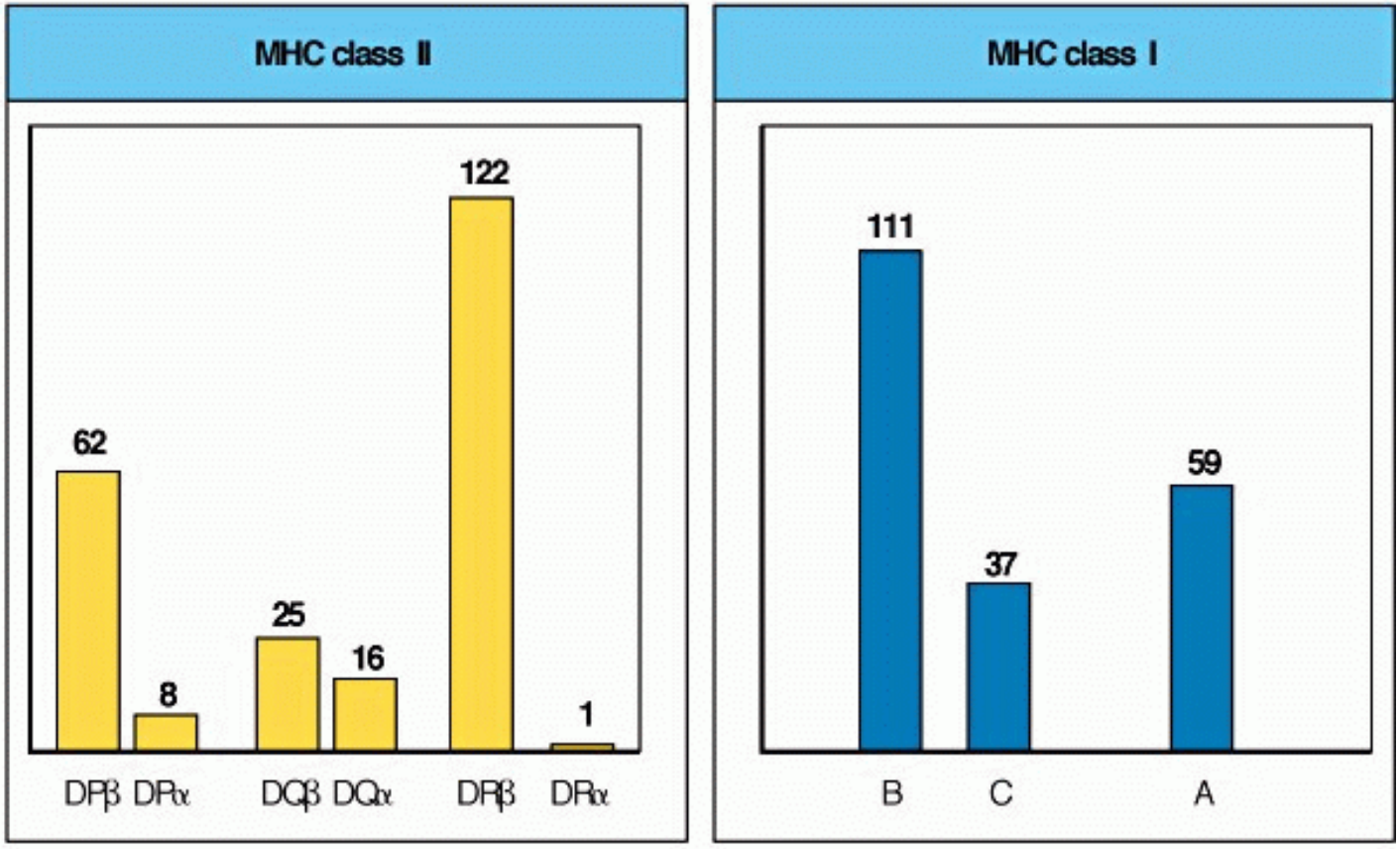
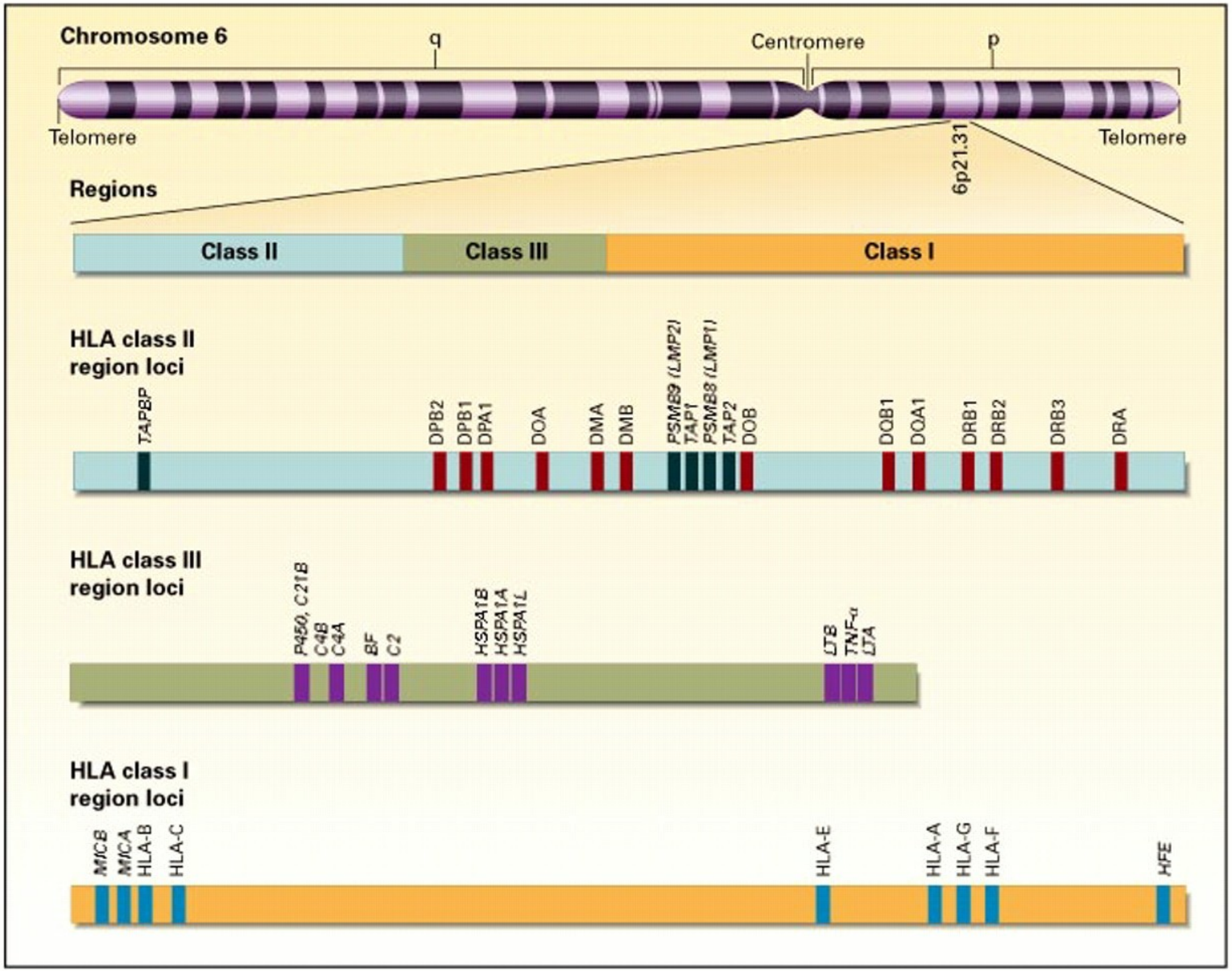
HLA antigens
(Human Leukocyte Antigens)

= human MHC
(Main Histocompatibility Complex)
antigens

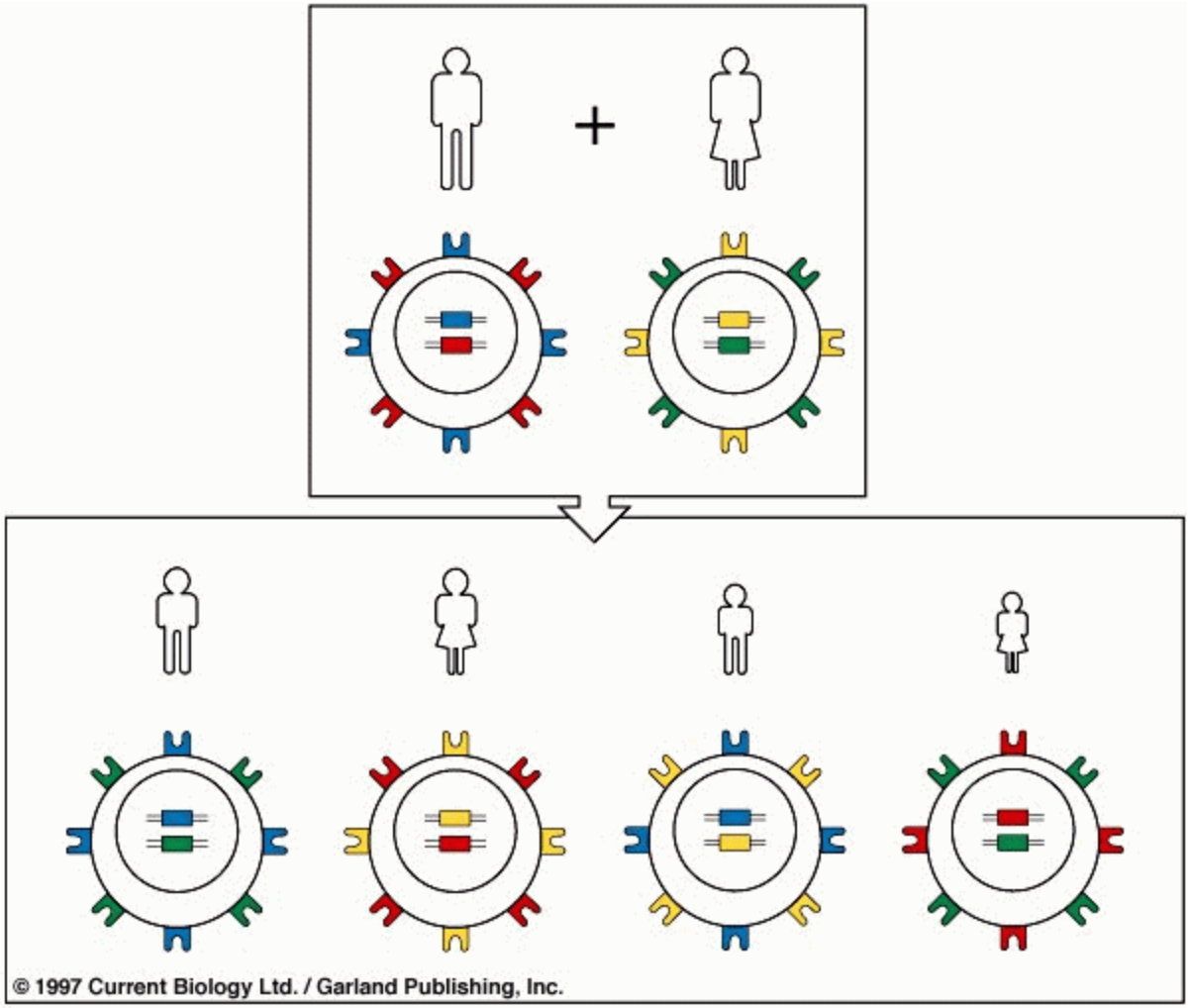
Polymorphism of human MHC antigens



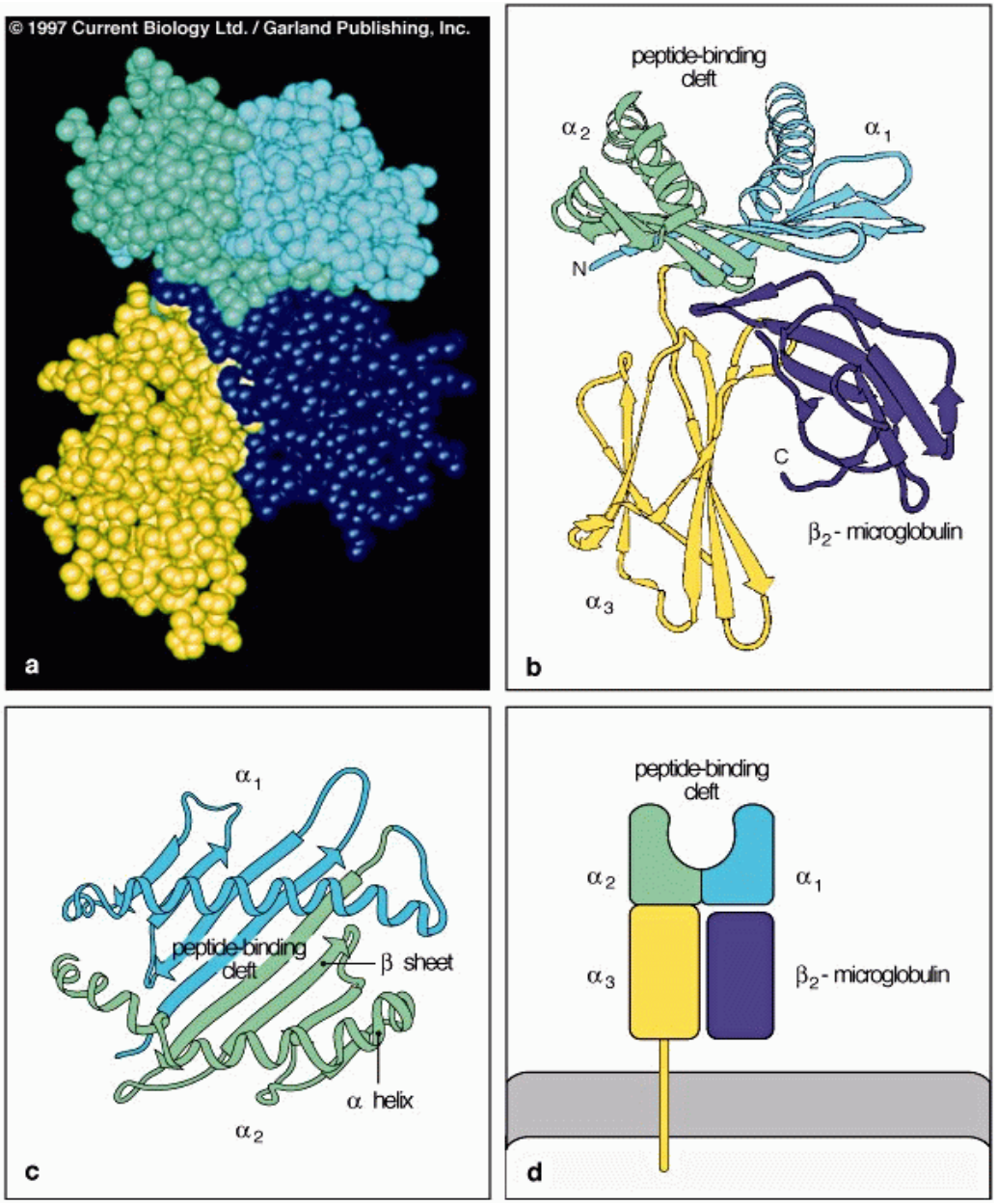
HLA genes are localized on 6p chromosome



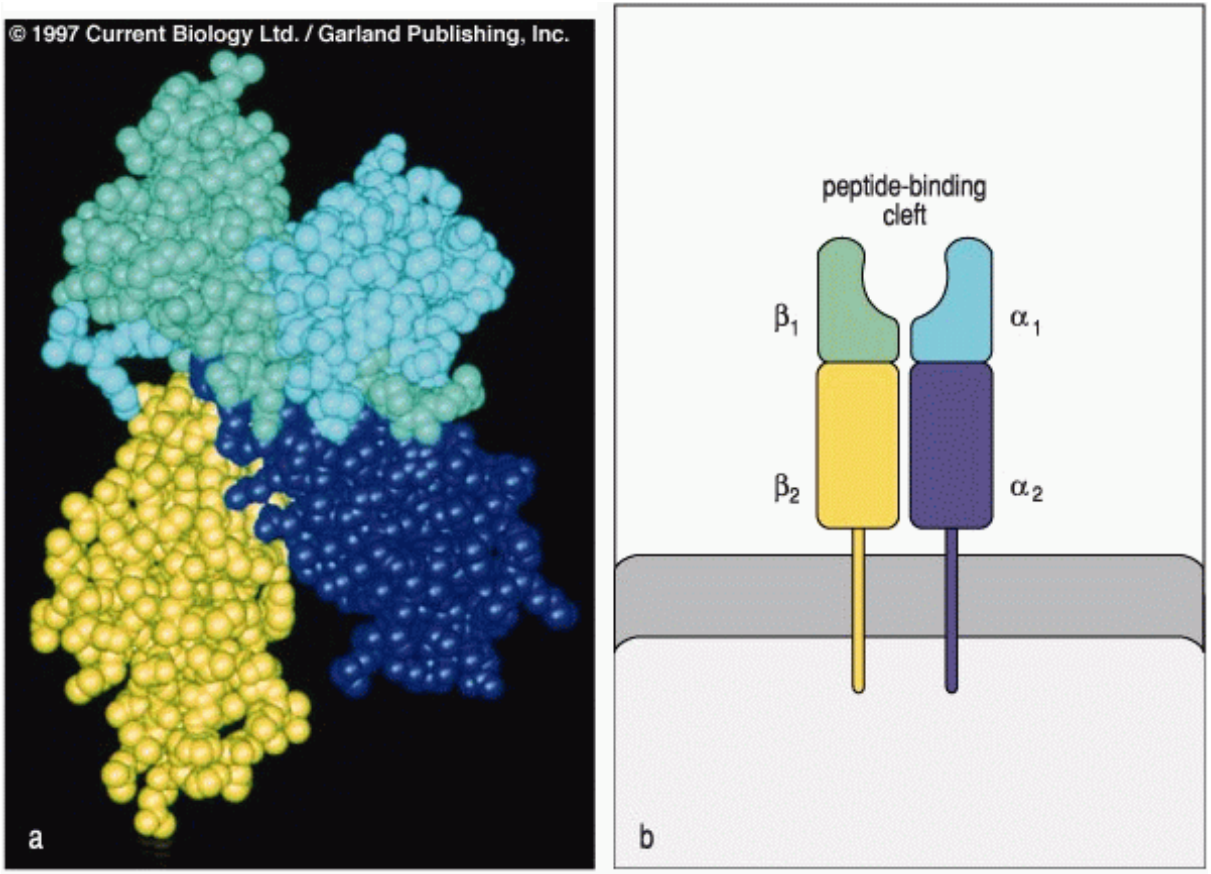
Co-dominant expression of HLA genes



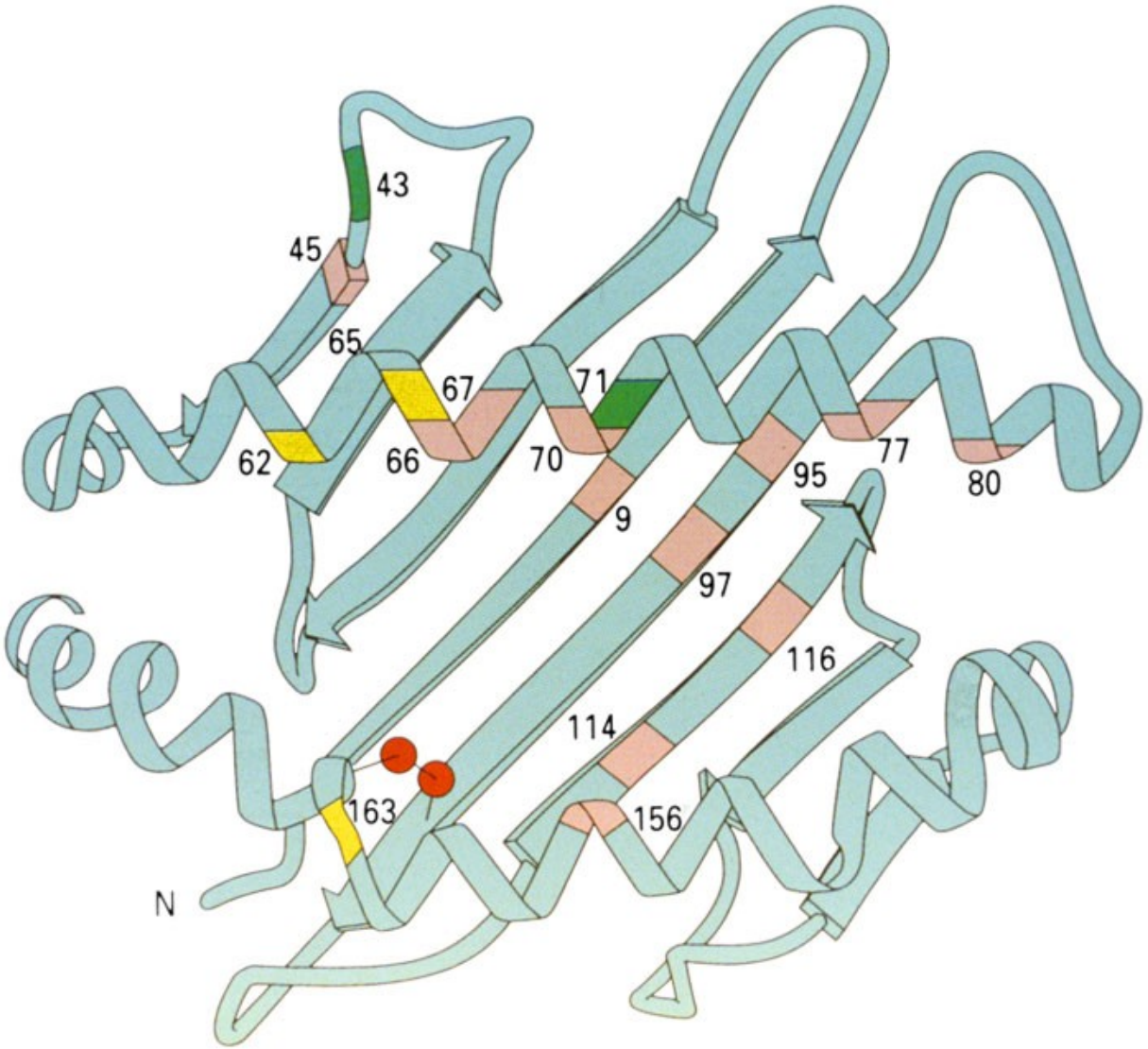
HLA-I antigens



HLA-II antigens

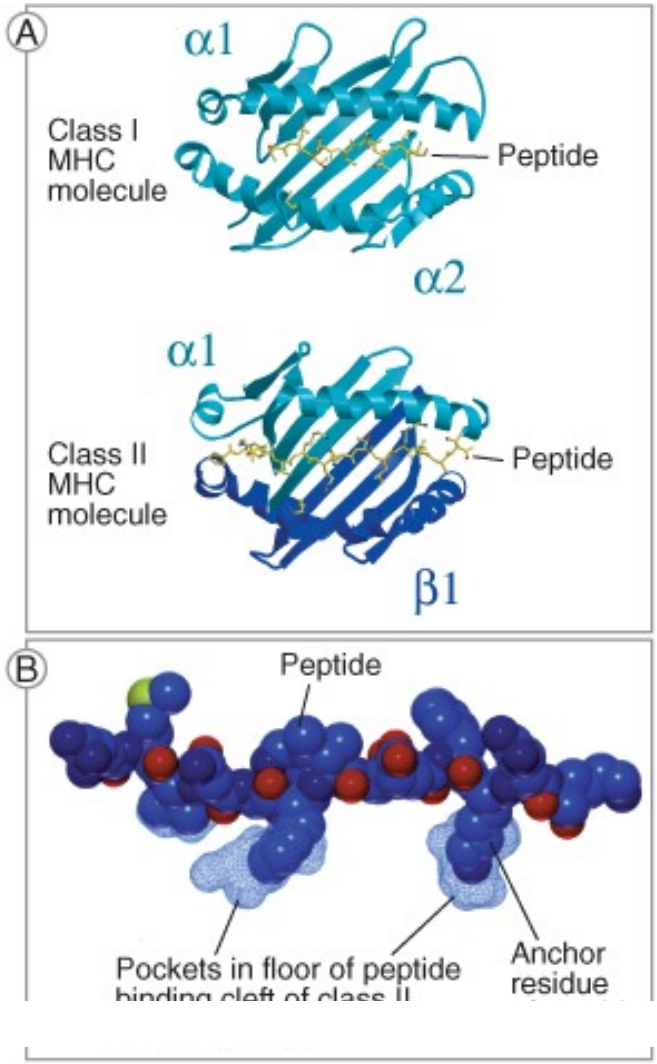


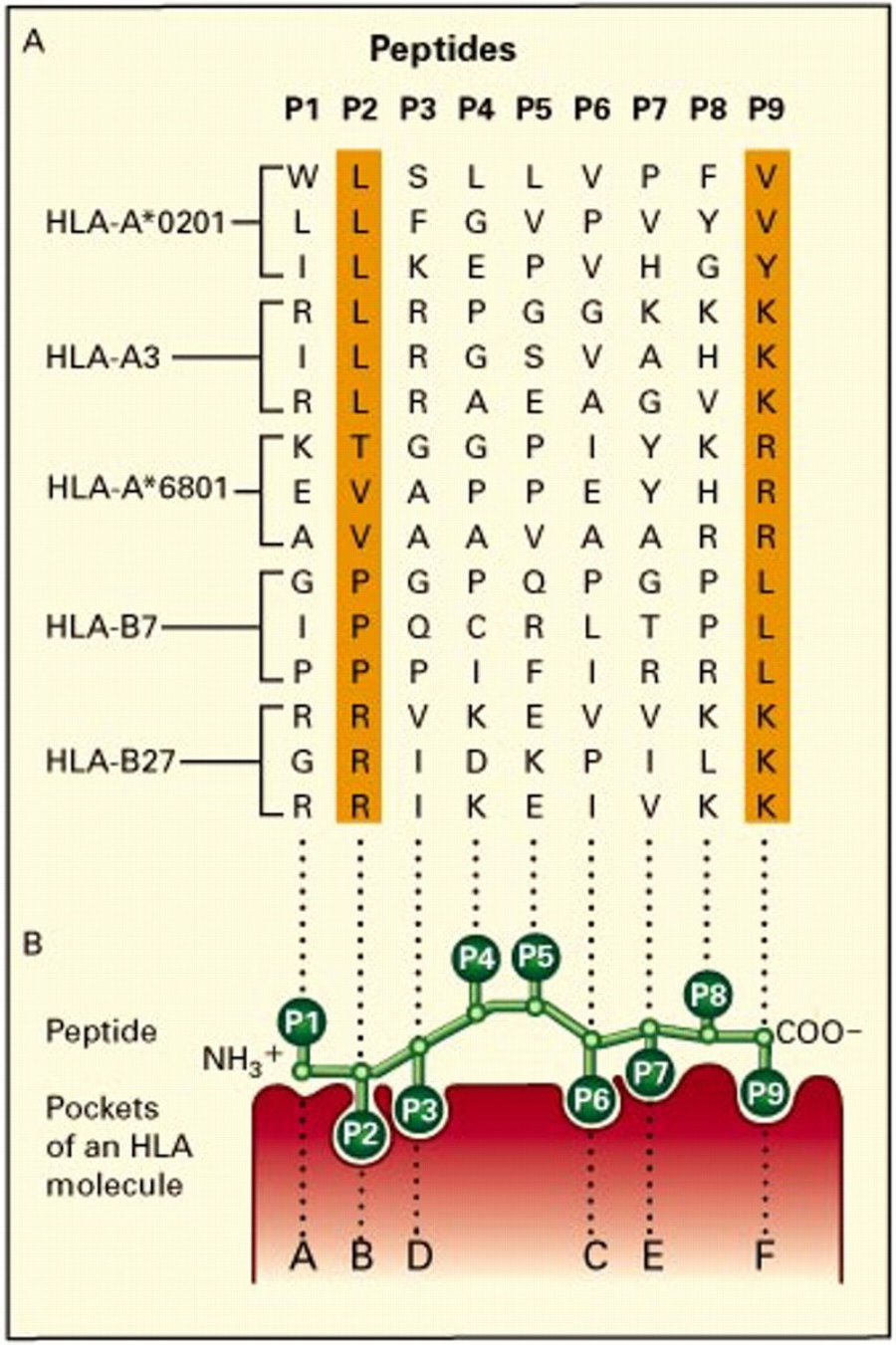
The top surface of HLA-A2



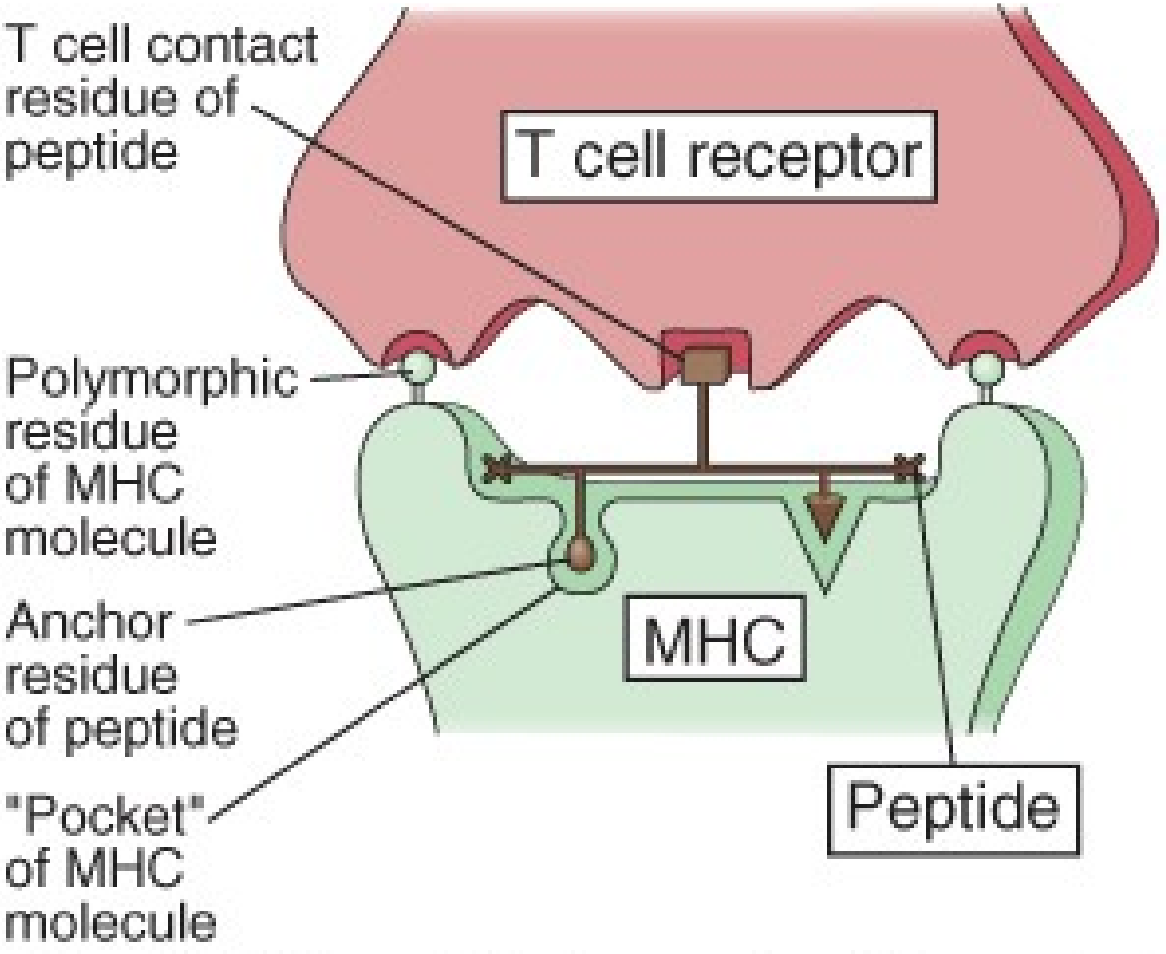
From: I. Roit et al: Slide atlas of Immunology. 3rd. edition

Binding of antigenic peptide to HLA molecule




A
Peptides
P1 P2 P3 P4 P5 P6 P7 P8 P9
HLA-A*0201
W L S L L V P F V
L L F G V P V Y V
I L K E P V H G Y
HLA-A3
R L R P G G K K K
I L R G S V A H K
R L R A E A G V K
HLA-A*6801
K T G G P I Y K R
E V A P P E Y H R
A V A A V A A R R
HLA-B7
G P G P Q P G P L
I P Q C R L T P L
P P P I F I R R L
HLA-B27
R R V K E V V K K
G R I D K P I L K
R R I K E I V K K
B
Peptide
NH3+
COO−
Pockets of an HLA molecule
P1
P2
P3
P4
P5
P6
P7
P8
P9
A
B
D
C
E
F

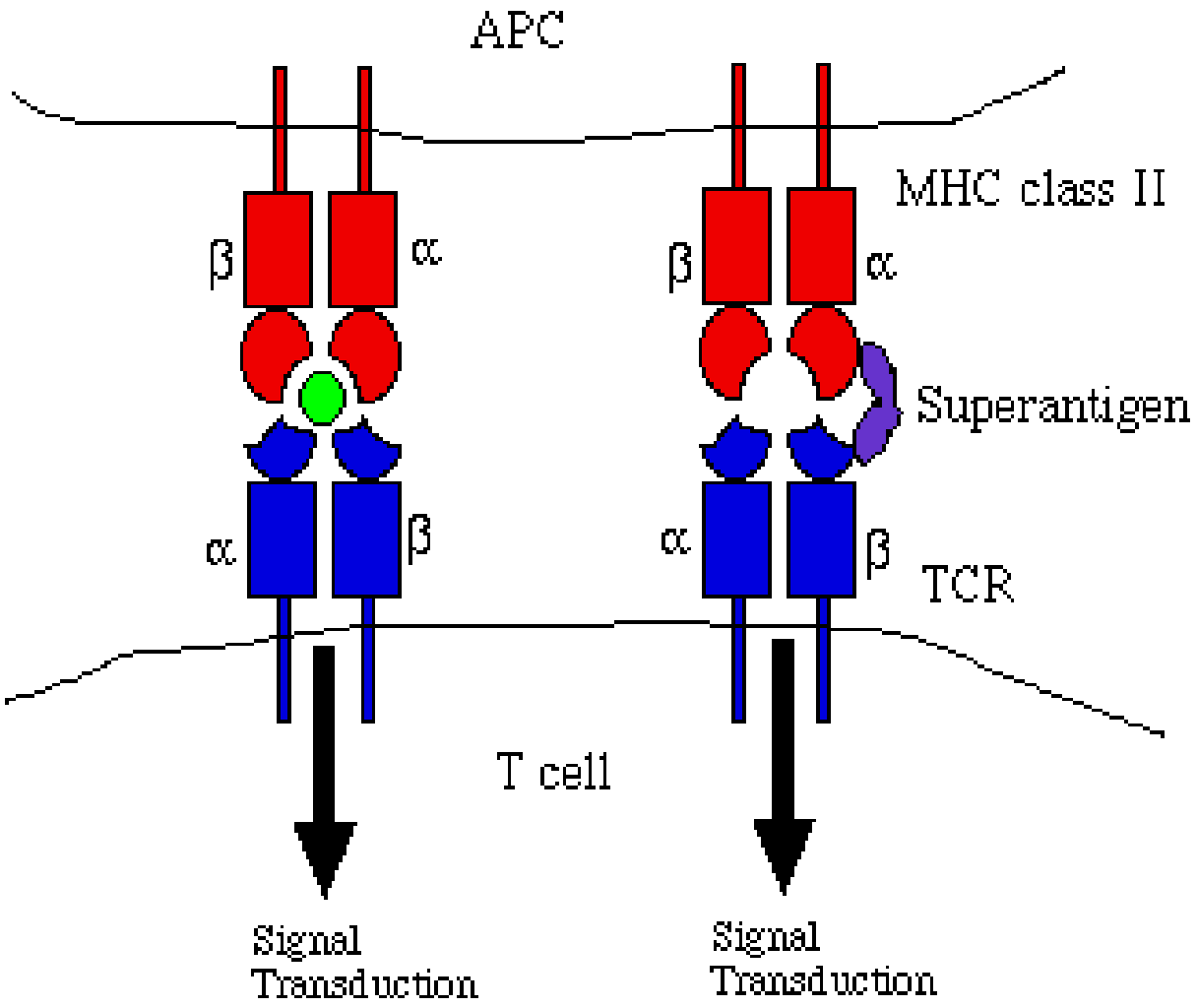
Interaction of TCR with HLA+antigen



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 by superantigen



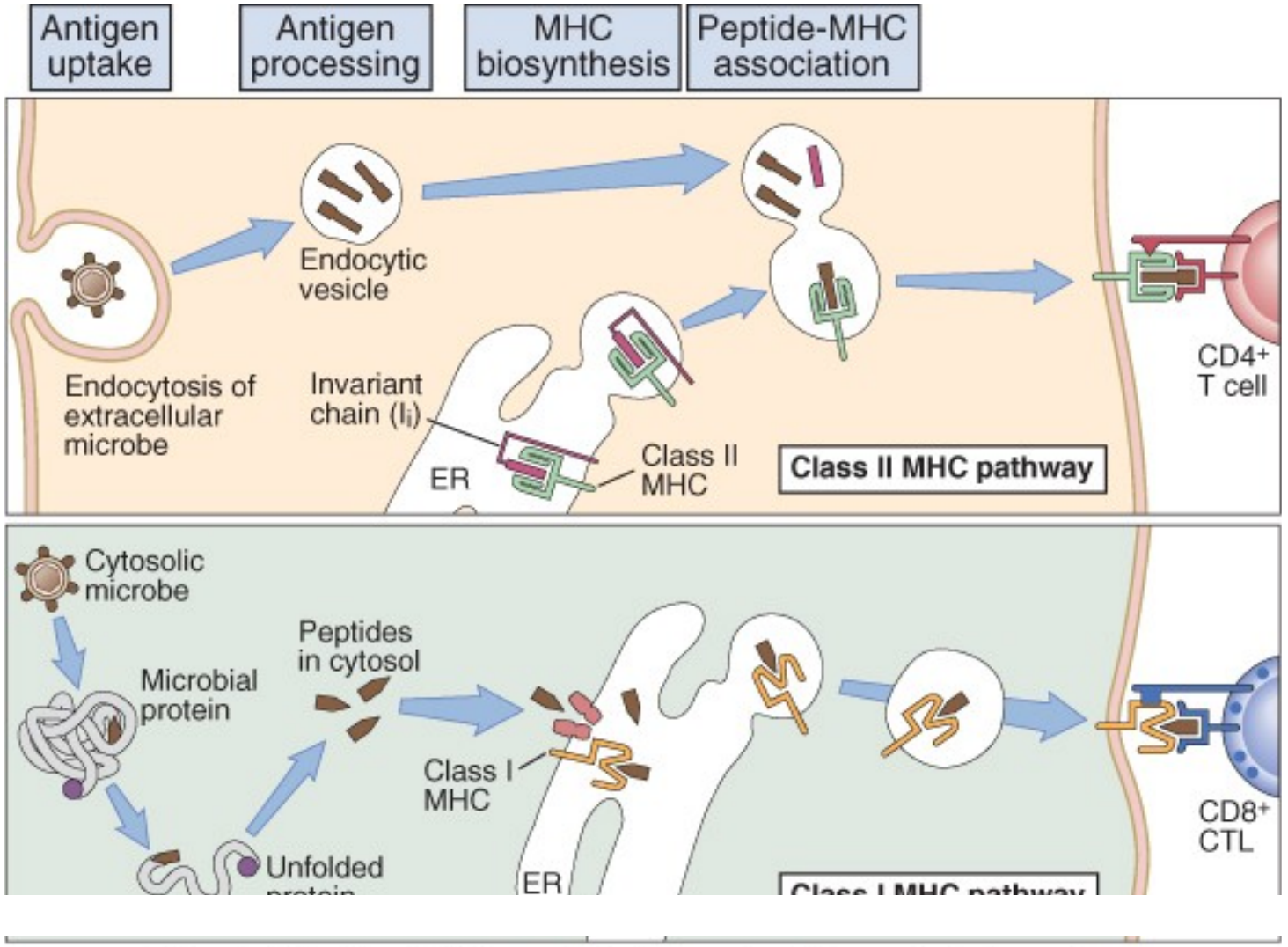
www.bio.davidson.edu/.../restricted/TSS.html

Initiation of the immune response, Role of HLA antigens

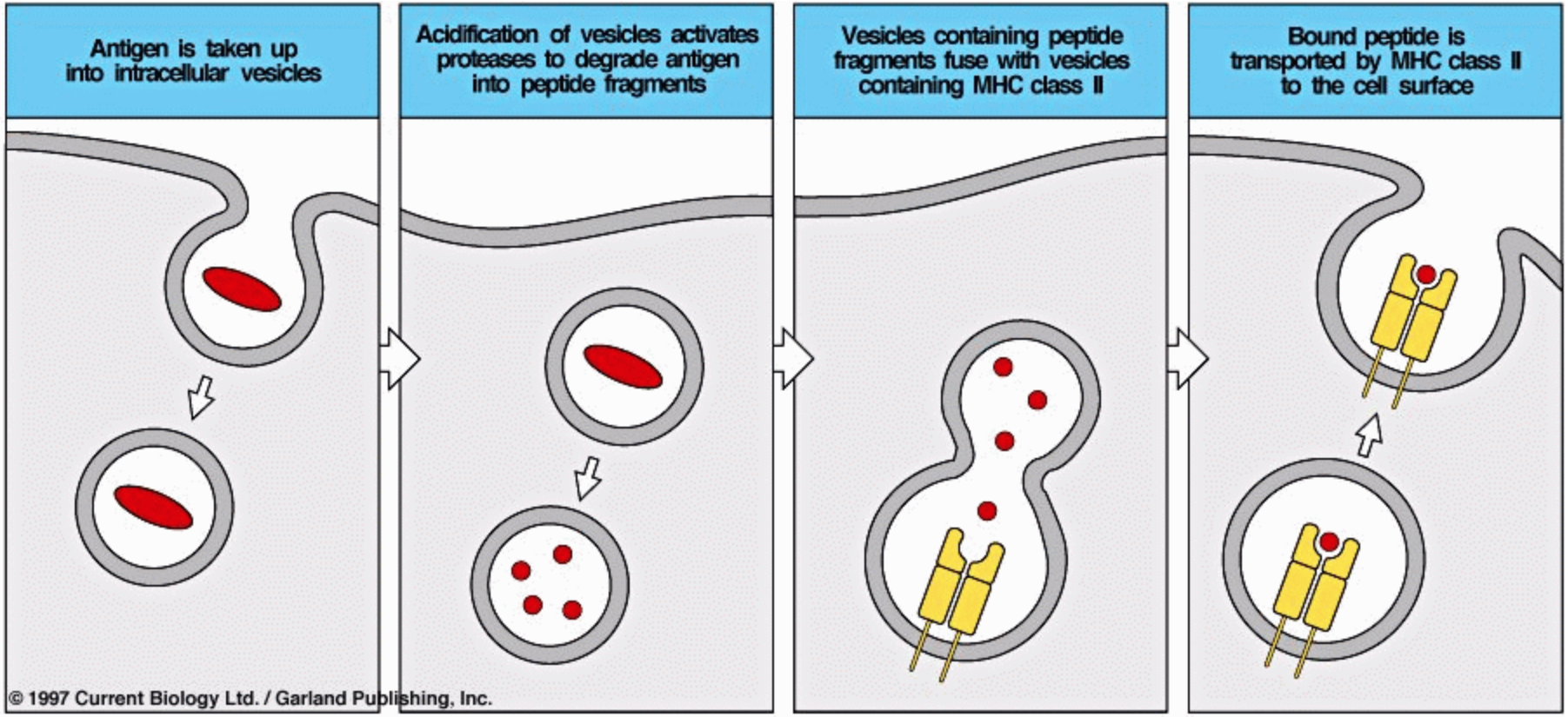
Two types of antigens as regards antibody production stimulation

- 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



Degradation and presentation of antigens on HLA-II molecules

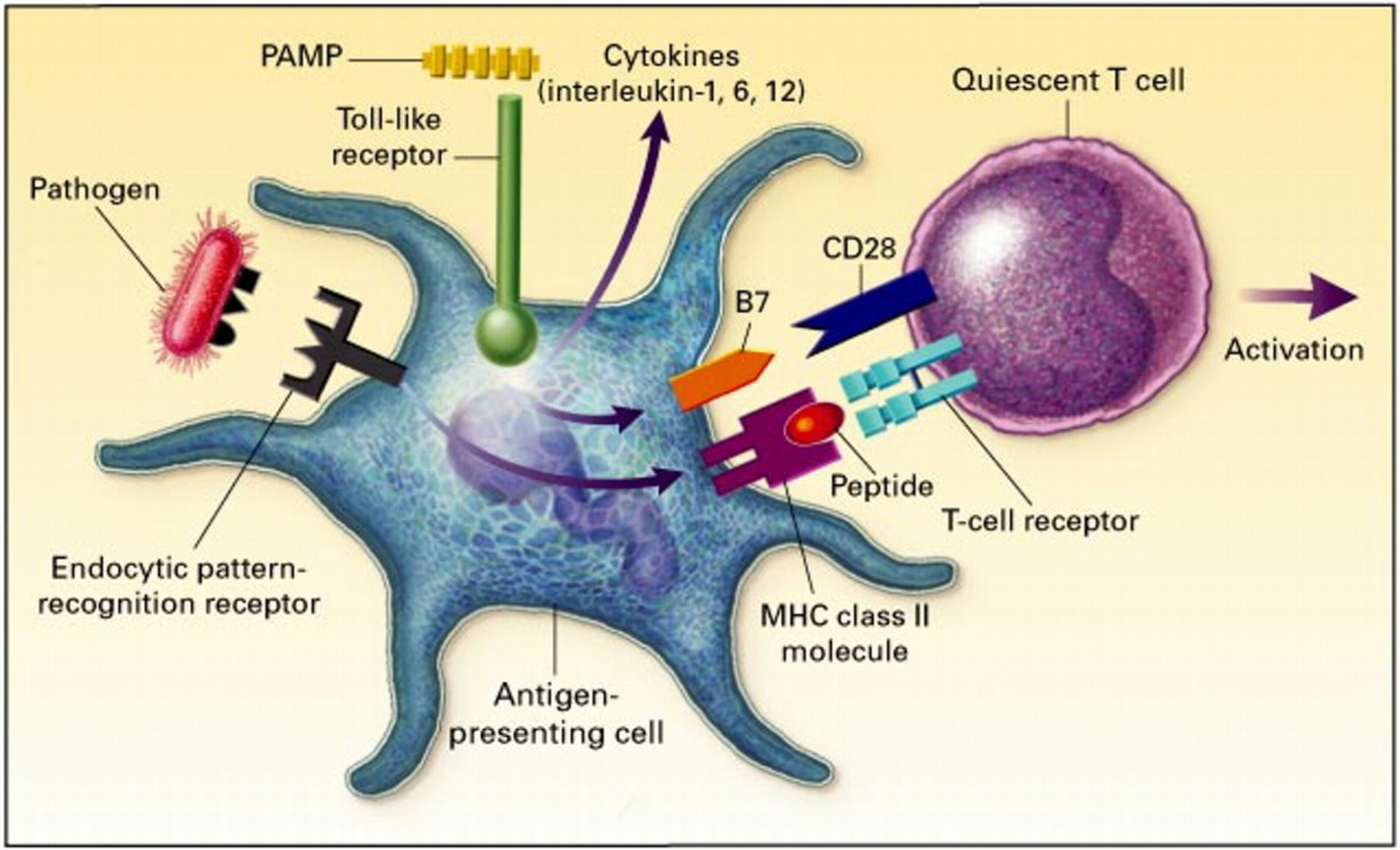


Role of HLA antigens in immune response

- 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.

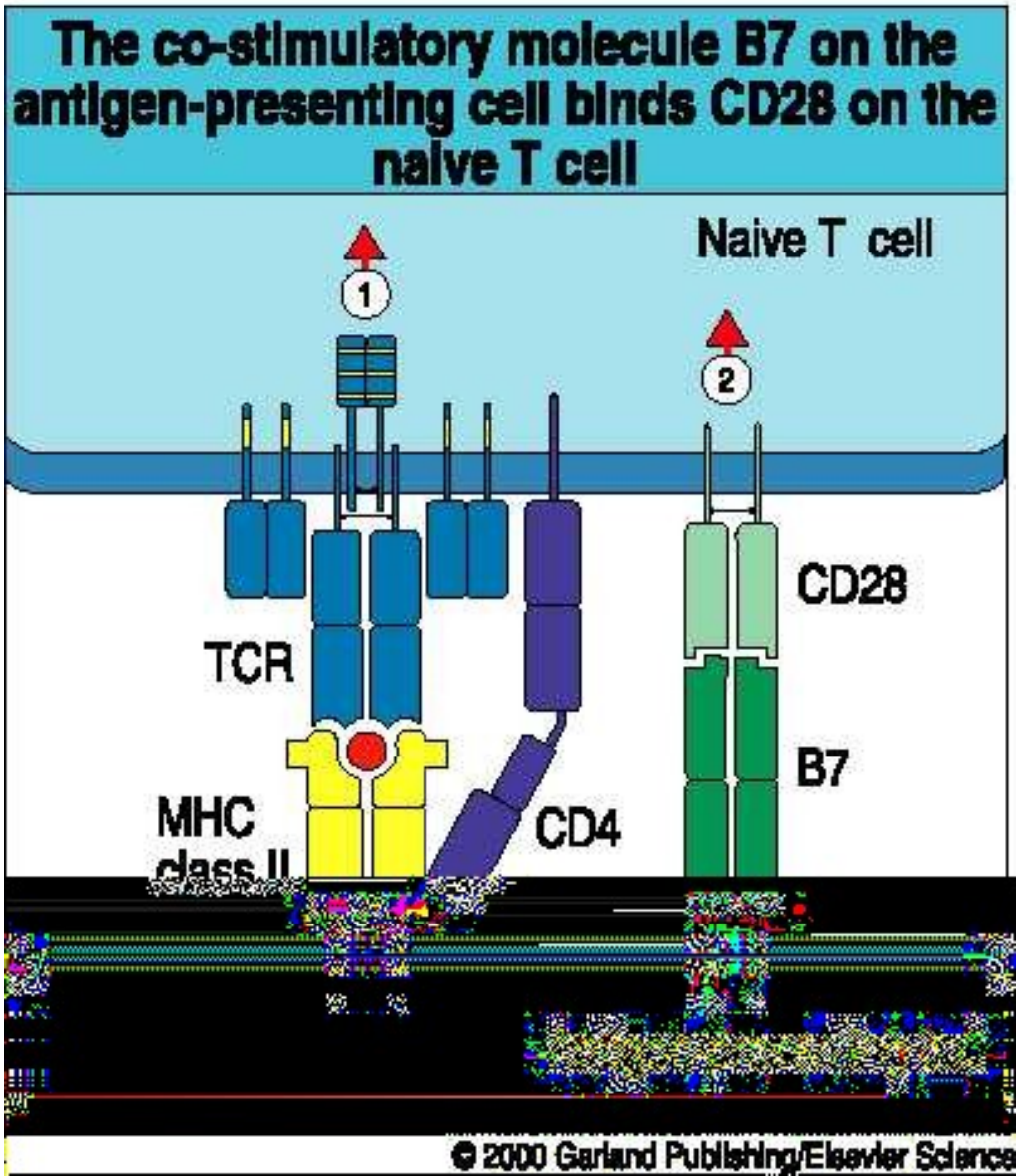
  Presentation of exogenous antigens to CD4+ cells. This leads to activation of the CD4+ (and also the antigen presenting cell).

Stimulation of a T-cell by an antigen is a complex reaction

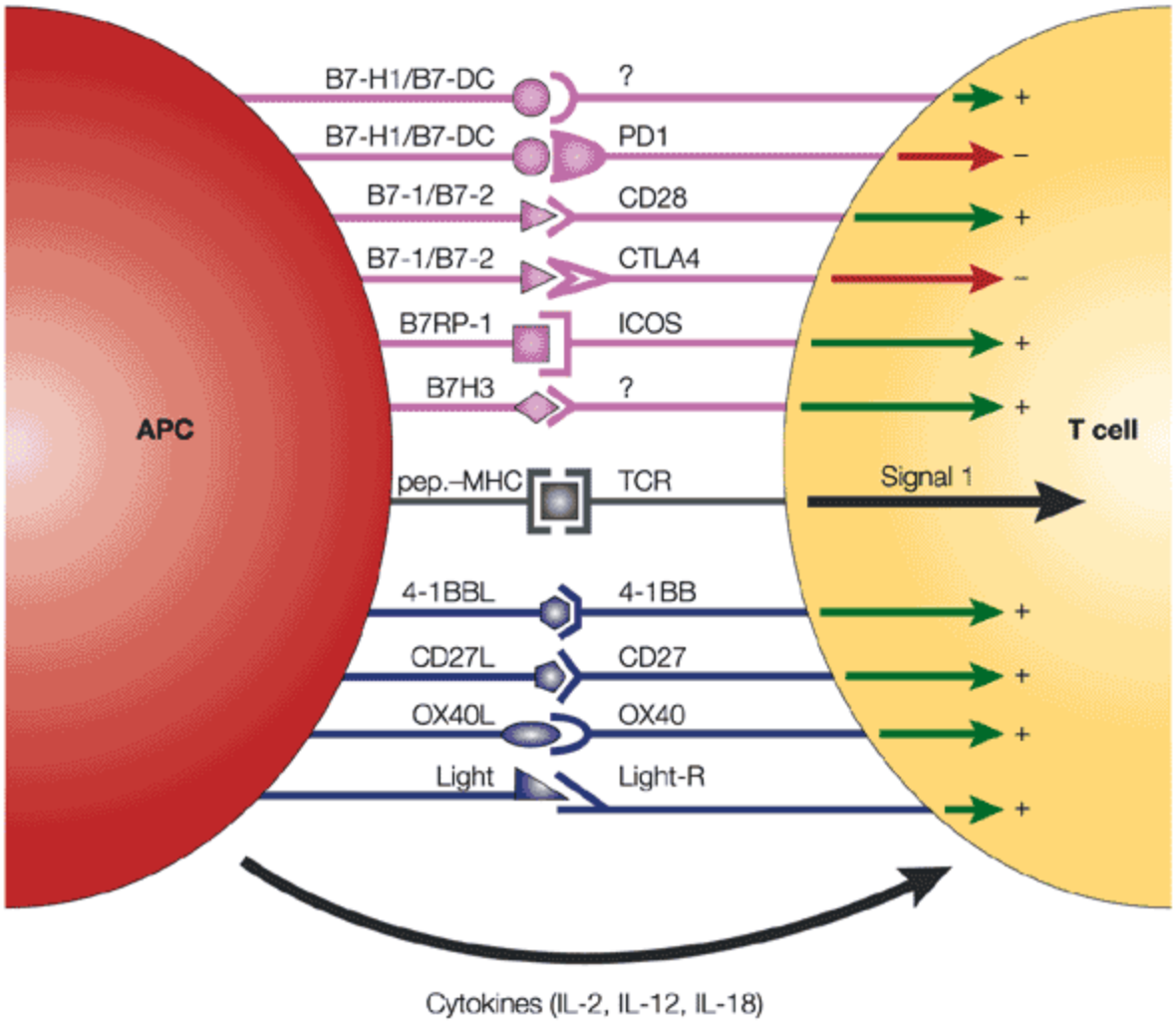


Costimulatory signals in T-cell activation

Figure 6.7



Costimulatory signals in T-cell activation



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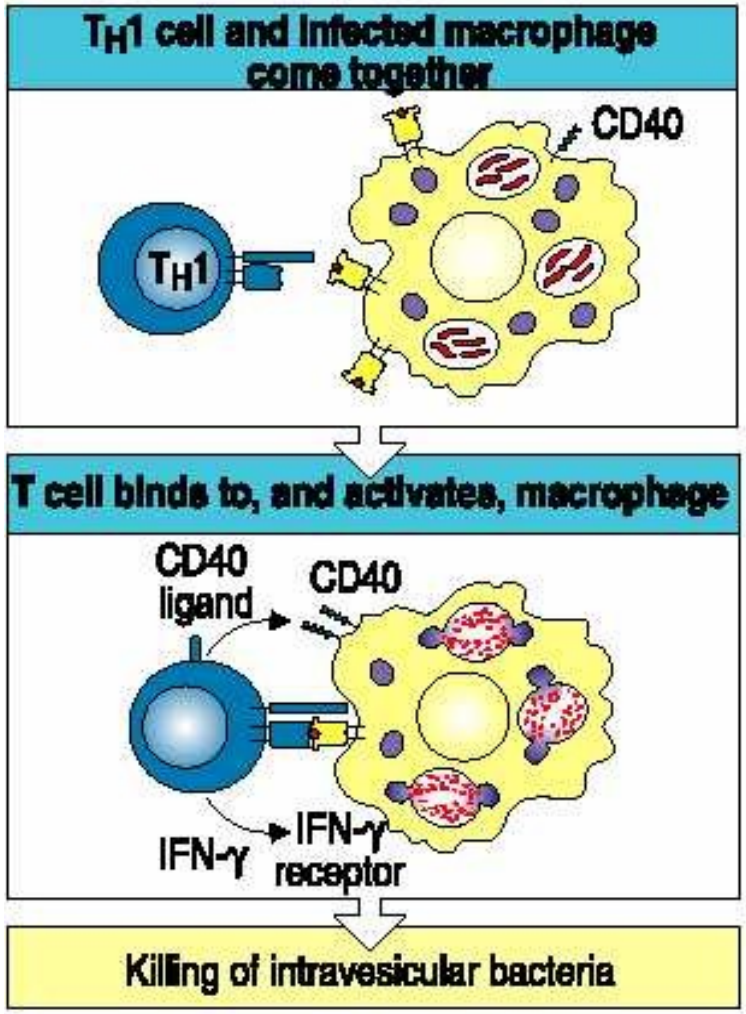
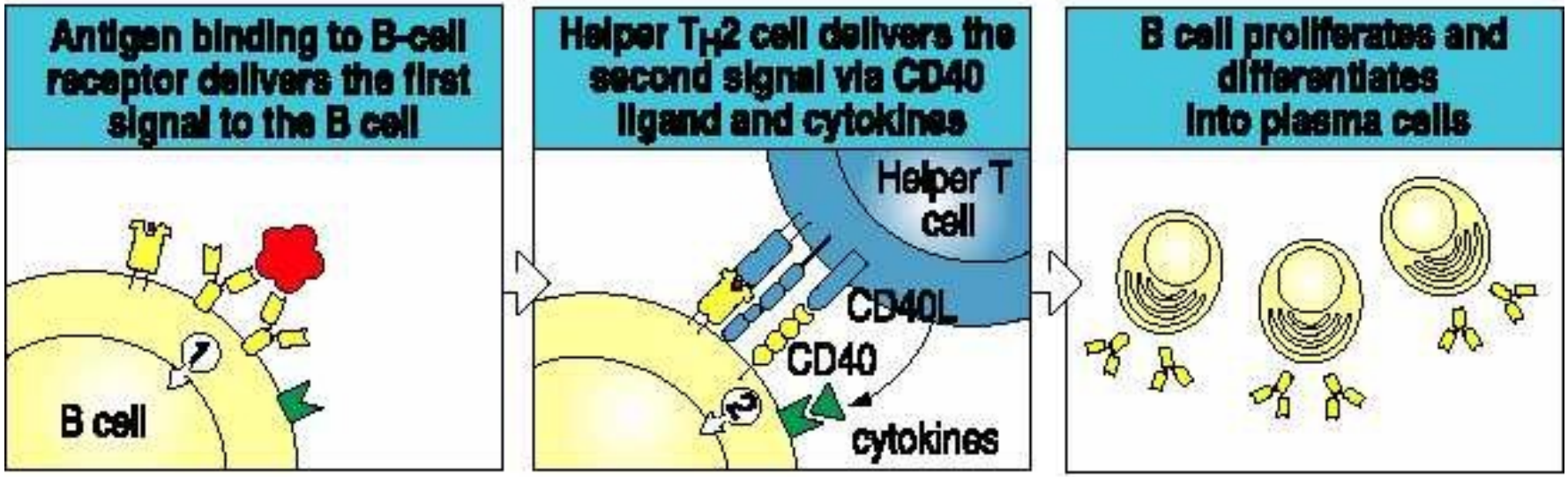
Function of Th1 cells

Figure 6.27



Initiation of antibody response in T-cell dependent antigens

Figure 7.8



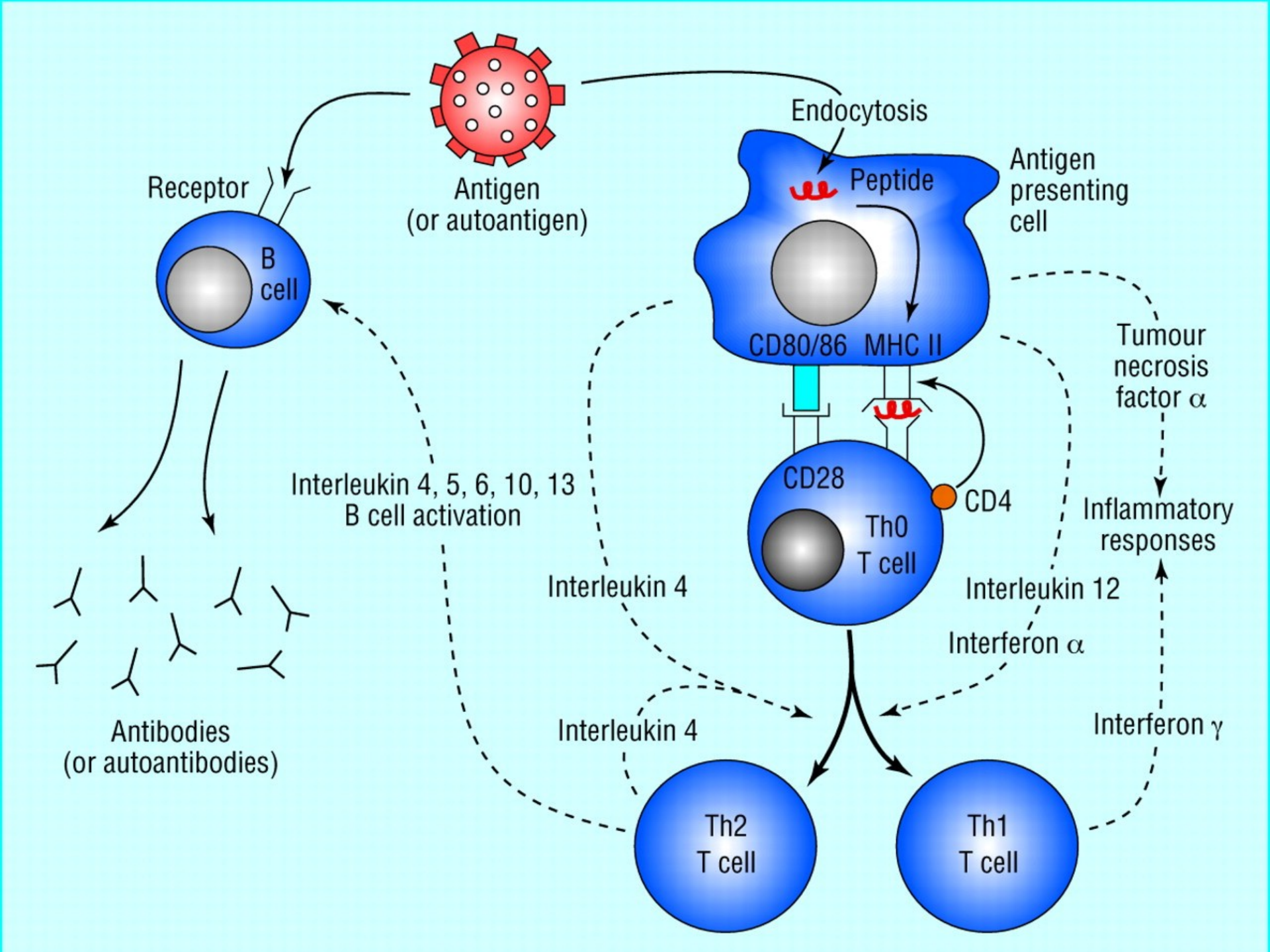
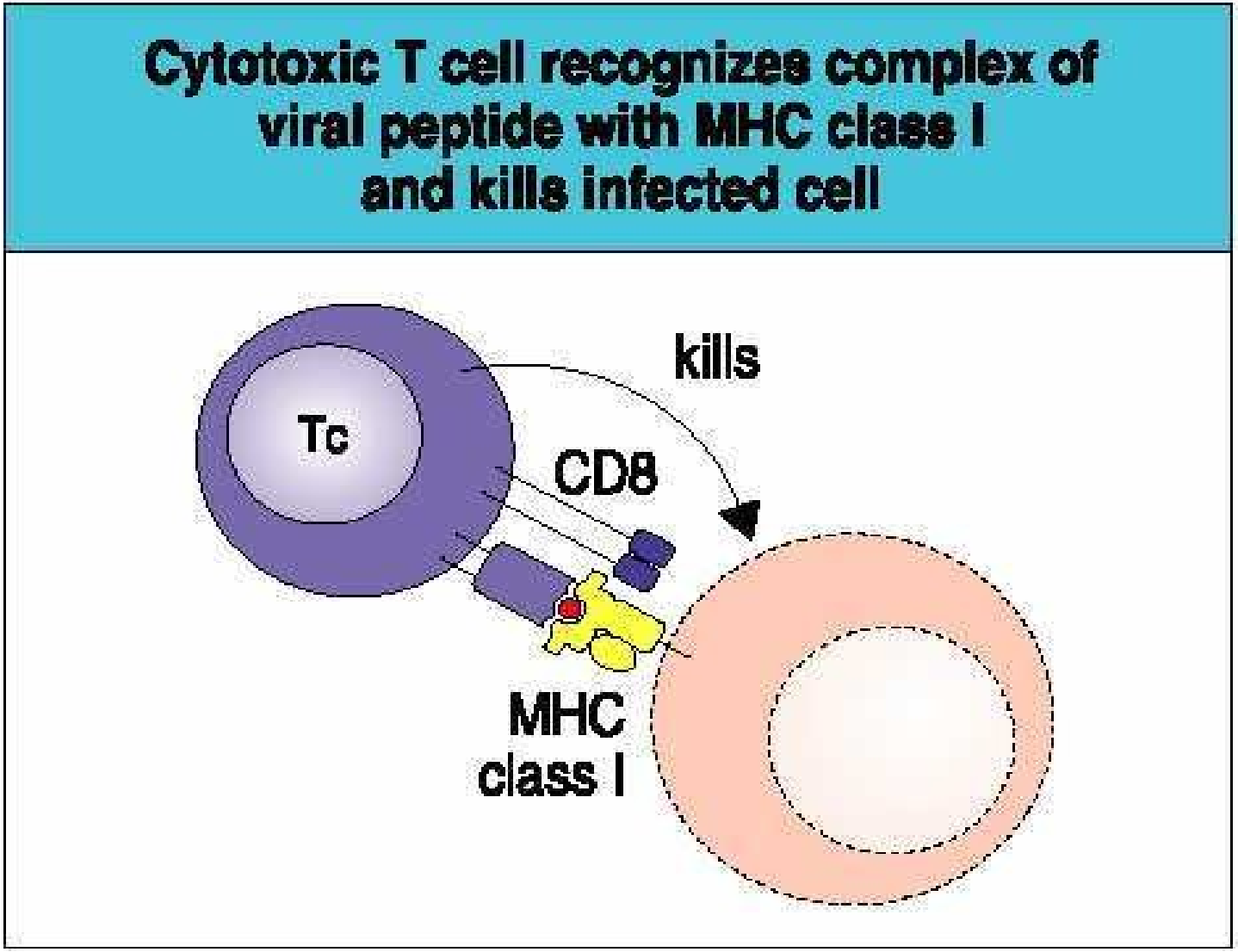
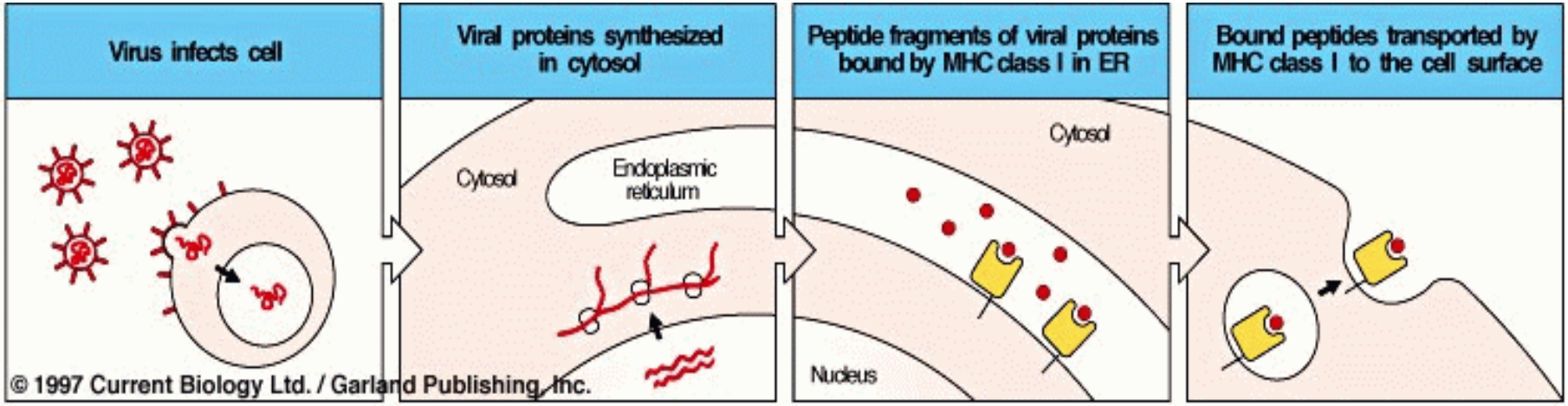

Antigen
(or autoantigen)
Endocytosis
Antigen
presenting
cell
Peptide
Receptor
B
cell
CD80/86
MHC II
Tumour
necrosis
factor α
CD28
CD4
Th0
T cell
Inflammatory
responses
Interleukin 4, 5, 6, 10, 13
B cell activation
Interleukin 4
Interleukin 12
Interferon α
Interleukin 4
Interferon γ
Antibodies
(or autoantibodies)
Th2
T cell
Th1
T cell

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 to development of the disease (increased relative risk), but not cause a disease.
- Majority of the carriers of the „disease associated antigen“ are healthy!

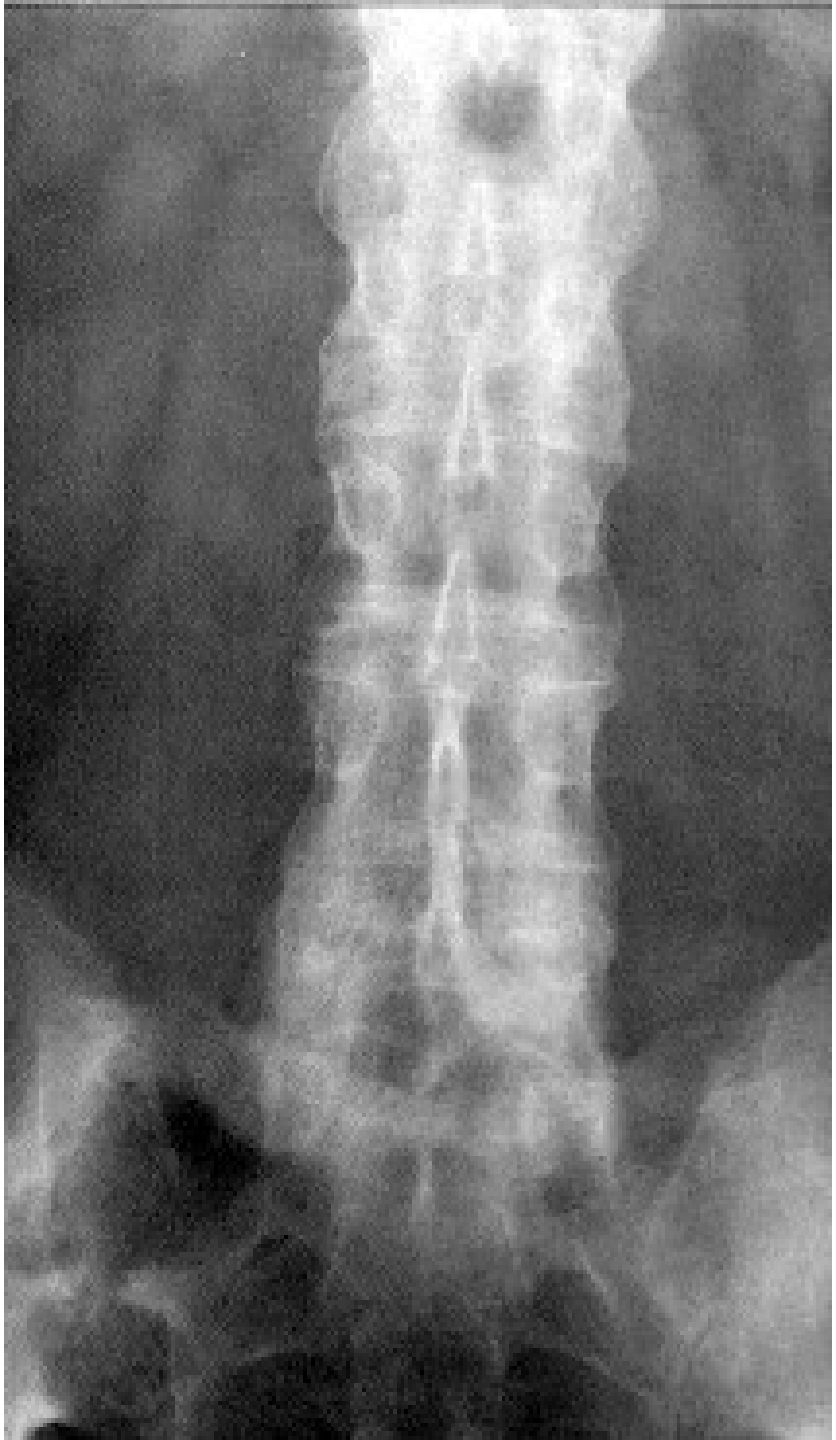
Association of diseases with particular HLA antigens

Disease	**HLA antigen**	**Relative risk***
Rheumatoud arthritis	DR4	6
Insulin-dependent diabetes	DR3	5
	DR4	6-7
	DR3/DR4	20
	DR3, DQw8/DQw2	30
Chronic aktive hepatitis	DR3	14
Coeliakia	DR3	12
Ankylozing spondylitis	B27	90-100

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!

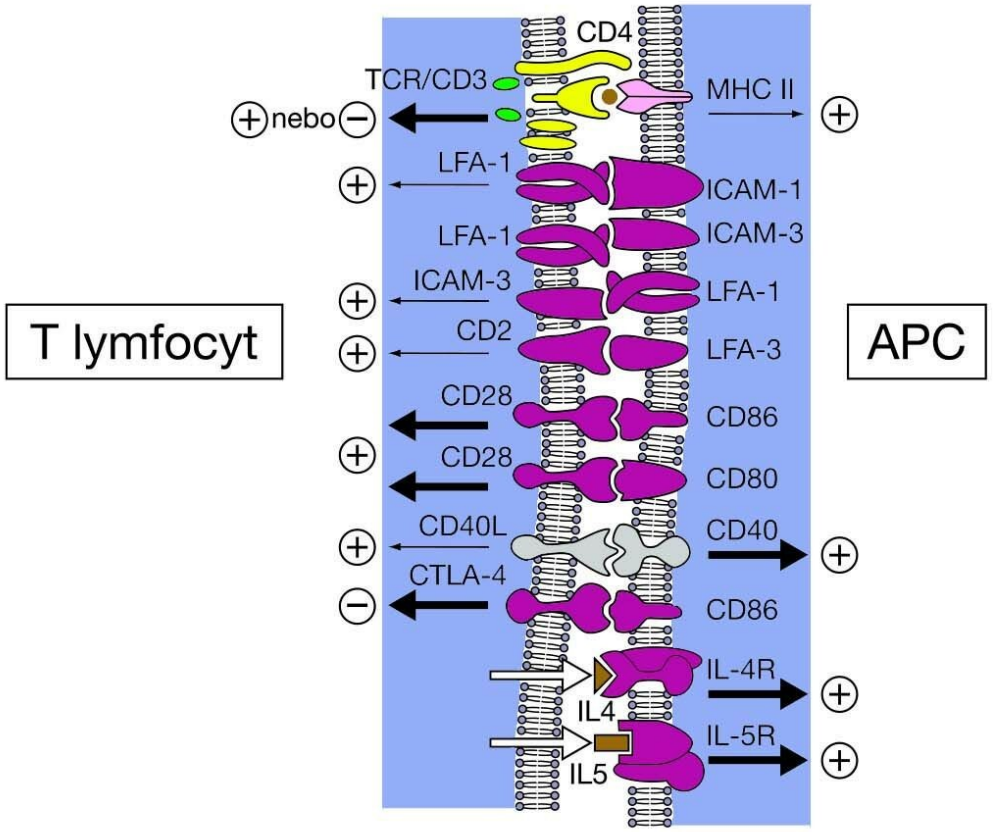
Regulation of the immune response

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

Regulation within the immune system

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

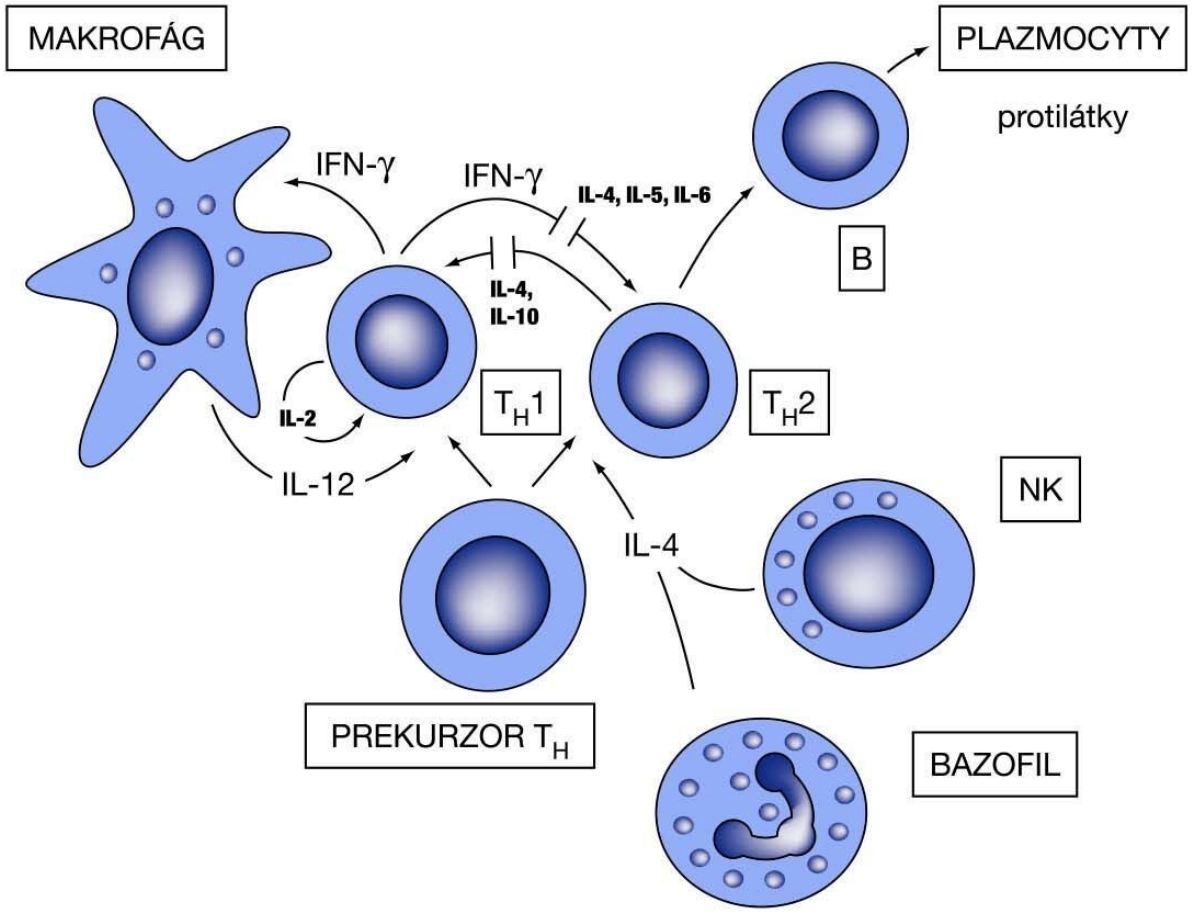
Costimulatory molecules involved in the interaction between APC and T-lymphocyte



Hořejší, Bartůňková:Základy imunologie, 3. vydání,Triton, 2005

Regulation by T-lymphocytes

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



Hořejší, Bartůňková:Základy imunologie, 3. vydání,Triton, 2005

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….

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.

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

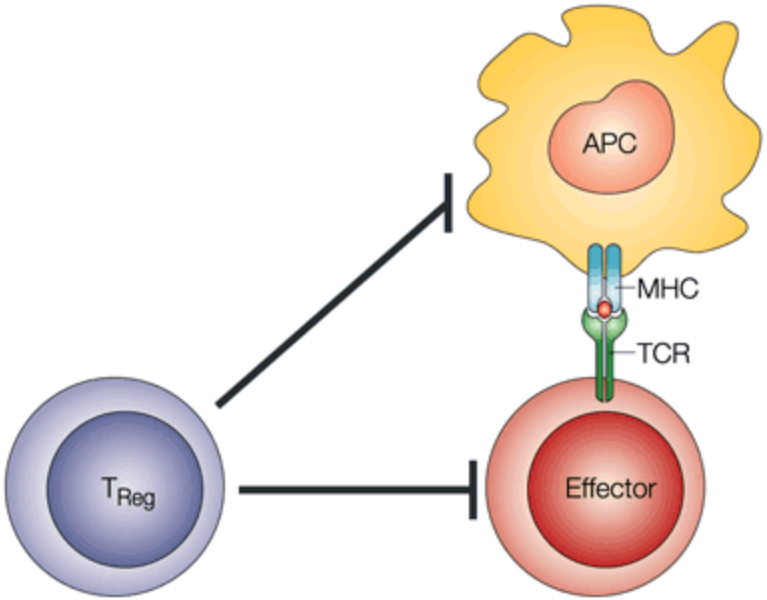
- IFN-α: anti-tumor treatment (malignancies of the lymphatic system, renal cancer, treatment of hepatitis B and C
- IL-2- anti-tumor treatment
- GM-CSF – treatment of granulocytopenia
- IFN-β: treatment of multiple sclerosis
- IFN-γ: treatment of some immunodeficiencies

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,
- Progenitor cells proliferation: IL-3, GM-CSF, M-CFS
- Negative regulators: IL-10, IL-13, TGF-β

T_{reg} lymphocytes

- Separate subgroup of regulatory T-cells
- Thymic development, although the development in periphery was also documented.
- CD4+CD25+
- Suppress immune reaction against self-antigens
- 5-10% of peripheral CD4+ cells



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