

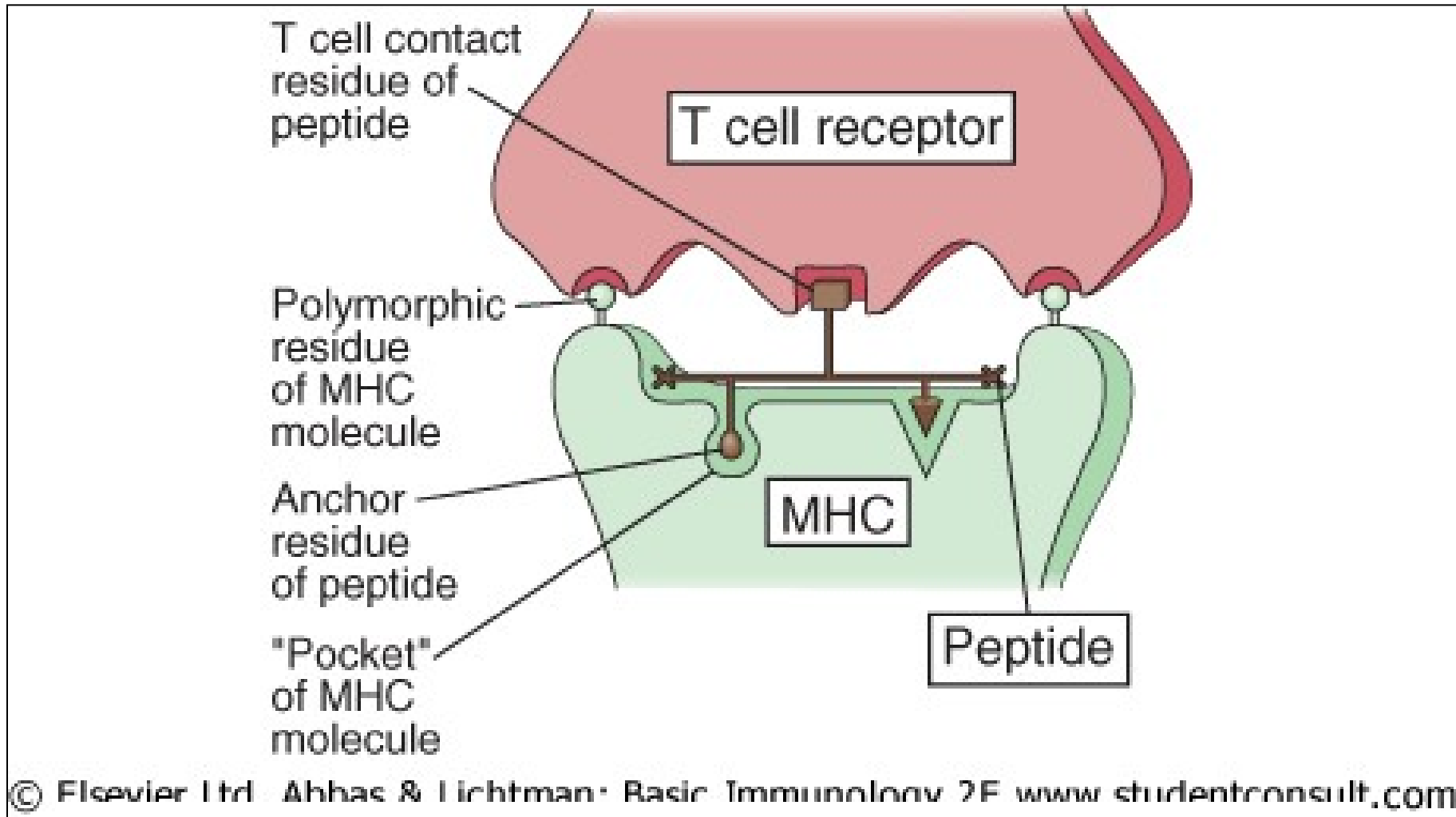
# **T-Lymphocytes**

**Function, Development, Subpopulations**

# Activation of T-lymphocytes

- T-lymphocytes can be stimulated only by complexes of antigen-HLA antigen.
- The HLA antigen must be the same as HLA antigens of the person from whom the lymphocytes originate= phenomenon of HLA restriction.

# Interaction TCR-polypeptide-HLA molecule



# Thymic education

- Positive selection: survival of cells reacting with low affinity with HLA antigens expressed on antigen-presenting cells in the thymus. Only those cells that recognize HLA antigen of the concrete person survive. The non-reacting cells die by neglect.
- Negative selection – those thymocytes that react with high affinity with complexes of HLA-autoantigens in thymus die by apoptosis.
- It is supposed that more than 90-95% of thymocytes die during these processes.

# Development of lymphocytes in the thymus

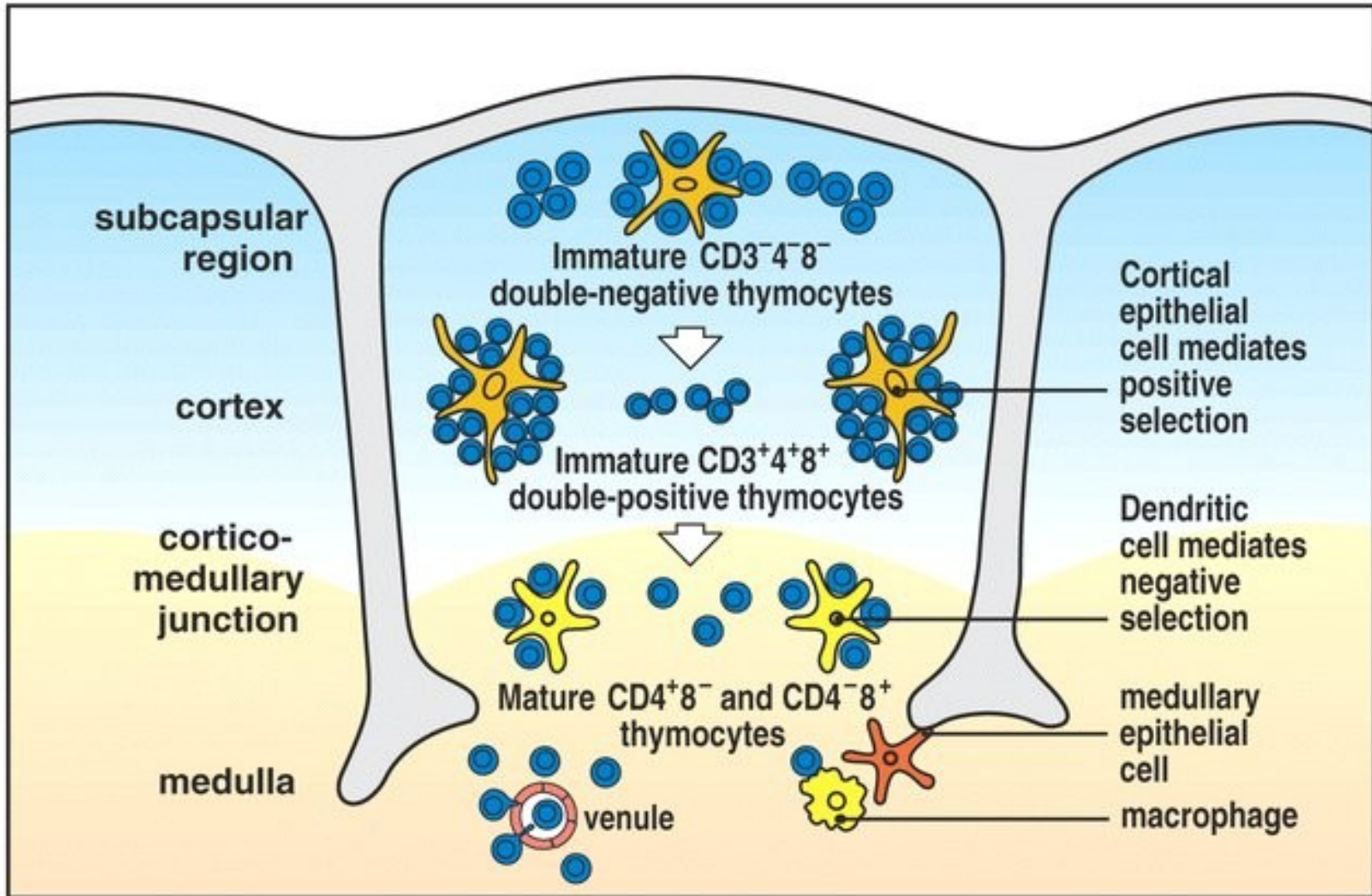
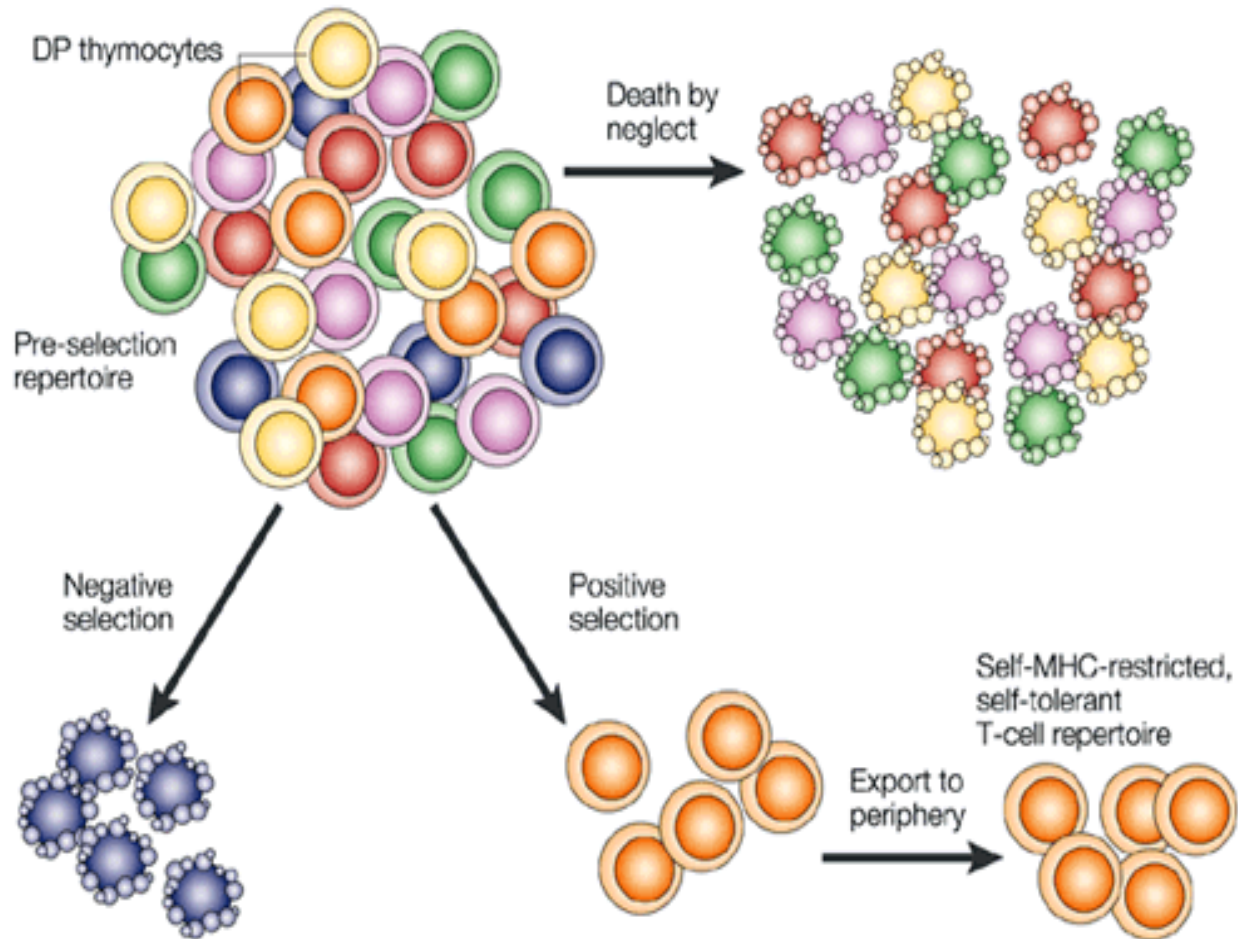
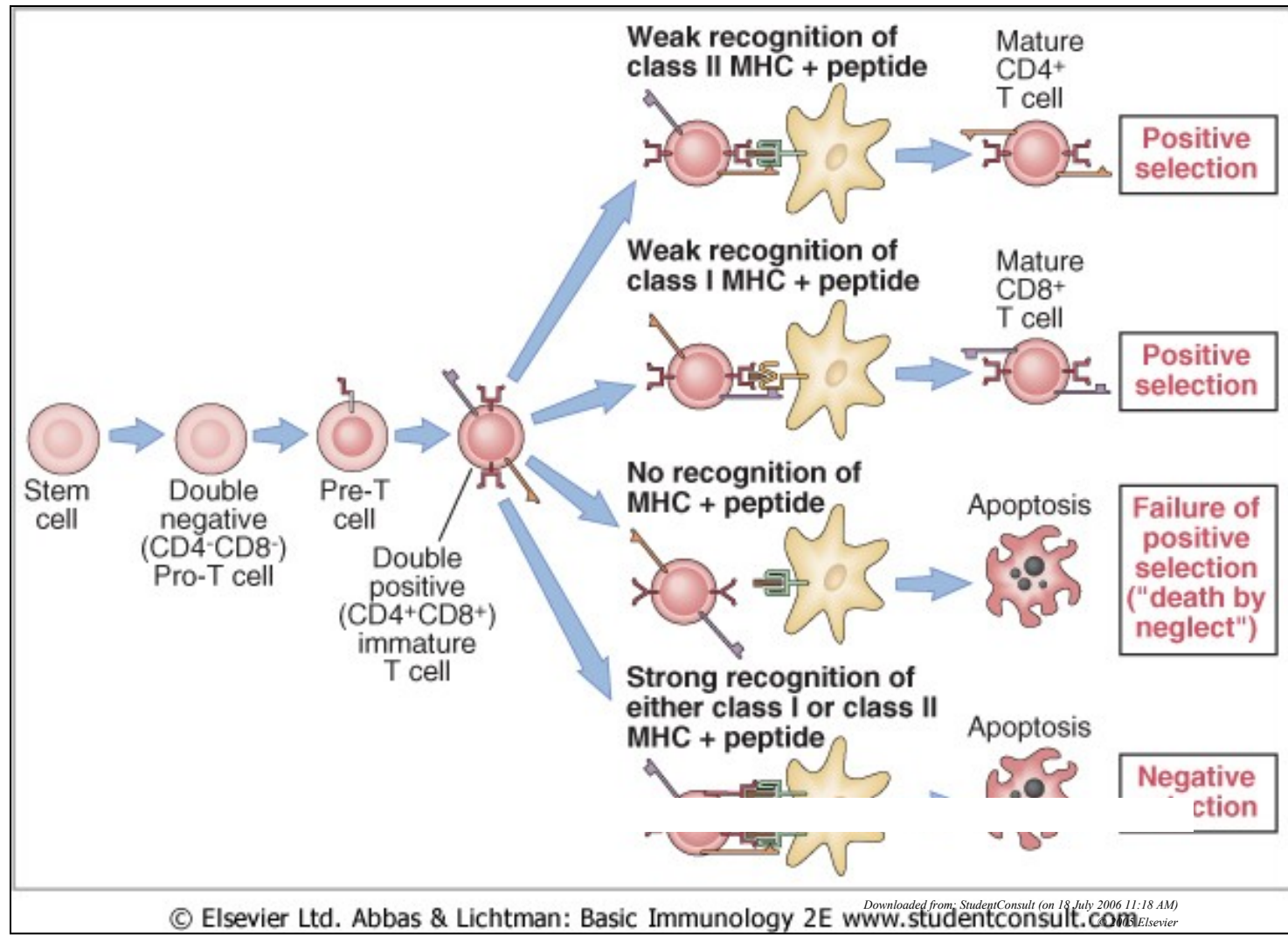


Figure 5-13 The Immune System, 2/e (© Garland Science 2005)

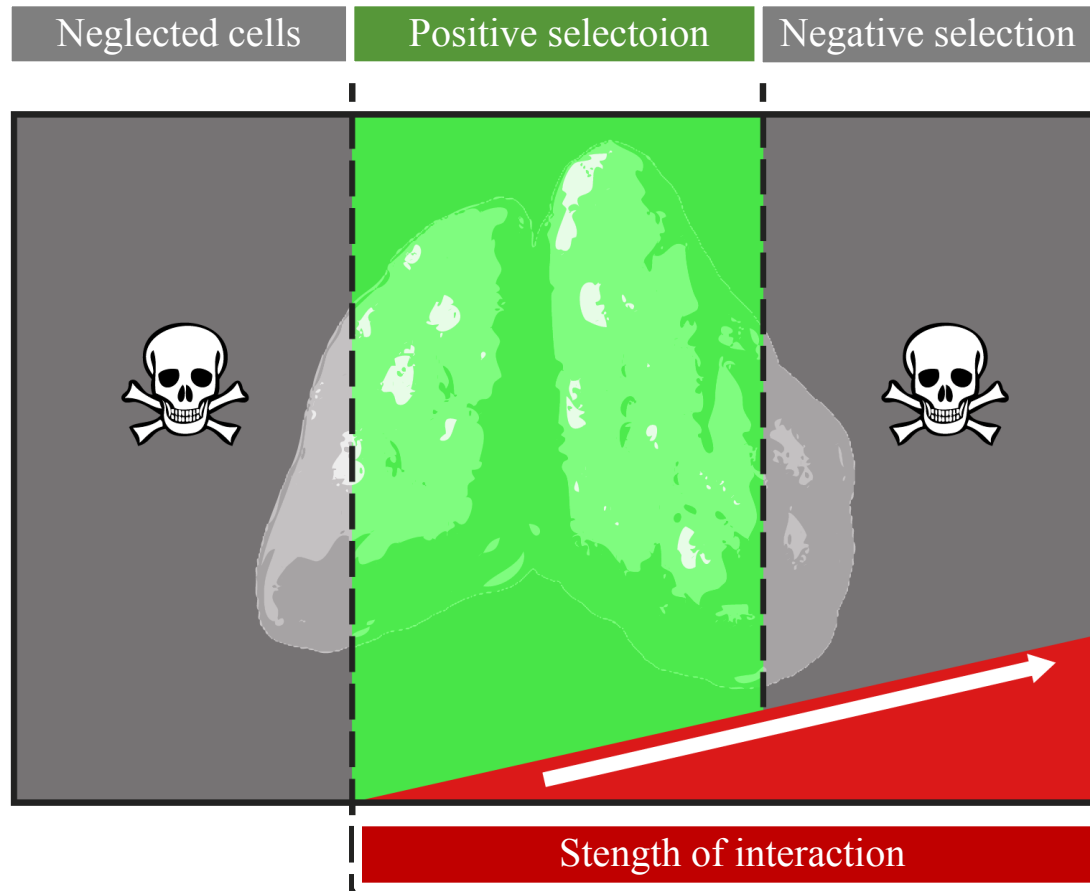
# The Fate of T-lymphocytes in the Thymus



# Thymic education of lymphocytes



# Strength of interaction between TCR and HLA-(antigen) complexes determines the fate of thymocytes



Cell death

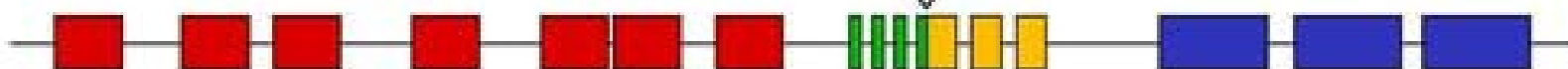


**Figure 5: V(D)J Recombination**

Germline configuration



D to J recombination



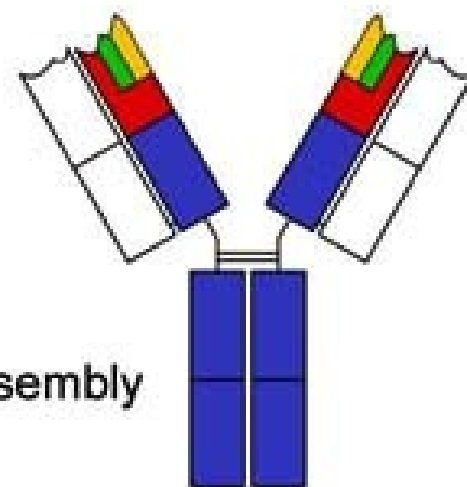
V to DJ recombination



transcription, splicing



translation, assembly



(adapted from Janeway 2001)

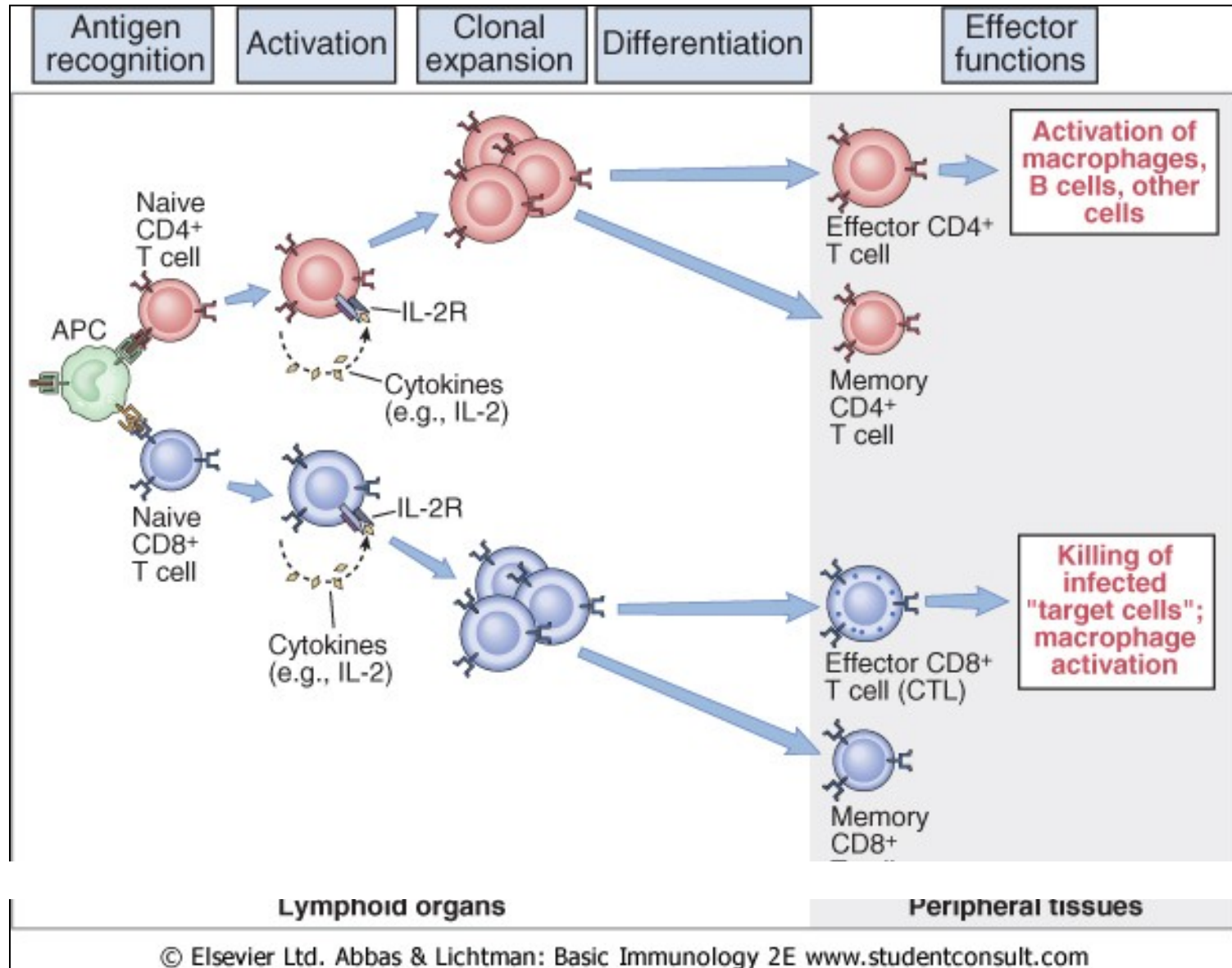
## V, D and J genes involved in T- and B- cell receptor formation

	Immunoglobulin		T cell receptor	
	Heavy chain	κ	α	β
Number of V gene segments	45	35	45	50
Number of diversity (D) gene segments	23	0	0	2
Number of joining (J) gene segments	6	5	~50	12

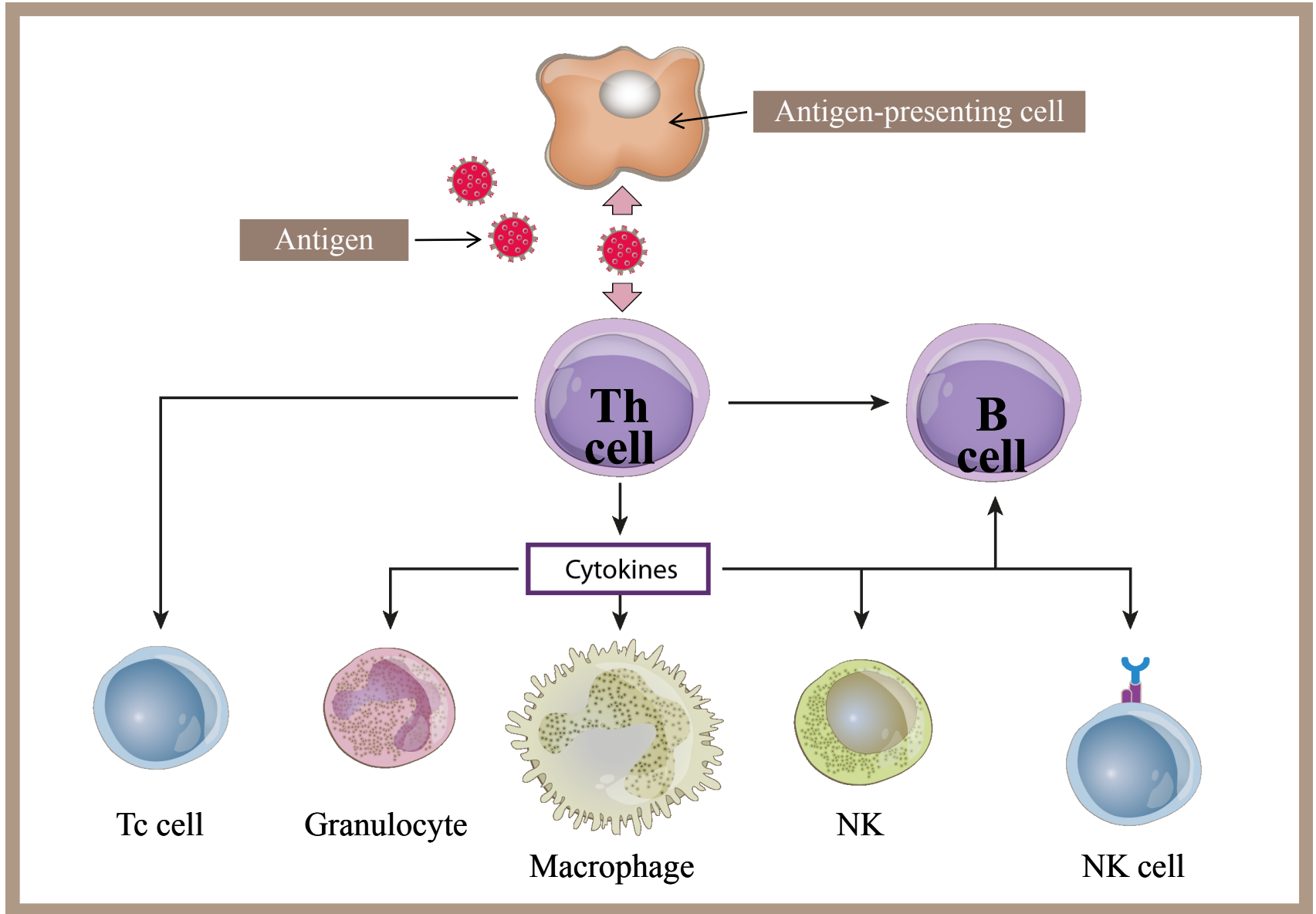
  

Mechanism	
Combinatorial diversity:	
Number of possible V-(D)-J combinations	Ig: $\sim 10^6$ TCR: $\sim 3 \times 10^6$
Junctional diversity:	
Total potential	
junctional diversity	

# Activation and differentiation of T-lymphocytes



# Central role of T-lymphocytes in specific immune response



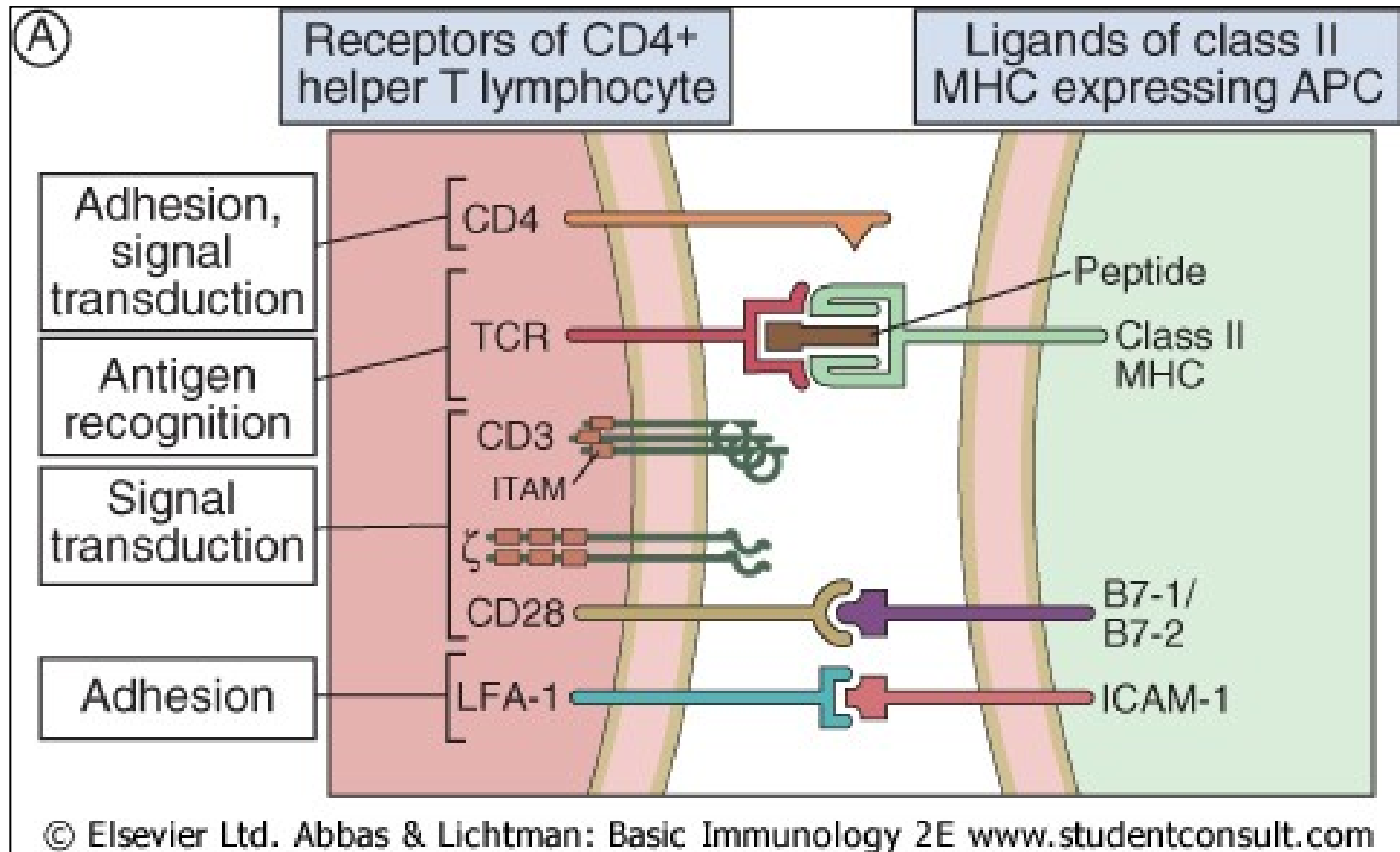
# Determination of lymphocytes using cell surface antigens

- CD (Cluster of Determination) antigens – antigens expressed on surface of leukocytes.
- More than 400 such markers has been determined.
- CD3<sup>+</sup> – all T-lymphocytes.
- CD3<sup>+</sup>CD4<sup>+</sup> – helper and majority of regulatory T-cells.
- CD3<sup>+</sup>CD8<sup>+</sup> – predominantly cytotoxic T-cells.
- Classical CD antigens cannot be used do determine Th1, Th2, Th 17 lymphocyte subsets – cytokine production must be used (usually intracytoplasmatic determination of cytokines).
- CD19<sup>+</sup> - B-lymphocytes.
- CD16<sup>+</sup>/CD56<sup>+</sup>(CD3<sup>-</sup>) - NK cells.
- Flow cytometry is used for CD markers determination.

# Surface structures on T-lymphocytes

- T-cell receptor (TCR):
  - Variable chains  $\alpha/\beta$  or  $\gamma/\delta$
  - Includes CD3 molecule – this part is responsible for signal transduction.
- Co-receptors CD4 and CD8 - binding to HLA I or HLA II molecules
- For T-cells activation co-stimulatory molecules are essential( the most important is CD28) – also signal transduction
- Adhesion molecules (e.g. LFA-1) – enables physical contact between T-cells and antigen presenting cells.

# Surface structures of T-lymphocytes



# Subpopulations of T-lymphocytes

- Cytotoxic T-lymphocytes (CD8<sup>+</sup>): kill target cells. Activated by complex HLA-I –antigenic peptide.
- Helper T-lymphocytes (CD4<sup>+</sup>): enable activation of macrophages (Th1) or B-cells (Th2) cells. They are activated by complexes HLA-II- antigenic peptide.
- Regulatory T-cells (CD4<sup>+</sup>): important in the maintenance of immune tolerance.



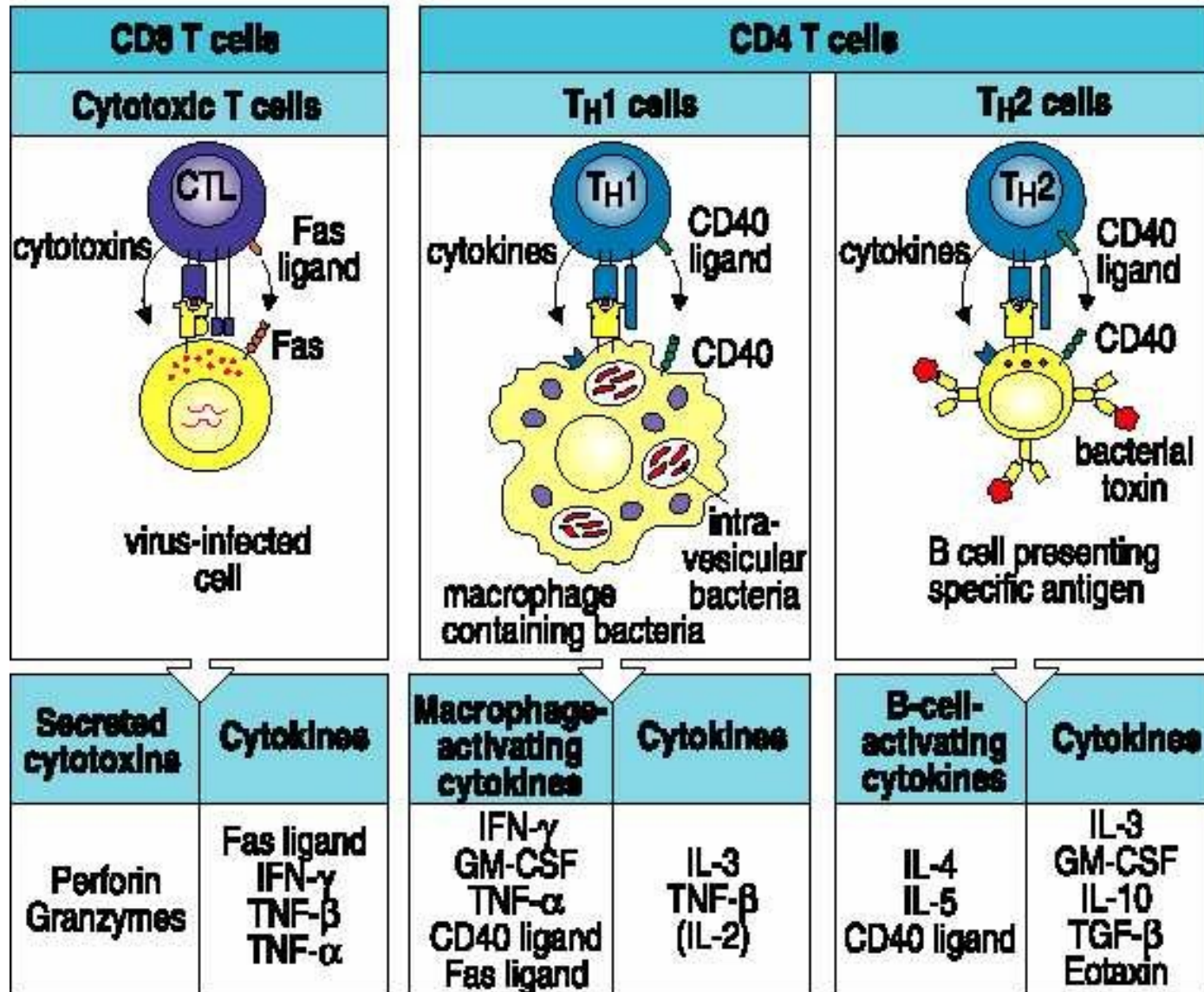
# Subpopulations of Th-lymphocytes

- $T_h1$  lymphocytes
  - Produce IFN- $\gamma$ , IL-2, IL-3,
  - Stimulation of macrophages, pro inflammatory effect
  - Probably pathogenic in multiple sclerosis...
- $T_h2$  lymphocytes
  - Produce IL-3, IL-4, IL-5, IL-6, IL-10, IL-13
  - Stimulation of antibody production, including IgE
  - Included in pathogenesis of allergic diseases
- $T_h17$  lymphocytes
  - Produce IL-17
  - Important in chronic inflammation

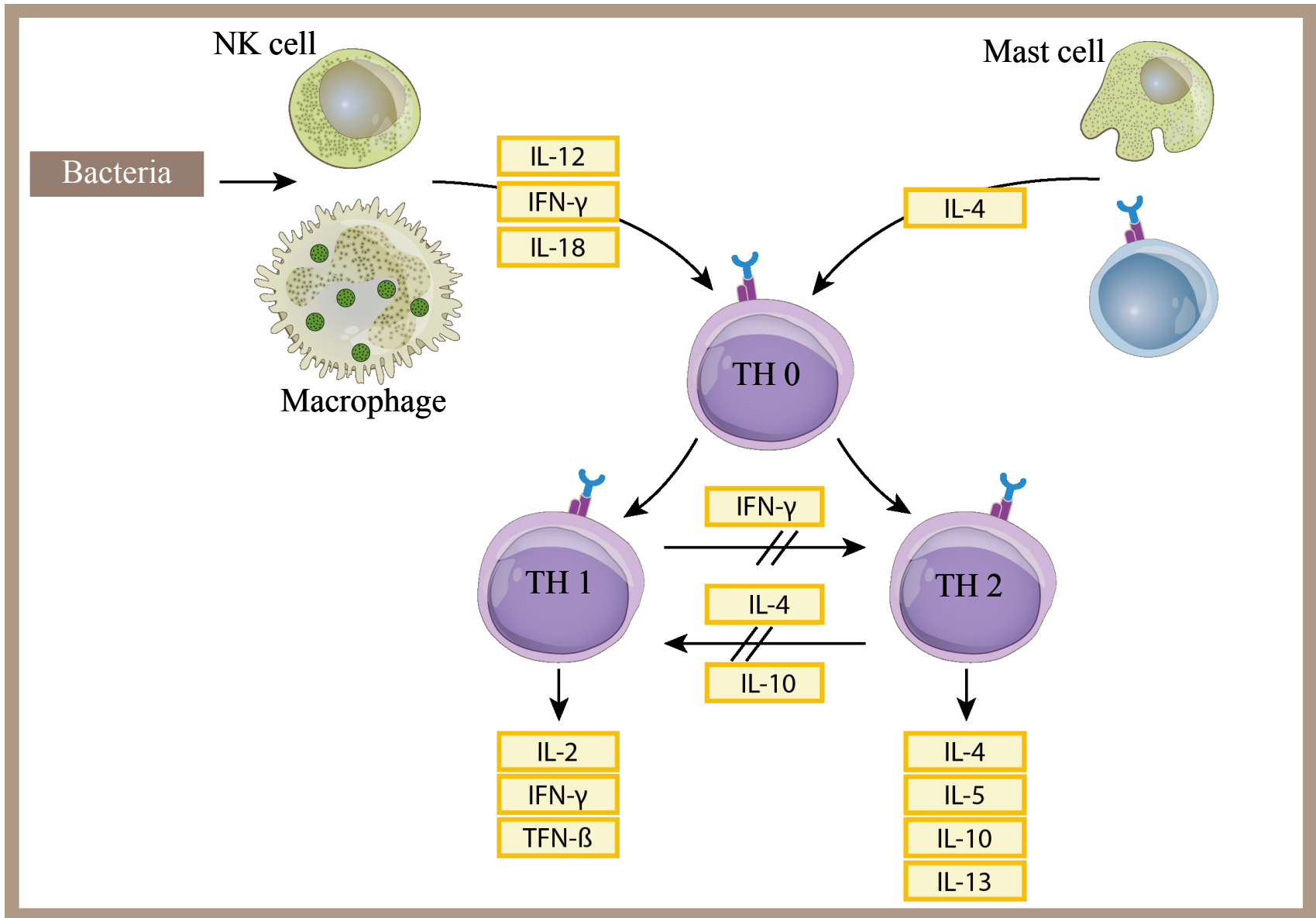
Also  $T_h9$ ,  $T_h22$  lymphocytes

# Functions of T-lymphocytes

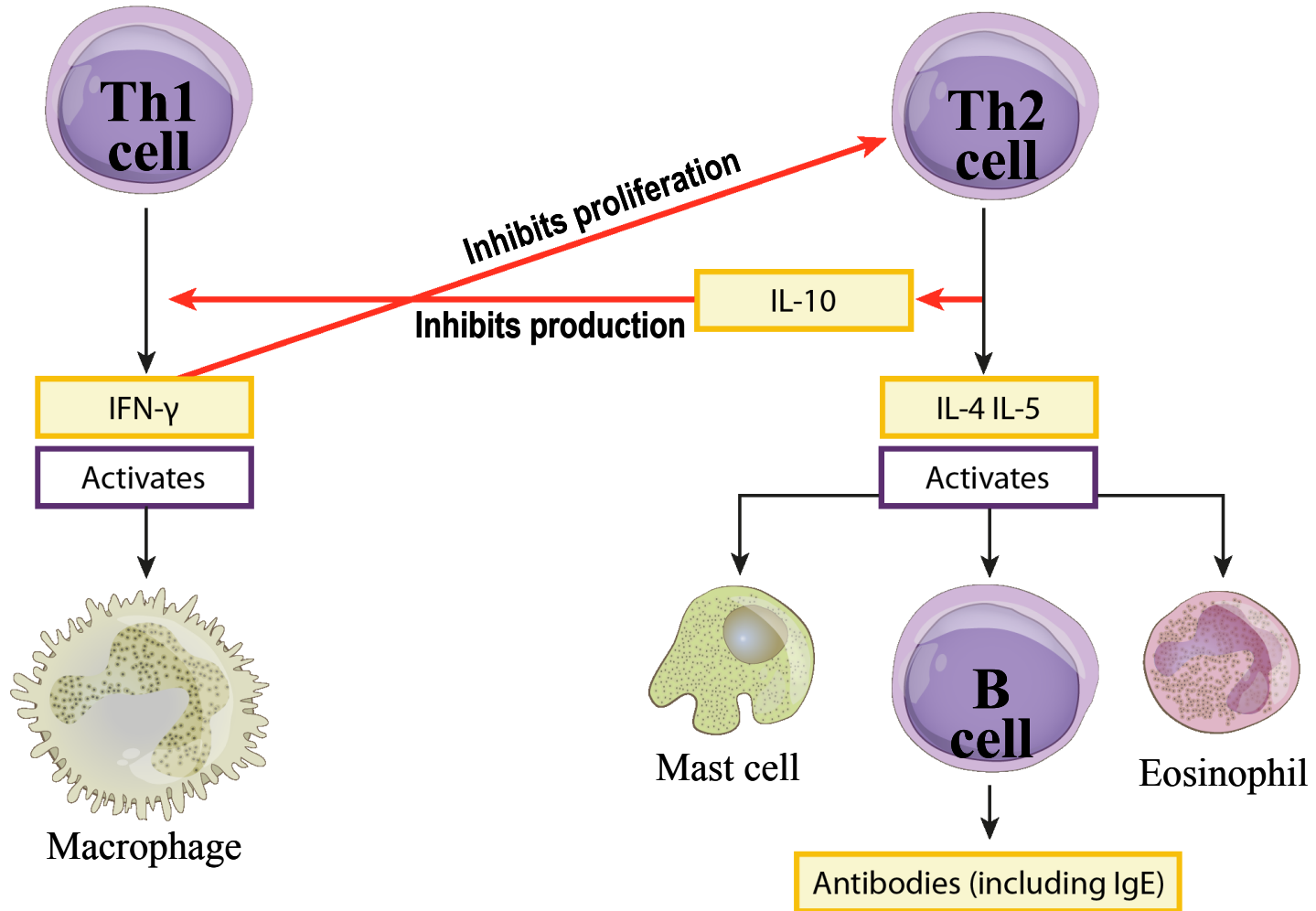
Figure 6.22



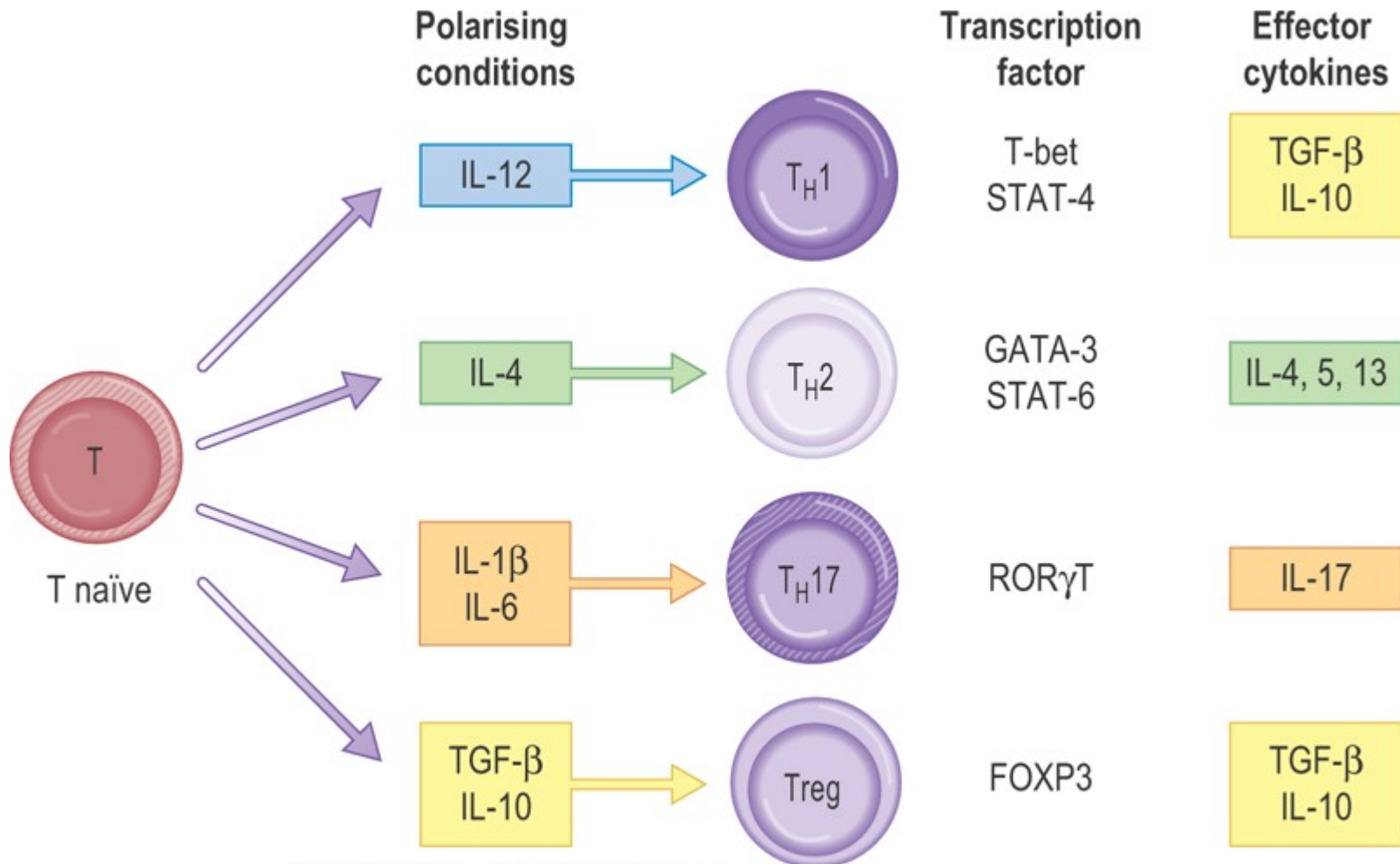
# Development of Th1 and Th2 cells



# Function of TH1 and Th2 cells



# Cytokine environment decides the future development of Th0 cells



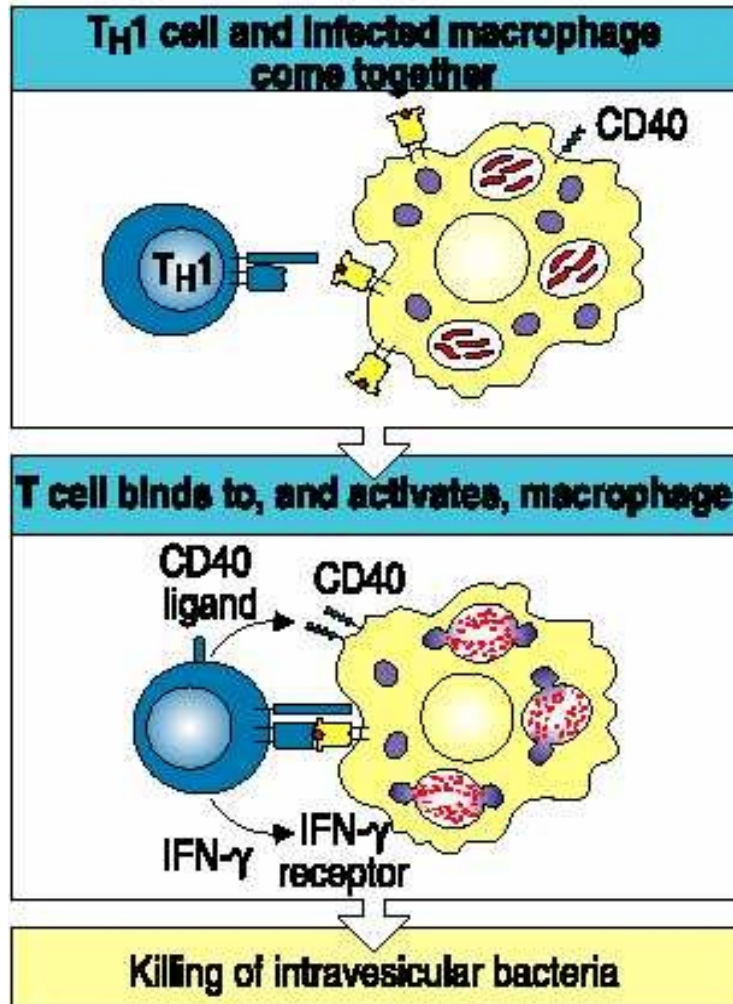
Vergani & Peakman: Basic & Clinical Immunology, 2nd Edition.  
Copyright © 2009 by Churchill Livingstone, an imprint of Elsevier, Ltd. All rights reserved.

# **T<sub>h</sub>1 lymphocytes**

- Secretion of IFN- $\gamma$ , IL-2, IL-3.
- Differentiate after stimulation by IL-12, IL-18, IFN- $\gamma$
- Pro-inflammatory effect, stimulate function of macrophages.
- Involved in pathogenesis of multiple sclerosis...
- Down-regulation of Th2 cells by production of IFN- $\gamma$
- Involved in acute graft rejection

# Function of Th1 cells

Figure 6.27



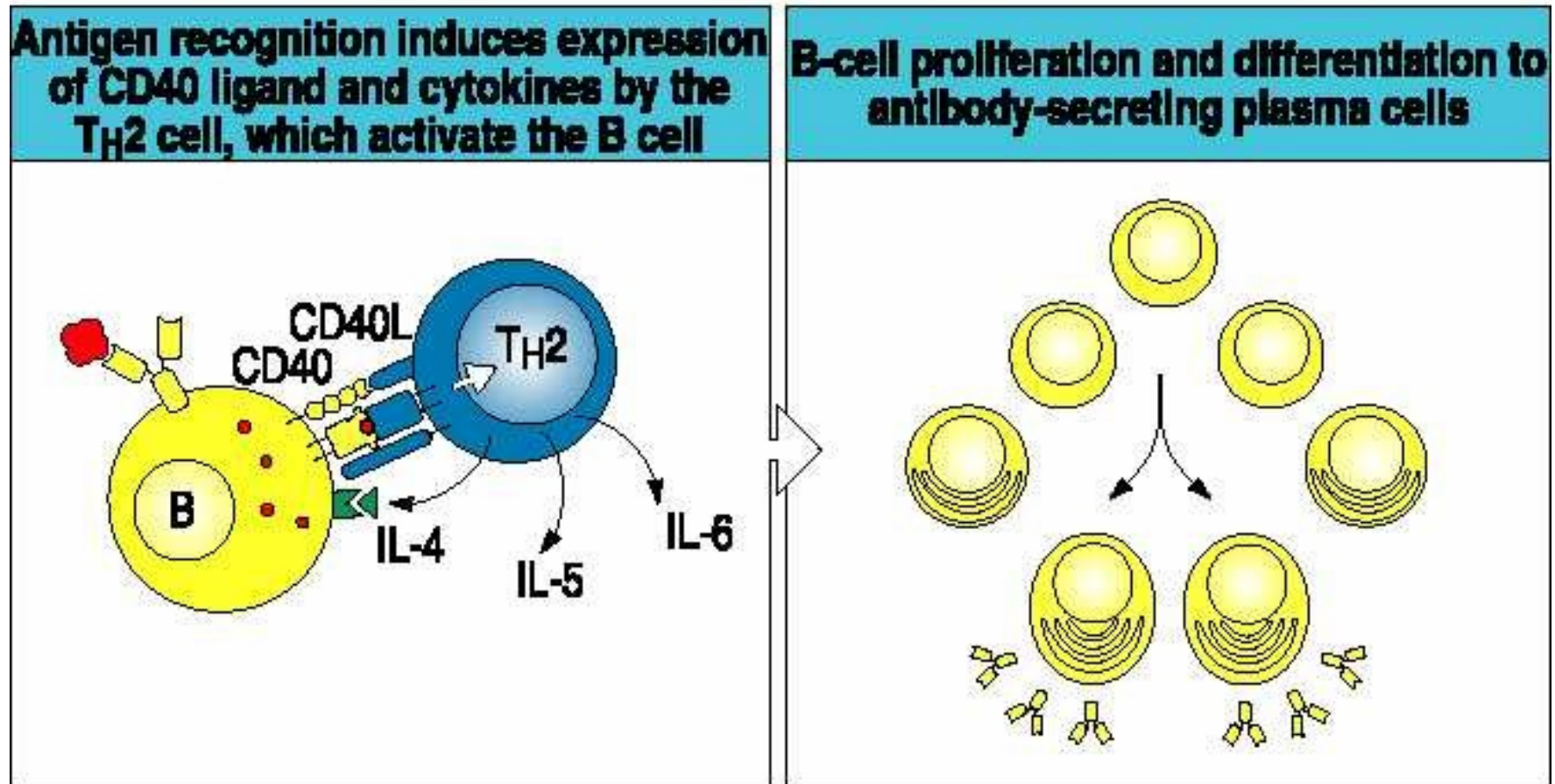
# T<sub>h</sub>2 lymphocytes

- Secrete IL-3, IL-4, IL-5, IL-6, IL-10, IL-13
- Differentiate after stimulation by IL-4
- Stimulation of antibody production, including IgE
- Important in protection against parasites
- Included in pathogenesis of allergic diseases
- By production of IL-10 suppress function of Th1 cells.
- Th2 predominance in pregnancy.



# Th2-lymphocytes are essential for stimulation of B-lymphocytes

Figure 6.30



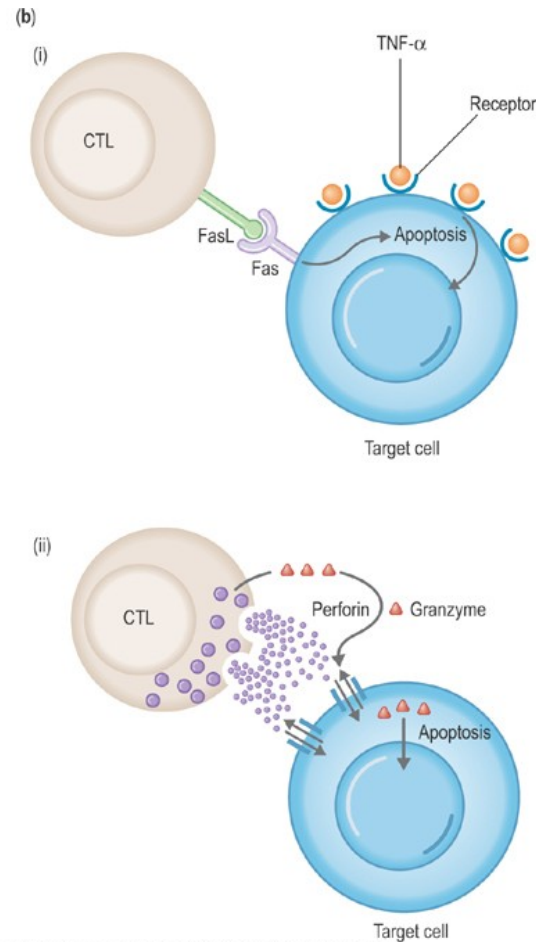
# Th 17 cells

- Important in protection against bacteria and fungi.
- Differentiate after stimulation by IL-6, TGF- $\beta$ , also IL-23 plays very important role
- Secretion of IL-17, IL-21, IL-22.
- Pathology – involved in chronic inflammatory states, including rheumatoid arthritis, Crohn disease.

# Cytotoxic T-lymfocytes

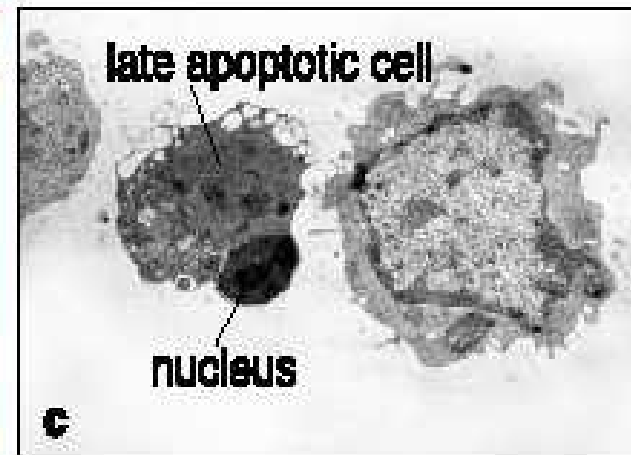
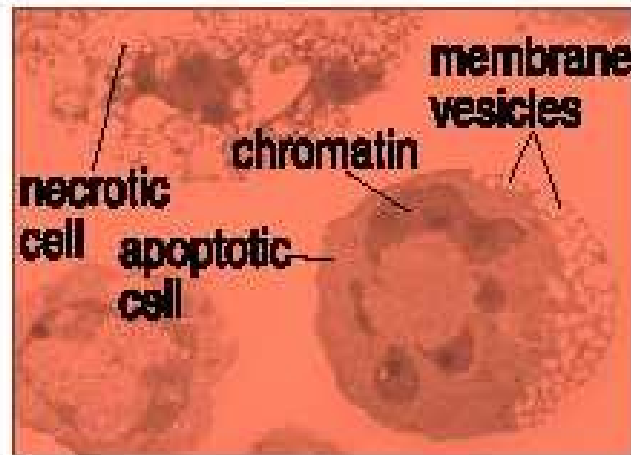
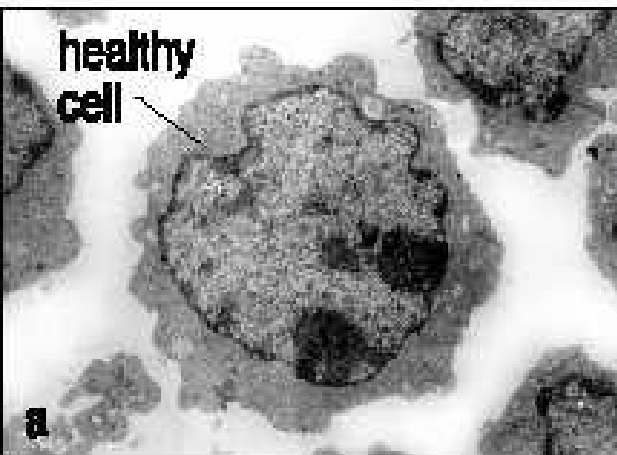
- CD8+
- Foreign antigens are recognized in complex with HLA-I class antigens.
- Mechanism of cytotoxicity: perforin (induction of membrane pores), various mechanism inducing apoptosis of the target cell (granzymes, FasL, lymfotoxin).
- Produce various cytokines (Tc1 and Tc2 cells)

# Cytotoxic effect of CD8+ cells

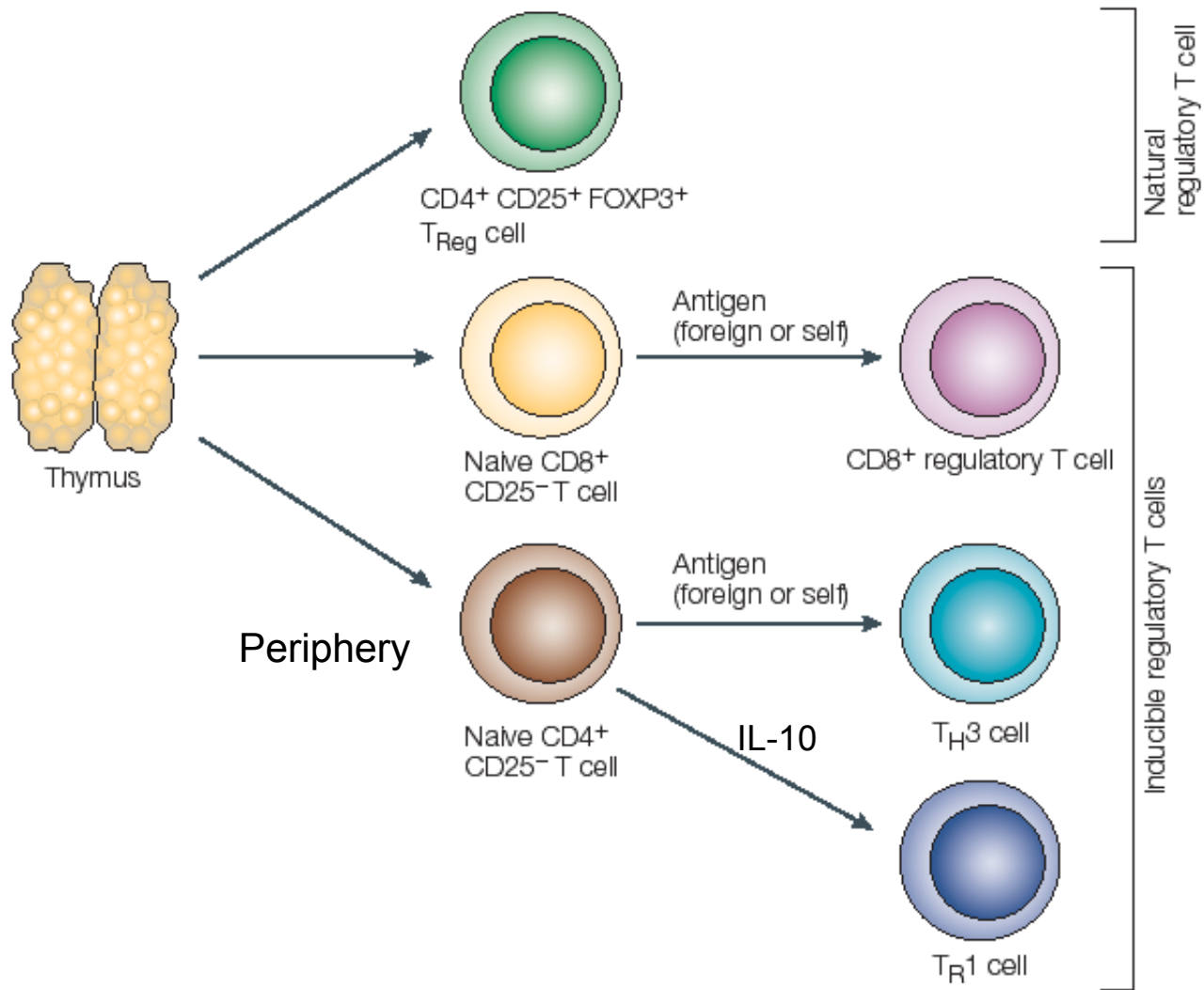


# CD8 lymphocytes induce apoptosis of target cells

Figure 6.25



# Types of regulatory T-lymphocytes



From: Nature Immunology

# T<sub>reg</sub> lymphocytes

- Thymic development
- Express CD4+CD25+
- Involved in tolerance of autoantigens
- Comprise approximately 5-10% of peripheral CD4+ lymphocytes
- Can be induced also in periphery by foreign antigens.

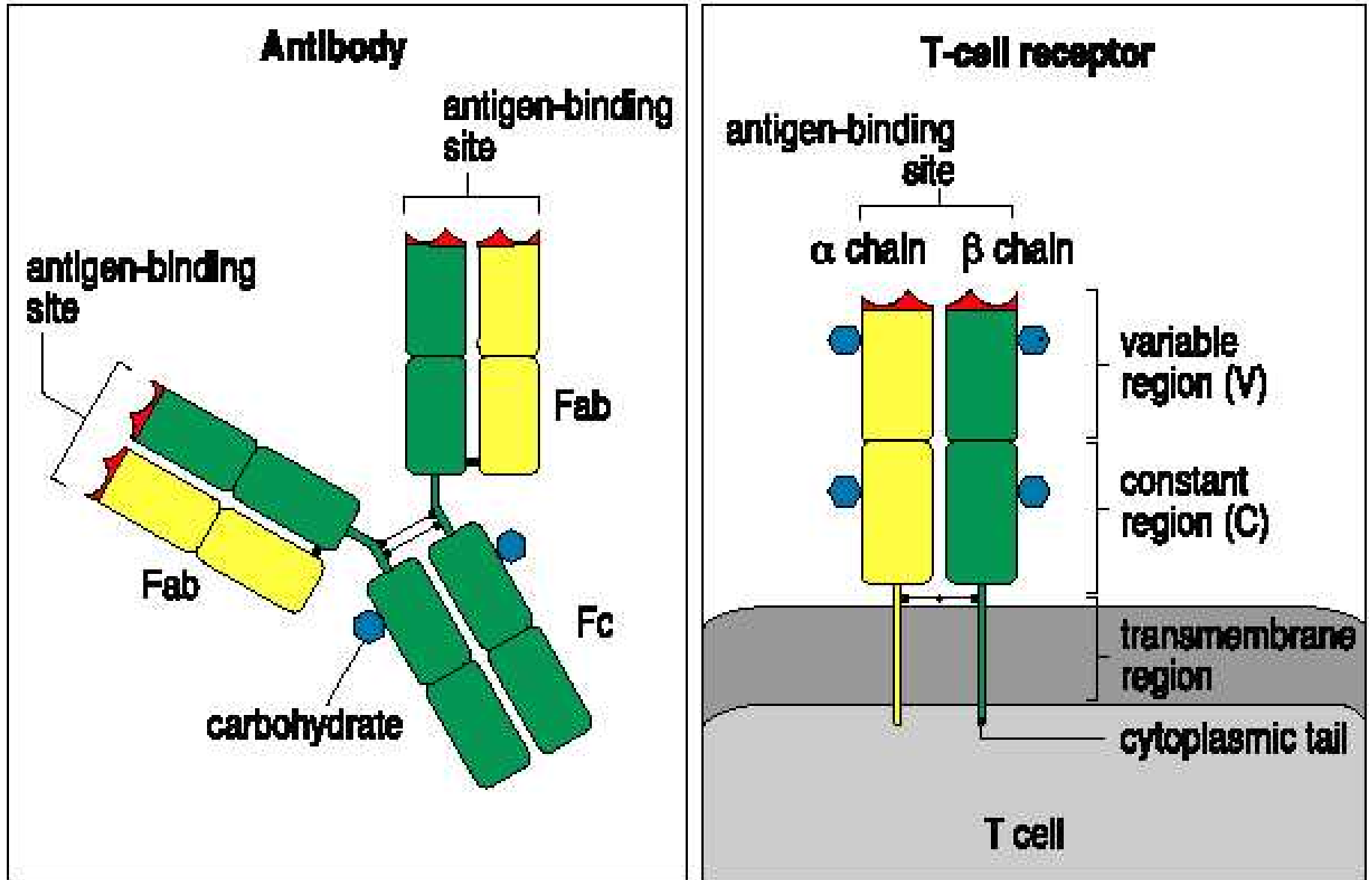
# TR-1 Lymphocytes

- Antigen-induced regulatory CD4<sup>+</sup> cells.
- Develop from antigen stimulated T-lymphocytes in the environment of IL-10.
- Tolerance of foreign antigens.
- Very similar are „Th3 cells“.



Figure 3.1

# T- and B-cells antigen-specific receptors



# $\gamma\delta$ -T-lymphocytes

- Comprise approximately 5% of peripheral lymphocytes.
- CD3+, CD4-CD8-
- Low antigenic specificity.
- Thymus is not necessary for their development.
- Other than HLA antigens may be involved in antigen presentation.
- Increased in mycobacterial infections, Erlichiosis, listeriosis.

# Intraepithelial T-lymphocytes

- TCR of  $\alpha\beta$  or  $\gamma\delta$  type
- Low antigenic specificity
- Extrathymic differentiation
- The first line of the specific immune response
- Usually CD8+