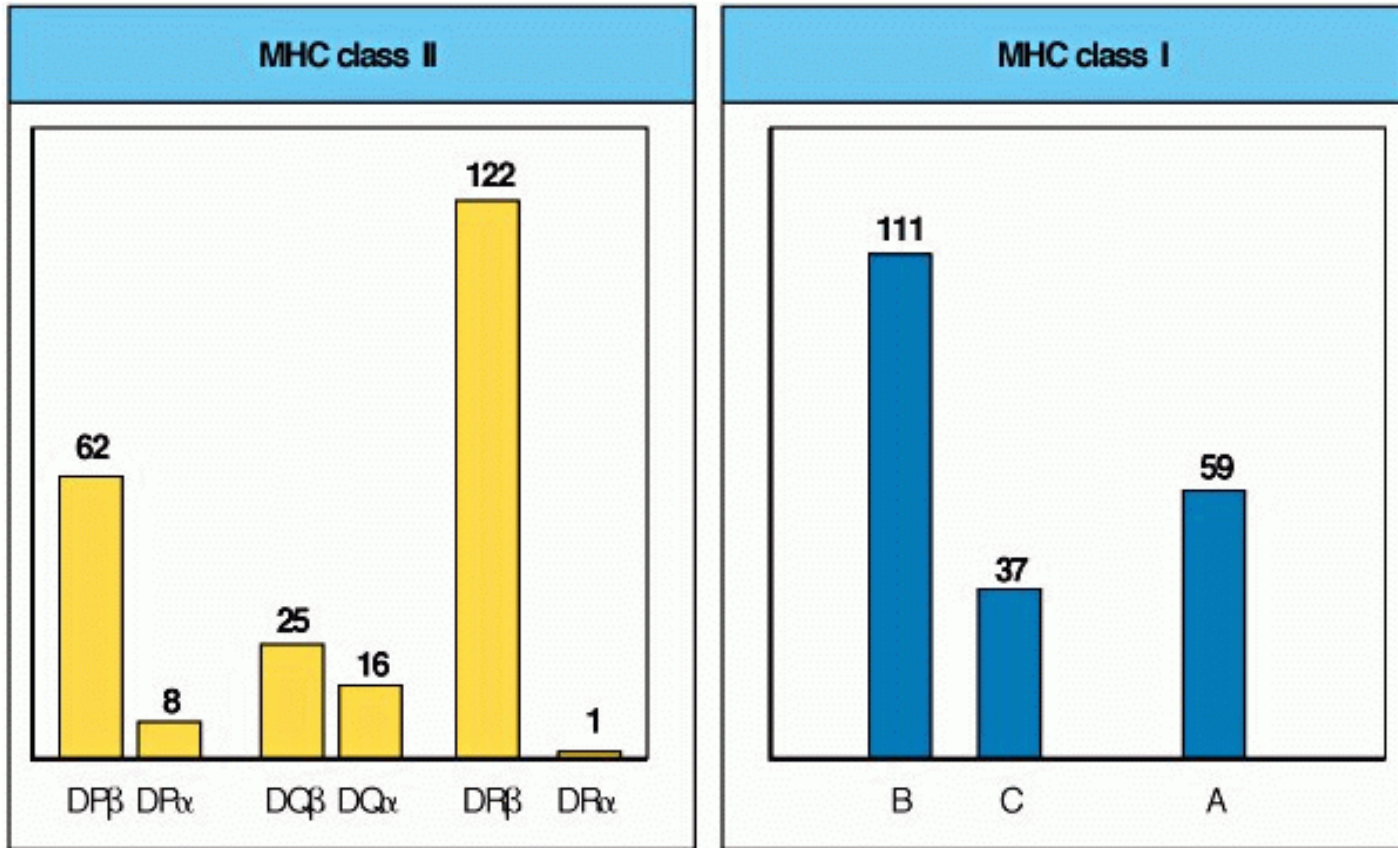


HLA antigens
(Human Leukocyte Antigens)

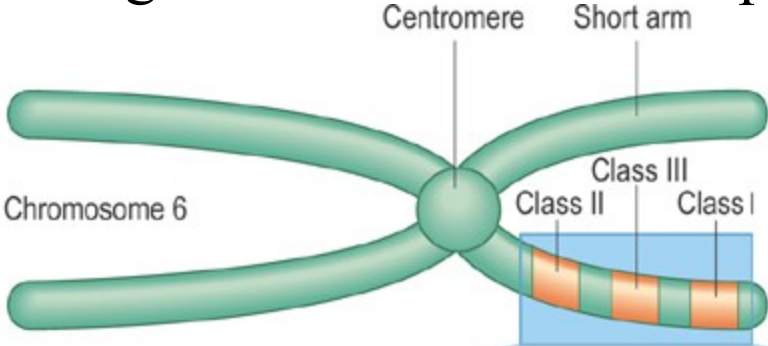
= human MHC
(Main Histocompatibility Complex)
antigens

Polymorphism of human MHC antigens

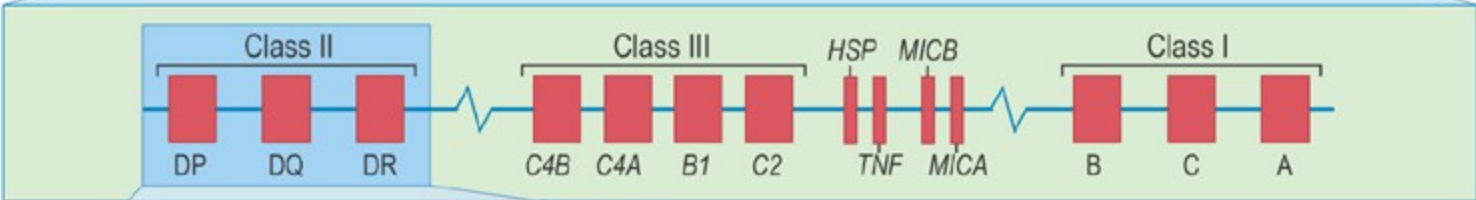


HLA genes are localized on 6p chromosome

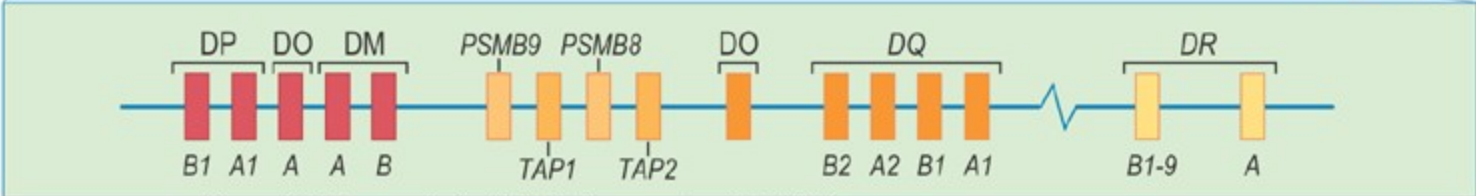
(a)



(b)

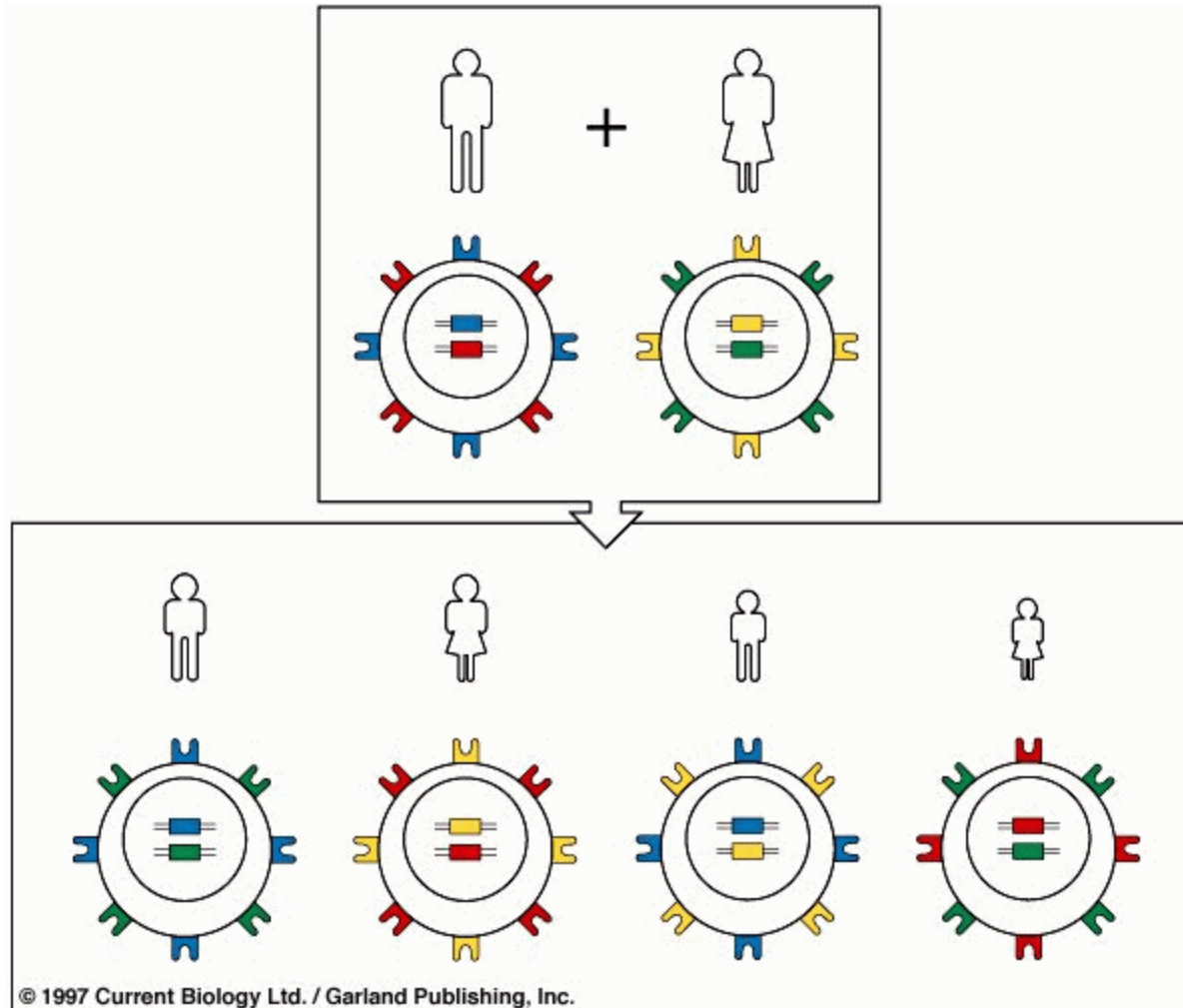


(c)



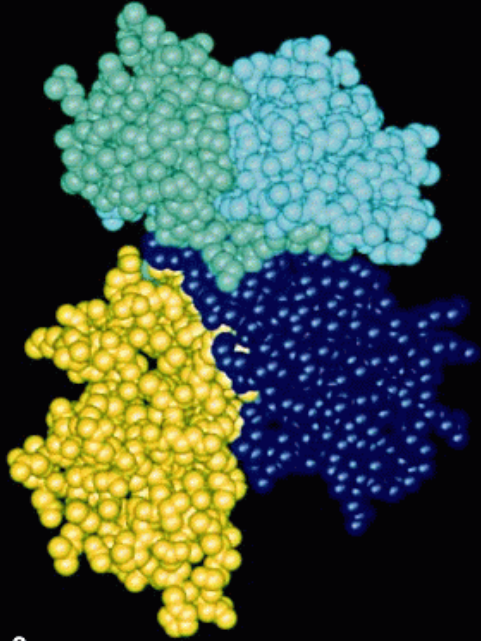
Vergani & Peakman: Basic & Clinical Immunology, 2nd Edition.
Copyright © 2009 by Churchill Livingstone, an imprint of Elsevier, Ltd. All rights reserved.

Co-dominant expression of HLA genes

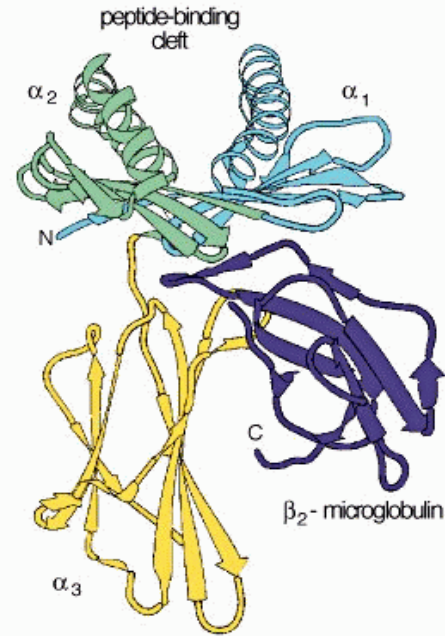


HLA-I antigens

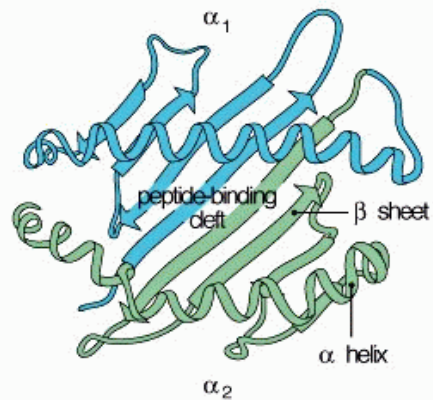
© 1997 Current Biology Ltd. / Garland Publishing, Inc.



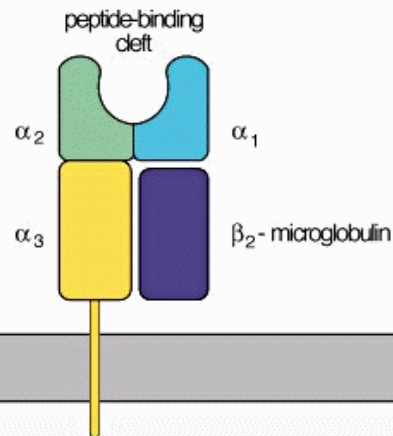
a



b

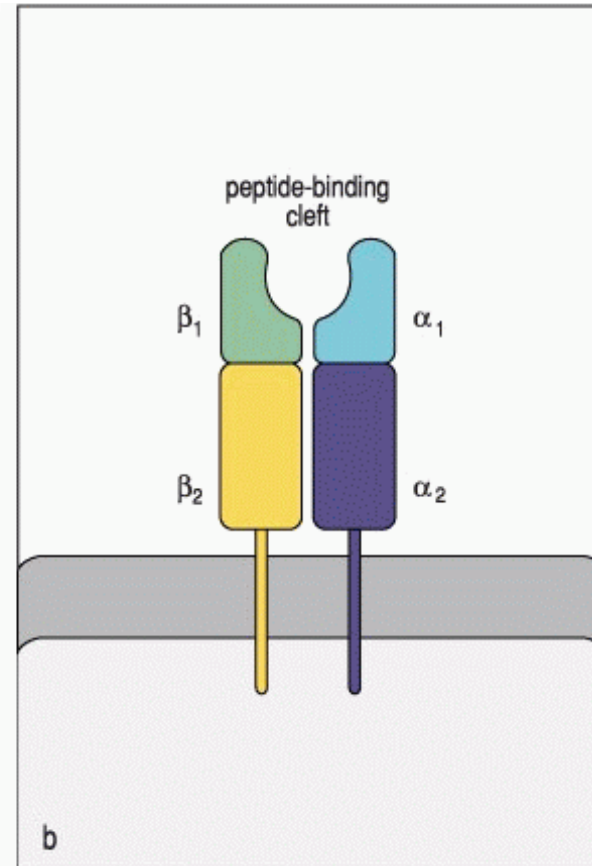
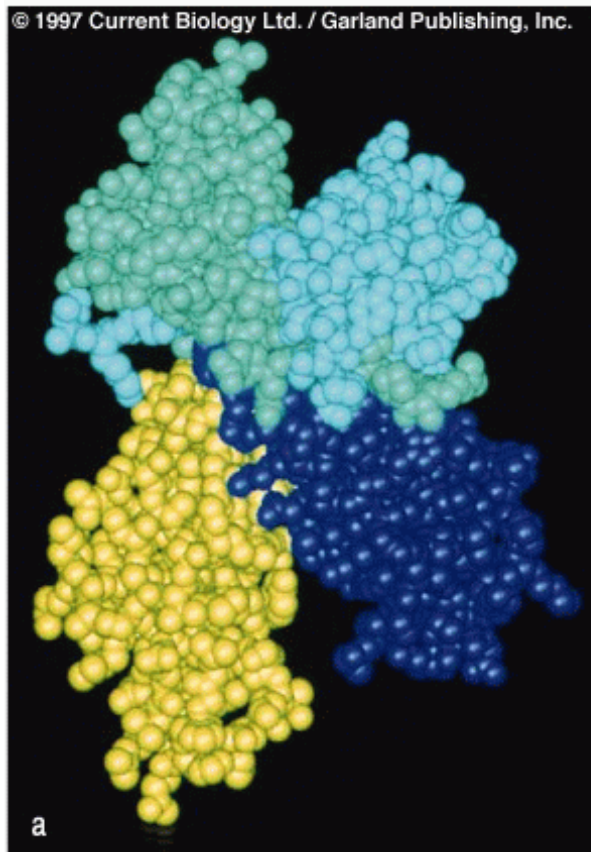


c

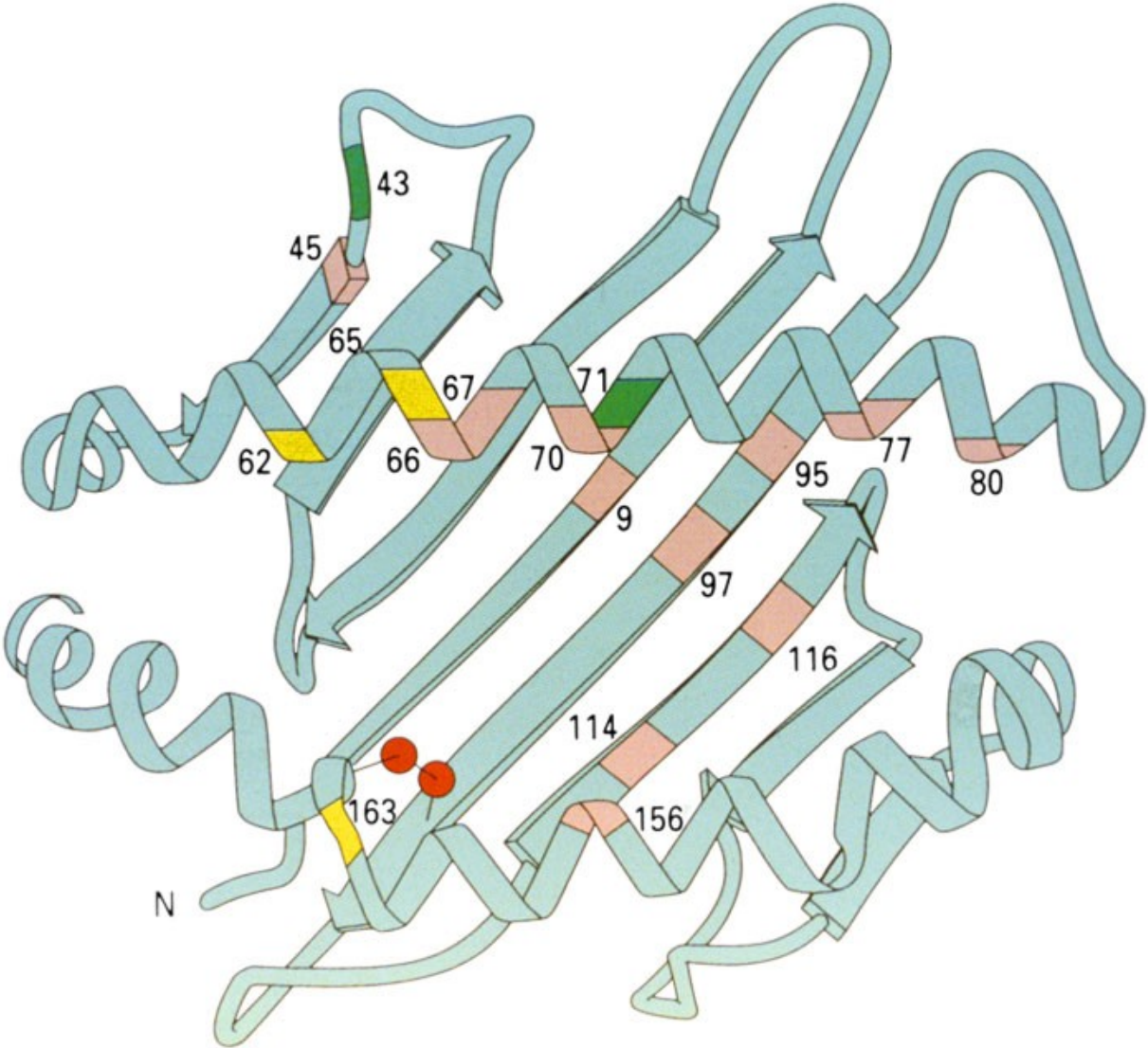


d

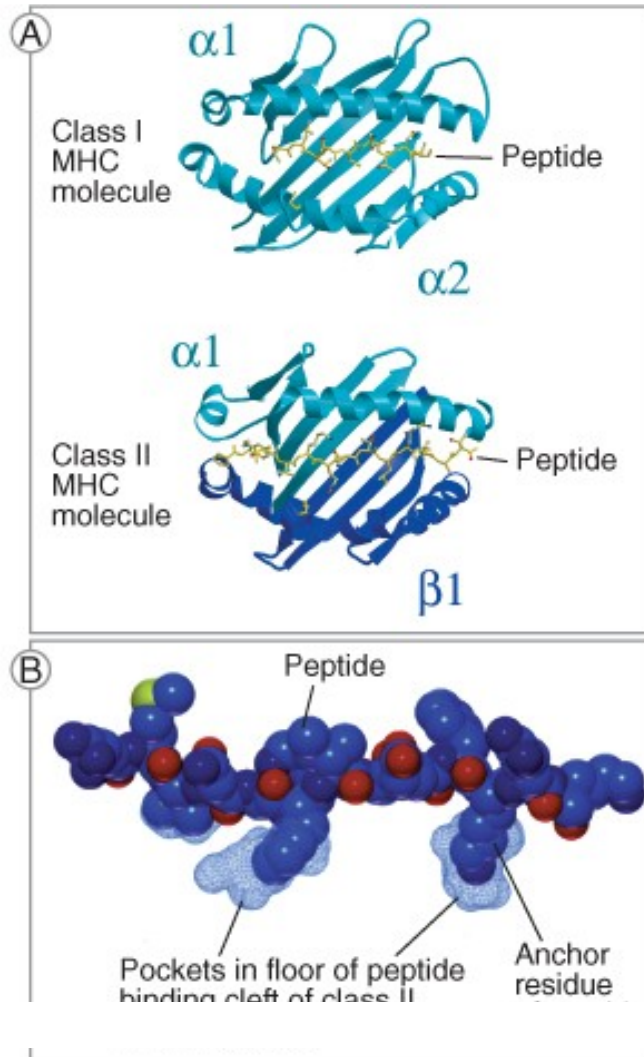
HLA-II antigens

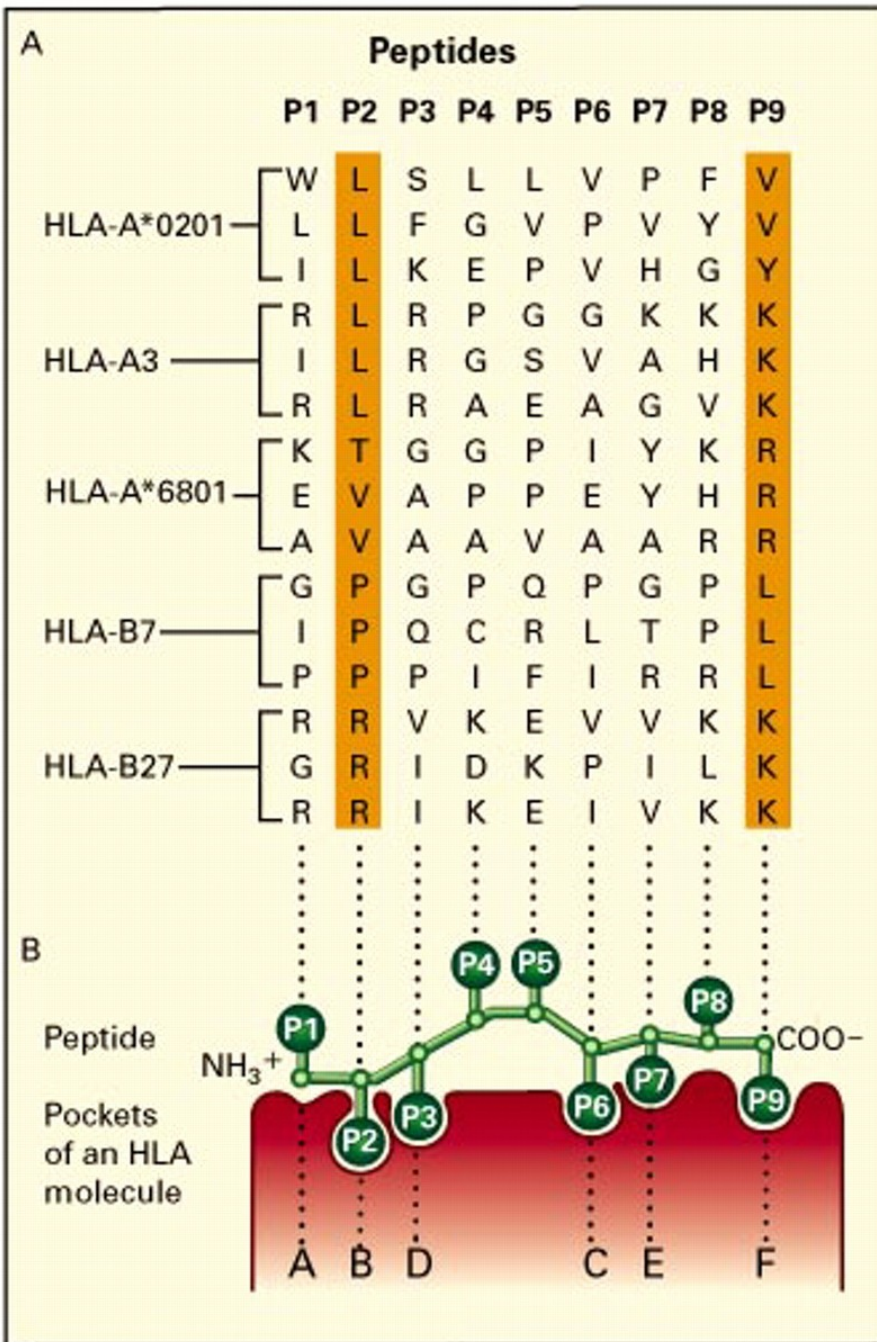


The top surface of HLA-A2



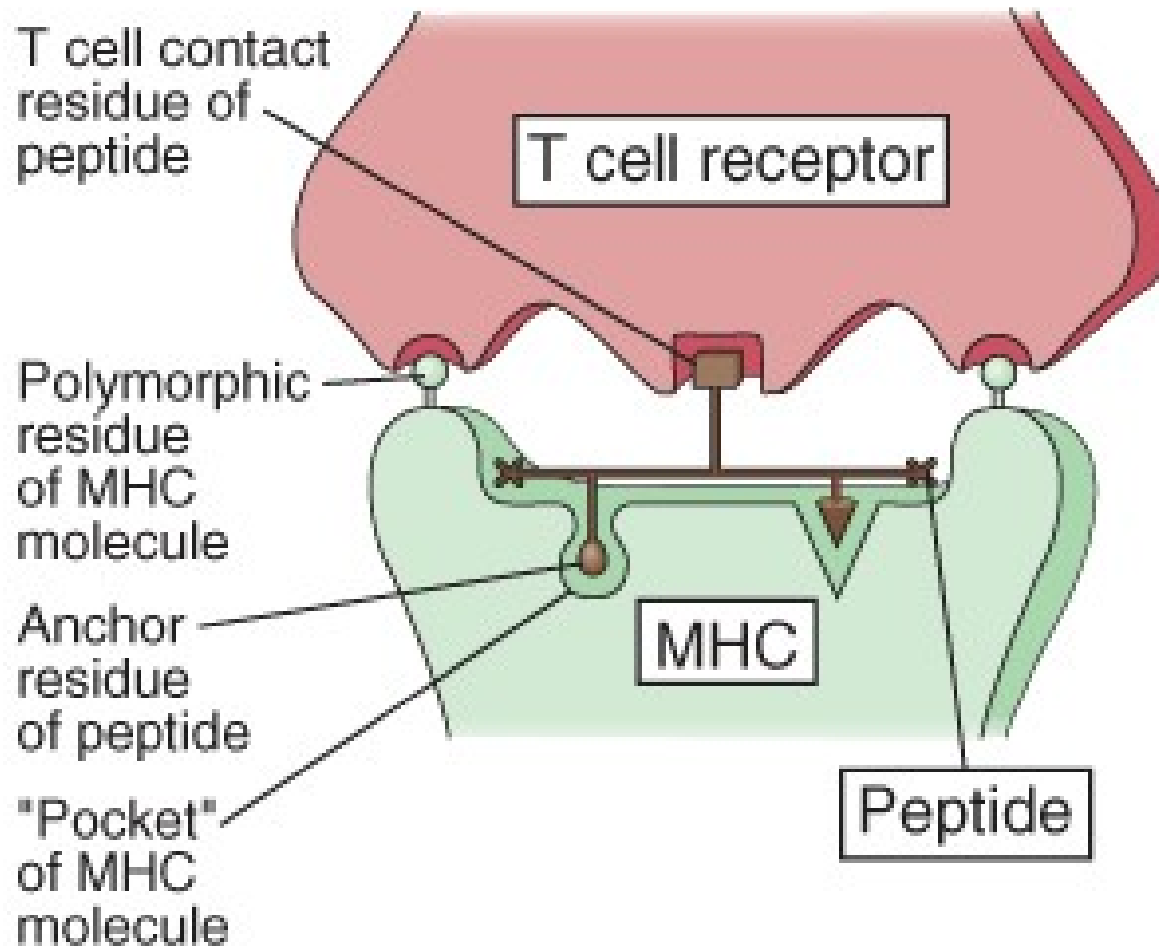
Binding of antigenic peptide to HLA molecule





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

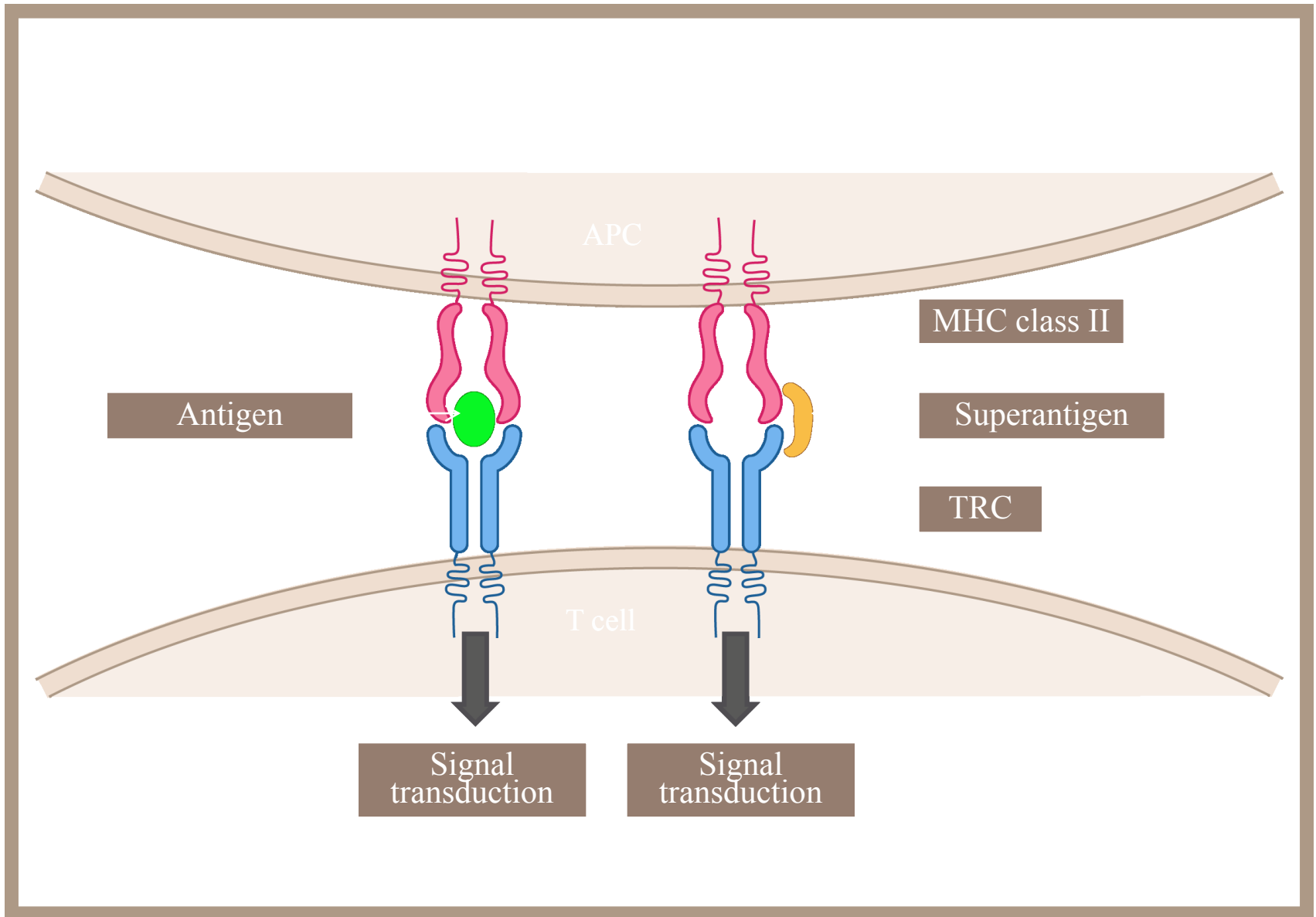
Interaction of TCR with HLA+antigen



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, erythrocytic toxin of Streptococcus

Activation of TCR by antigen and superantigen

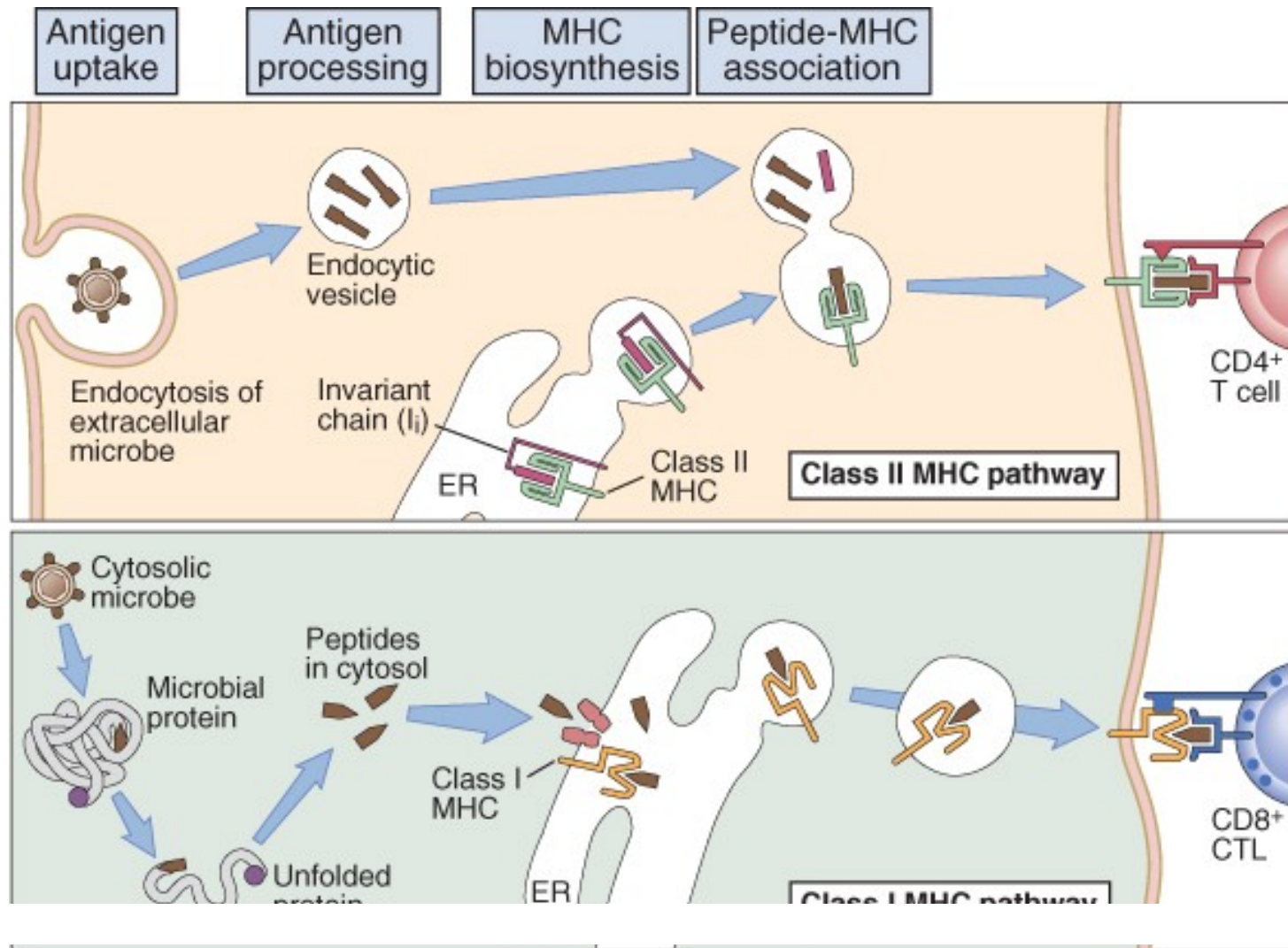


Initiation of the immune response, Role of HLA antigens

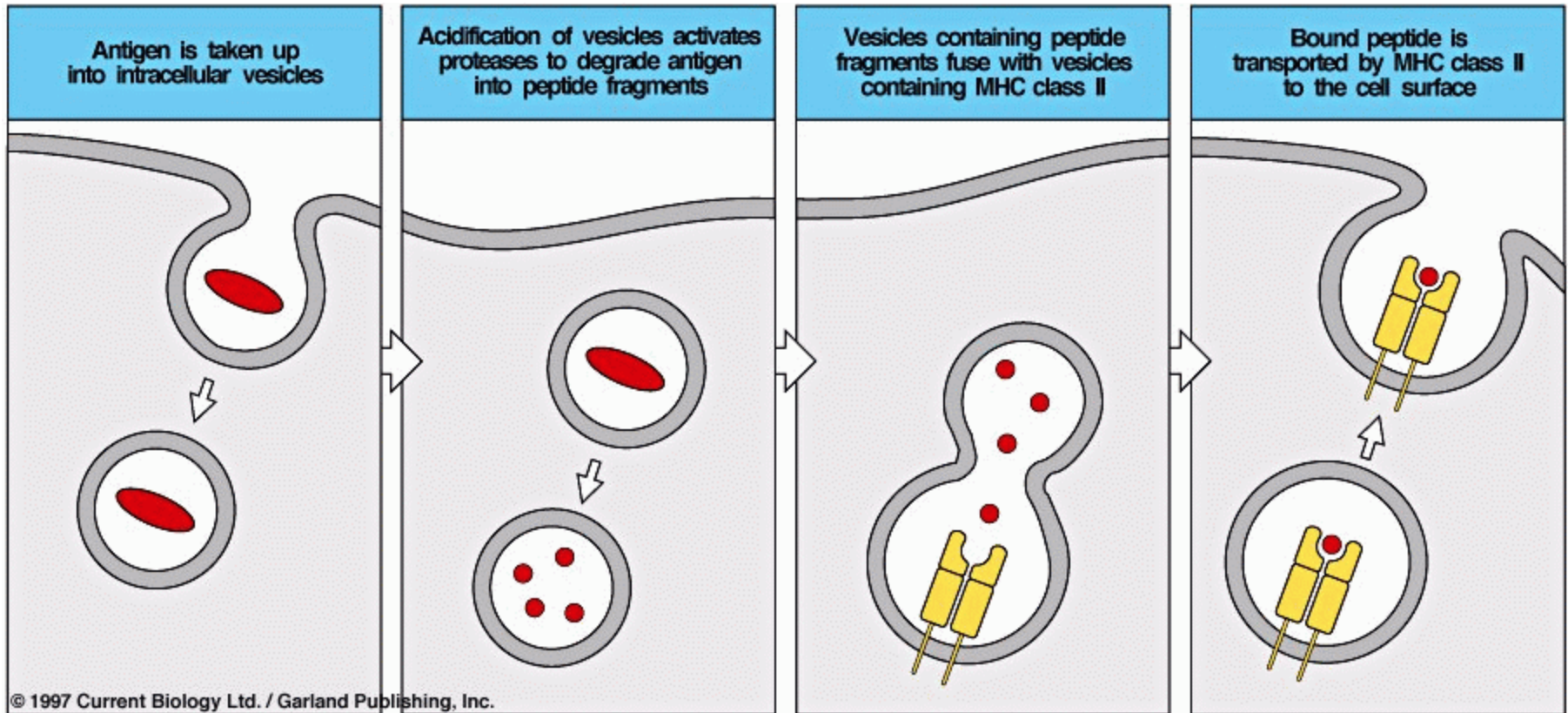
Two types of antigens as regards antibody production stimulation

- 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.

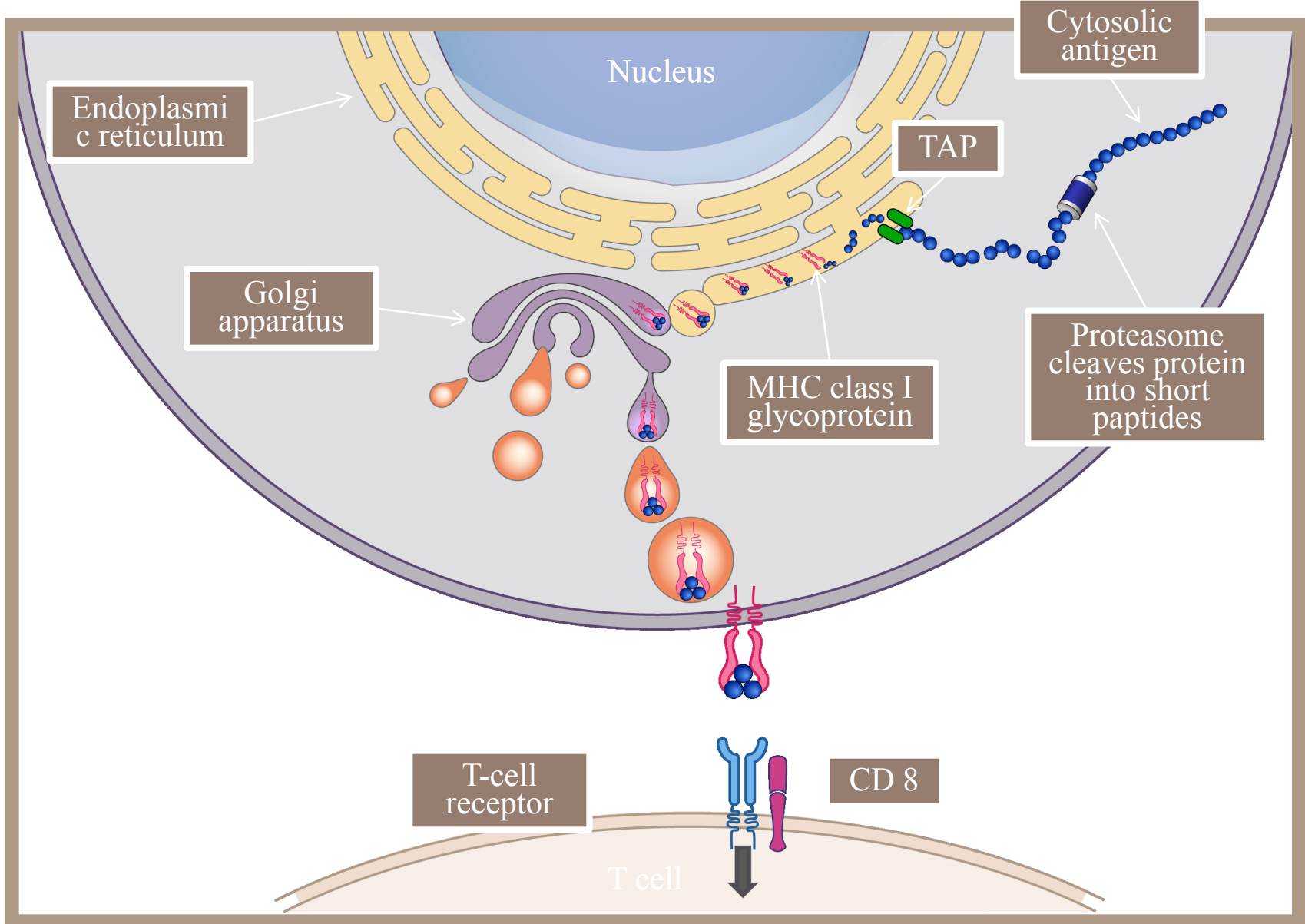
Role of HLA antigens in immune response



Degradation and presentation of antigens on HLA-II molecules



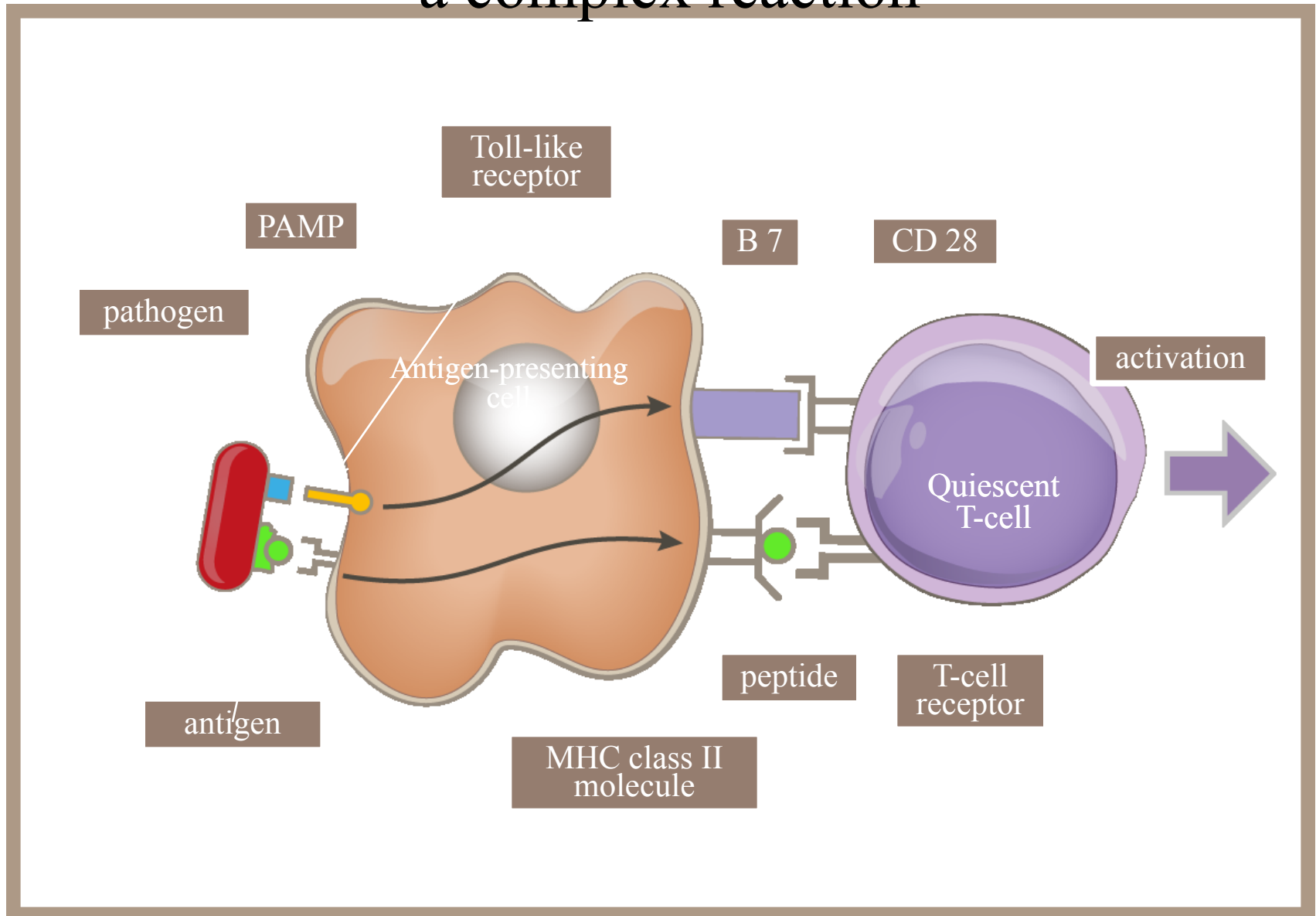
Presentation of endogenous antigens by HLA-I



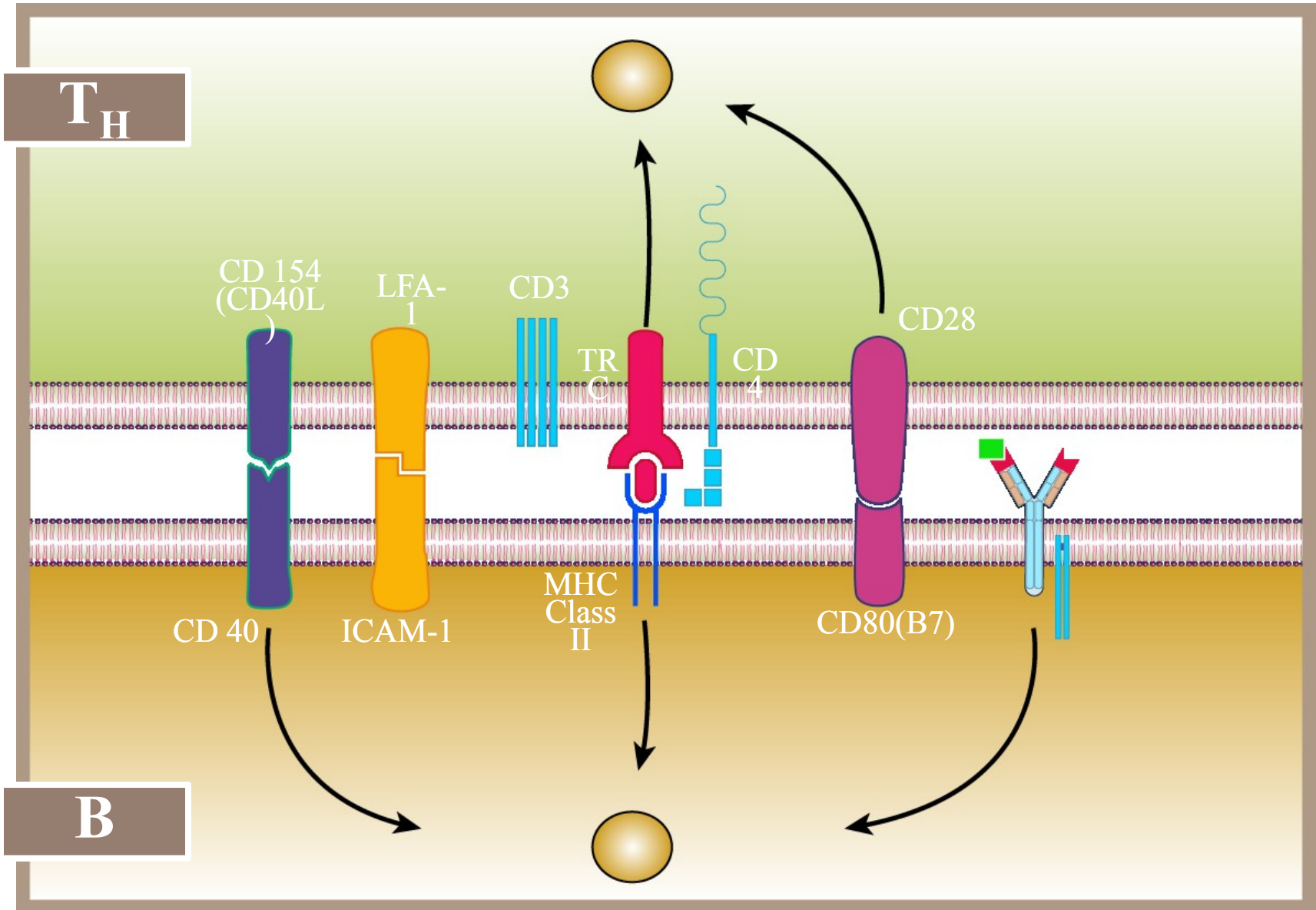
Role of HLA antigens in immune response

- 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).

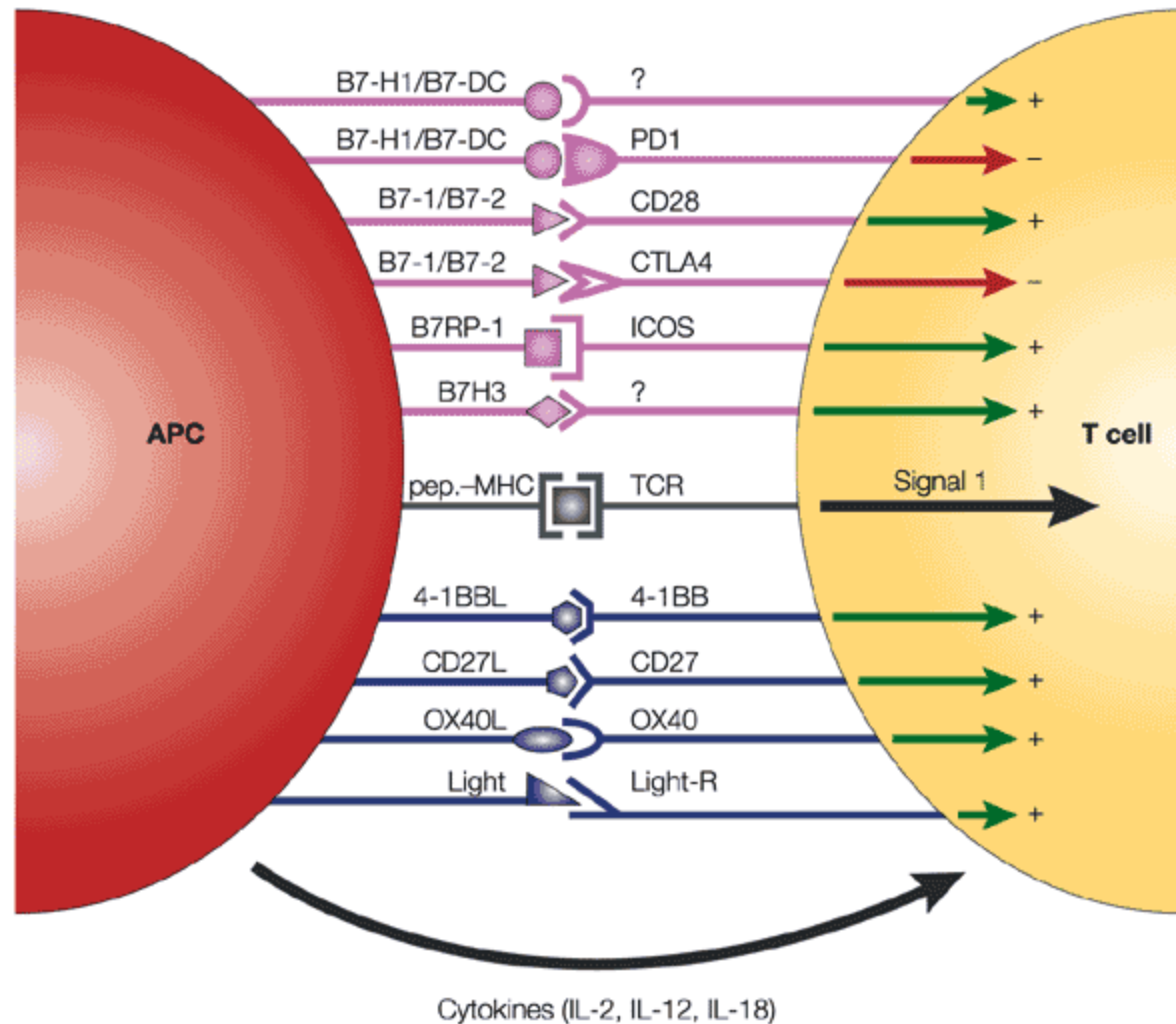
T-cell stimulation by antigen is a complex reaction



Costimulatory molecules in T-cell activation

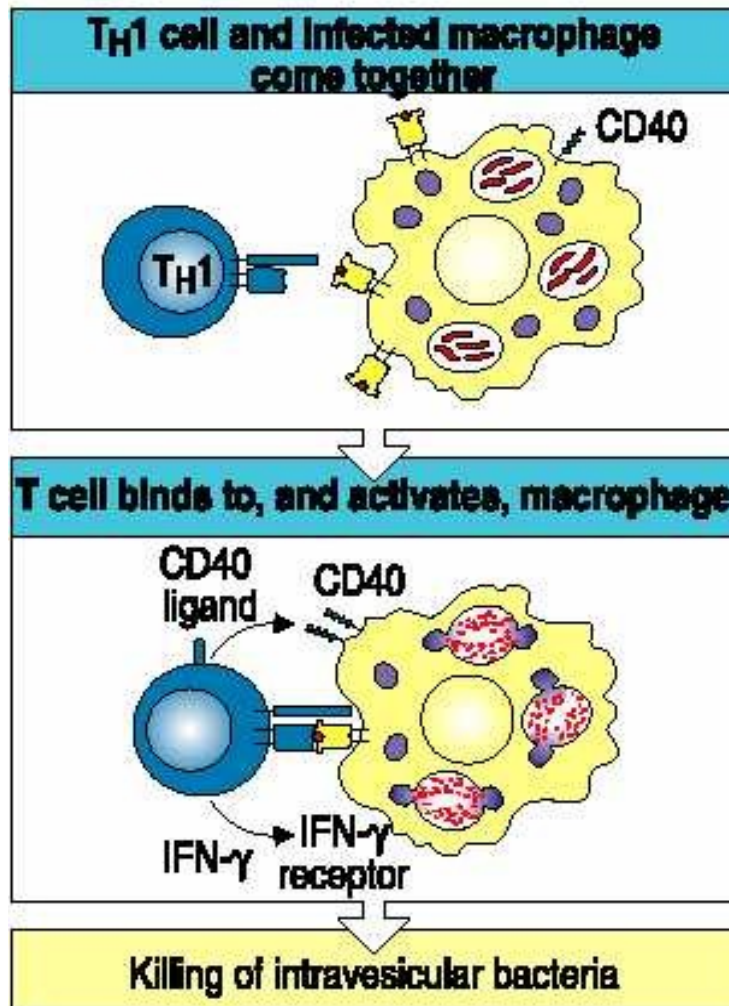


Costimulatory signals in T-cell activation



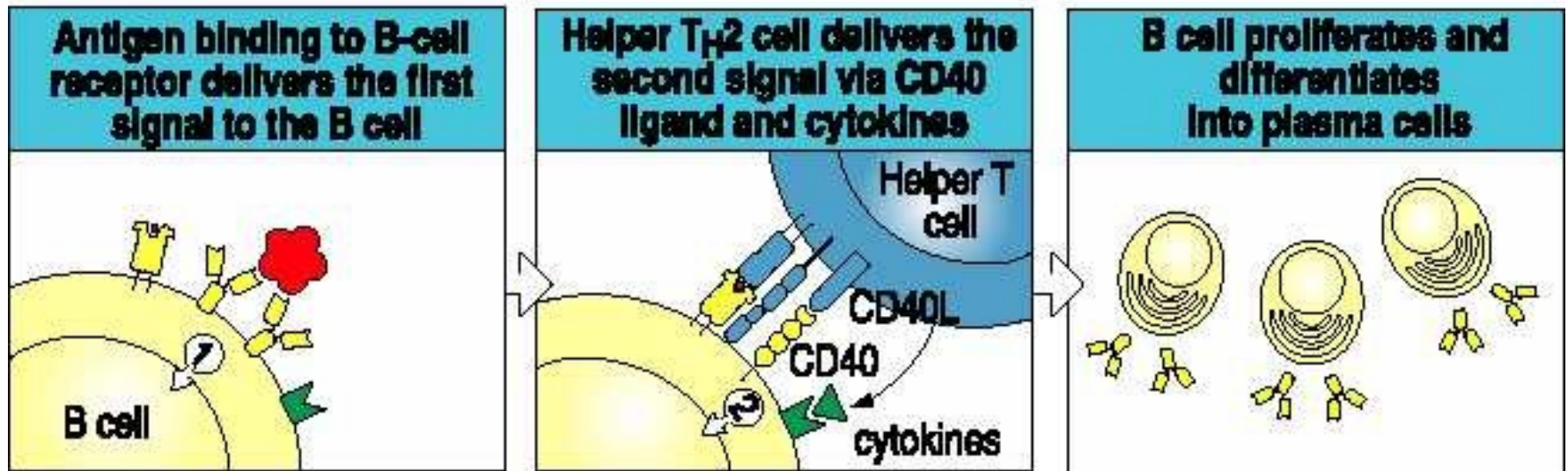
Function of Th1 cells

Figure 8.27



Initiation of antibody response in T-cell dependent antigens

Figure 7.8



Activation of immune system by antigen

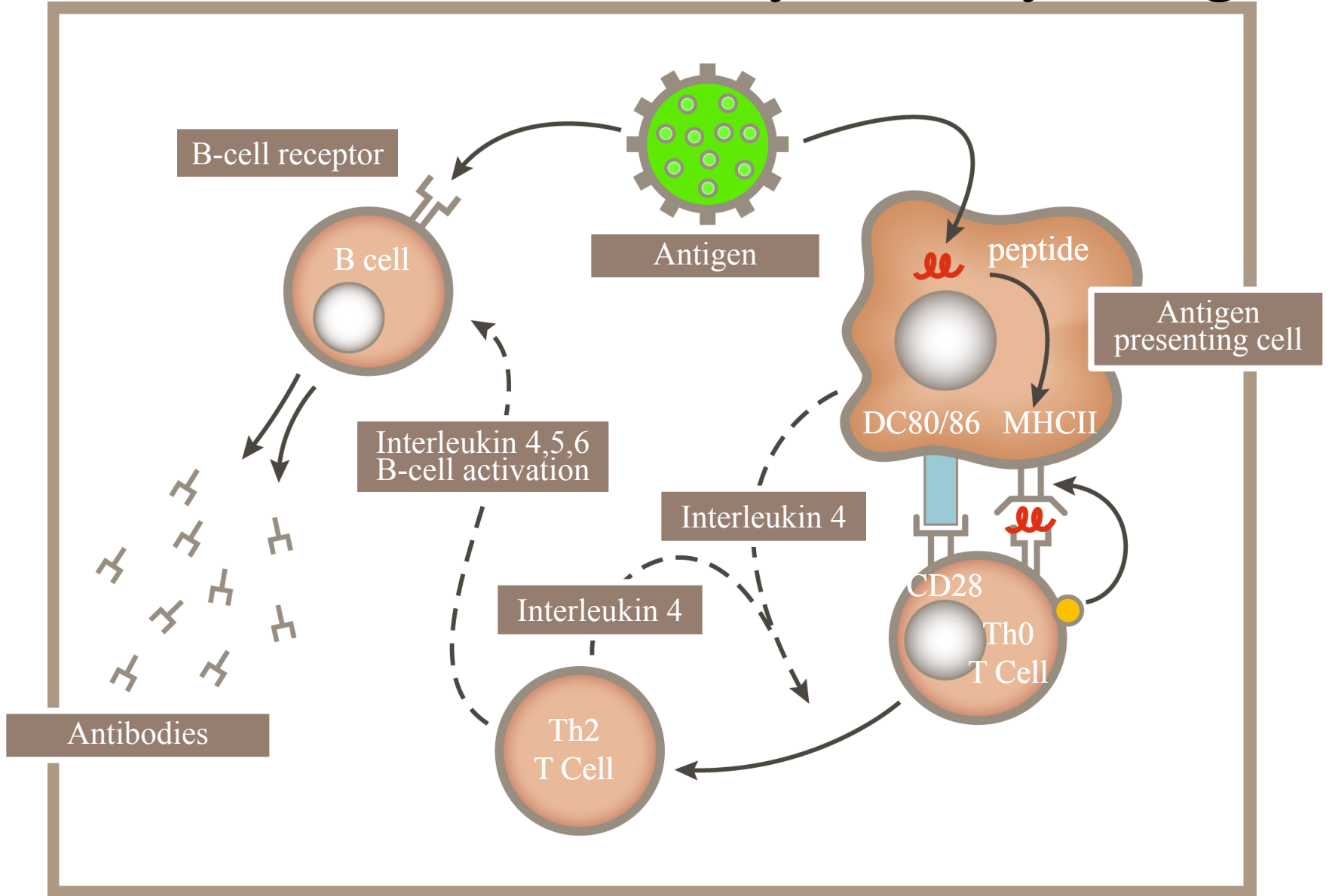
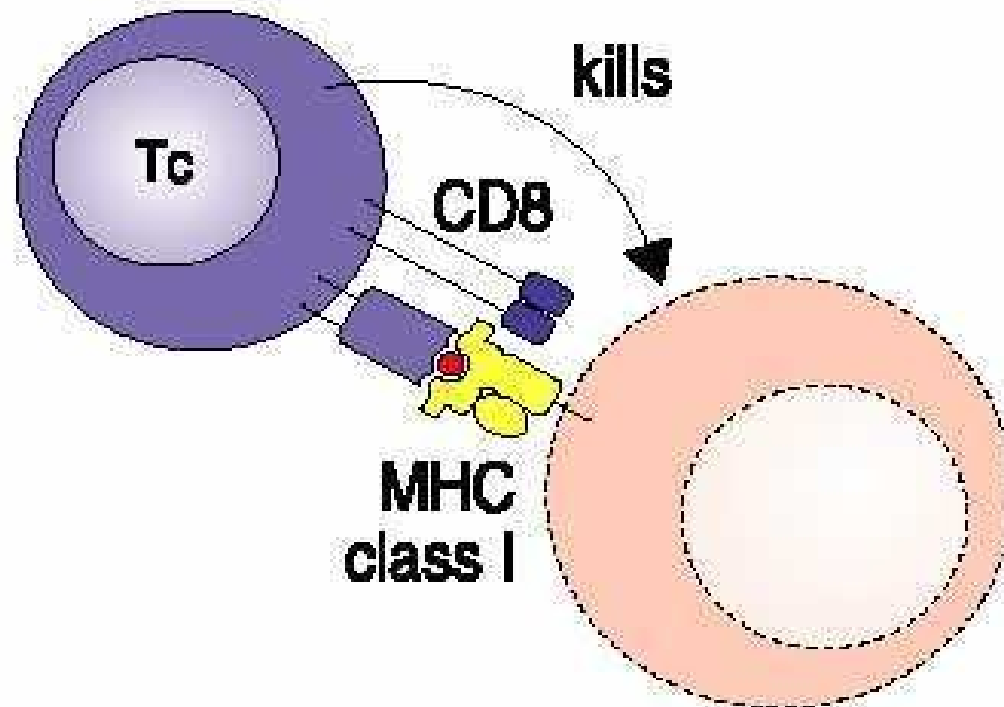
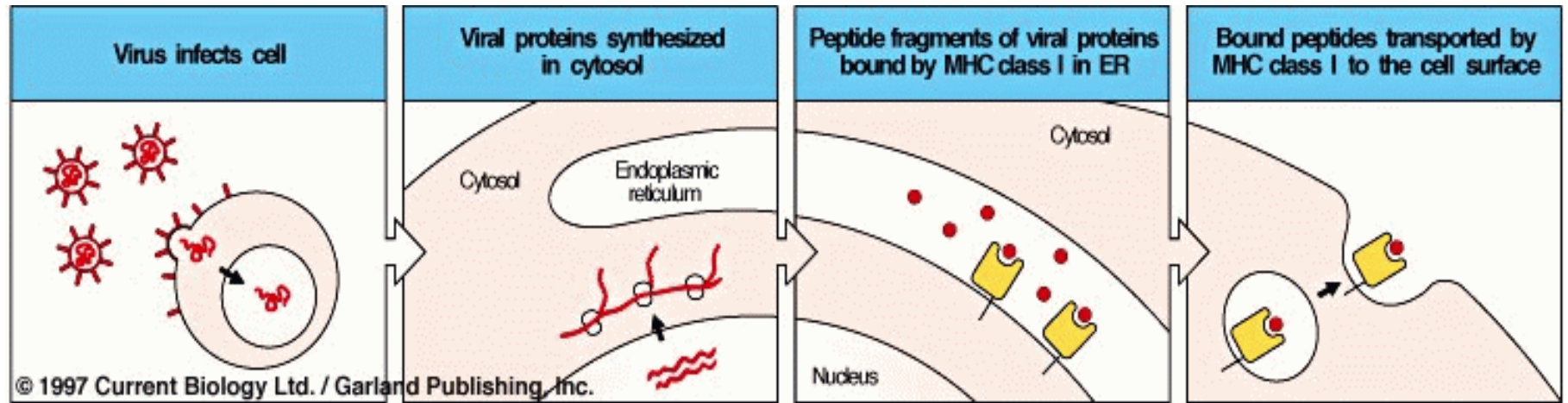


Figure 1.24

Cytotoxic T cell recognizes complex of viral peptide with MHC class I and kills infected cell



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*
Rheumatoid arthritis	DR4	6
Insulin-dependent diabetes	DR3	5
	DR4	6-7
	DR3/DR4	20
	DR3, DQw8/DQw2	30
Chronic active hepatitis	DR3	14
Coeliacia	DR3	12
Ankylosing 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 joints 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!

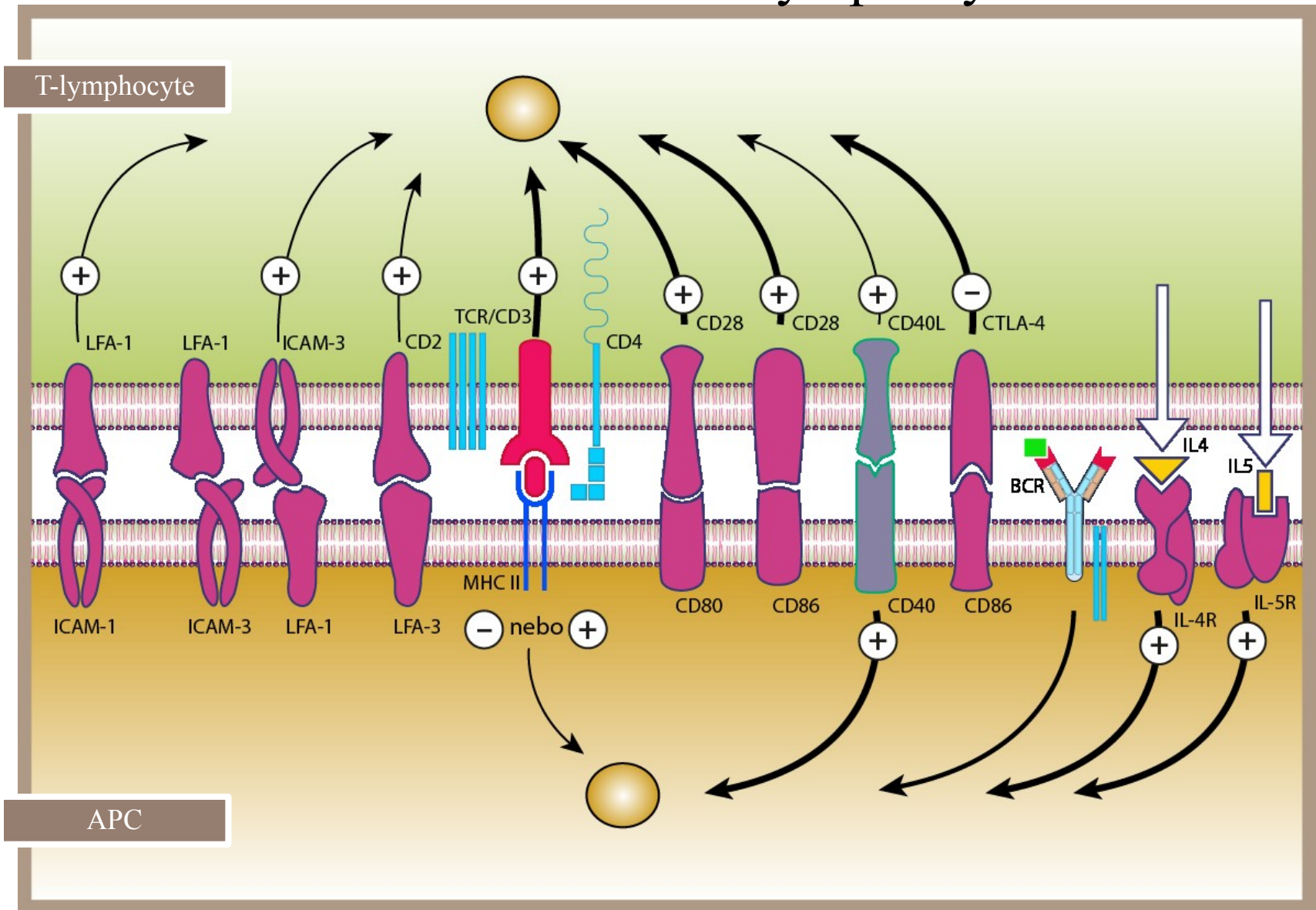
Regulation of the immune response

- Interactions of the components of the immune system
- Characteristics 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)

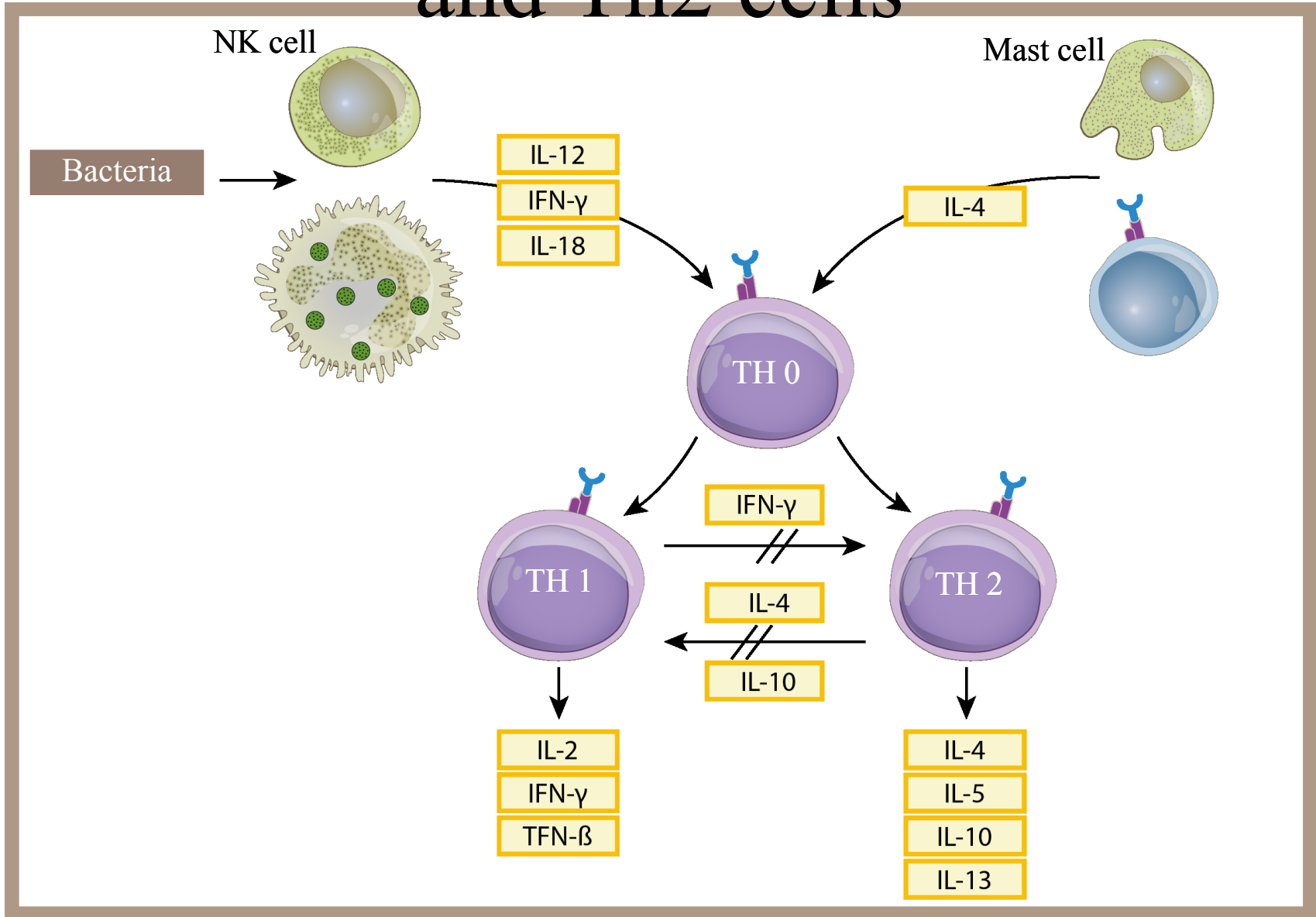
Costimulatory molecules involved in the interaction between APC and T-lymphocyte



Regulation by T-lymphocytes

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

Development and function of Th1 and Th2 cells



Cytokines

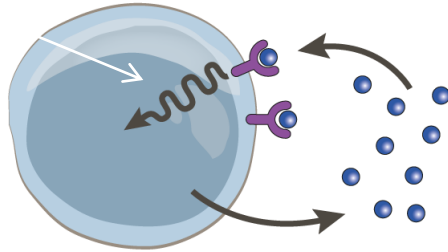
- Mediators, „tissue hormones“, main regulators of the cells of the immune system.
- Produced mainly by the cells of the immune system, also the cells of the immune system predominate as the target cells.
- The effect on the target cell is based on the interaction with specific receptors.
- Usually short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

Cytokines

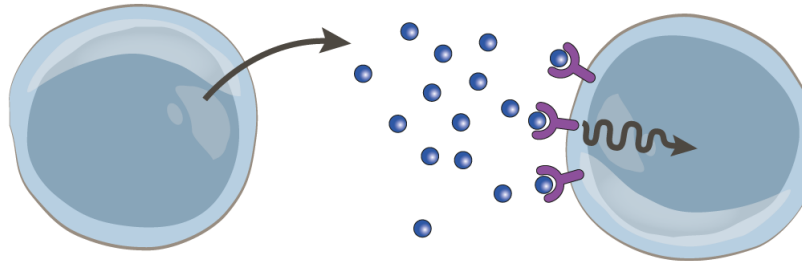
- Usually produced by a broad range of cells, but some cells are usually „main producers“ of the concrete cytokine..
- Pleiotropic effect.
- Cytokine network is formed.
- A concrete cytokine may have both stimulatory and inhibitory effect, depending on the the interaction with other cytokines, concentration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

Effect of cytokines on cells

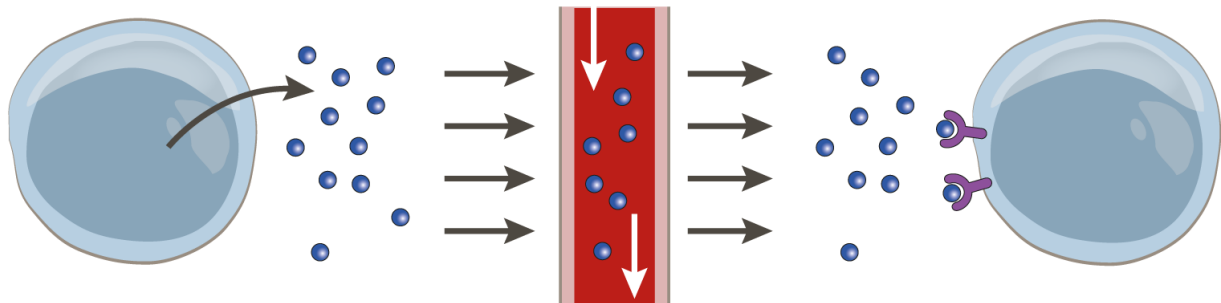
Autokrine



Parakrine



Endokrine



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-CSF
- 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.

Cytokines in pathogenesis of diseases

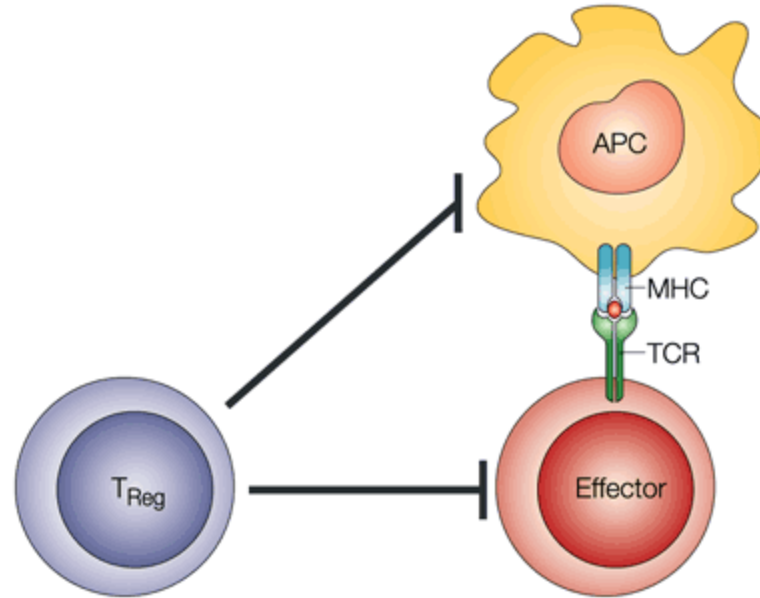
- Atopic diseases: IL-4 stimulates IgE production, IL-5 stimulates eosinophils production.
- Inflammatory diseases (rheumatic, Crohn's disease), systemic response in sepsis – various pro-inflammatory cytokines, TNF- α seems to be the most important.
- Immunodeficiency diseases may be caused by disturbed production of various cytokines (IFN γ , 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

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

TR-1 lymphocytes

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

Interaction idiotype-antiidiotype

