

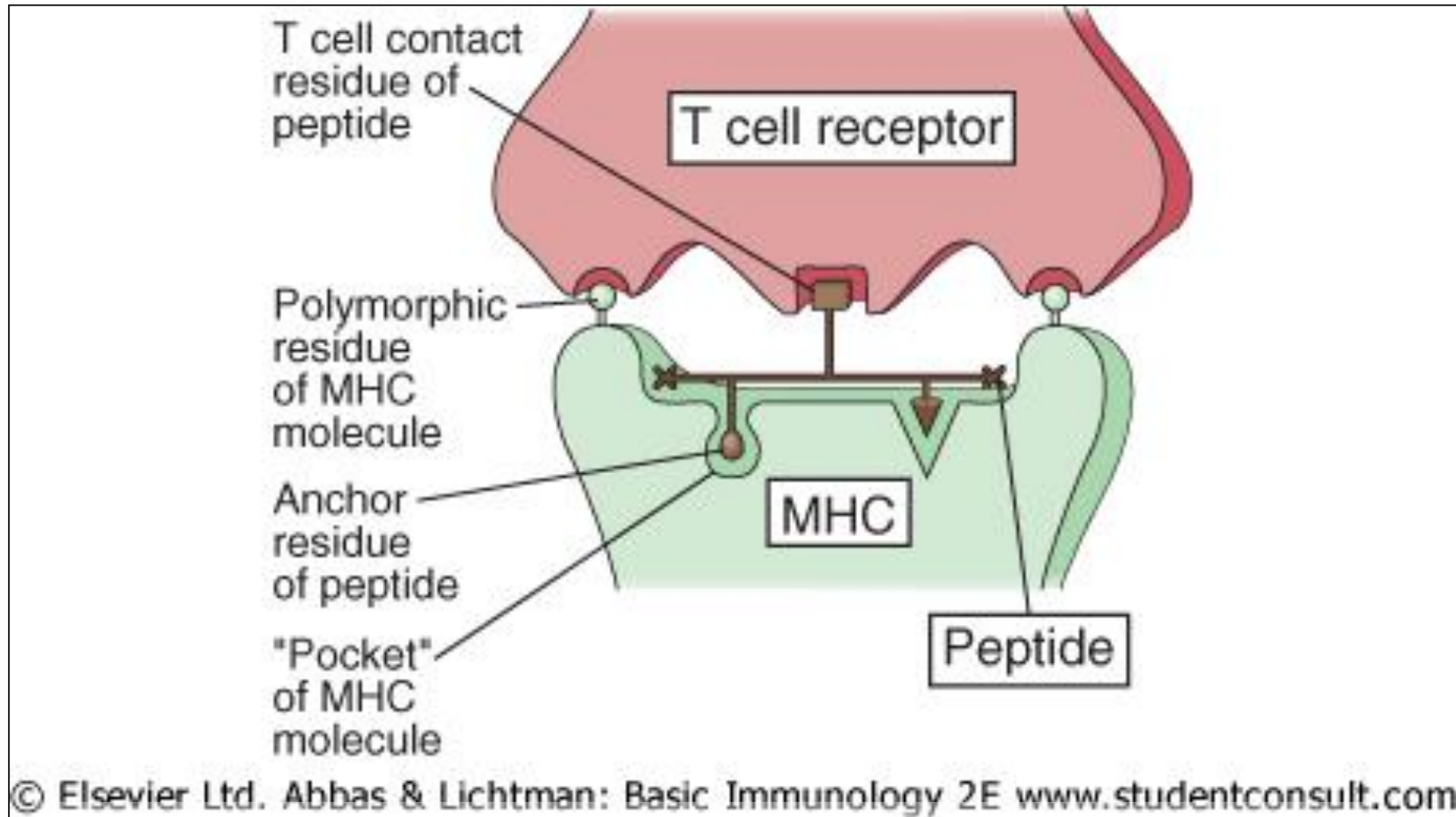
T-Lymphocytes

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

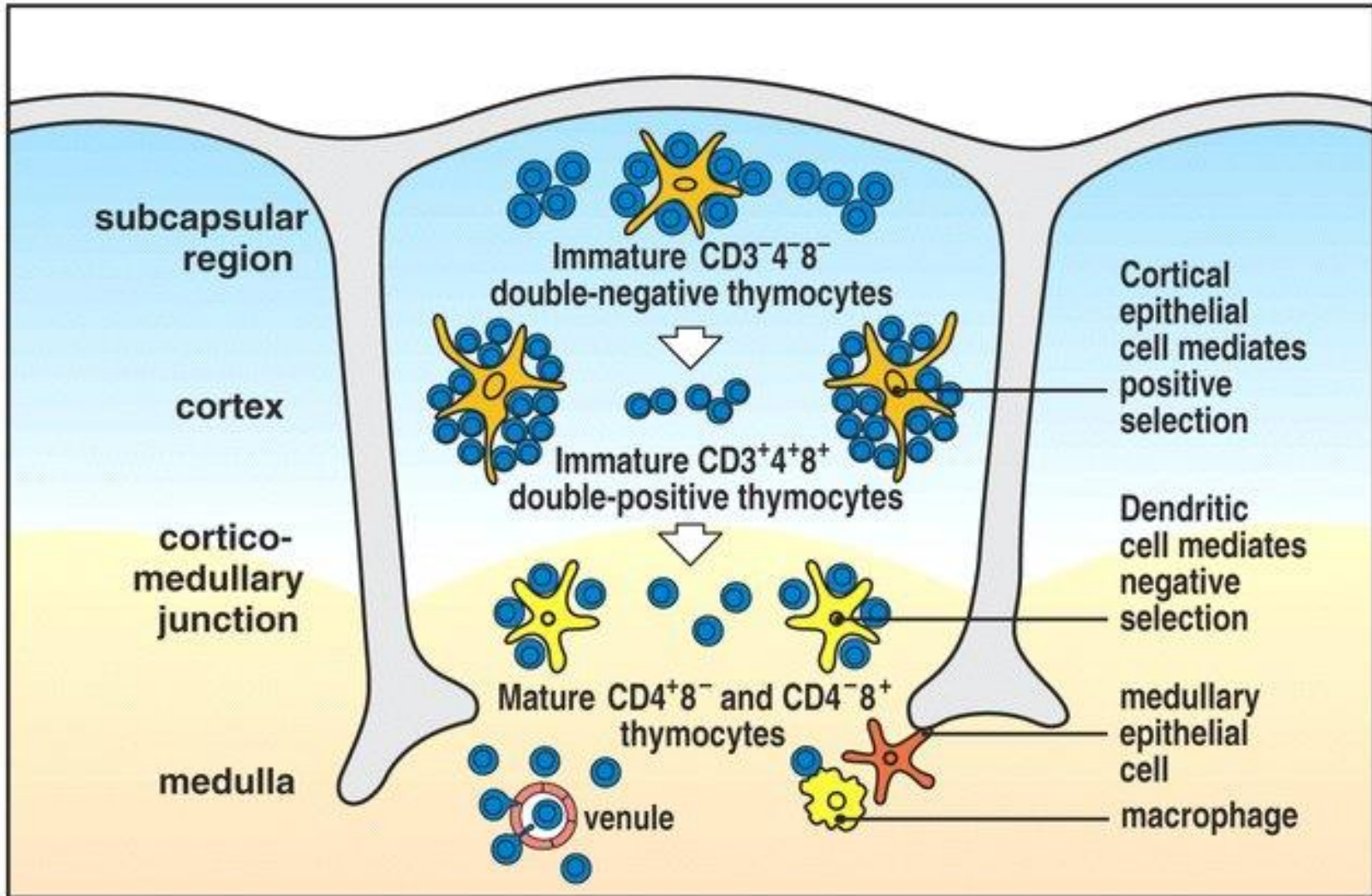
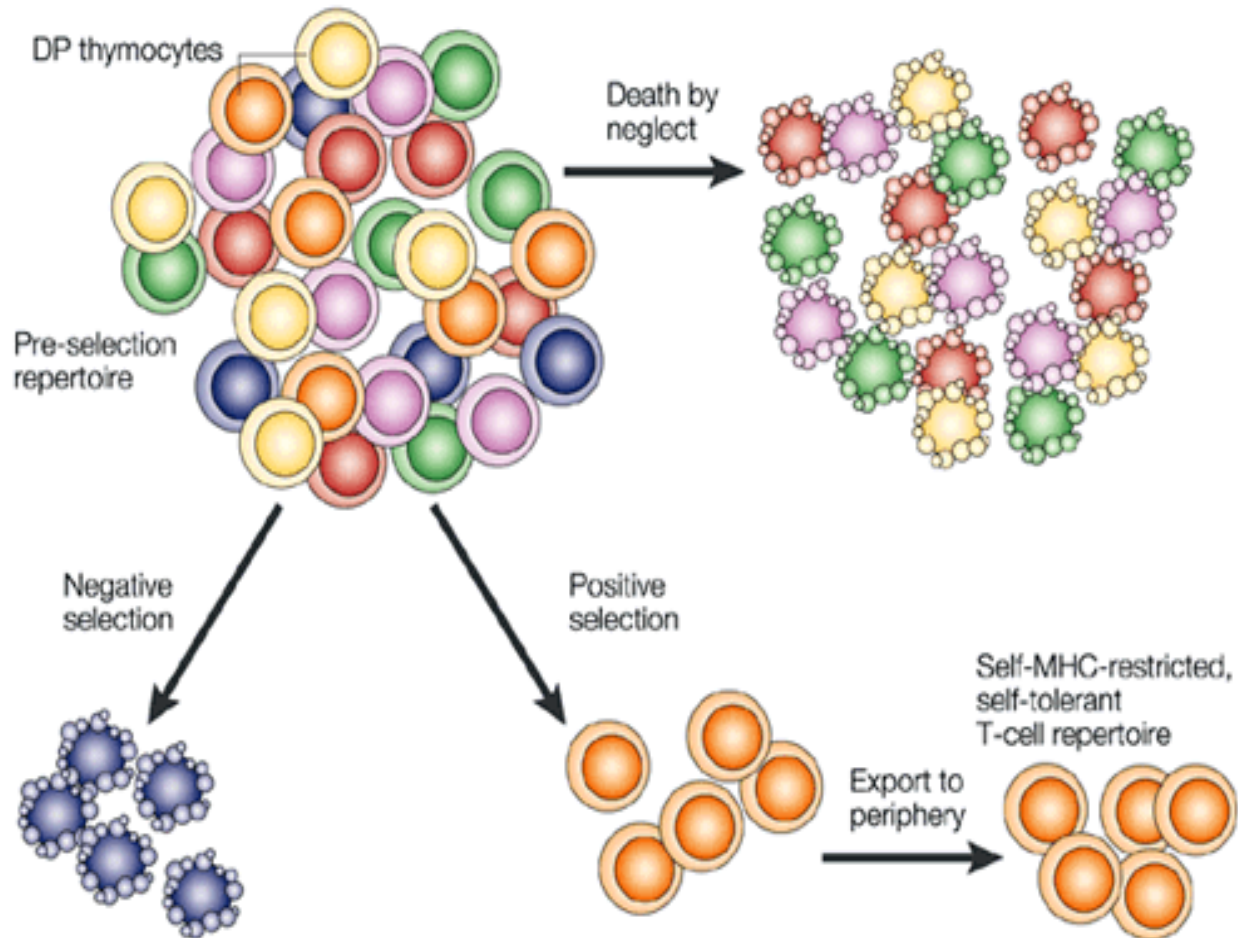
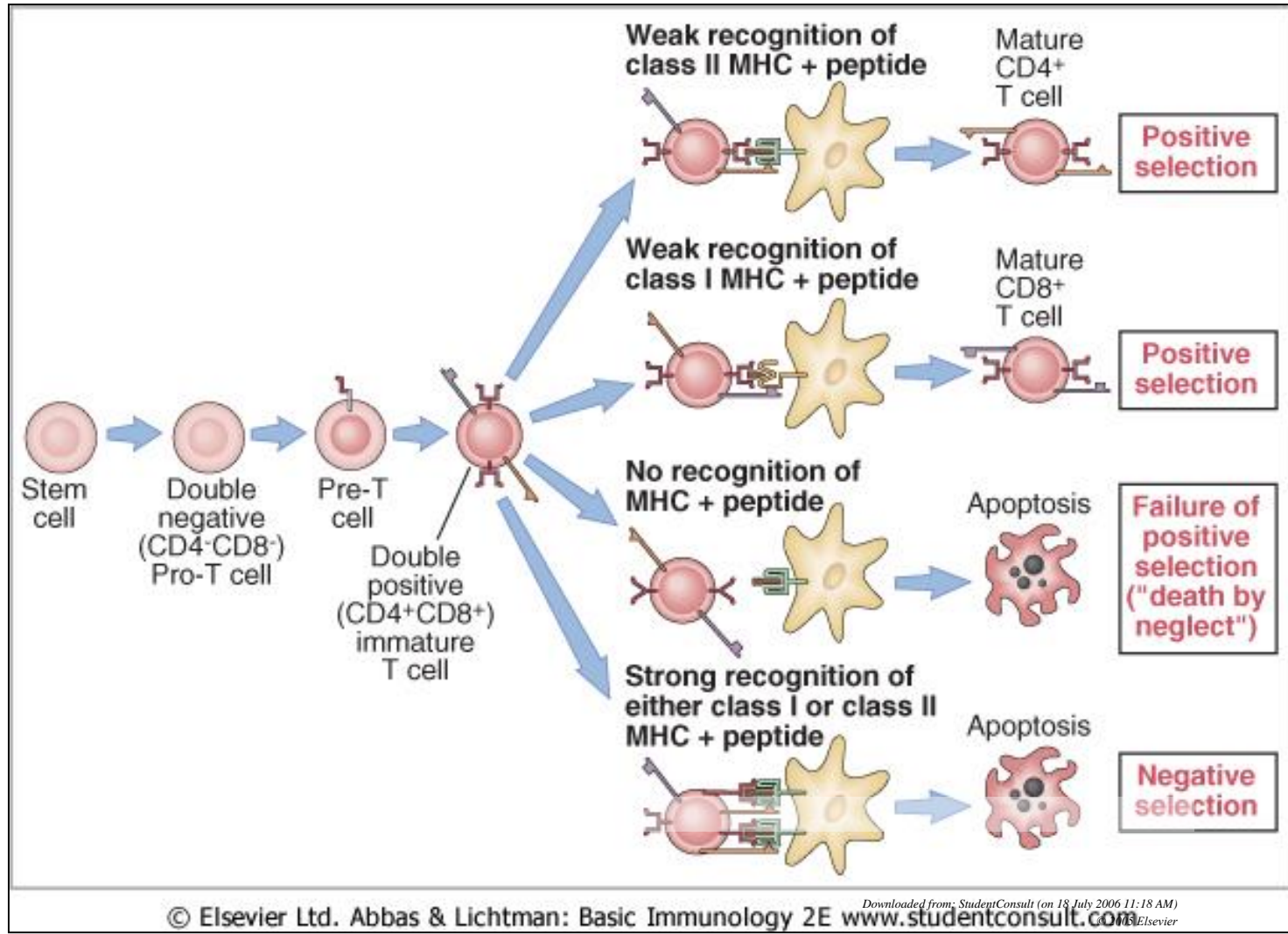


Figure 5-13 The Immune System, 2/e (© Garland Science 2005)

The Fate of T-lymphocytes in the Thymus



Thymic education of lymphocytes

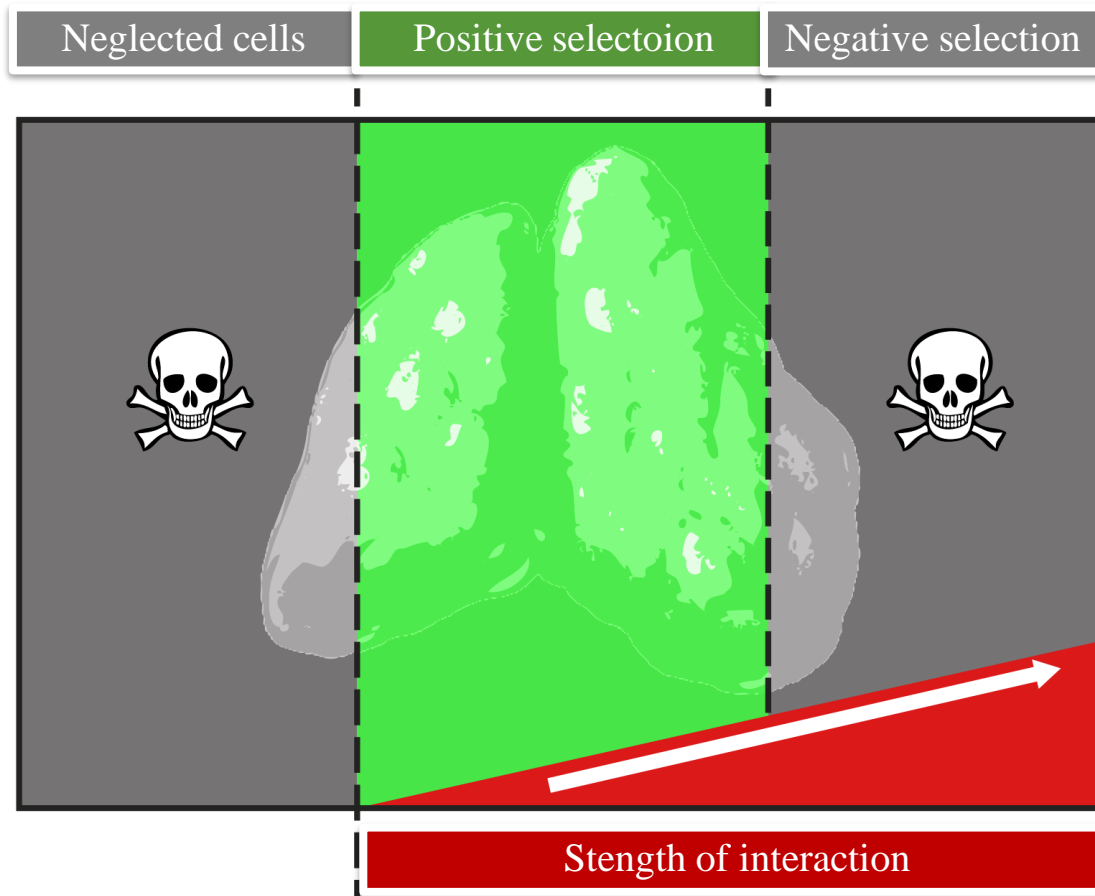


The significance of the AIRE (Autoimmune regulator)

- Transcription factor, in the thymus leads to expression of many somatic proteins of various organs .
- The expression of autoantigens on HLA-antigens leads to a negative selection of T-lymphocytes.
- AIRE deficiency leads to development of various autoimmune diseases (endocrine glands, liver, stomach), autoantibodies against IL-17 lead to mucocutaneous candidiasis (so called APECED syndrome).



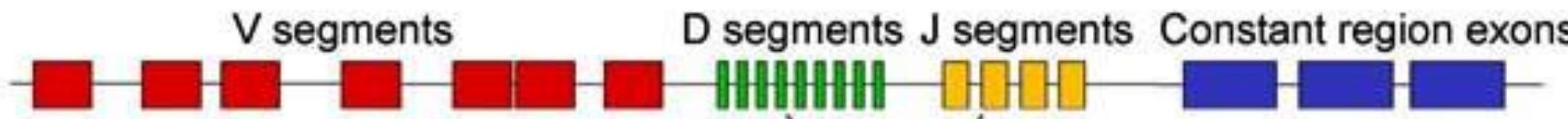
Strength of interaction between TCR and HLA-(antigen) complexes determines the fate of thymocytes



Cell death

Figure 5: V(D)J Recombination

Germline configuration



D to J recombination



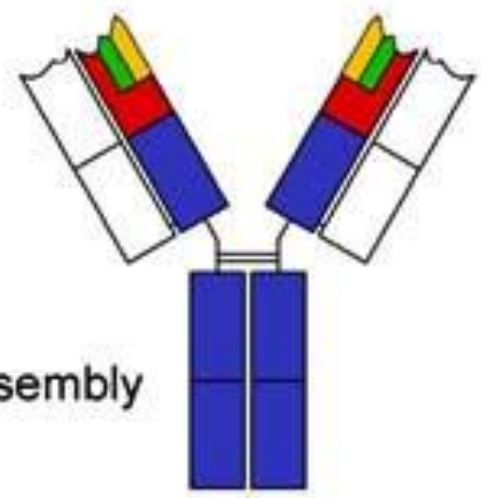
V to DJ recombination



transcription, splicing



translation, assembly

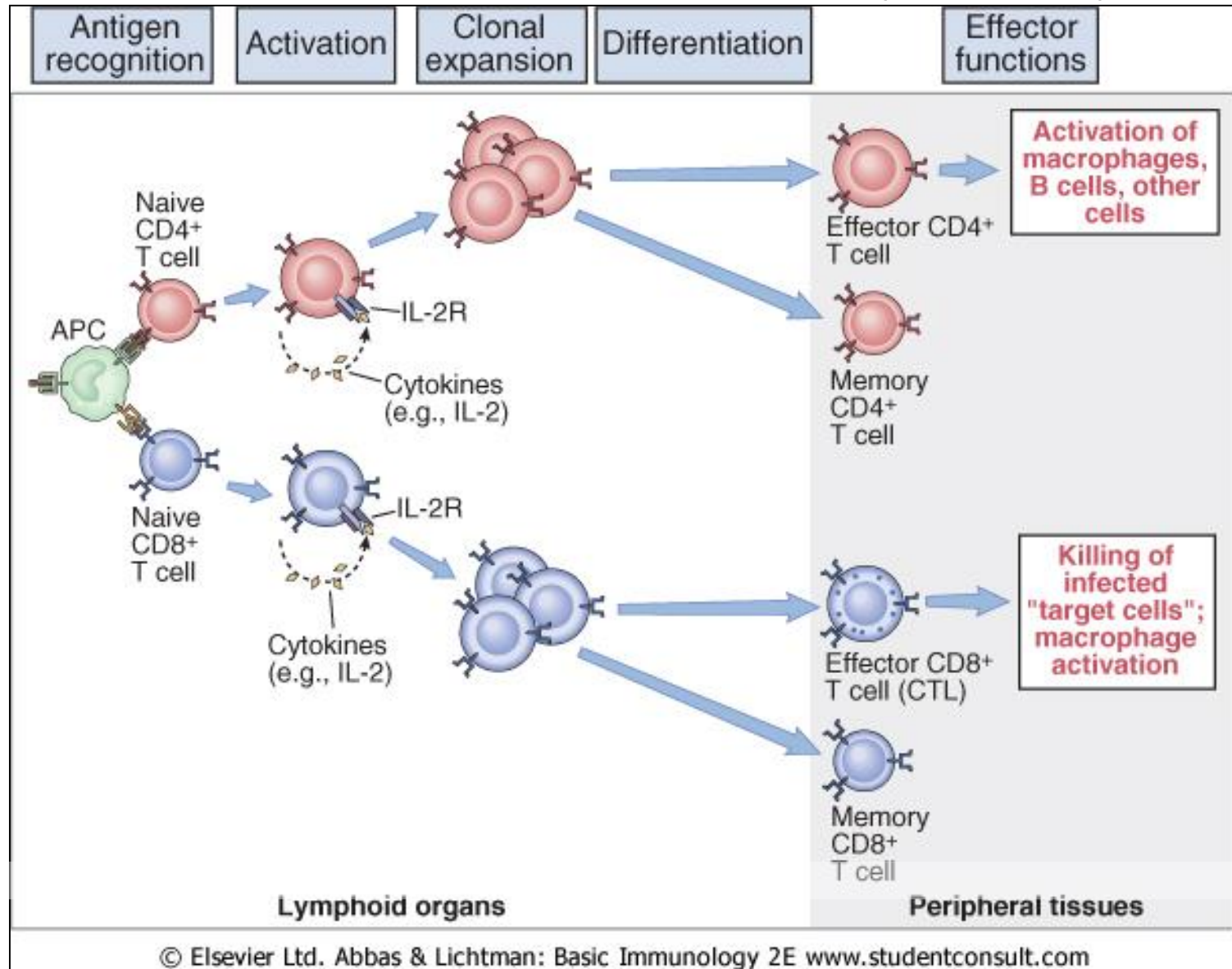


(adapted from Janeway 2001)

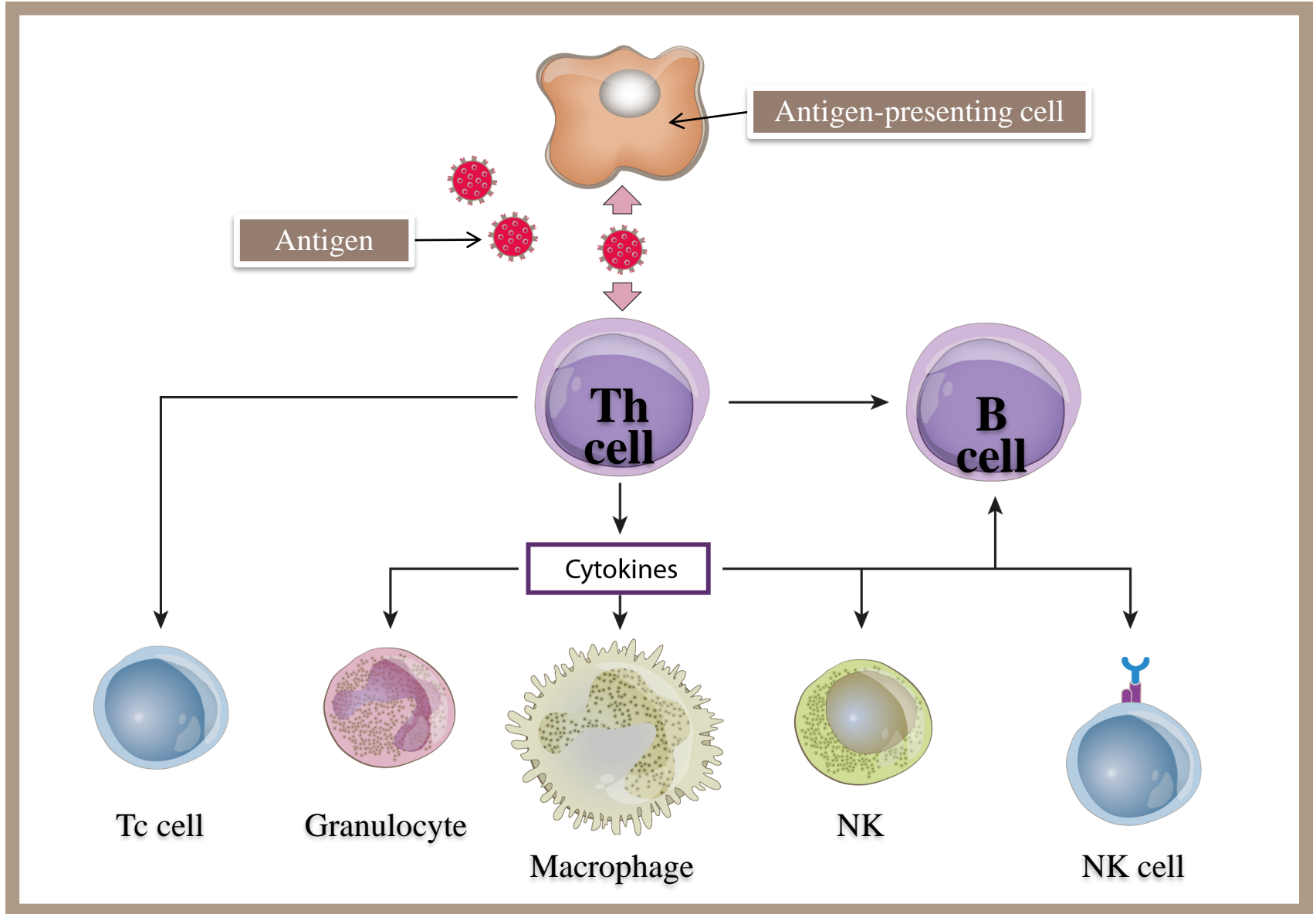
V, D and J genes involved in T- and B- cell receptor formation

	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 repertoire with junctional diversity	Ig: $\sim 10^{11}$	TCR: $\sim 10^{16}$		
© Elsevier Ltd. Abbas & Lichtman: Basic Immunology 2E www.studentconsult.com				

Activation and differentiation of T-lymphocytes



Central role of T-lymphocytes in specific immune response



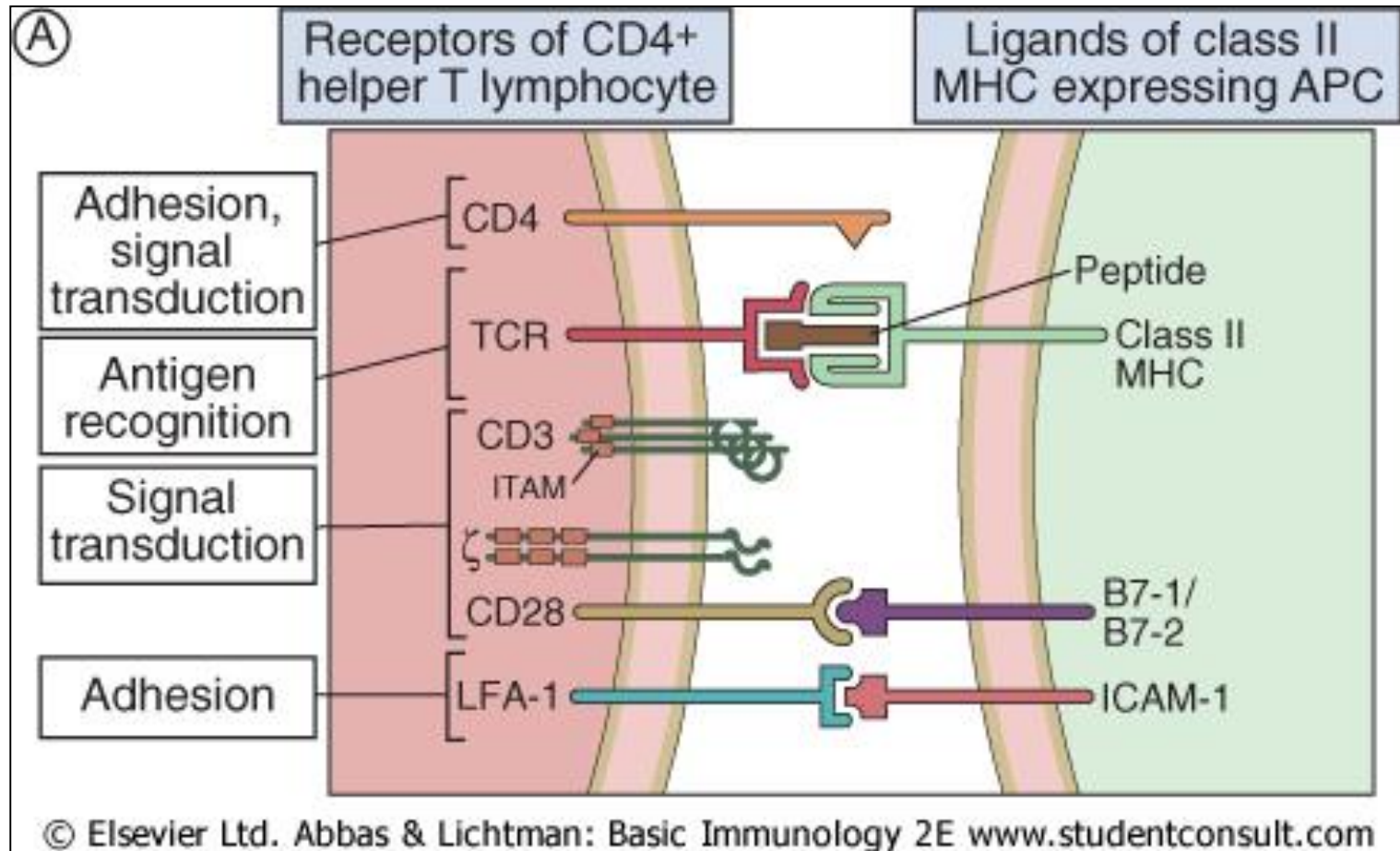
Determination of lymphocytes using cell surface antigens

- CD (Cluster of Determination) antigens – antigens expressed on surface of leukocytes.
- More than 400 such markers has been determined.
- CD3⁺ – all T-lymphocytes.
- CD3⁺CD4⁺ – helper and majority of regulatory T-cells.
- CD3⁺CD8⁺ – 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⁺ - B-lymphocytes.
- CD16⁺/CD56⁺(CD3⁻) - NK cells.
- Flow cytometry is used for CD markers determination.

Surface structures on T-lymphocytes

- T-cell receptor (TCR):
 - Variable chains α/β or γ/δ
 - 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⁺): kill target cells. Activated by complex HLA-I –antigenic peptide.
- Helper T-lymphocytes (CD4⁺): enable activation of macrophages (Th1) or B-cells (Th2) cells. They are activated by complexes HLA-II- antigenic peptide.
- Regulatory T-cells (CD4⁺): important in the maintenance of immune tolerance.

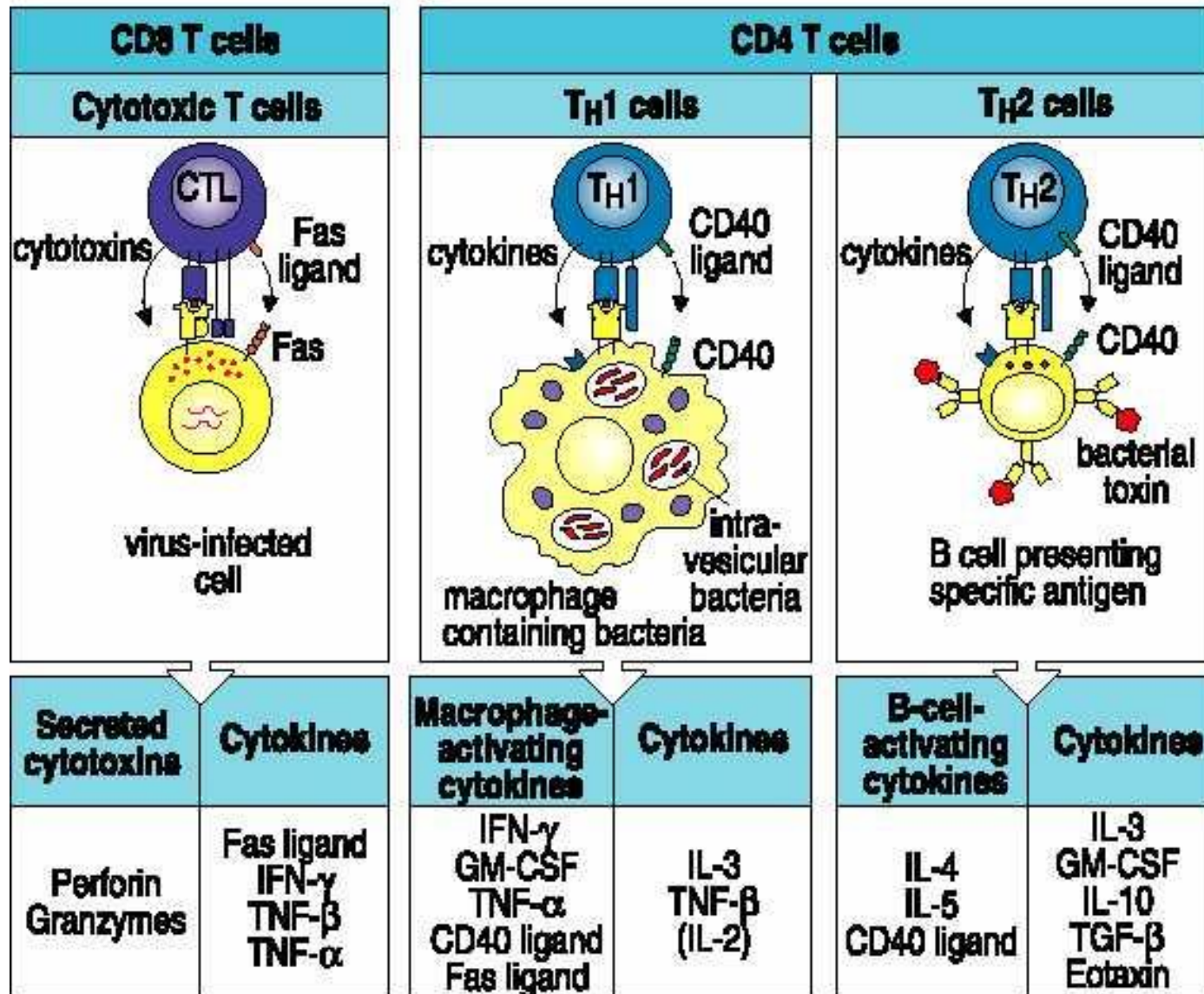
Subpopulations of Th-lymphocytes

- T_h1 lymphocytes
 - Produce IFN- γ , 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

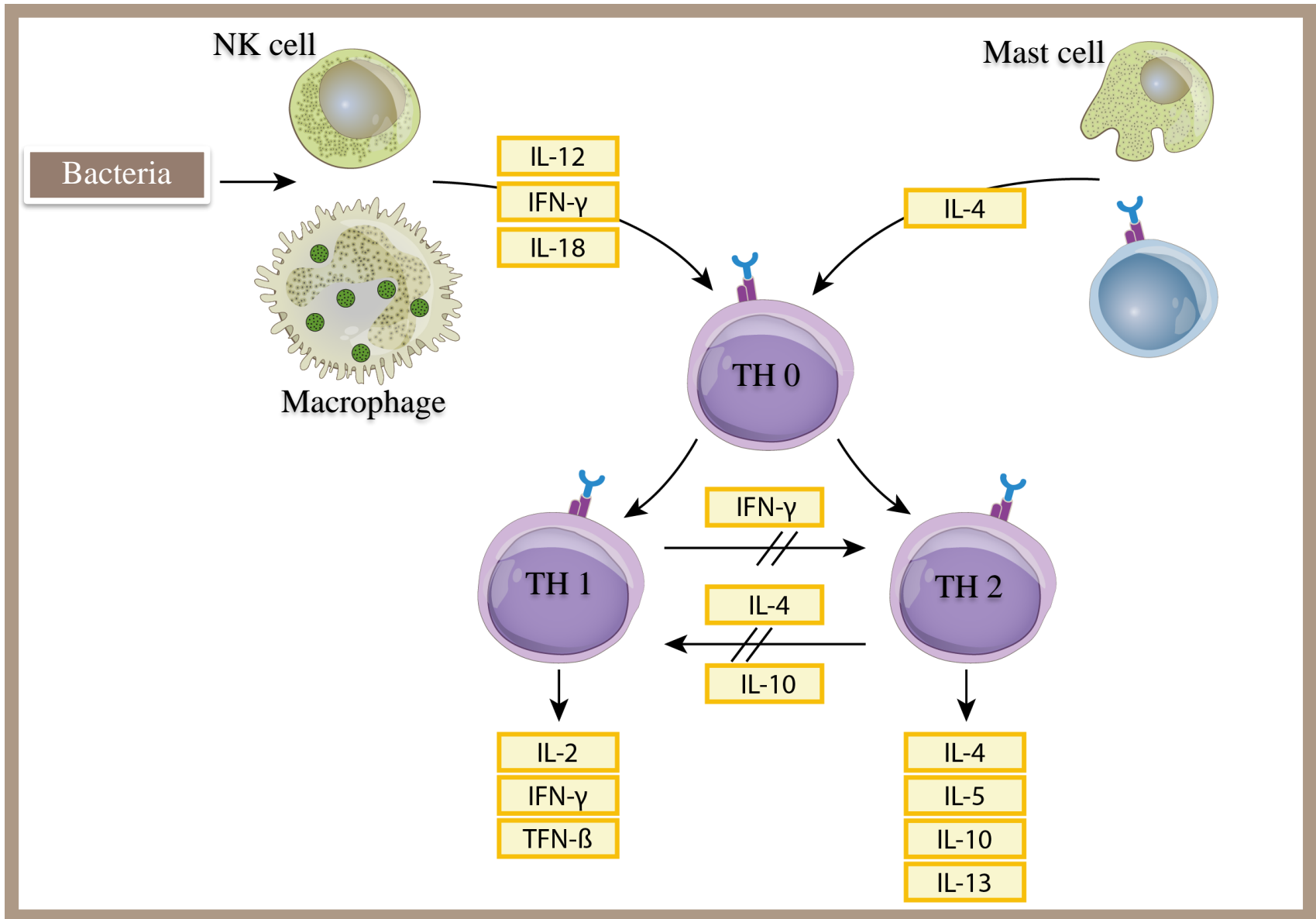
Also T_h9 , T_h22 lymphocytes

Functions of T-lymphocytes

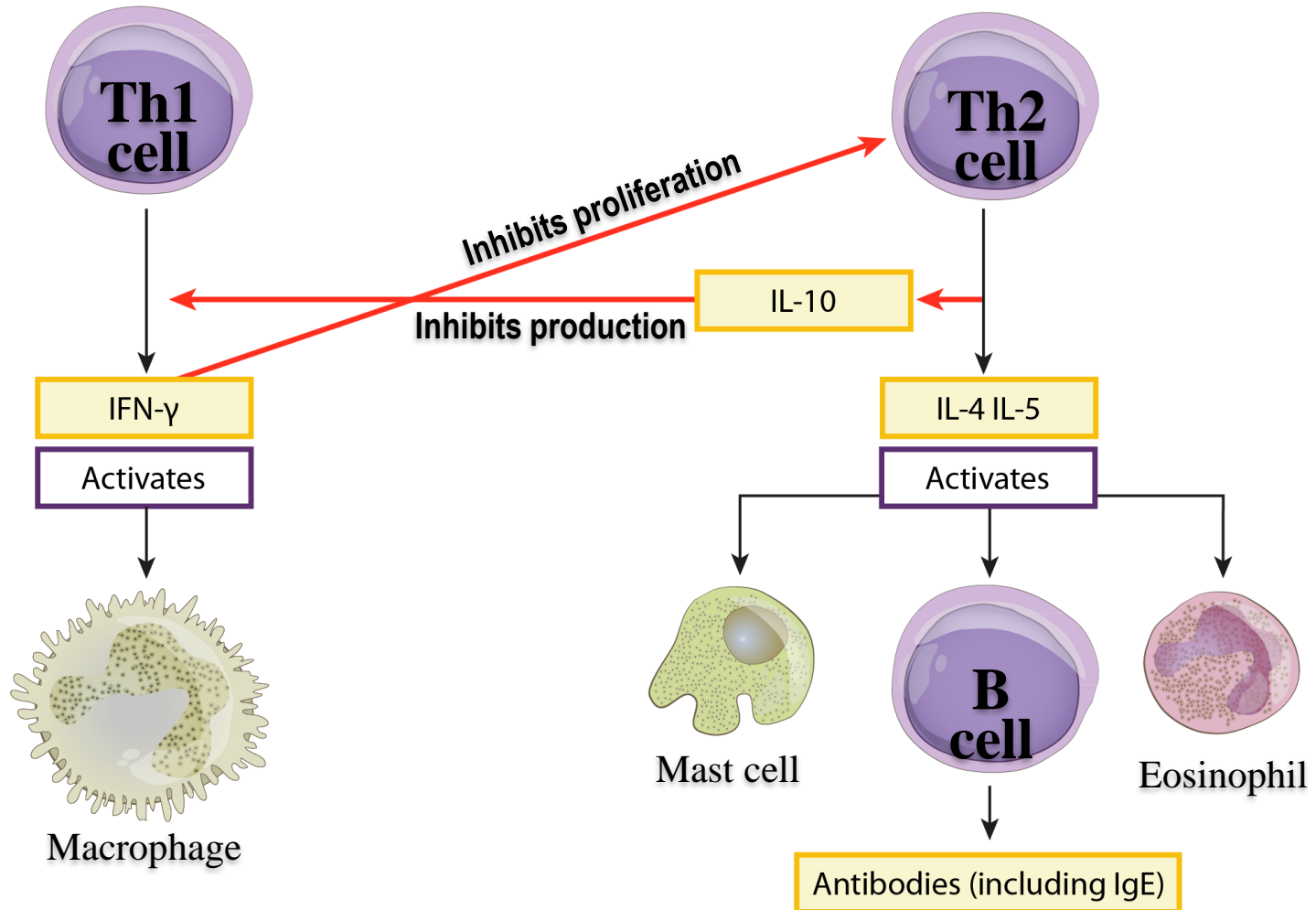
Figure 6.22



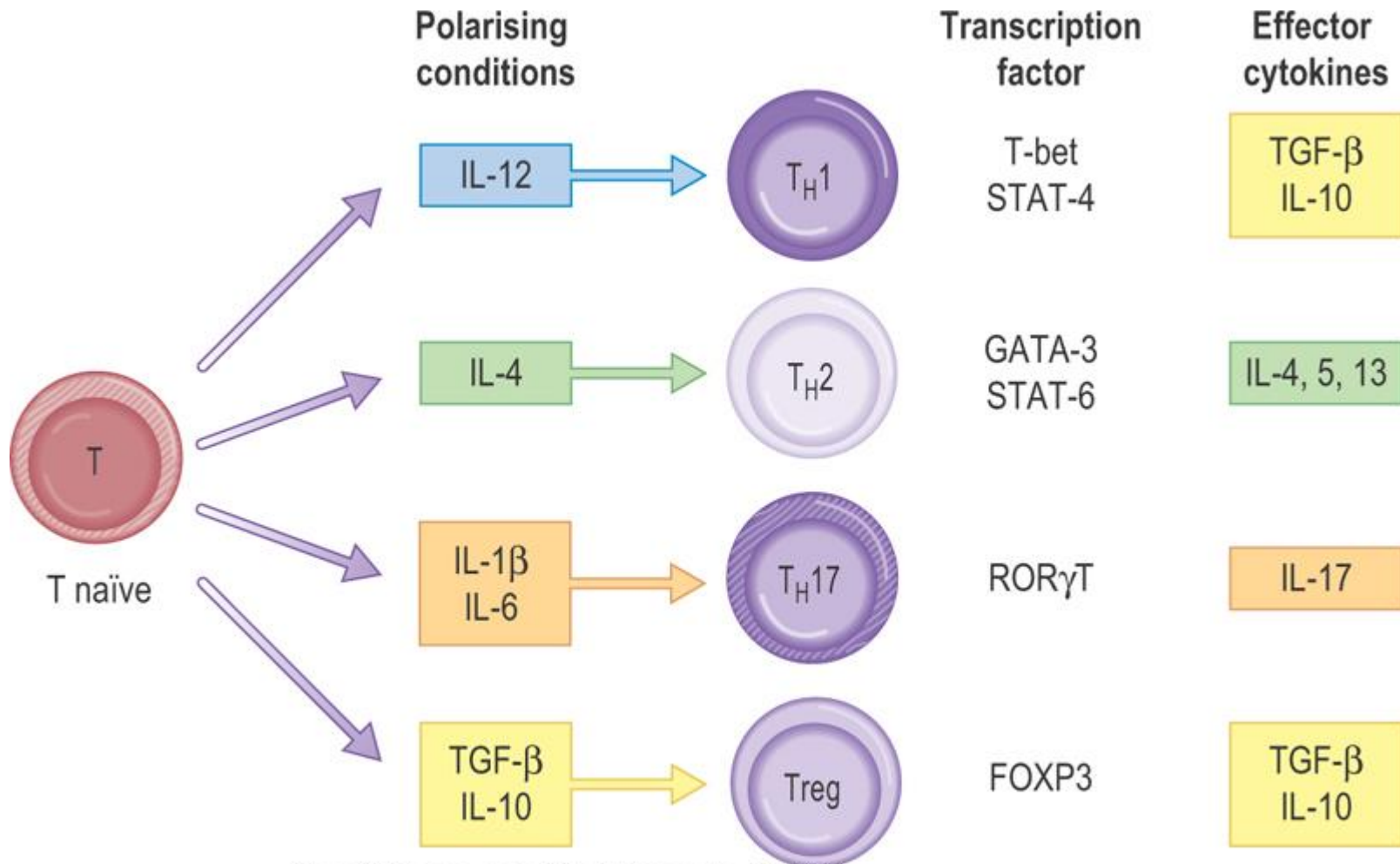
Development of Th1 and Th2 cells



Function of TH1 and Th2 cells



Cytokine environment decides the future development of Th0 cells

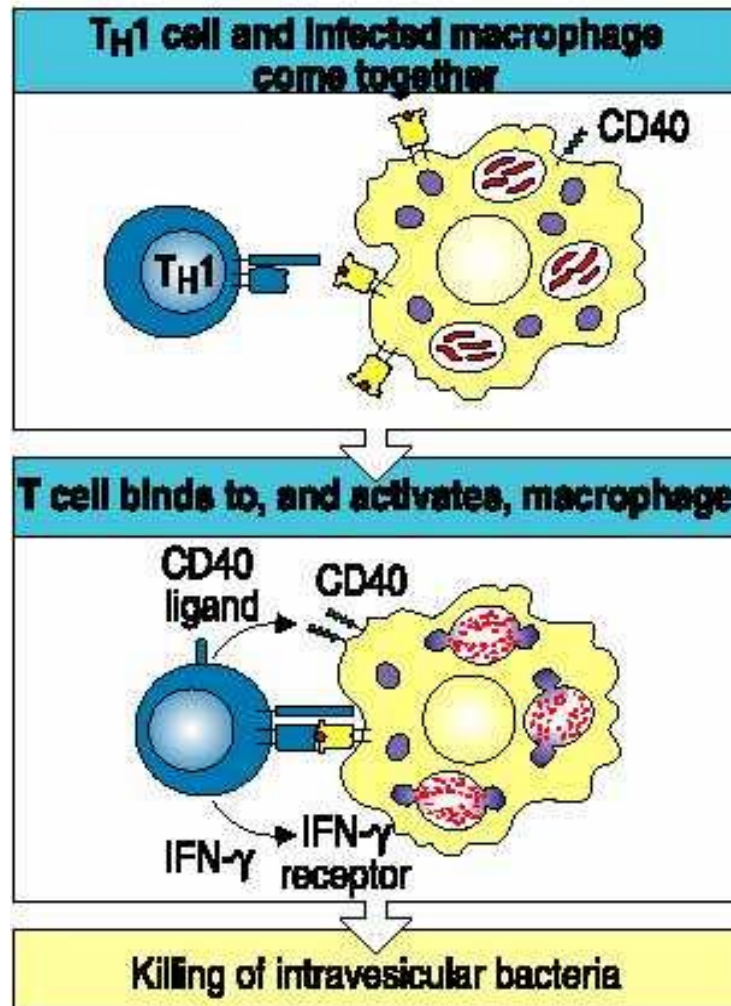


T_h1 lymphocytes

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

Function of Th1 cells

Figure 8.27

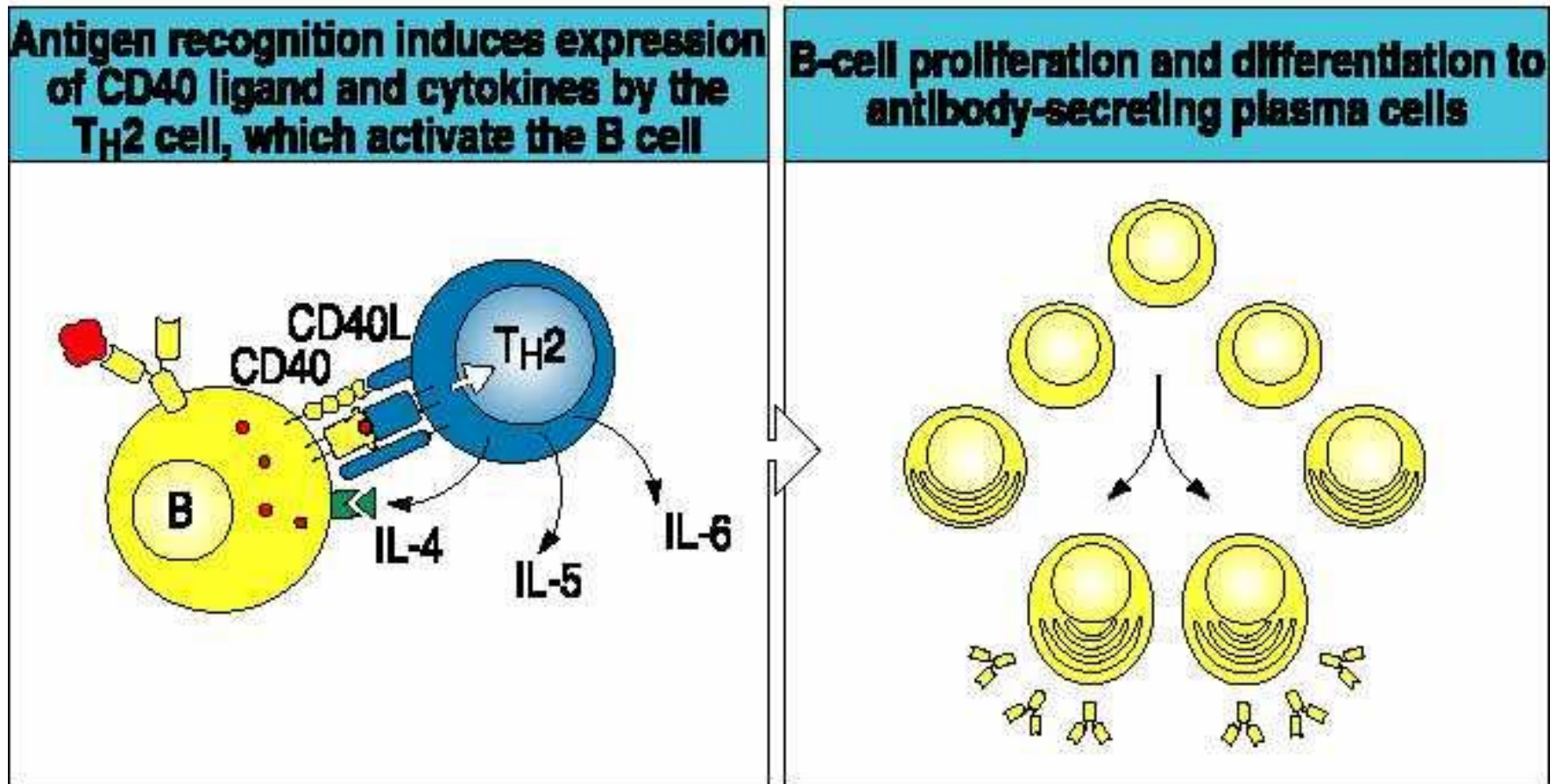


T_h2 lymphocytes

- 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



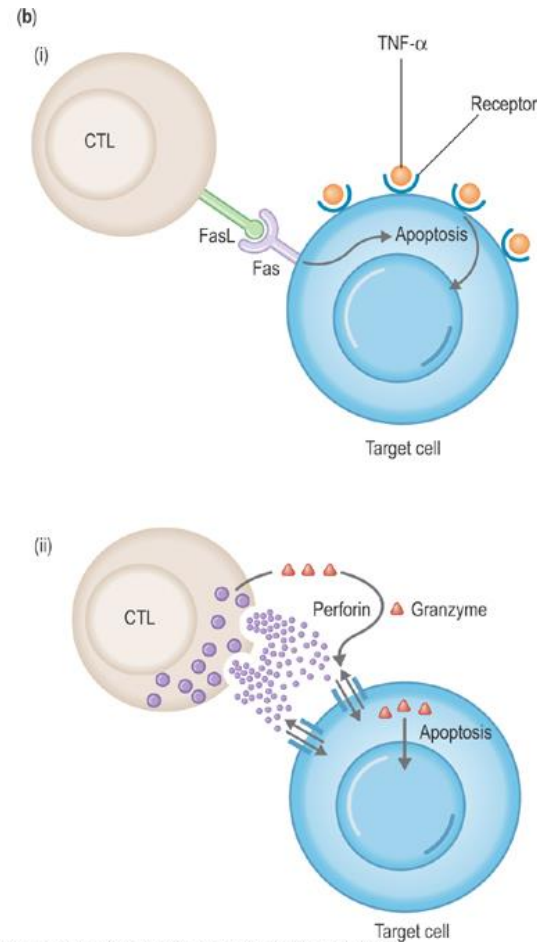
Th 17 cells

- Important in protection against bacteria and fungi.
- Differentiate after stimulation by IL-6, IL-1 β , also IL-23 plays very important role
- Secretion of IL-17, IL-21, IL-22.
- Pathology – involved in chronic inflammatory processes, including rheumatoid arthritis, Crohn disease.

Cytotoxic T-lymfocytes

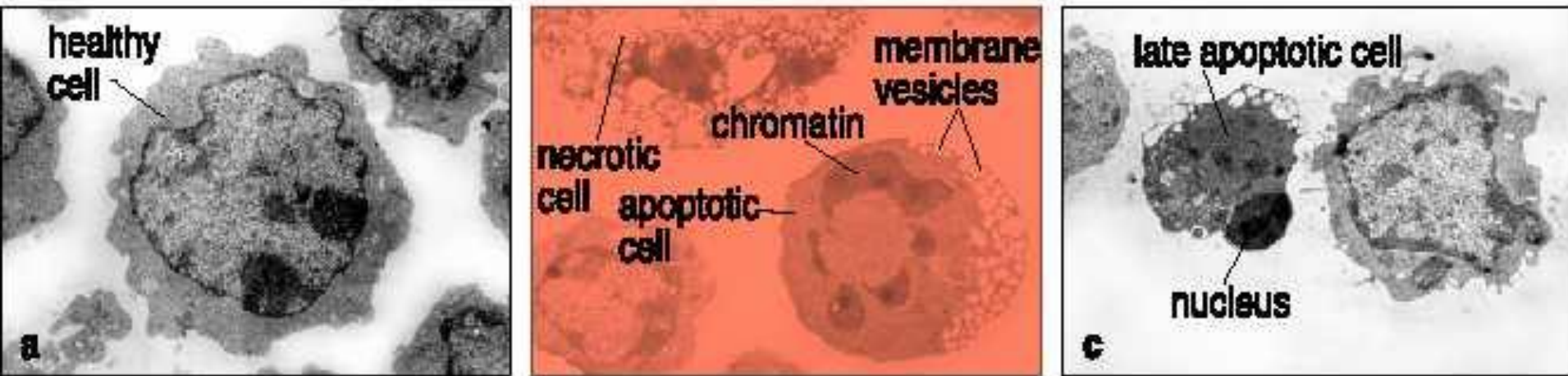
- CD8+
- Foreign antigens are recognized in complex with HLA-I class antigens.
- Mechanism of cytotoxicity: perforin (induction of membrane pores), various mechanism inducing apoptosis of the target cell (granzymes, FasL, lymfotoxin).
- Produce various cytokines (Tc1 and Tc2 cells)

Cytotoxic effect of CD8+ cells

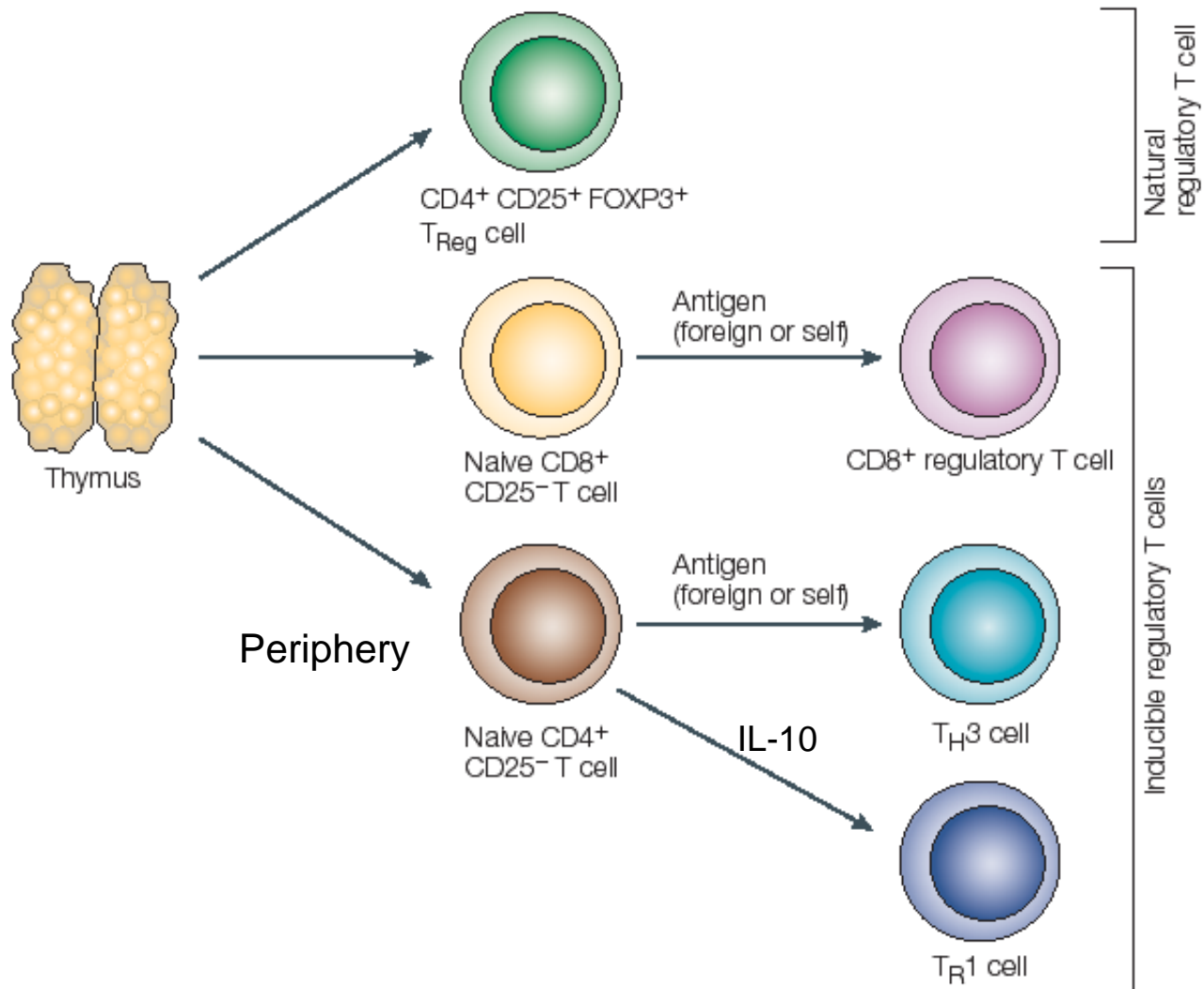


CD8 lymphocytes induce apoptosis of target cells

Figure 6.25



Types of regulatory T-lymphocytes



From: Nature Immunology

T_{reg} lymphocytes

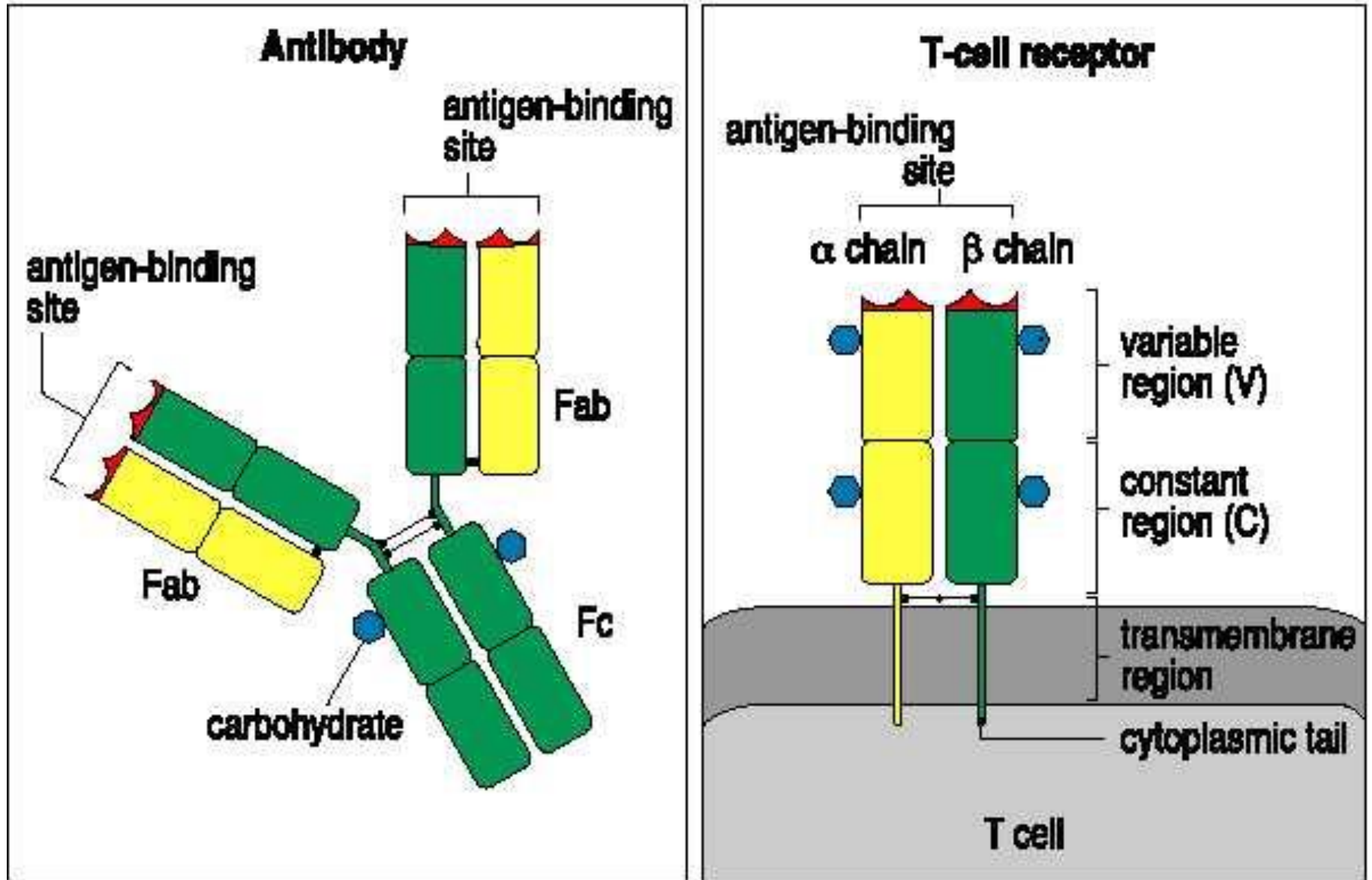
- Thymic development
- Express CD4+CD25+
- Involved in tolerance of autoantigens
- Comprise approximately 5-10% of peripheral CD4+ lymphocytes
- Can be induced also in periphery by foreign antigens (i-Treg).
- Mechanisms of regulation: Production of TGF β, expression of CTLA-4

TR-1 Lymphocytes

- Antigen-induced regulatory CD4+ 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+