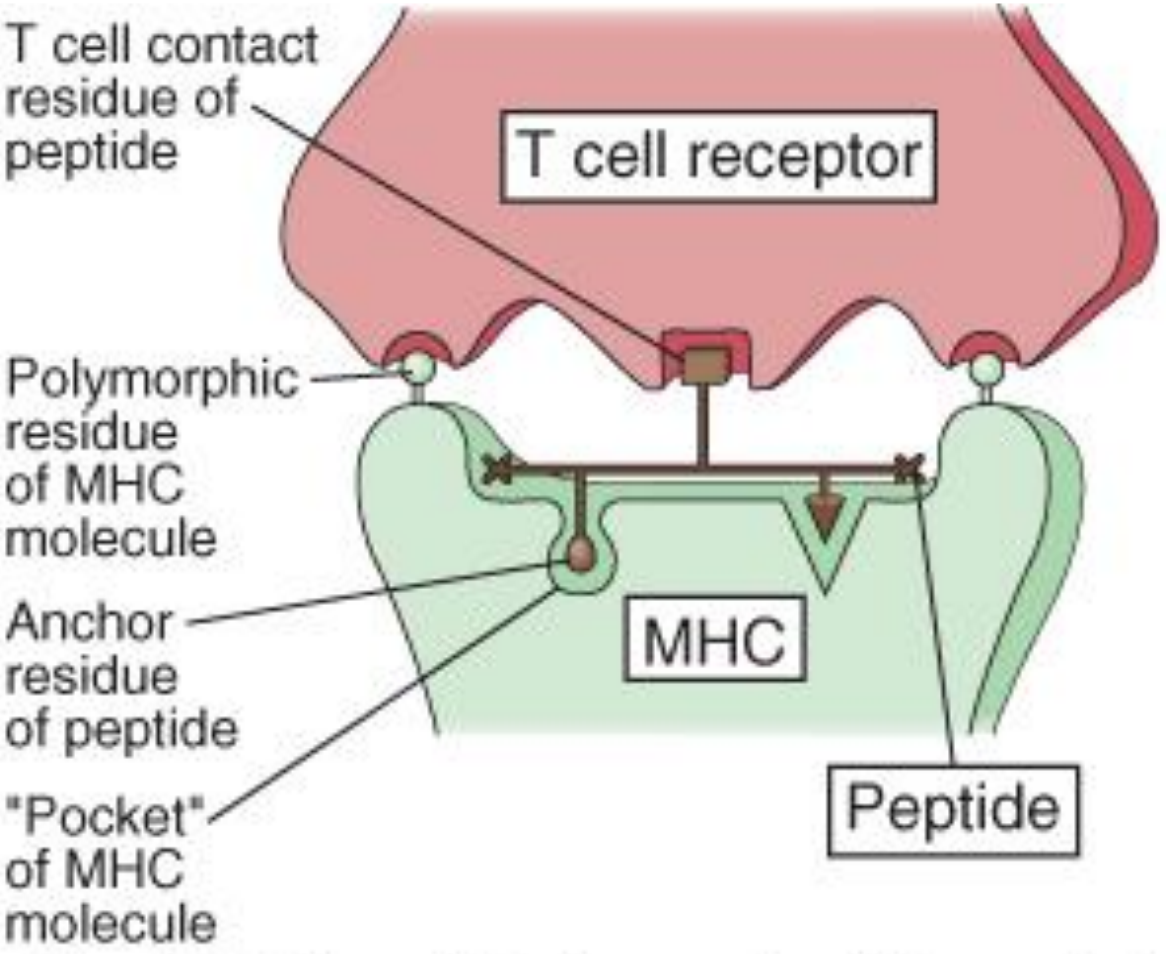
Binding of antigenic peptide to HLA molecule





Jan Klein, Ph.D., and Akie Sato, Ph.D.: *The HLA System.* N Engl J Med 2000; 343:702-709

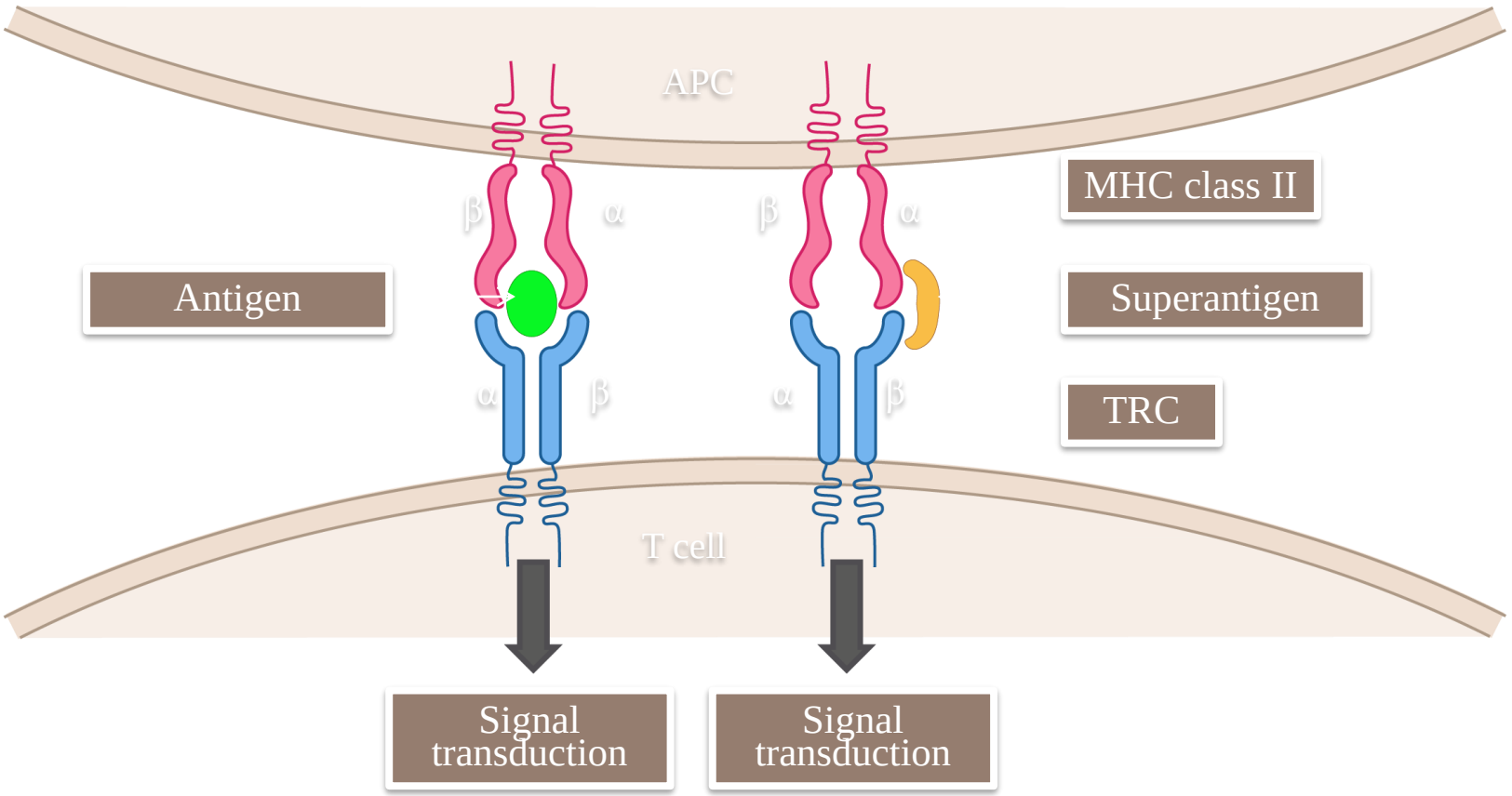
Interaction of TCR with HLA+antigen



Superantigens

- Bind to invariant regions of HLA-II and TCR.
- The consequence is a polyclonal stimulation of lymphocytes without presence of antigen.
- This stimulation may lead to autoimmune reaction.
- High quantity of released cytokines may lead to a severe damage of the organism.
- Examples: staphylococcal enterotoxin, erytrogenic toxin of Streptococcus

Activation of TCR by antigen and superantigen



Initiation of the immune response, Role of HLA antigens

Two types of antigens as regards antibody production stimulation

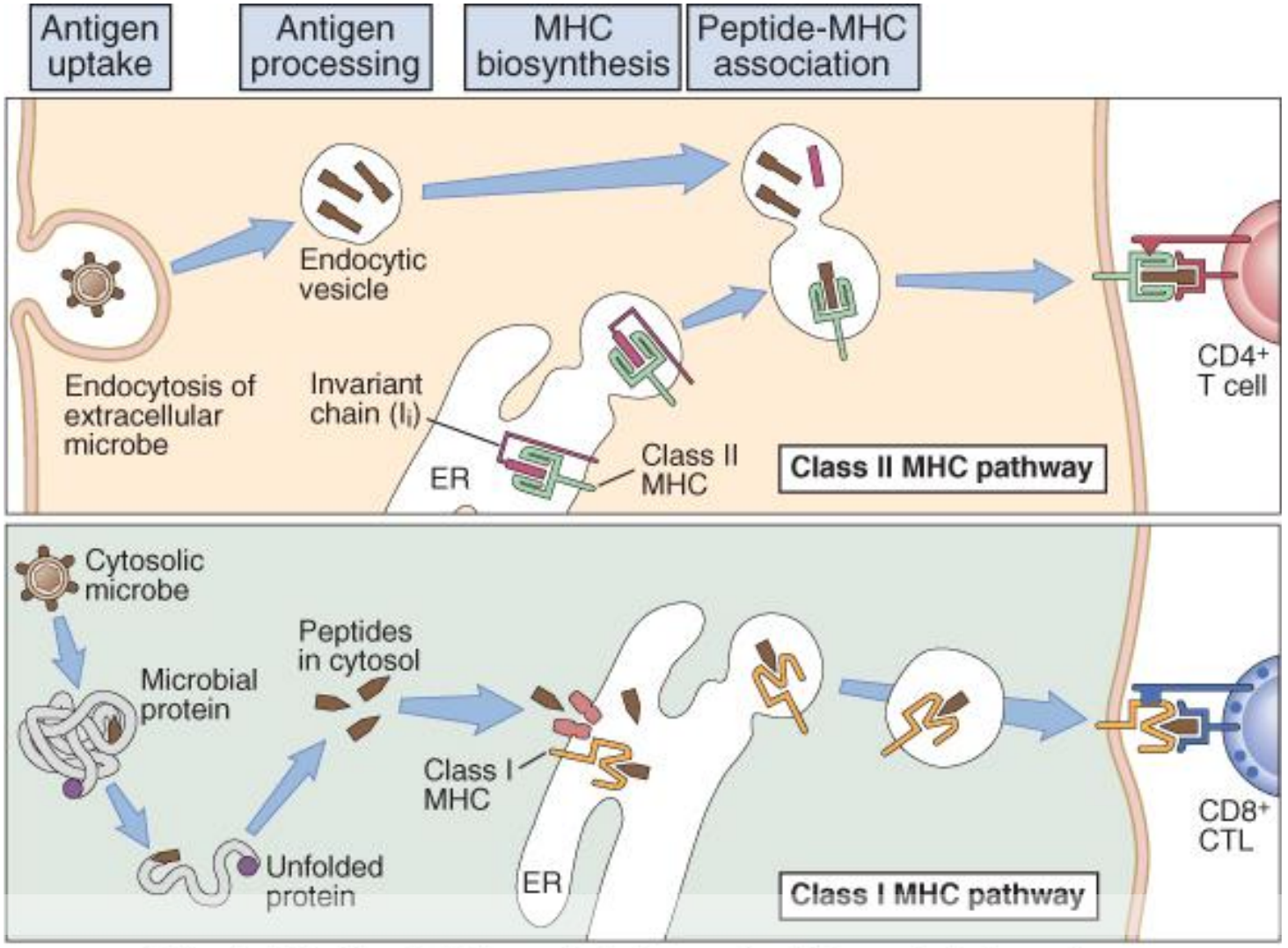
- T- dependent. Initiation of immune response requires antigen presenting cells, T-lymphocytes. Includes majority of antigens.
- T-independent. For the stimulation of B-cells T-lymphocytes (and APC) are not necessary. Polysacharides are typical examples. Only IgM is produced (not other isotypes). No immune memory is induced.

Role of HLA antigens in immune response

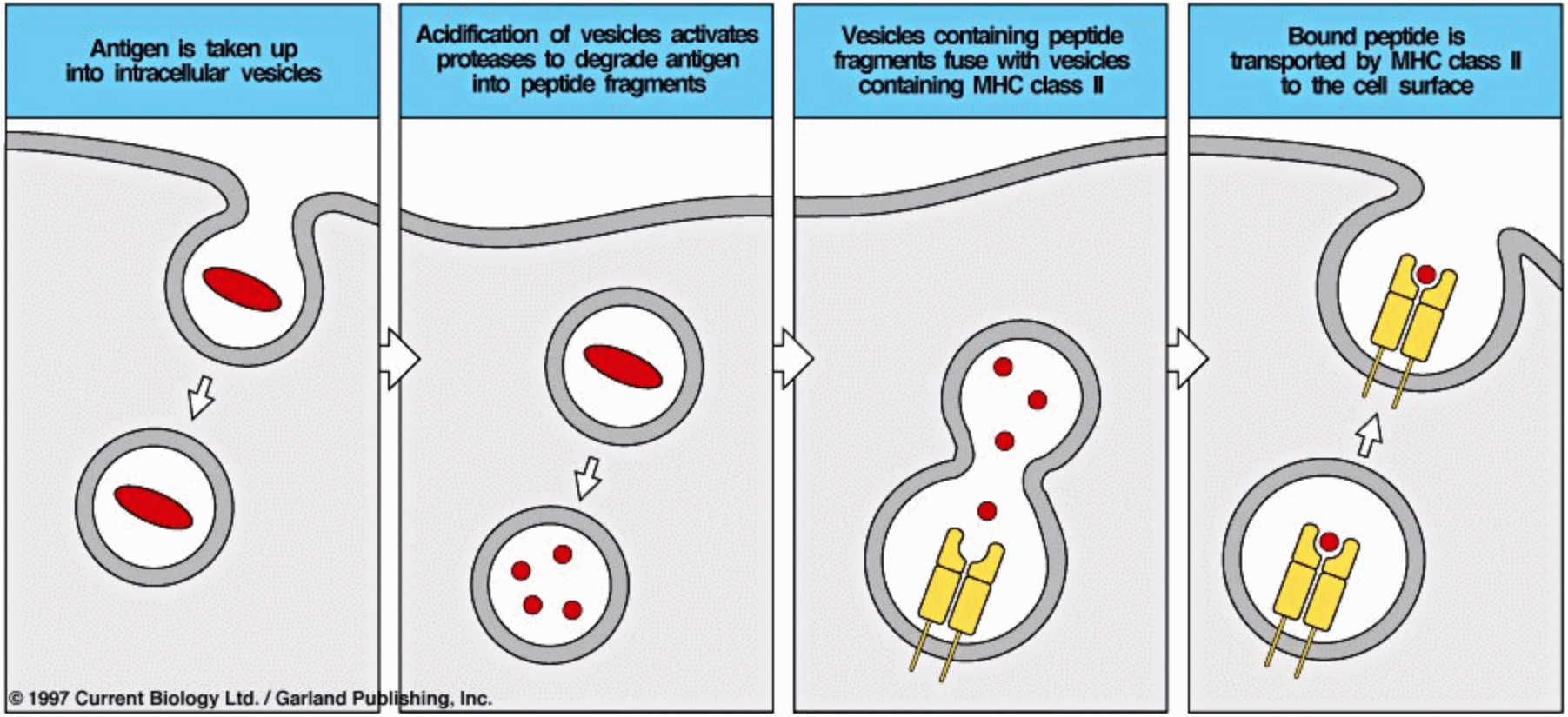
- HLA-I: Expressed on all nucleated cells. Presentation of endogenous antigens to CD8+ cells. This leads to activation of the CD8+ cell and cytotoxic effect on antigen-presenting cell.
- HLA-II Expressed on professional antigen-presenting cells – monocytes, macrophages, dendritic cells, B-cells.

  Presentation of exogenous antigens to CD4+ cells. This leads to activation of the CD4+ (and also the antigen presenting cell).

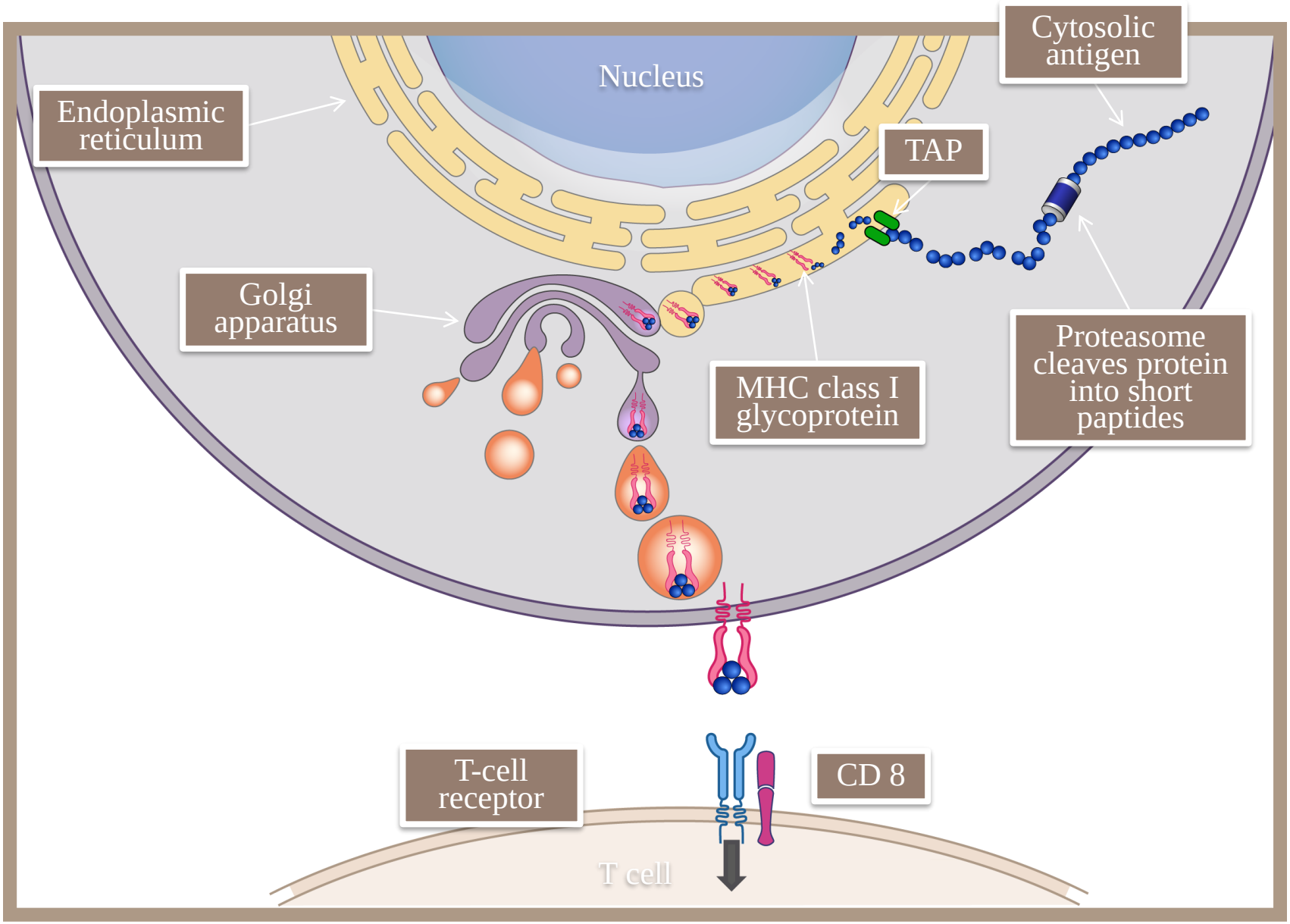
Role of HLA antigens in immune response



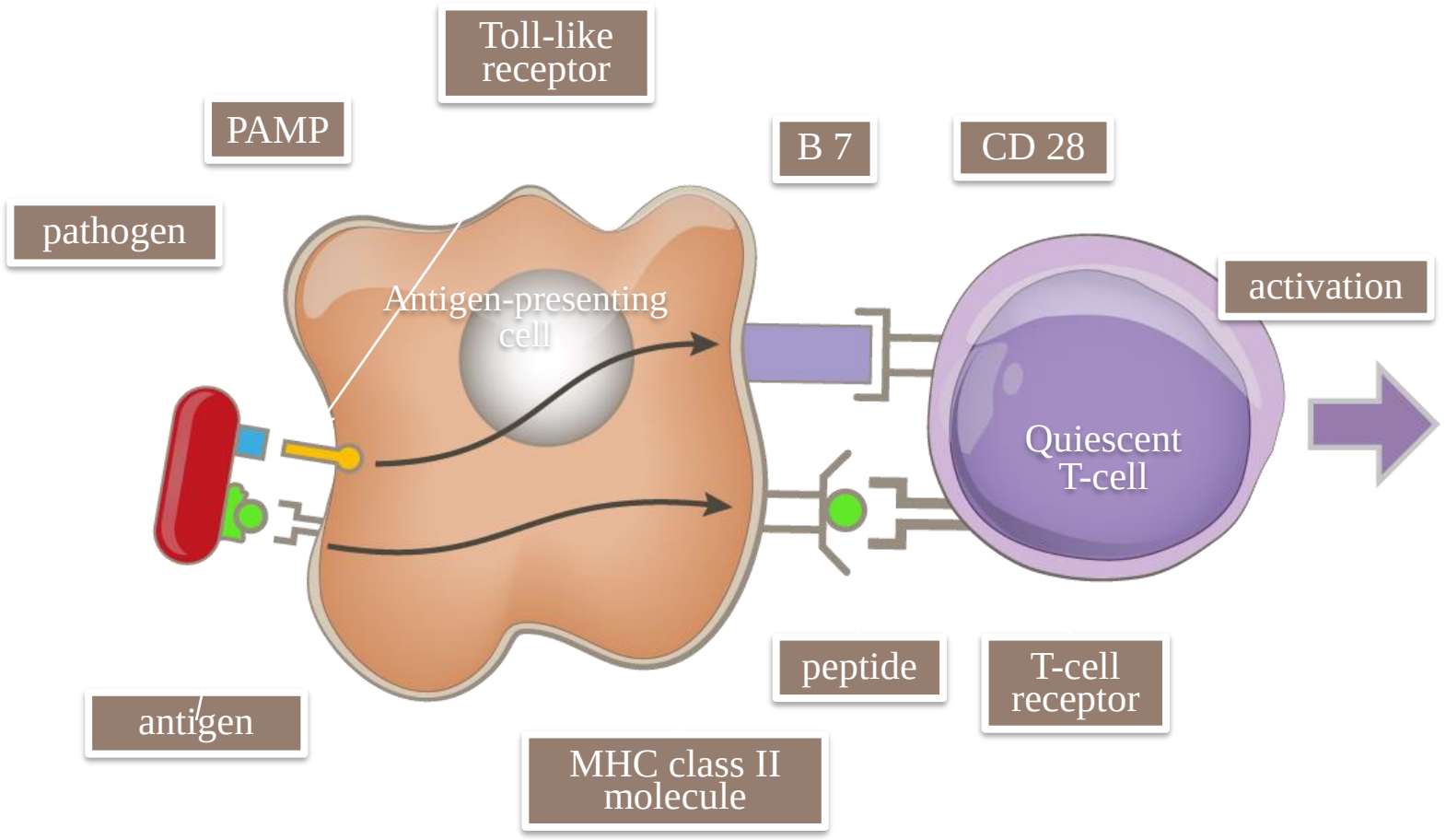
Degradation and presentation of antigens on HLA-II molecules



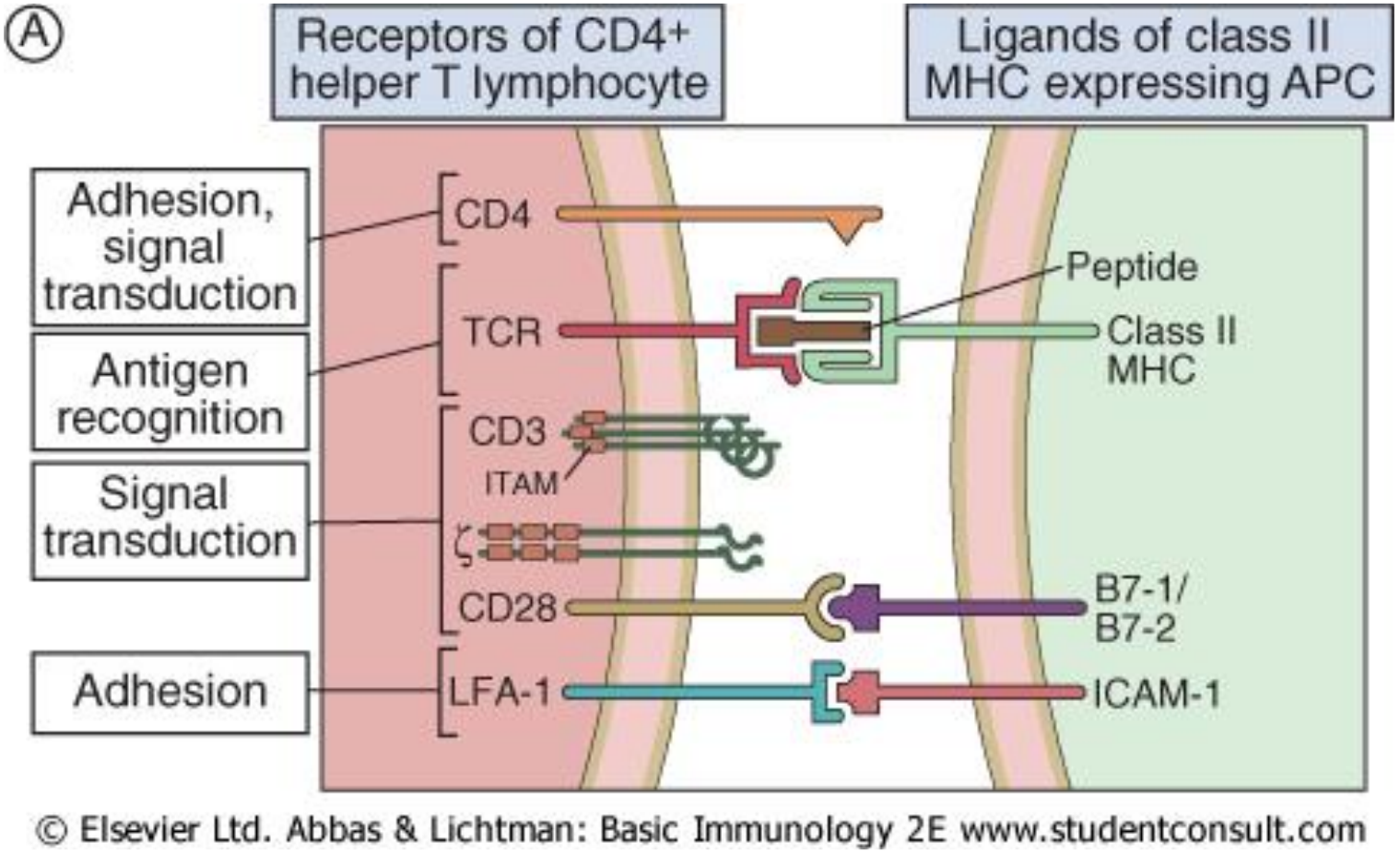
Presentation of endogenous antigens by HLA-I



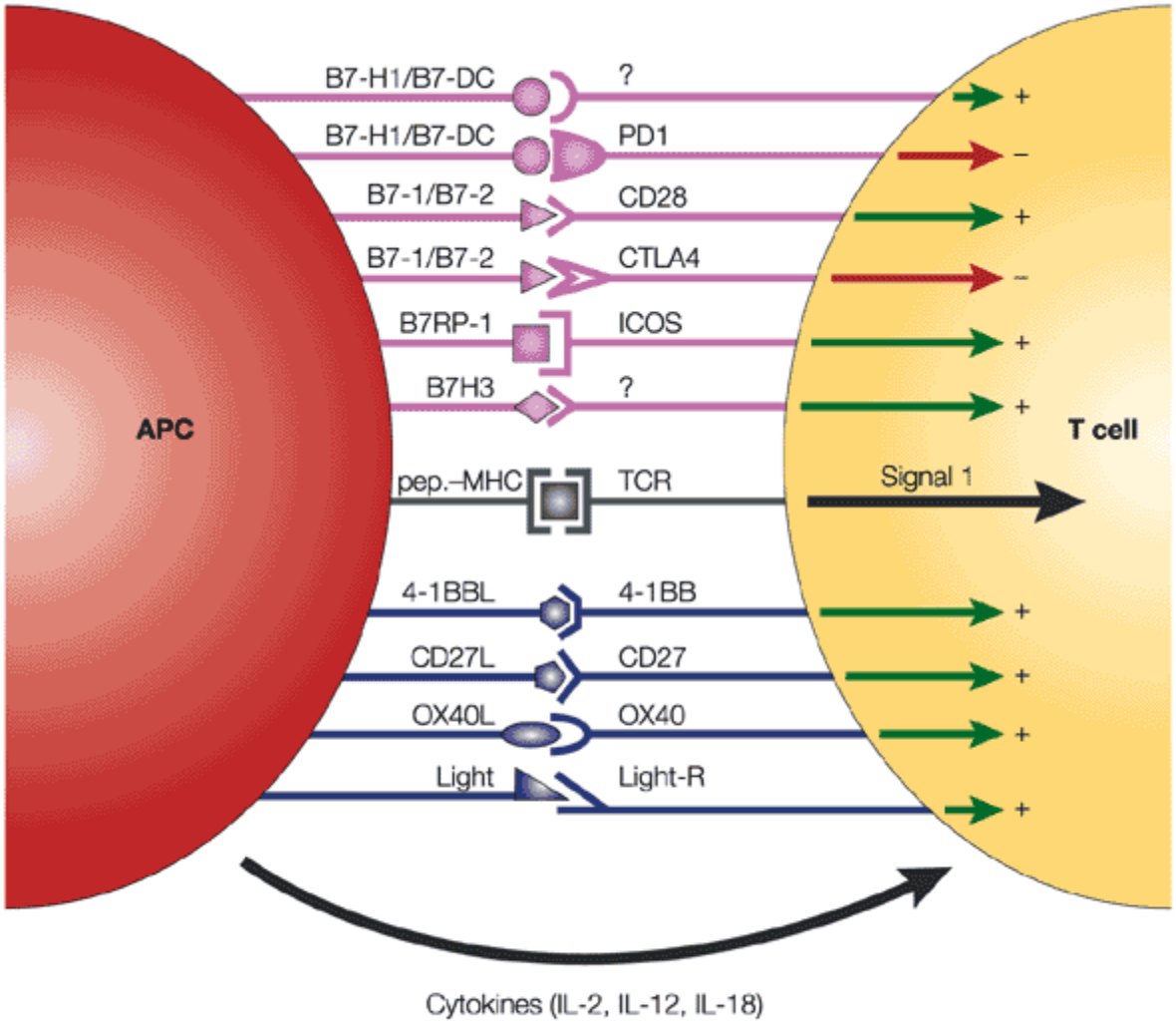
T-cell stimulation by antigen is a complex reaction



Surface structures of T-lymphocytes



Costimulatory signals in T-cell activation



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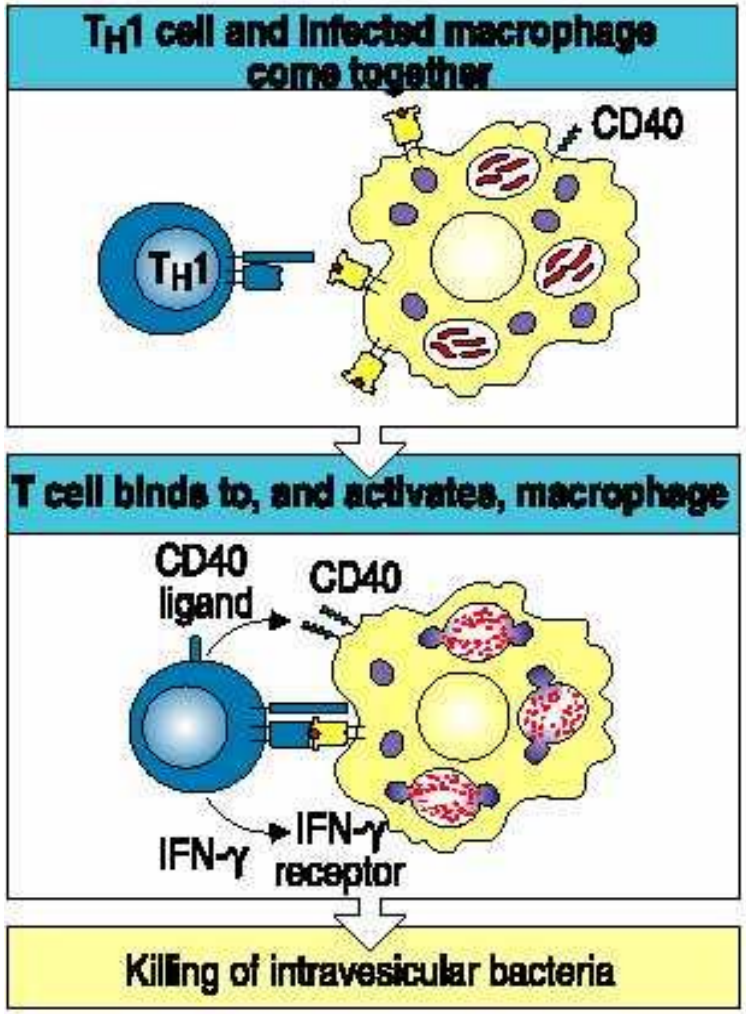
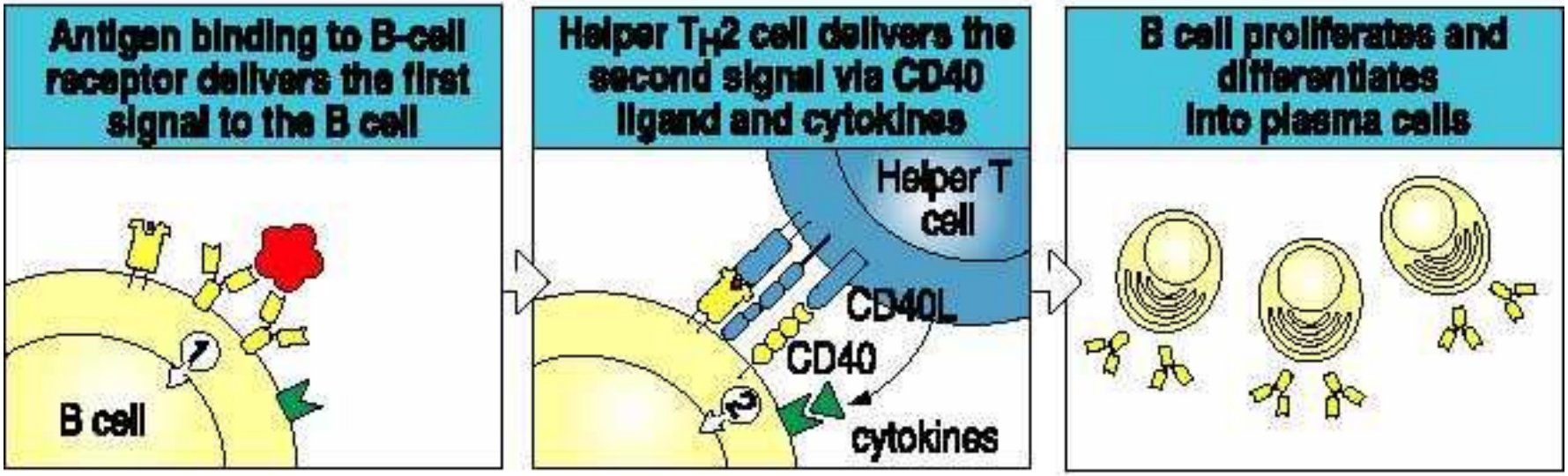
Function of Th1 cells

Figure 6.27



Initiation of antibody response in T-cell dependent antigens

Figure 7.8



Activation of immune system by antigen

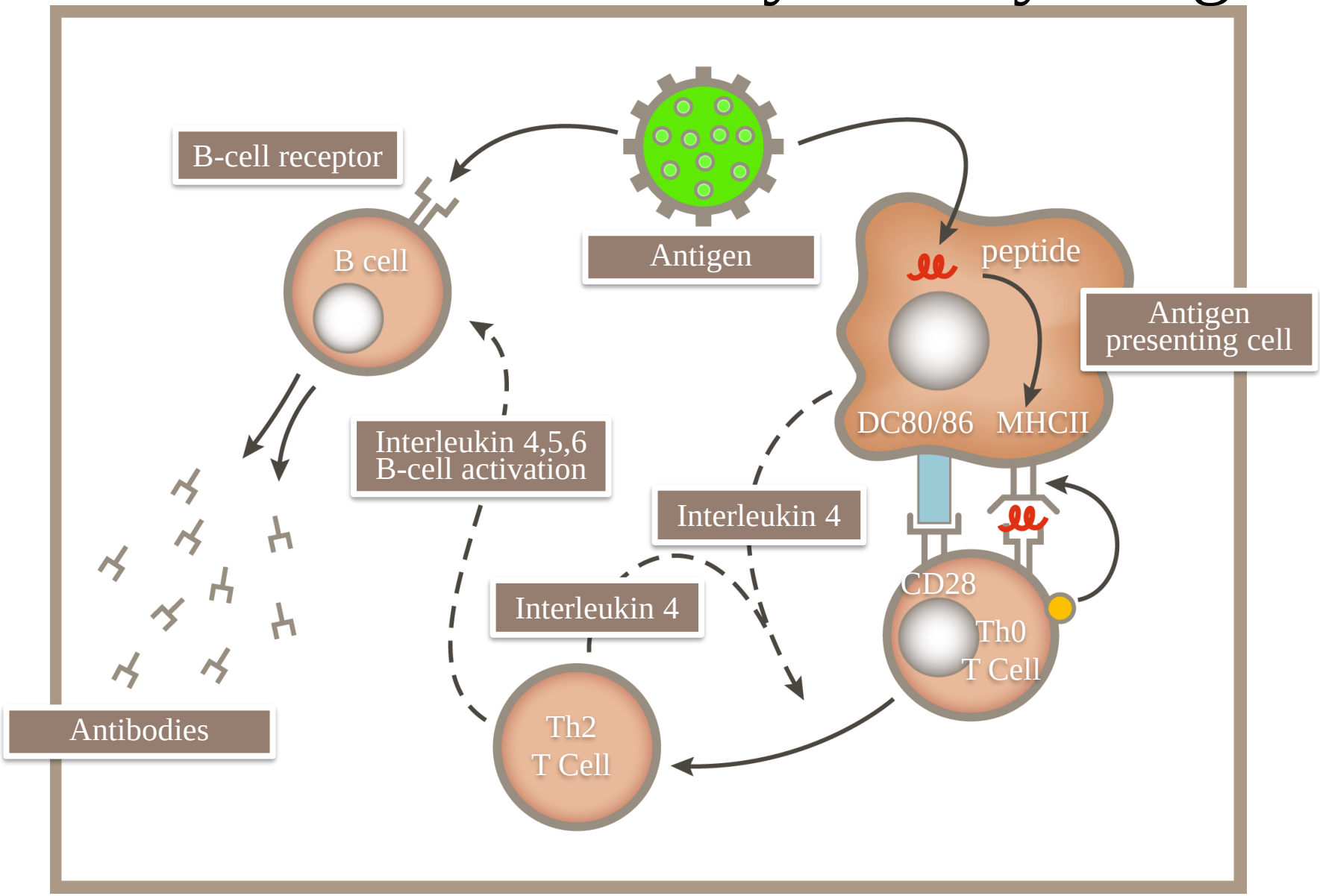
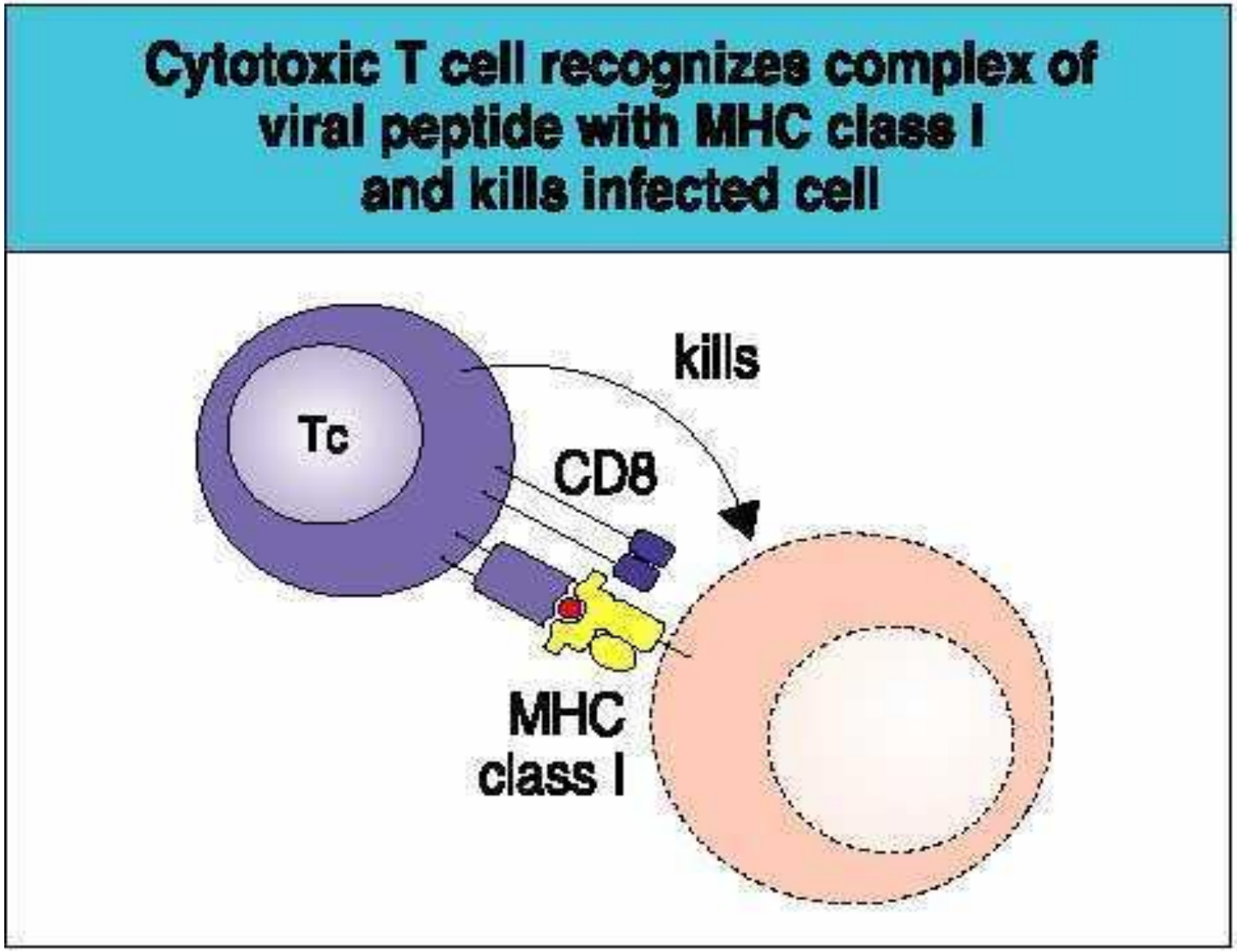
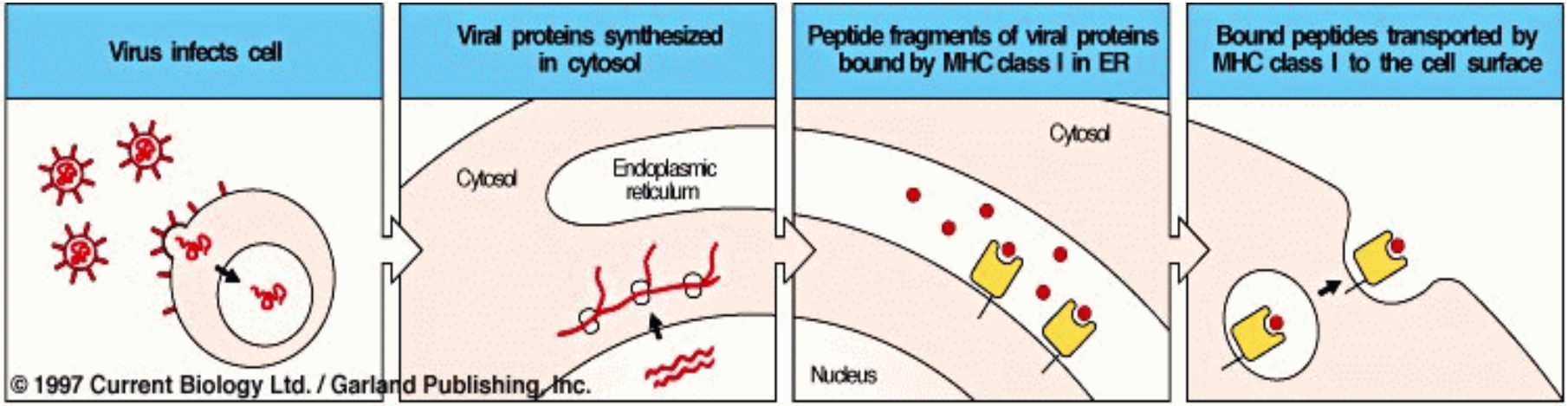


Figure 1.24



Expression of viral antigens on HLA-I molecules



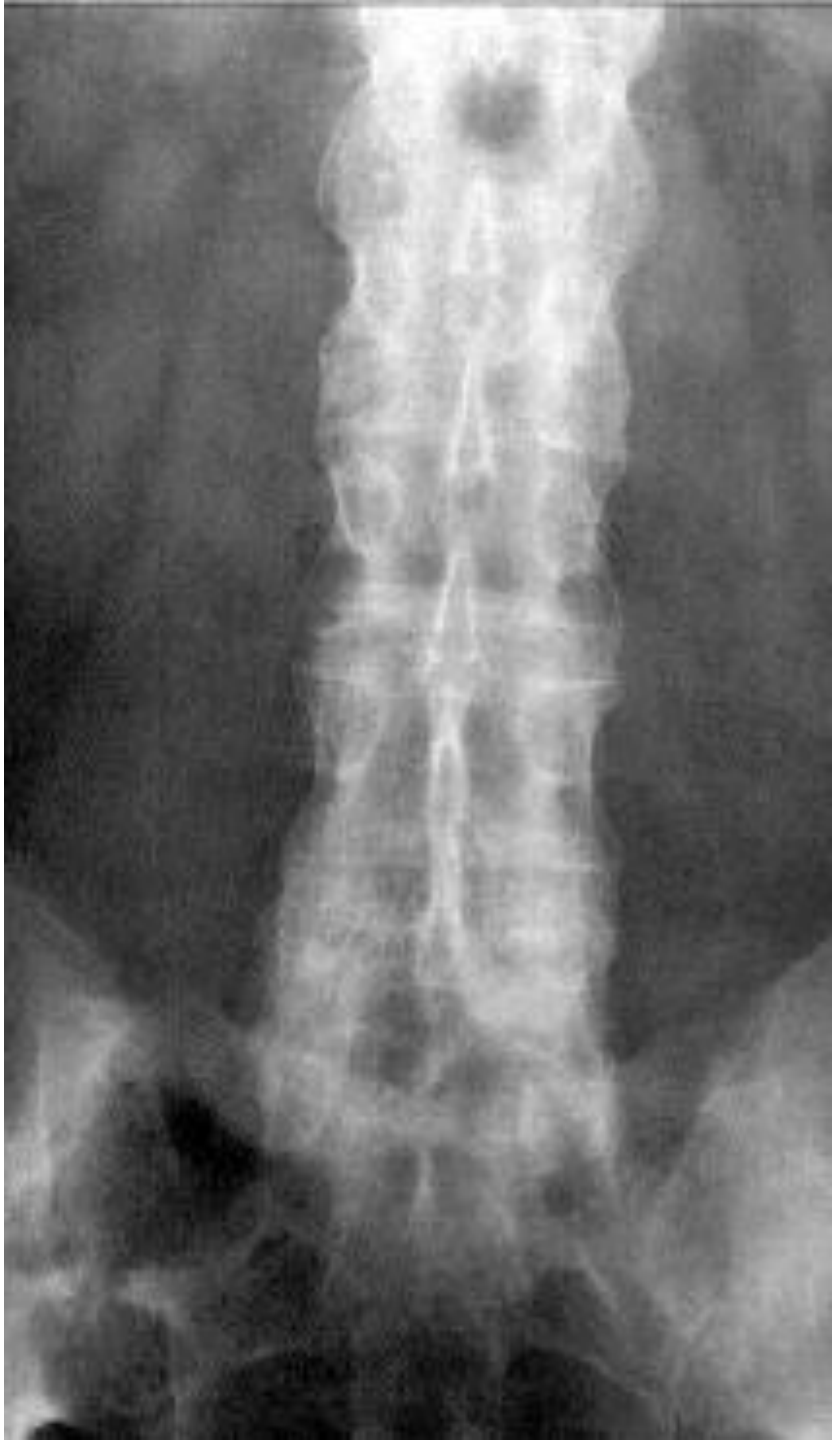
HLA antigens and diseases

- Various, predominantly immunopathologic, diseases are more frequent in persons with some HLA antigens.
- Presence of the HLA antigen makes a predisposition for development of the disease (increased relative risk), but not cause a disease.
- Majority of the carriers of the „disease associated antigen“ are healthy!

Ankylosing spondylitis

- Males predominantly affected, frequency 1:1000.
- Usually starts with sacroileitis, consequently vertebral column is affected.
- Fibrotisation and ossification of intervertebral joins and filaments.
- The process leads to decreased mobility and ankylosis in terminal state.
- Ninety-five percent of patients are HLA-27 positive.

Ankylosing spondylitis

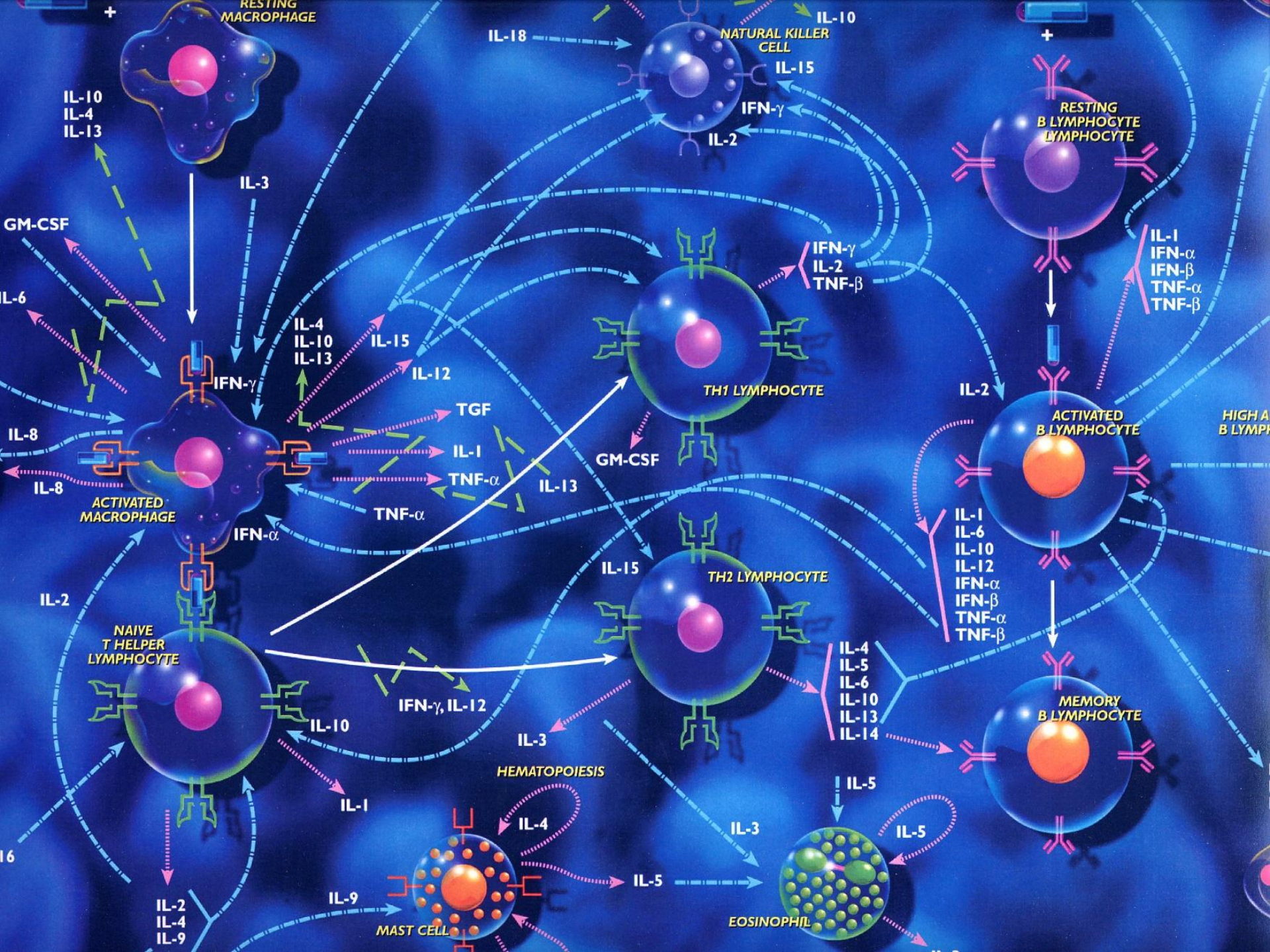


Ankylozing spondylitis and HLA B-27

- Frequency of the disease is 1:1000.
- Ninety-five percent of patients are HLA-27 positive (in Caucasian population).
- But: HLA-27 is present in approximately 5% of people $\Rightarrow$only 1 / 50 HLA B-27+ persons will develop ankylosing spondylitis!
- Negativity of HLA-B27 almost excludes the diagnosis of ankylosing spondylitis.
- Pozitivity – only shows that the patient has the predisposition! It does not make a diagnosis!

Coeliac disease

- Haplotype HLA-DQ2 / HLA-DQ8 is expressed in majority of patients with coeliac disease.
- However these HLA genes are present in approximately 40% of general population. Only in 3-4% of them will develop the celiac disease.
- The test for HLA DQ2/DQ8 has high negative predictive value (can exclude the disease) but minimal positive predictive value (cannot make a diagnosis).


RESTING MACROPHAGE
IL-10
IL-4
IL-13
IL-3
GM-CSF
IL-6
IL-8
IL-8
ACTIVATED MACROPHAGE
IFN-γ
IL-4
IL-10
IL-13
IL-15
IL-12
IFN-γ
TGF
IL-1
TNF-α
TNF-α
IL-13
IFN-α
IL-18
NATURAL KILLER CELL
IL-10
IL-15
IFN-γ
IL-2
TH1 LYMPHOCYTE
IFN-γ
IL-2
TNF-β
GM-CSF
IL-15
TH2 LYMPHOCYTE
IL-4
IL-5
IL-6
IL-10
IL-13
IL-14
IL-2
NAIVE T HELPER LYMPHOCYTE
IFN-γ, IL-12
IL-10
IL-1
IL-3
HEMATOPOIESIS
IL-4
IL-5
IL-9
MAST CELL
IL-2
IL-4
IL-9
IL-5
IL-3
IL-5
EOSINOPHIL
RESTING B LYMPHOCYTE LYMPHOCYTE
IL-1
IFN-α
IFN-β
TNF-α
TNF-β
IL-2
ACTIVATED B LYMPHOCYTE
IL-1
IL-6
IL-10
IL-12
IFN-α
IFN-β
TNF-α
TNF-β
MEMORY B LYMPHOCYTE

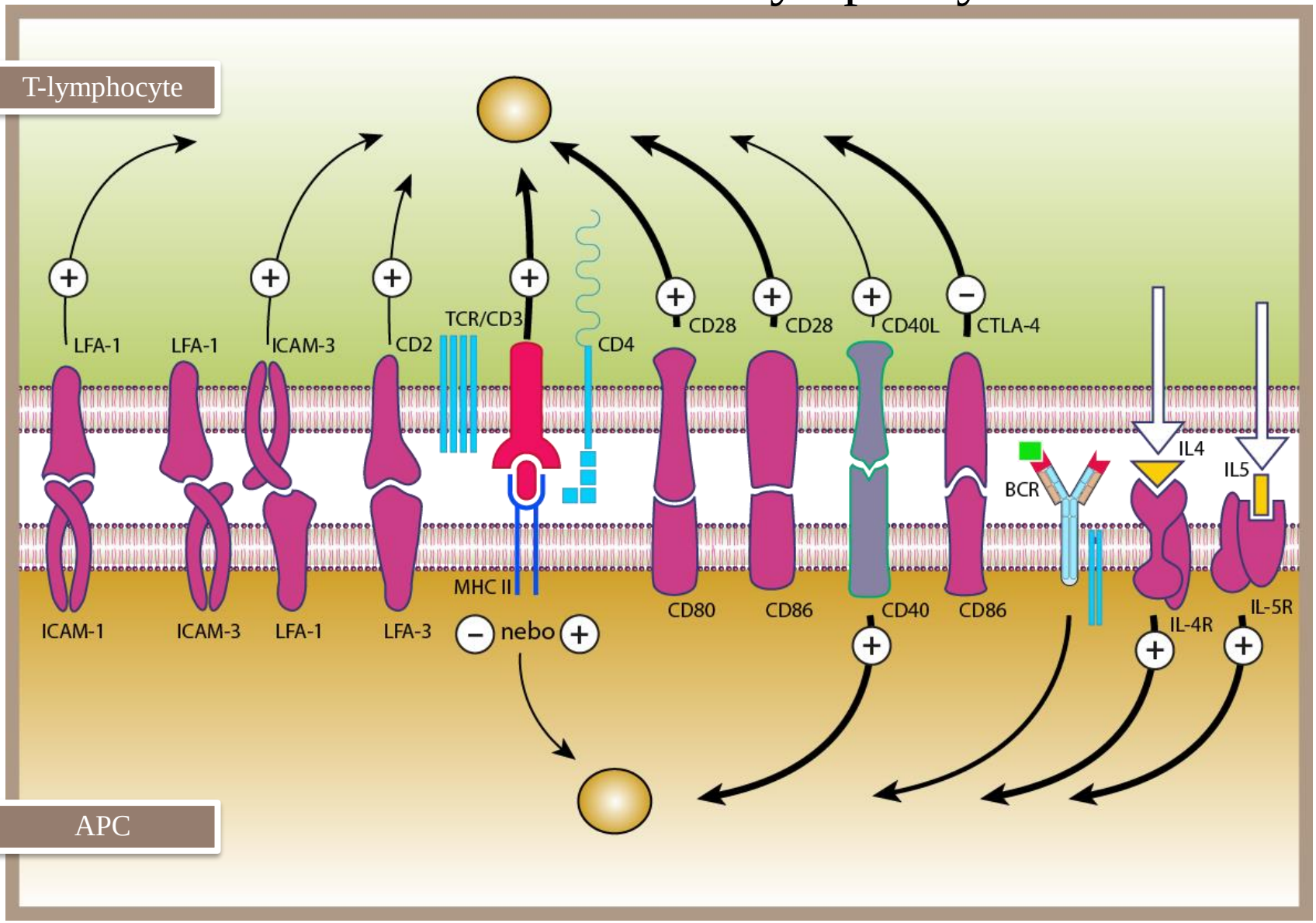
Regulation of the immune response

- Interactions of the components of the immune system
- Characteristcs of the stimulating antigen (PAMPs, T-dependent and T-independent antigens)
- Neuroendocrine interactions

Regulation inside the immune system

- Physical interactions among cells – through surface molecules transmitting positive or negative signals.
- Chemical signals – cytokines, regulation by antibodies (idiotype-antiidiotype interactions)

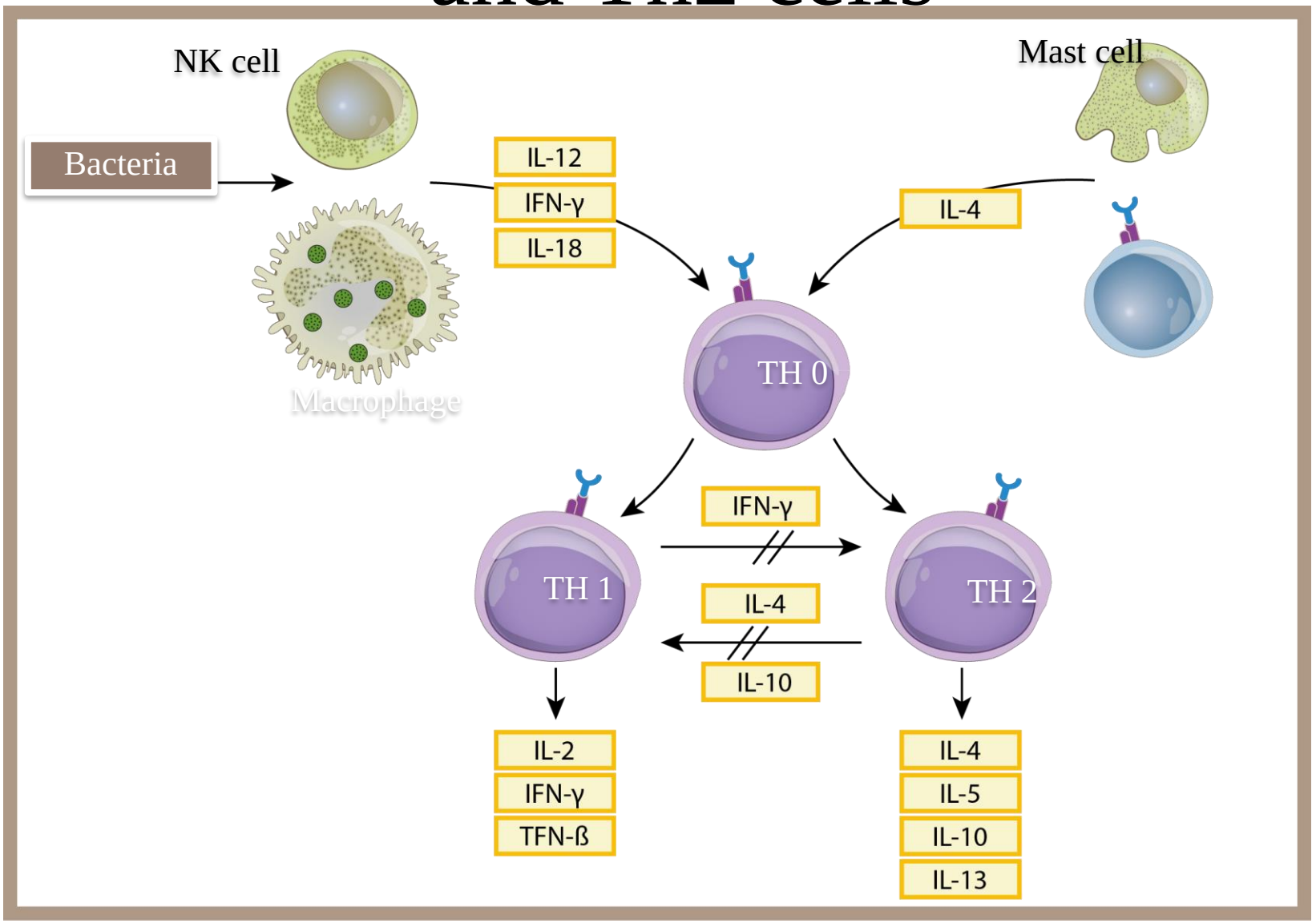
Costimulatory molecules involved in the interaction between APC and T-lymphocyte



Regulation by T-lymphocytes

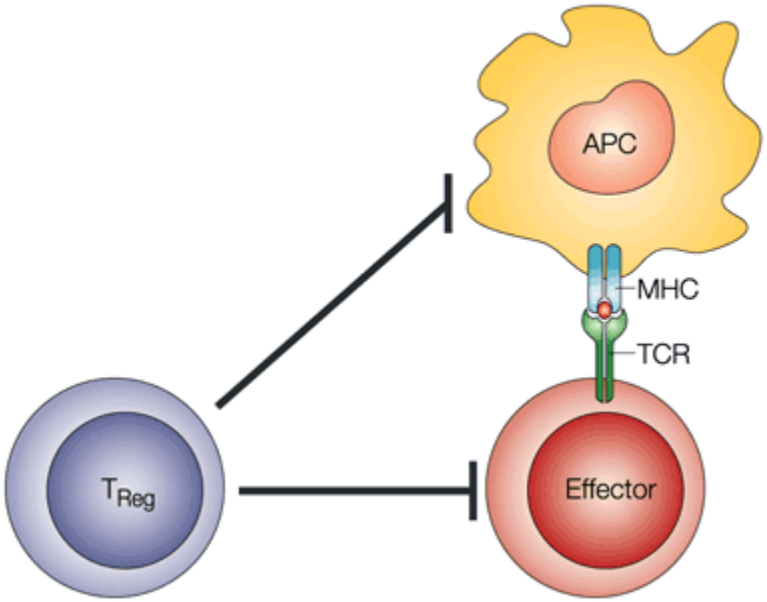
- Relation between Th1 and Th2 cells
- Various types of regulatory cells

Development and function of Th1 and Th2 cells



T_{reg} lymphocytes

- Separate subgroup of regulatory T-cells
- Thymic development, although the development in periphery was also documented (i-Treg).
- CD4+CD25+
- Suppress immune reaction against self-antigens
- 5-10% of peripheral CD4+ cells
- Mechanisms of regulation: Production of TGF β, expression of CTLA-4 ….



Benefits:
- T-cell homeostasis
- prevents autoimmune disease
- tolerance after transplantation
- prevents GVHD
- prevents allergy
- prevents hypersensitivity

Detrimental effects:
- down-regulation of tumour immunity
- down-regulation of immunity to infection

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TR-1 lymphocytes

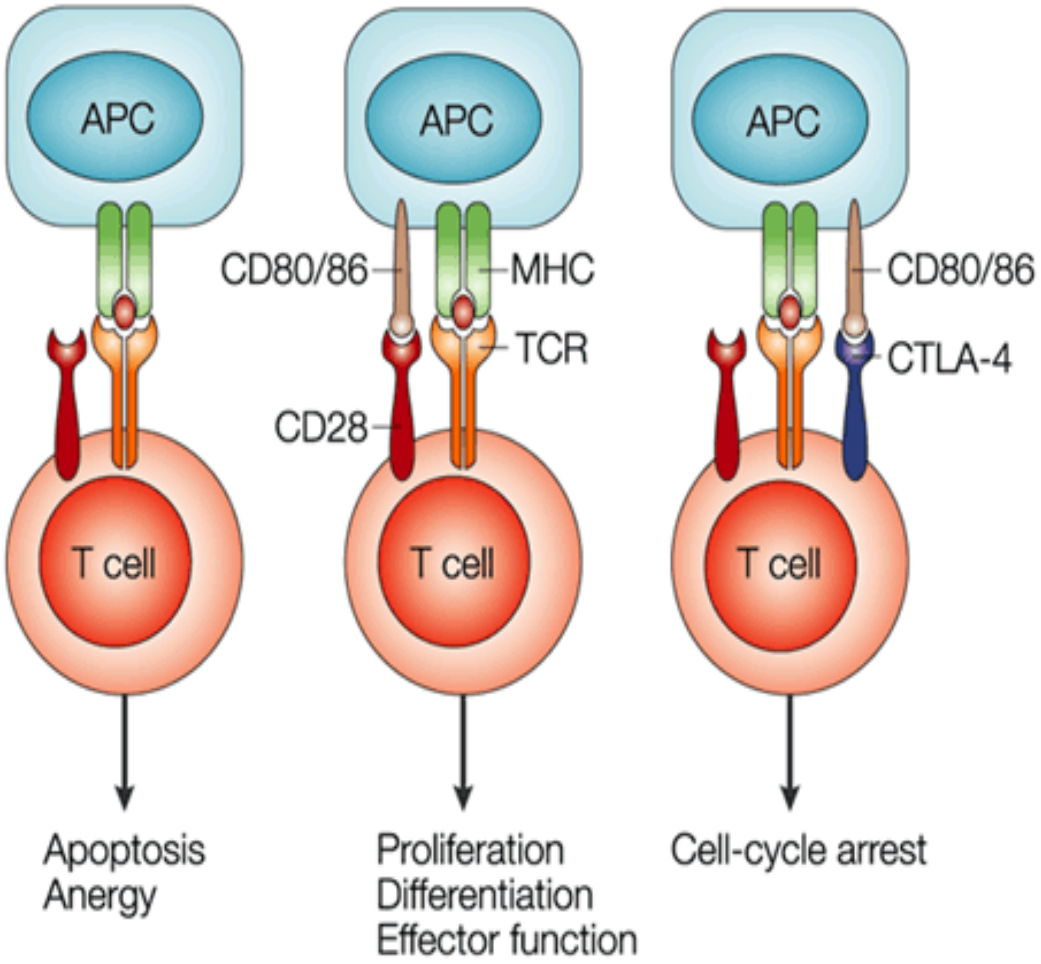
- Induced i periphery by antigen.
- CD4+
- Production of high levels of IL-10, IFN-γ, TGF-β, but not IL-2.
- Similar function have Th3 cells

T-lymphocyte checkpoints

- Stimulatory
  - CD27 (ligand CD70 - APC),
  - CD28 (Ligand CD80, 86 - APC),
  - CD40 – expressed on APC, B-ly (ligand CD154 = CD40L – T-ly) ,
  - OX40 – activates and memory T-ly (ligand OX49L),
  - GITR - Treg (ligand GITRL – mainly APC)
- Inhibitory
  - CTLA-4 expressed on activated T-lymphocytes, Treg (ligand CD80,86) ,
  - PD-1 expressed on activated T-lymphocytes (ligand PDL1, PDL2,- activated macrophages, granulocytes)

CTLA-4

- Expressed mainly on the surface of activated helper T cells.
- Transmits an inhibitory signal to T-cells.
- Similar to the T-cell co-stimulatory protein,CD28 both molecules bind to CD80 and CD86, (B7-1 and B7-2)
- Intracellular CTLA4 is also found in regulatory T-cells and may be important to their function.
- CTLA-4 binds its ligands, captures them from the surface of APC and internalizes them *via* a process that is called transendocytosis, leading to a reduction of APC-mediated T cell activation.
- **Ipilimumab** – monoclonal antibody that blocks CTLA-4 function, is used for „stimulation“ of immune system during immunotherapy of several tumors.
- **Abatacept** – fusion protein IgG+CTLA-4 – binds CD80/86, prevents T-cell activation, is used as immunosuppressive agent.


APC
APC
APC
CD80/86
MHC
TCR
CD28
CD80/86
CTLA-4
T cell
T cell
T cell
Apoptosis
Anergy
Proliferation
Differentiation
Effector function
Cell-cycle arrest

PD-1
(Programmed cell death protein-1)

- Expressed on activated T-lymphocytes
- Binding to is ligands (PD-L1, PD-L2, expressed mainly on activated macrophages, granulocytes, dendritic cells) leads to apoptosis of antigen specific lymphocytes.
- An important check-point in T-cell regulation.
- PD-L1 is expressed on many cancer cells.
- Monoclonal antibody against PD-1 (e.g. **nivolumab**) is used in immunotherapy of tumors.

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2018

Illustrations: Niklas Elmehed

James P. Allison • Tasuku Honjo

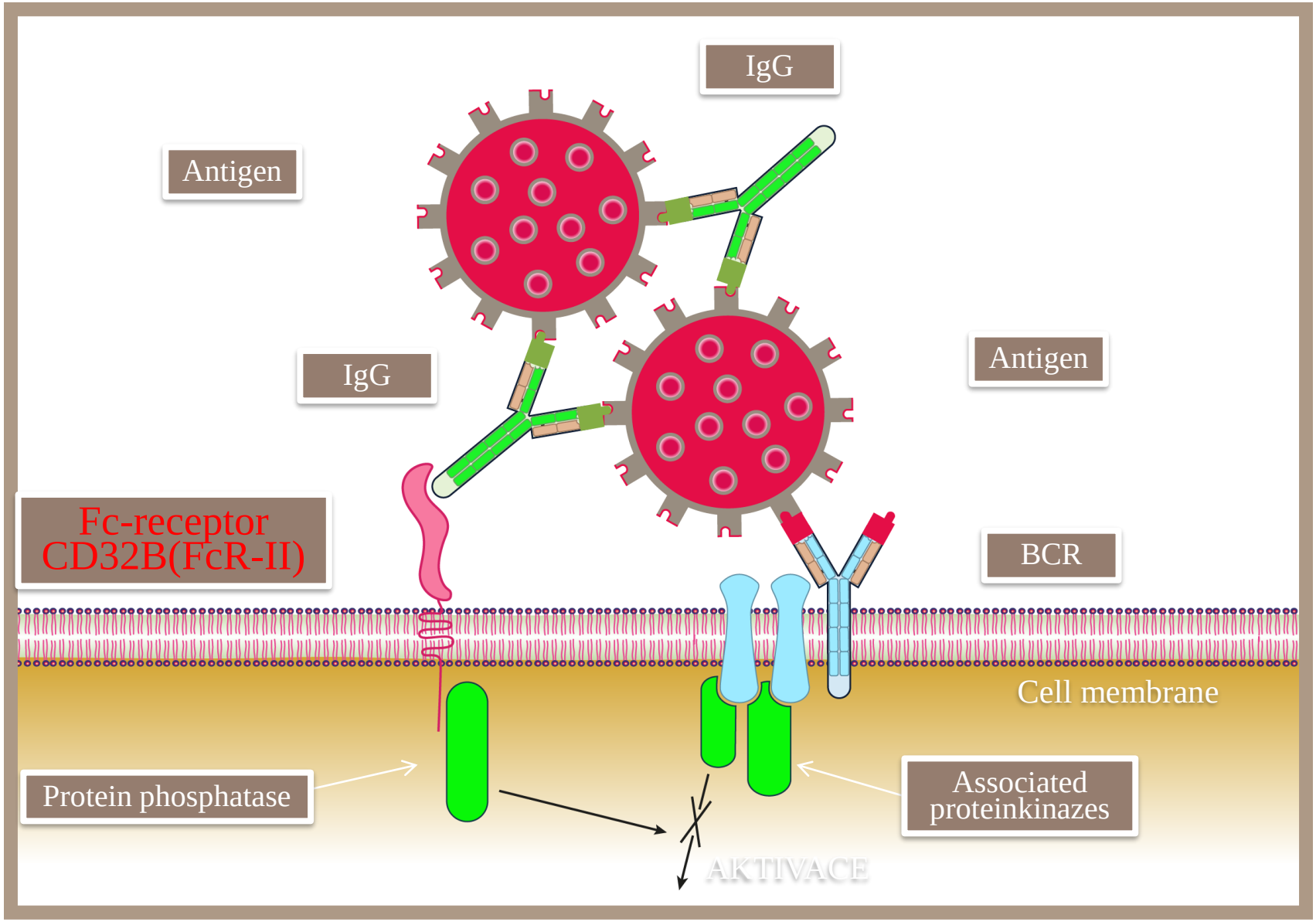
"for their discovery of cancer therapy by inhibition of negative immune regulation"

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

Regulation by antibodies

- Negative regulation after IgG binding to FcγRII on B-cells.
- Binding of the immune complex during the presentation of antigens by dendritic follicular cells to B-lymphocytes in germinal centers significantly increases immunogenicity.

Inhibition of B-cells by antigen-antibody complexes



Cytokines

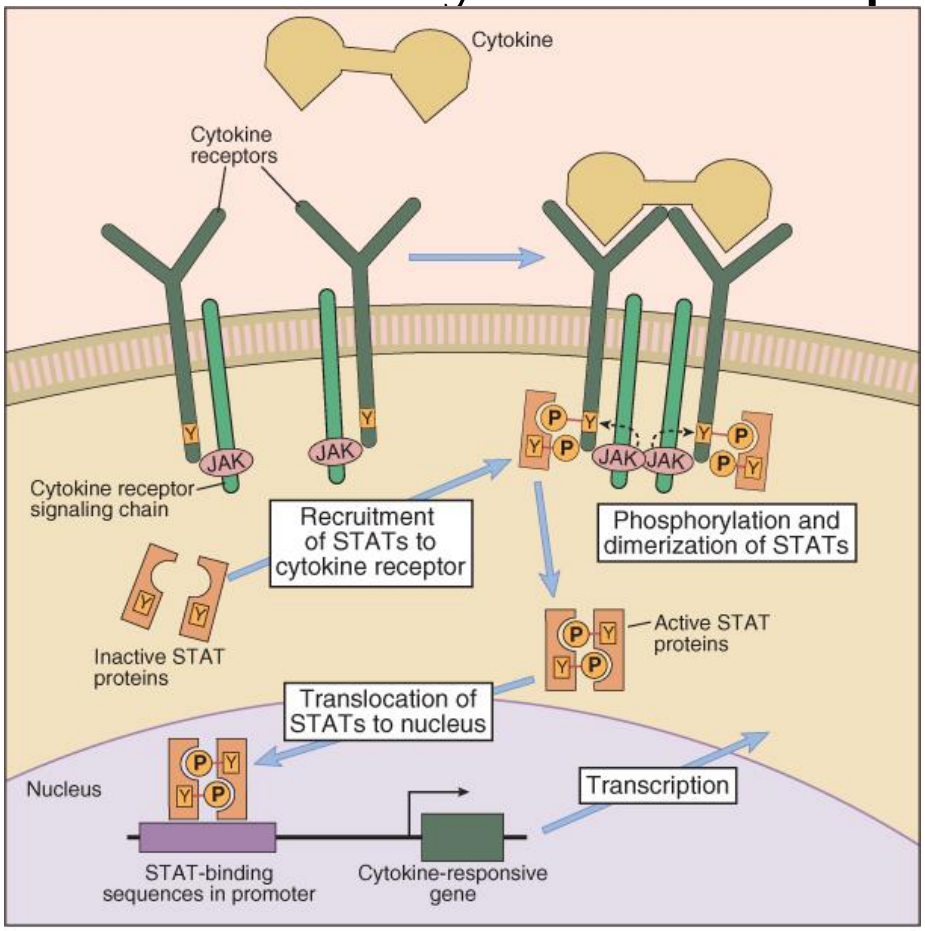
- Mediators, „tissue hormons“, main regulators of the cells of the immune system.
- Produced mainly by the cells of the immune system, also the cells of the immune system predominate as the target cells.
- The effect on the target cell is based on the interaction with specific receptors.
- Usually short half-life
- Nomenclature:
  - IL-1 - IL-36 (?)
  - Historical names: interferons, TNF, CSF..

Cytokines

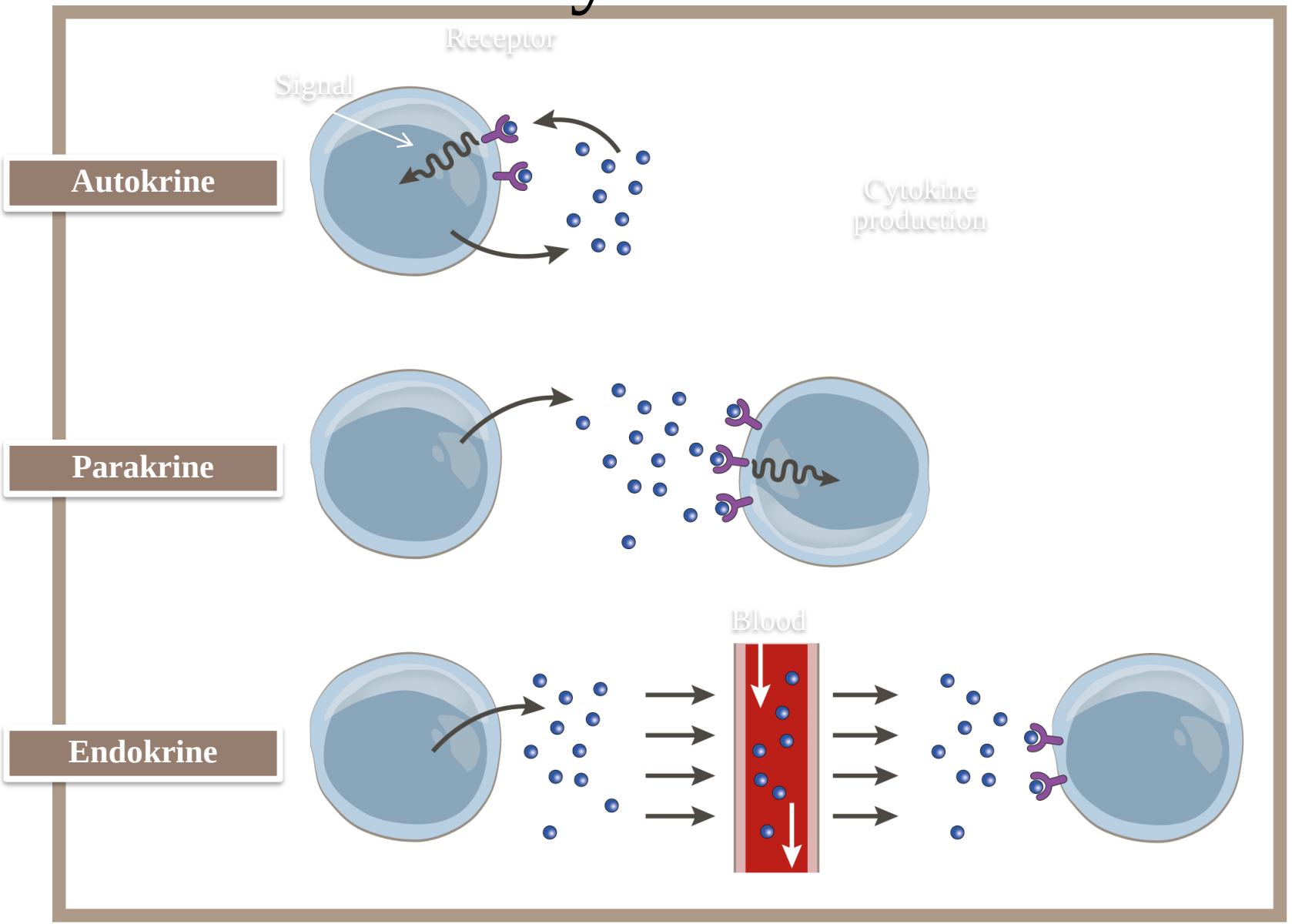
- Usually produced by a broad range of cells, bus some cells are usually „main producers“ of the concrete cytokine..
- Pleiotropic effect.
- Cytokine network is formed.
- A concrete cytokine may have both stimulatory and inhibitory effect, depending on the the interaction with other cytokines, concentration of the cytokine….

JAK-SAT signalisation plays a crucial role in signal transduction from cytokine receptors

A roman god JANUS had two faces



Effect of cytokines on cells



Effects of cytokines

- Pro-inflammatory cytokines: IL-1, IL-6, TNF-α, IL-18
- Stimulation of macrophages: IFN-γ
- Stimulation of granulocytes: IL-8
- T-lymphocytes stimulation: IL-2
- B-lymphocytes stimulation, production of antibodies: IL-4, IL-5, IL-6, BAFF
- Progenitor cells proliferation: IL-3, GM-CSF, M-CFS
- Negative regulators: IL-10, IL-13, TGF-β

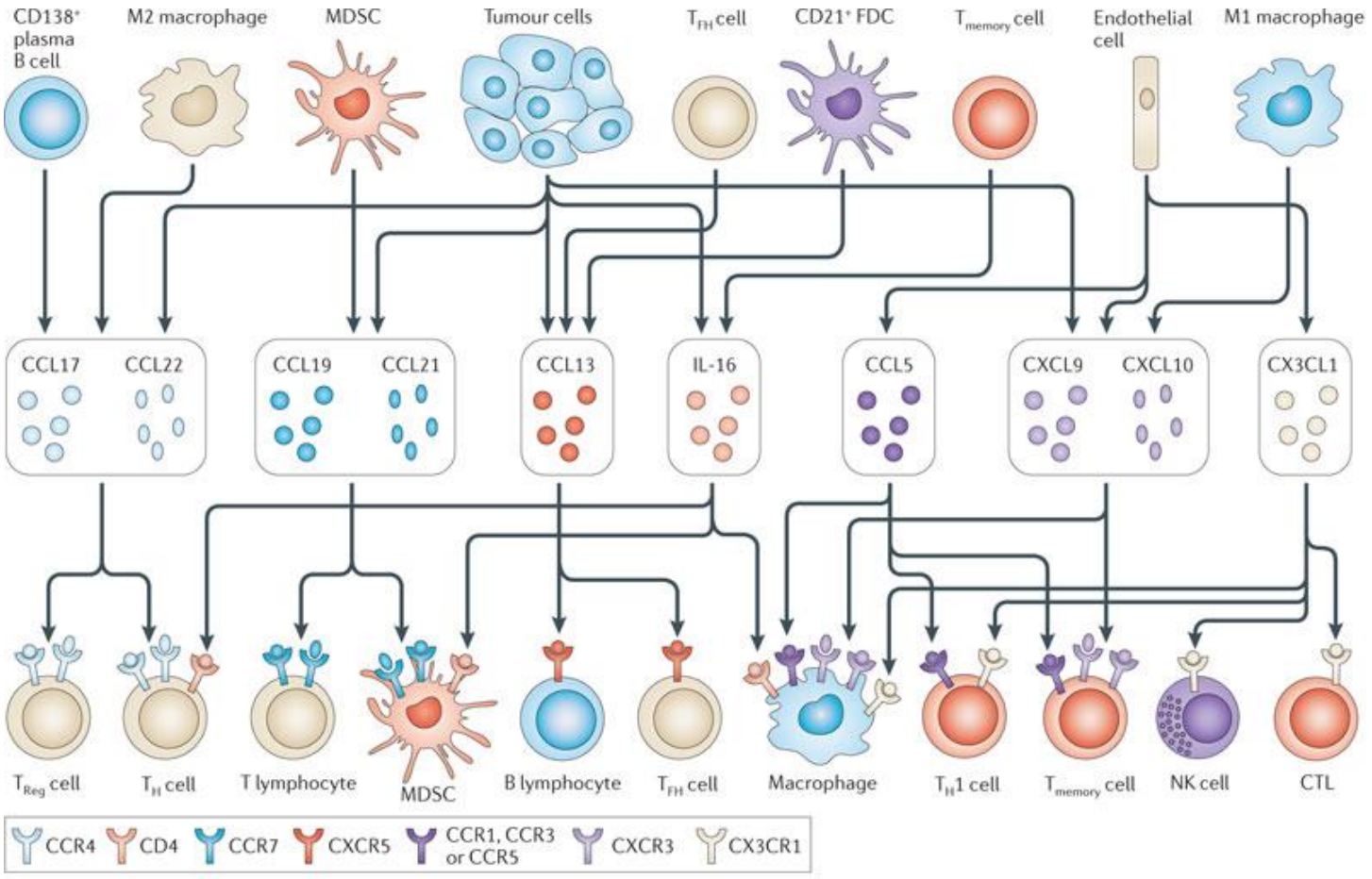
Interferons (IFN)

- Type I: IFN α, IFN β : produced by the virus infected cells (fibroblasts, macrophages). In the target cells they inhibit viral replication.
- Type II „Immune“: IFN γ: produced by activated T_H1 cells, causes activation of macrophages.

Chemokines

- Low molecular weight polypeptides.
- Based on the concentration gradient, they control migration of inglammatory cells to sites of inflammation (inflammatory chemokines).
- Chemokineds regulate migration of cells even in physiological conditions (homeostatic chemokines).
- They can also affect other functions of vatious cells of the immune system.
- According to the location of cysteines at the N-terminus, they are divided into 4 families: CC, CXC, CX3C and C.
- About 45 chemokines and 19 different chemokine receptors have been described..

Chemokines in anti-tumor response



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Cytokines in pathogensis of diseases

- Atopic diseases: IL-4 stimulates IgE production, IL-5 stimulates eosinophils production.
- Inflammatory diseases (rheumatic, Crohn´s disease), systemic response in sepsis – various pro-inflammatiory cytokines, TNF-α seems to be the most important.
- Immunodeficiency diseases may be caused by disturbed production of various cytokines (IFNγ, IL-12), or defect of cytokine receptors.

Therapeutic use of cytokines

- IFN-α: anti-tumor treatment (malignancies of the lymphatic system, renal cancer, treatment of hepatitis B and C
- IL-2- anti-tumor treatment
- GM-CSF – treatment of granulocytopenia
- IFN-β: treatment of multiple sclerosis
- IFN-γ: treatment of some immunodeficiencies

Anti-cytokine treatment

- Blockade of function of cytokines by various approaches:
  - Direct blockade of cytokines.
  - Blockade of cytokine receptors.
  - Soluble artificial receptors binding cytokines.
- Most frequently monoclonal antibodies, various fusion proteins…
- Anti-inflammatory treatment: directed against TNF-α, IL-1, IL-6, IL-17, IL-23..
- Anti-tumor treatment – blockade of various growth factors (e.g. EGF)