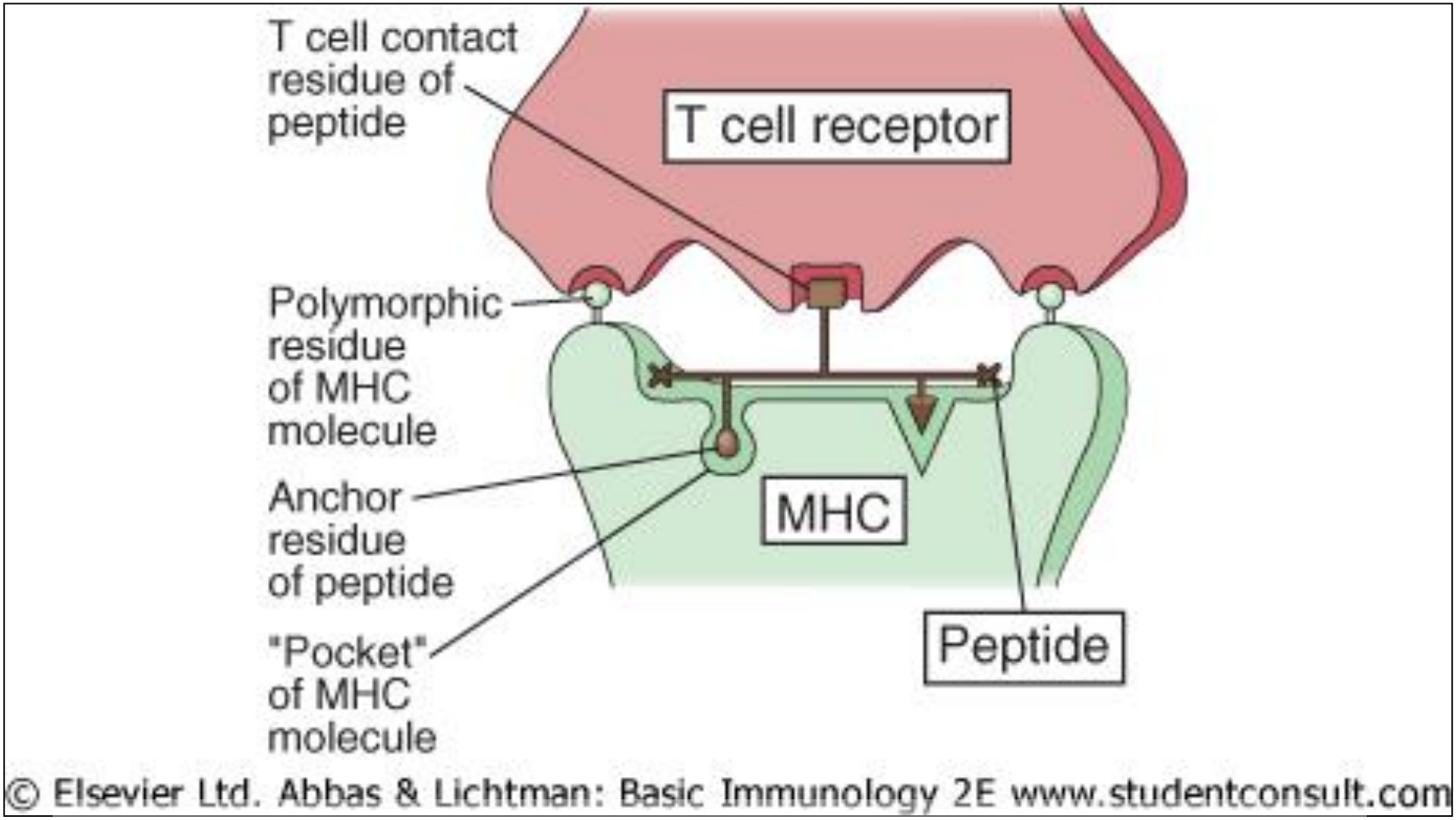
T-Lymphocytes

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

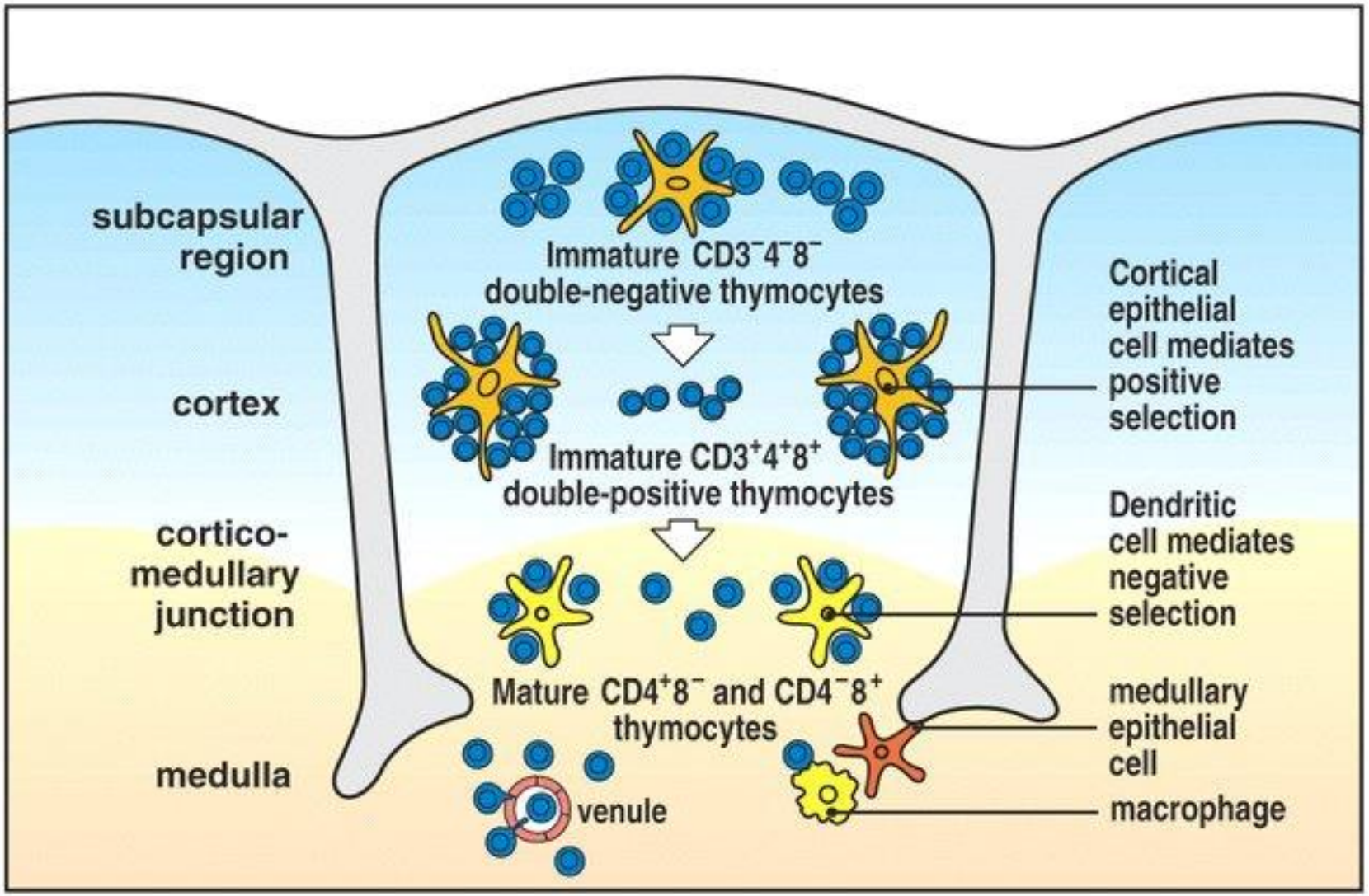
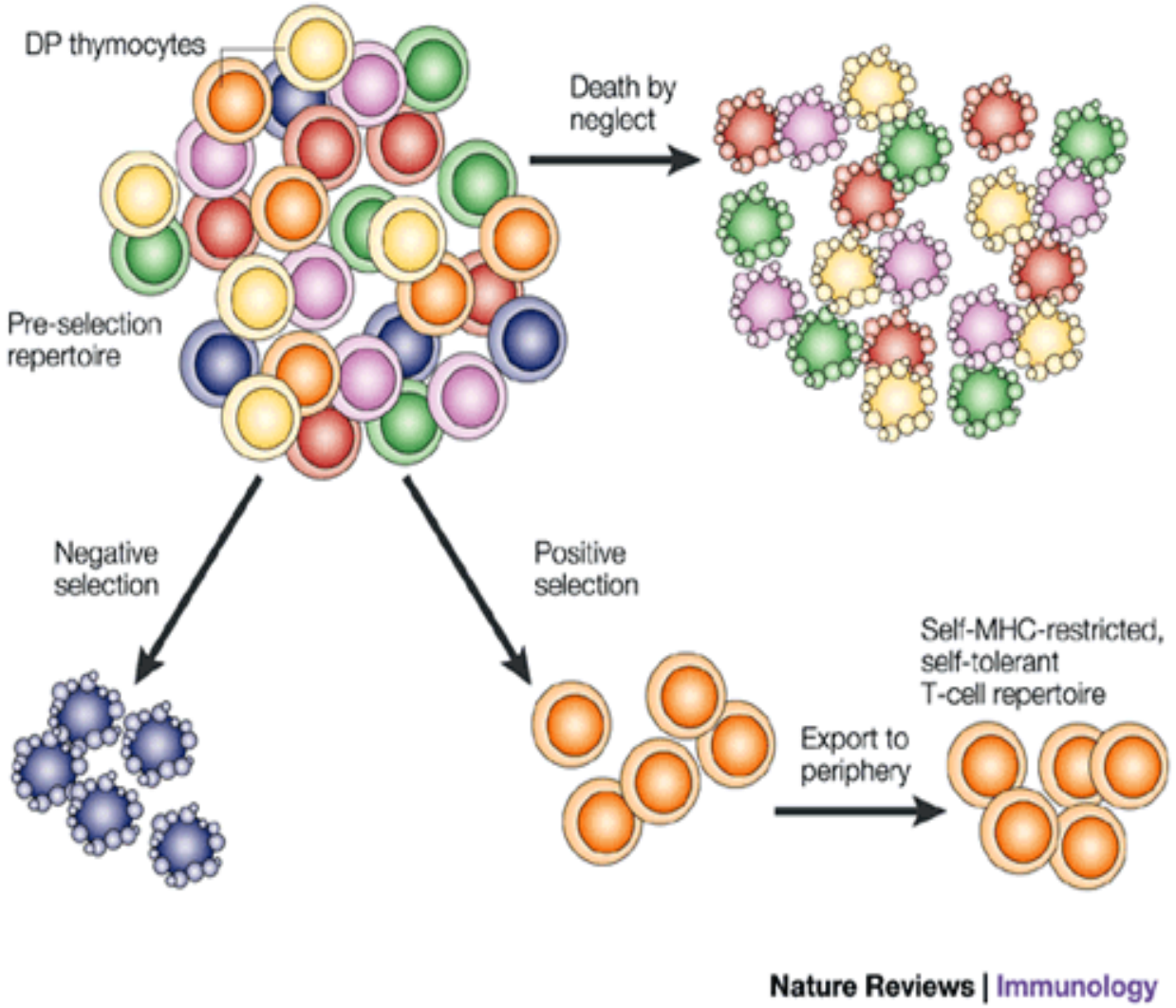
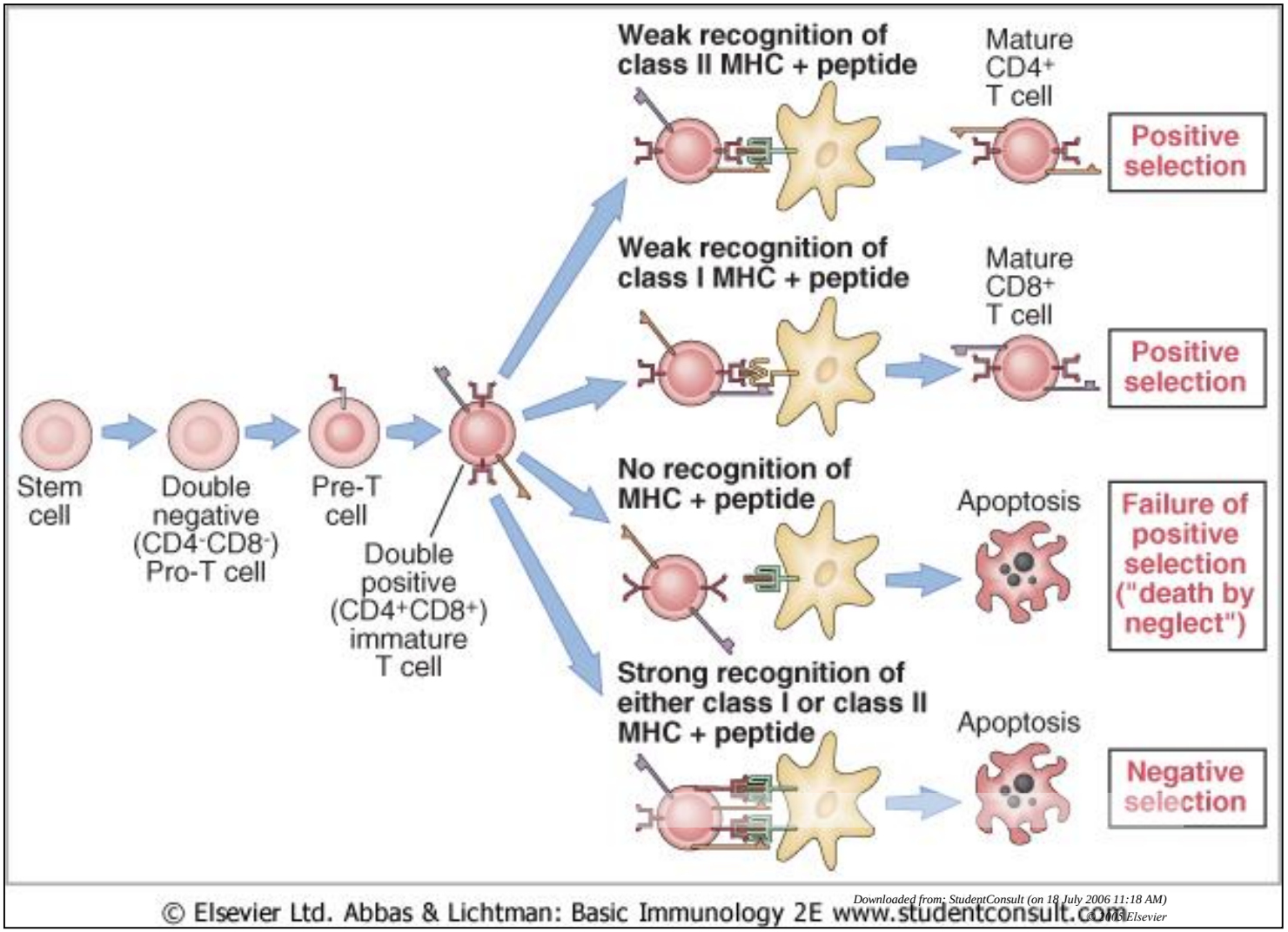


Figure 5-13 The Immune System, 2/e (© Garland Science 2005)

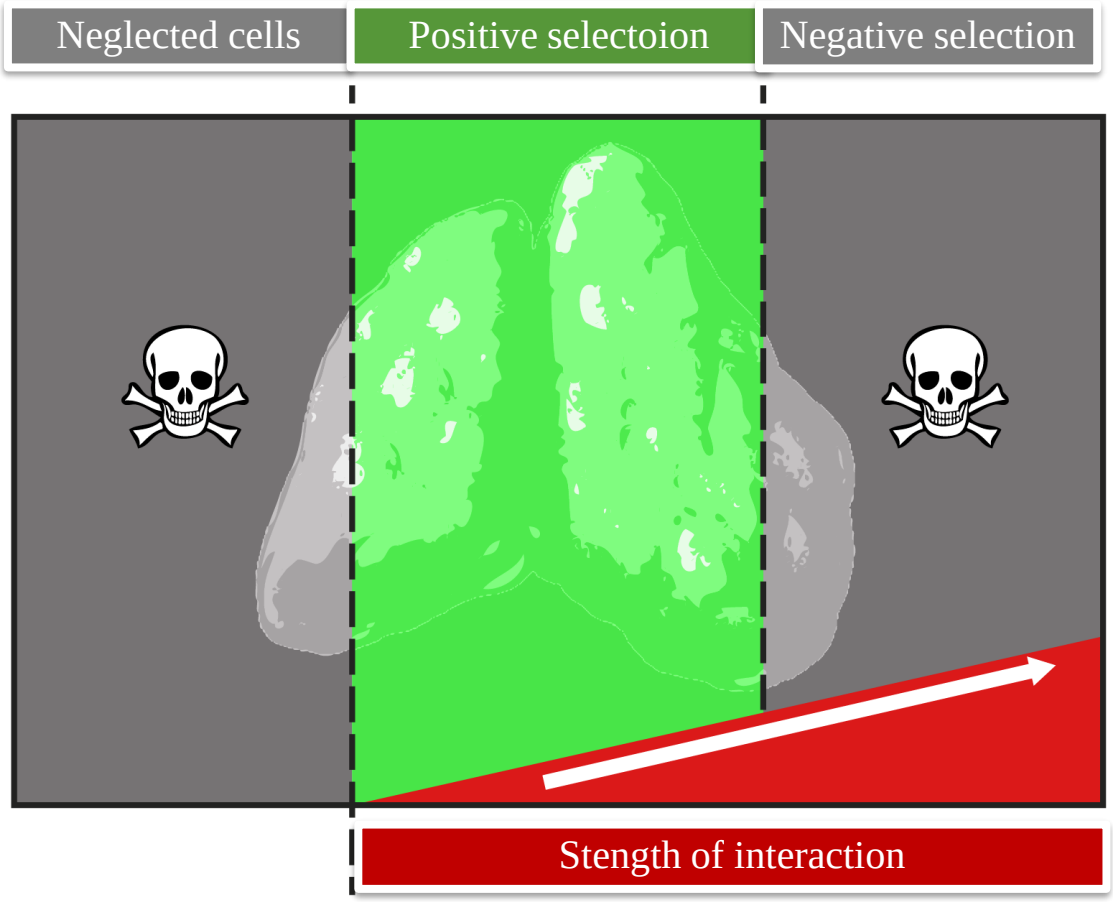
The Fate of T-lymphocytes in the Thymus



Thymic education of lymphocytes

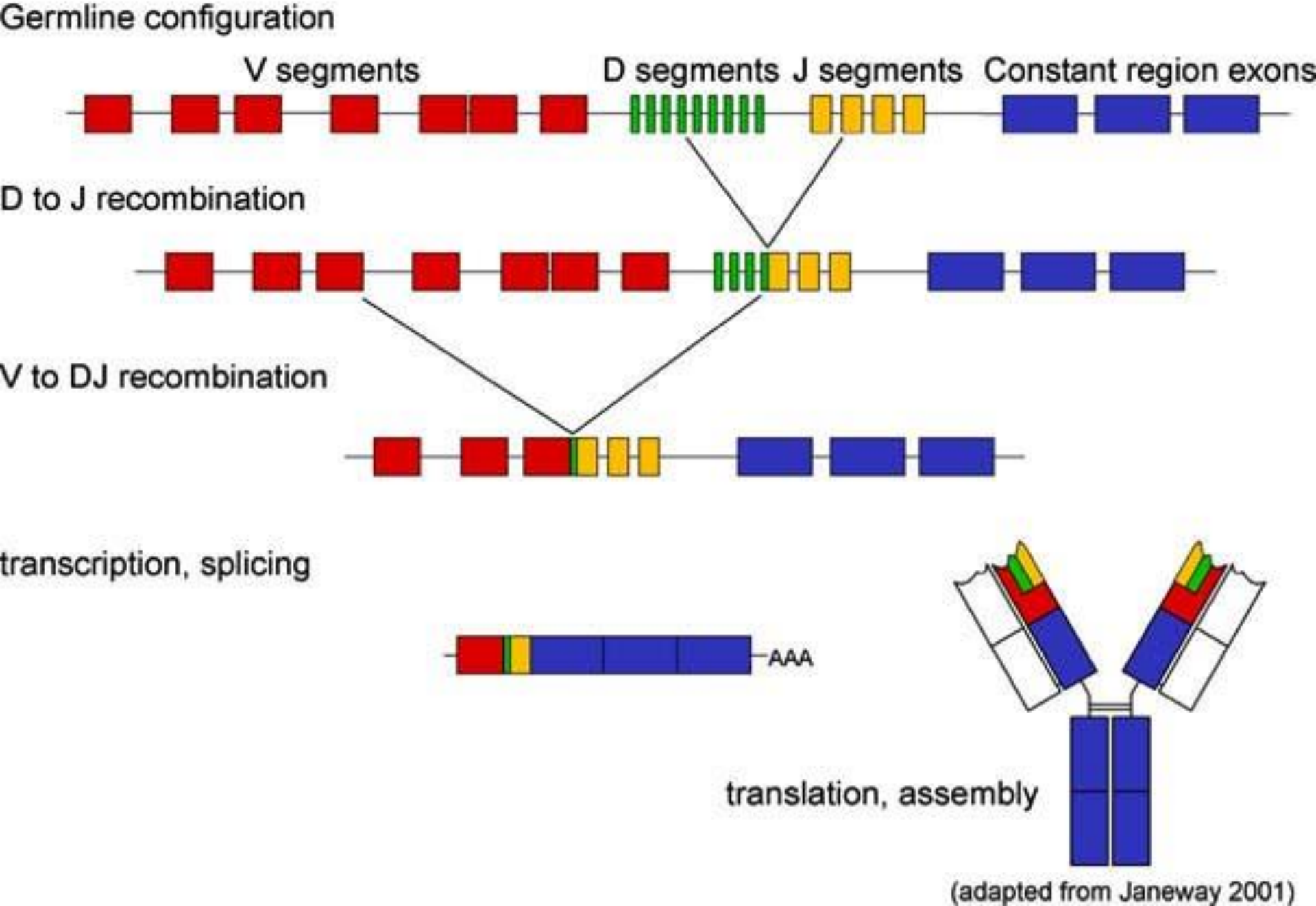


Strength of interaction between TCR and HLA-(antigen) complexes determines the fate of thymocytes



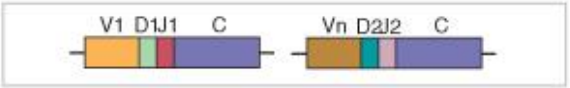
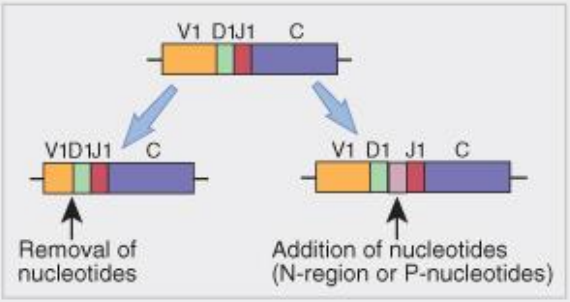
Cell death

Figure 5: V(D)J Recombination

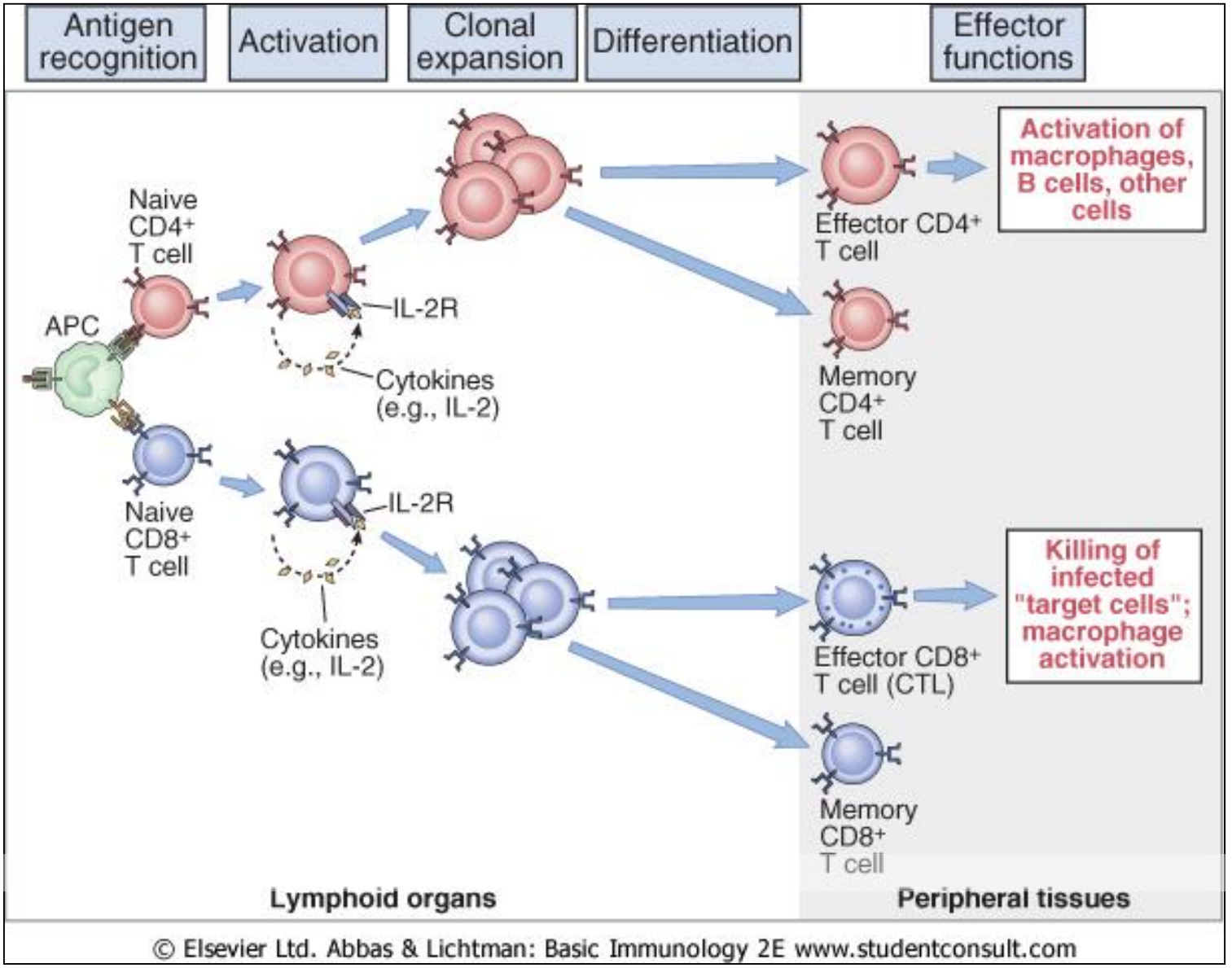


(adapted from Janeway 2001)

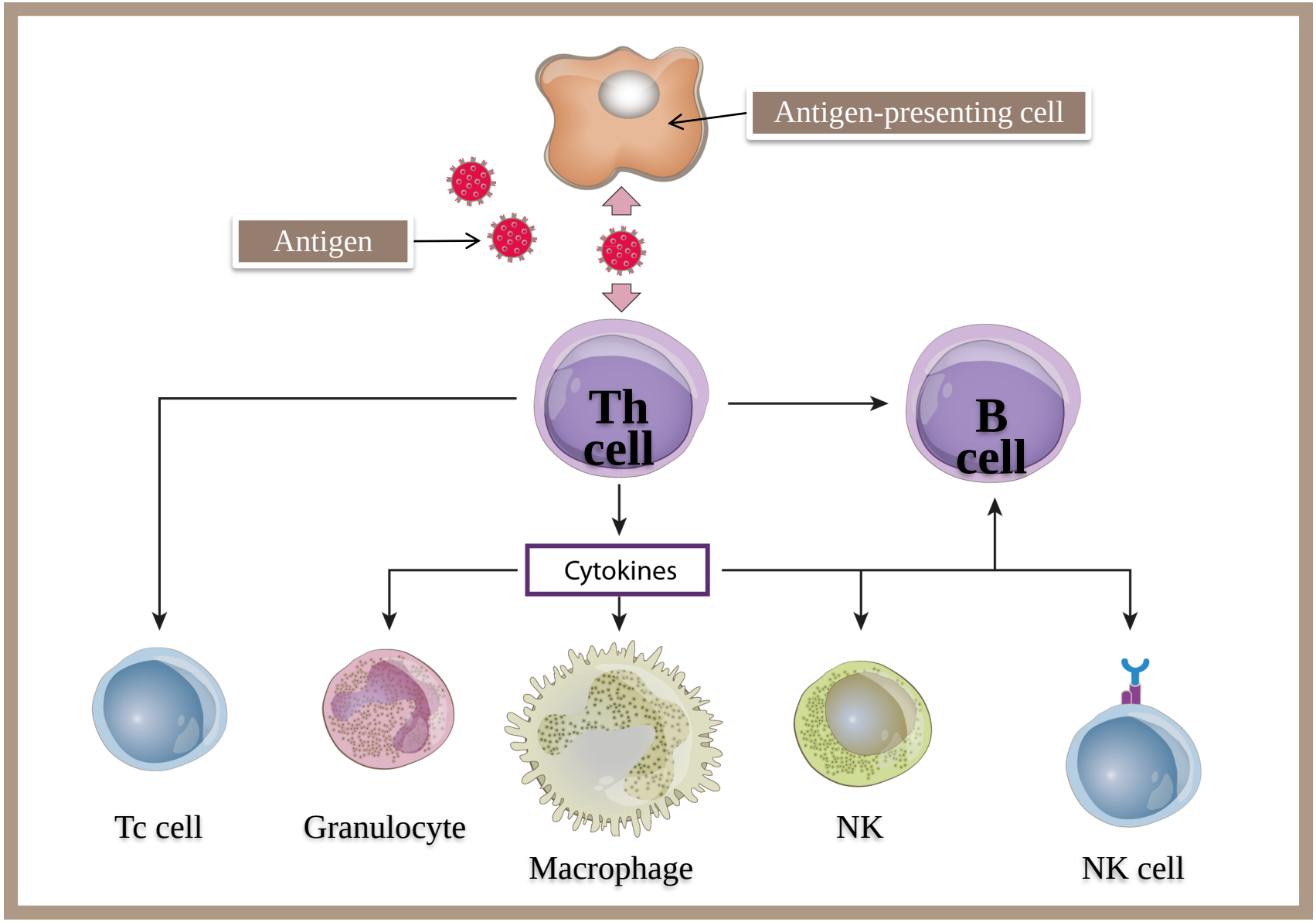
V, D and J genes involved in T- and B- cell receptor formation

	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: ~10^6		TCR: ~3×10^6	
Junctional diversity: Total potential repertoire with junctional diversity	 Ig: ~10^{11}		TCR: ~10^{16}	

Activation and differentiation of T-lymphocytes



Central role of T-lymphocytes in specific immune response



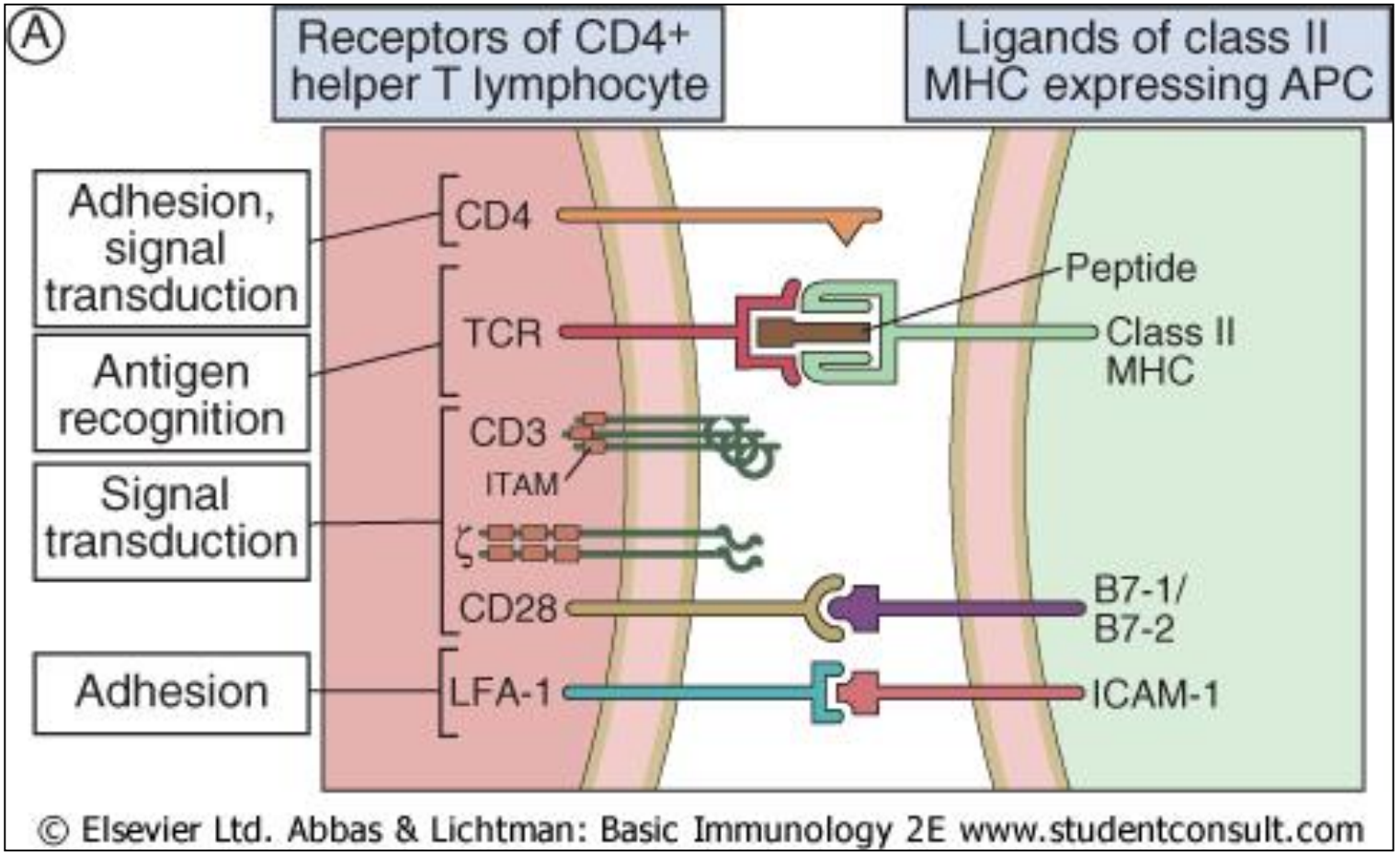
Determination of lymphocytes using cell surface antigens

- 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 stuctures 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.

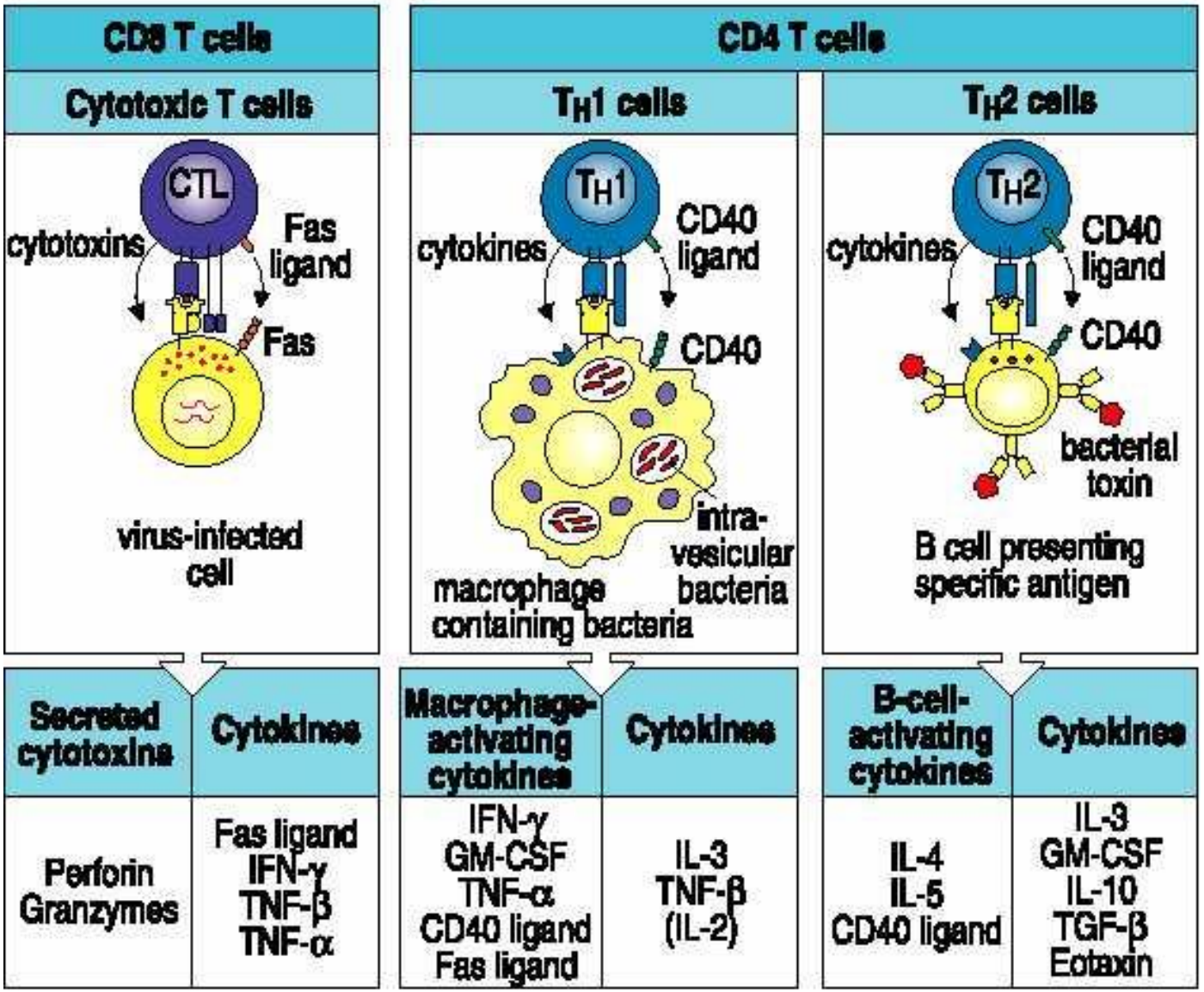
Subpopulations of Th-lymphocytes

- 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**

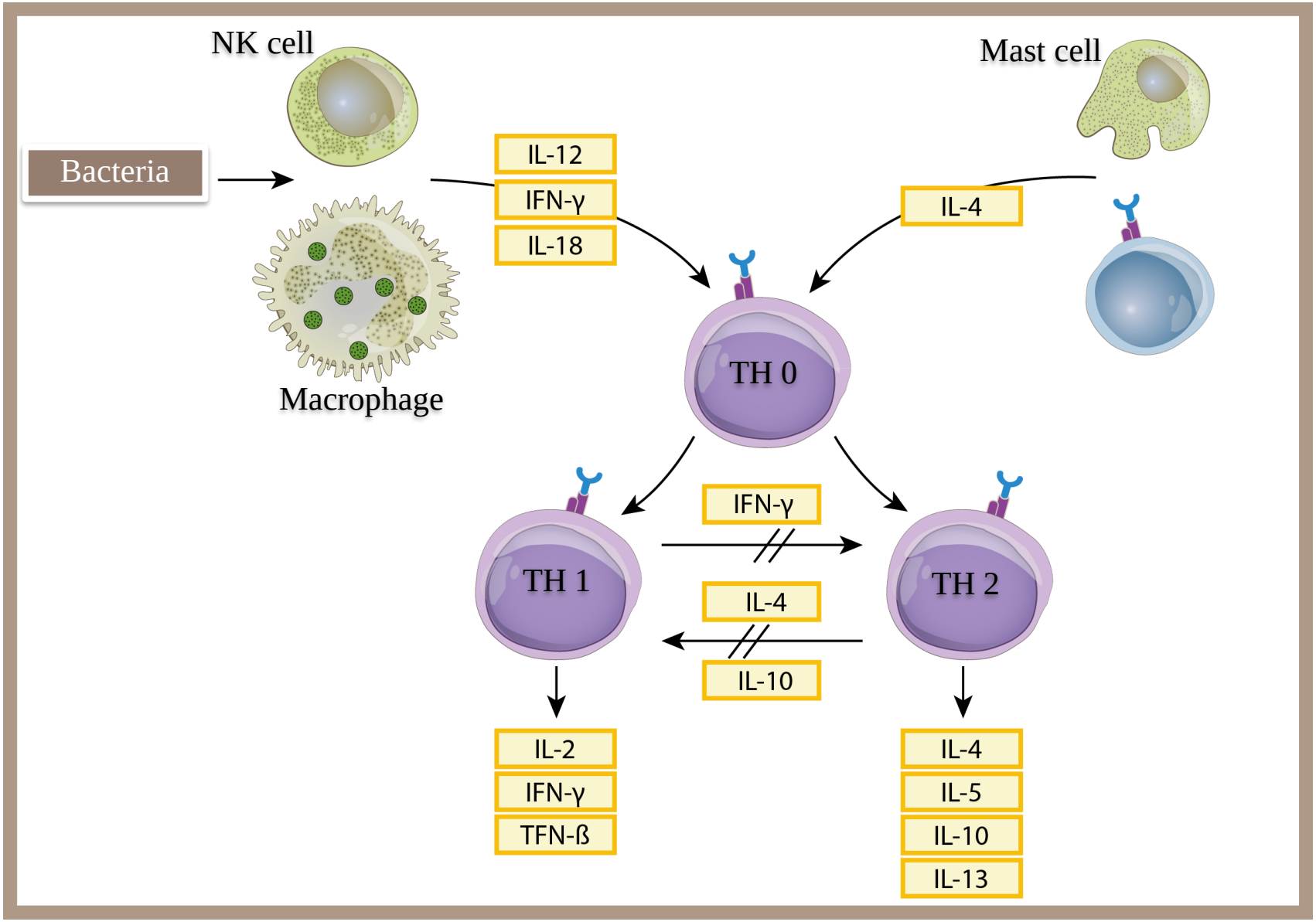
Also T_h9, $T_h22$lymphocytes

Functions of T-lymphocytes

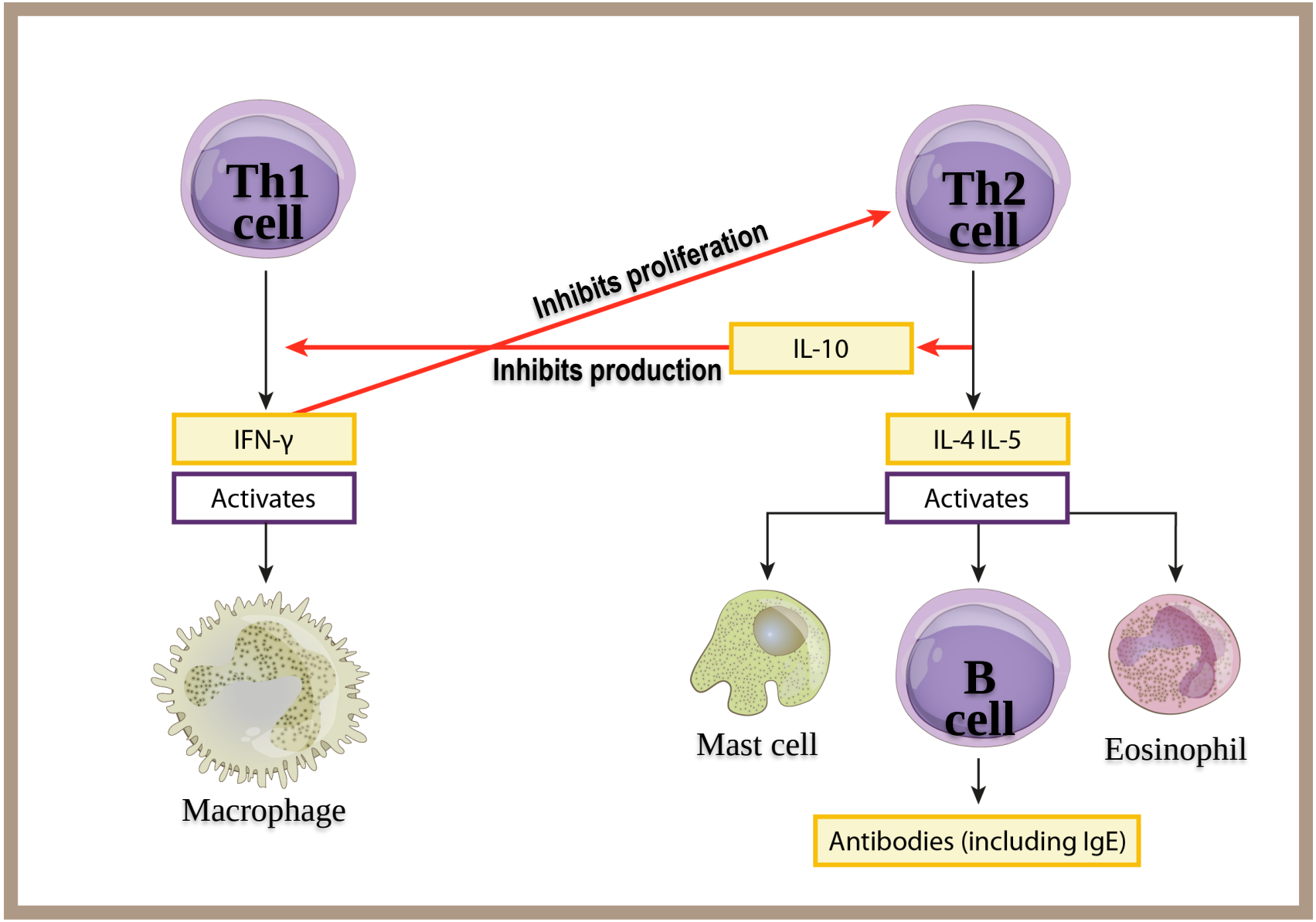
Figure 6.22



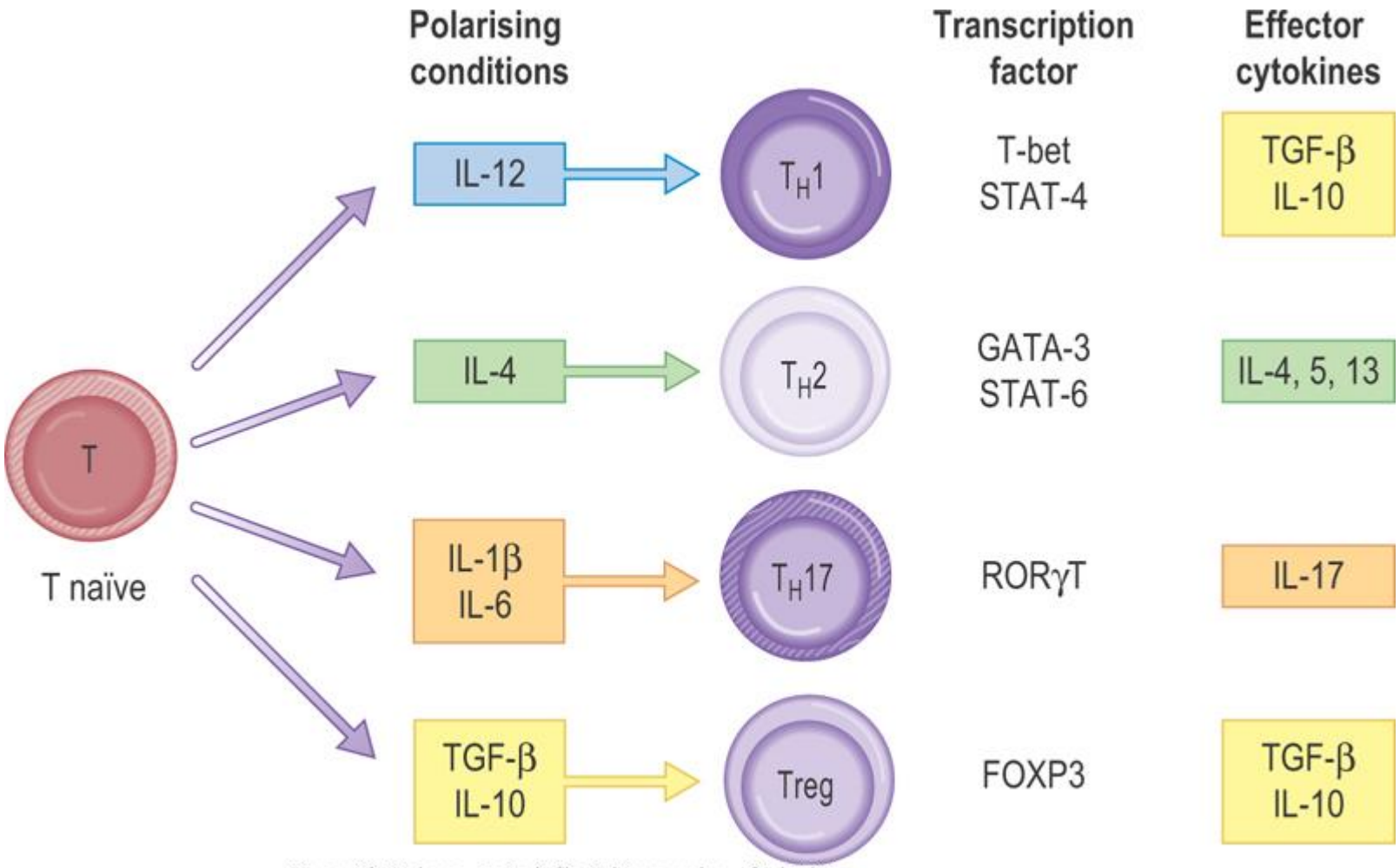
Development of Th1 and Th2 cells



Function of TH1 and Th2 cells



Cytokine environment decides the future development of Th0 cells

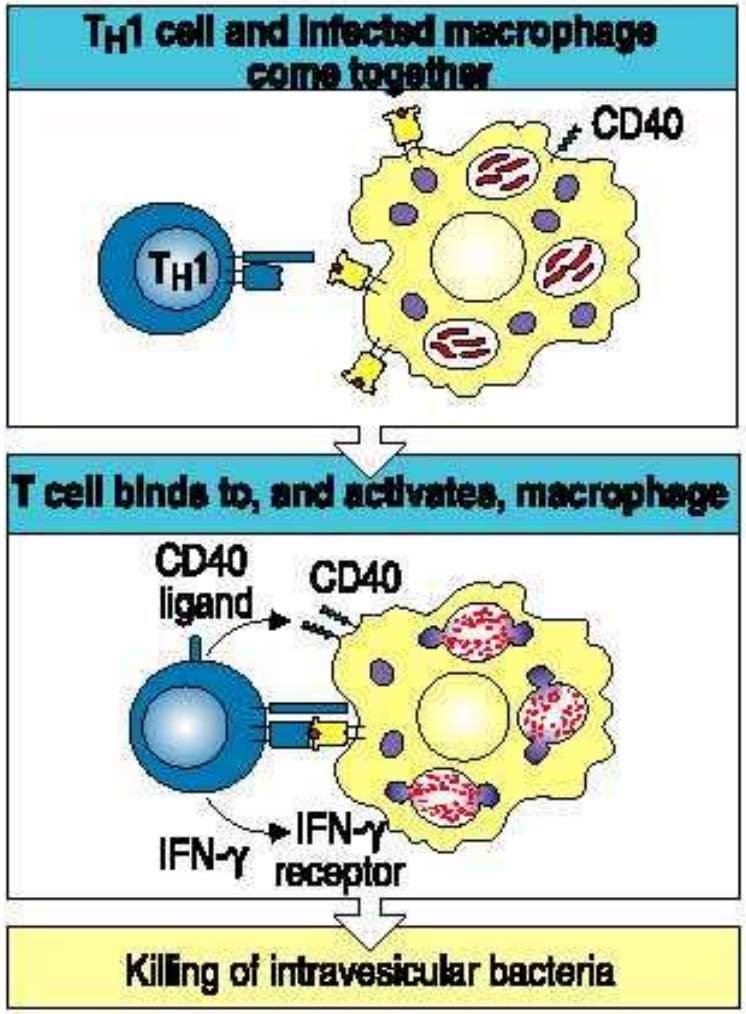


T_h1 lymphocytes

- 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 accute graft rejection

Function of Th1 cells

Figure 6.27

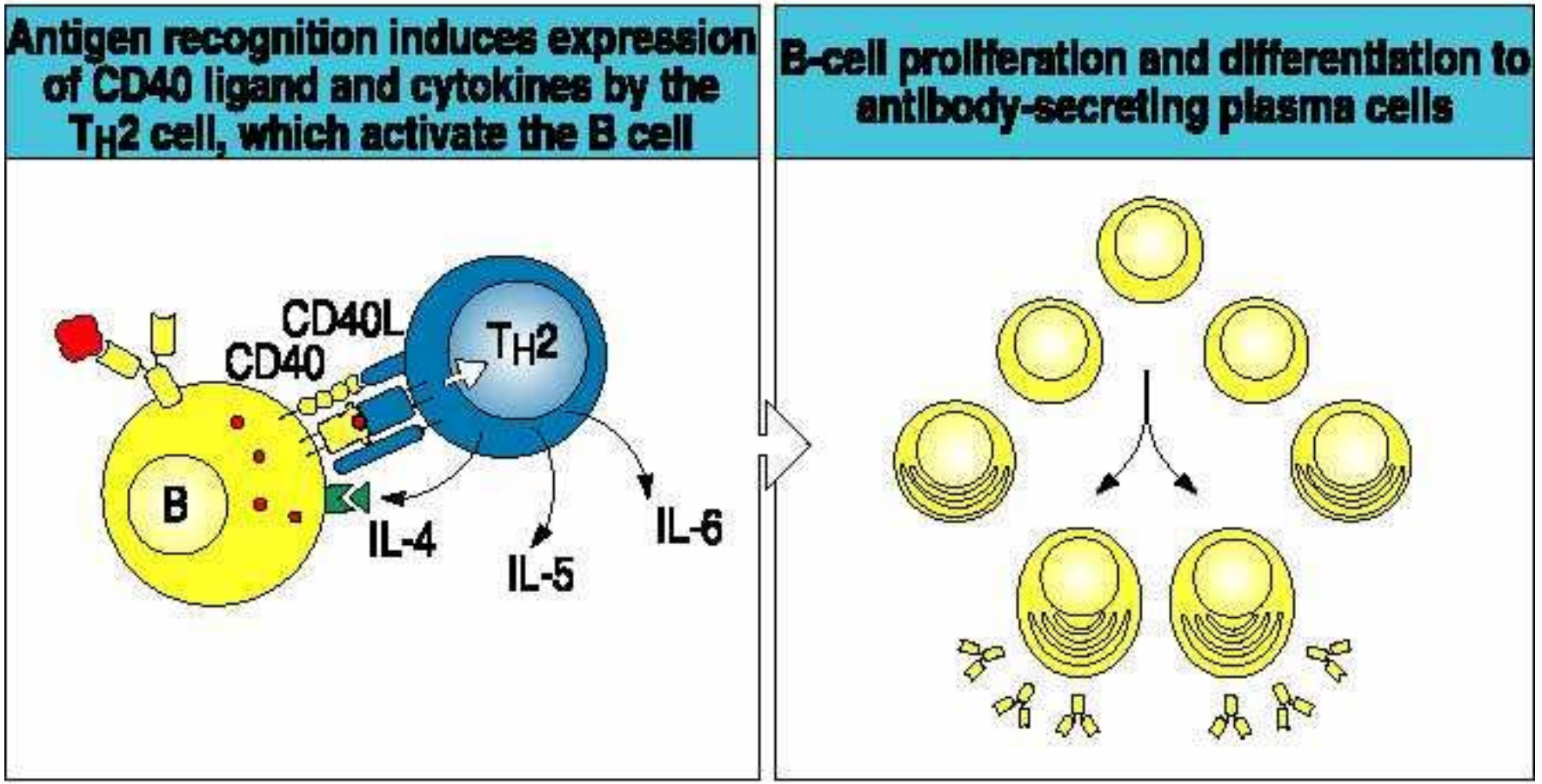


T_h2 lymphocytes

- 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 parazites
- 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



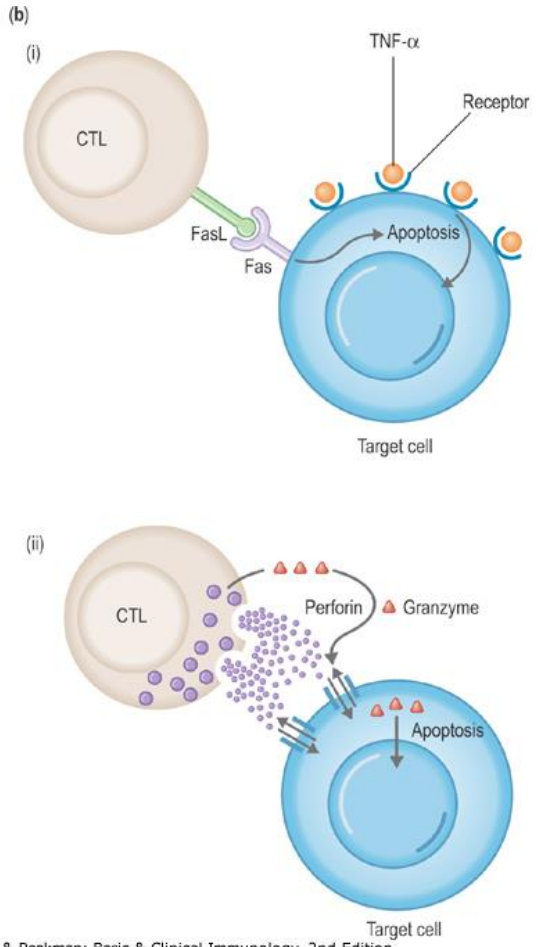
Th 17 cells

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

Cytotoxic T-lymfocytes

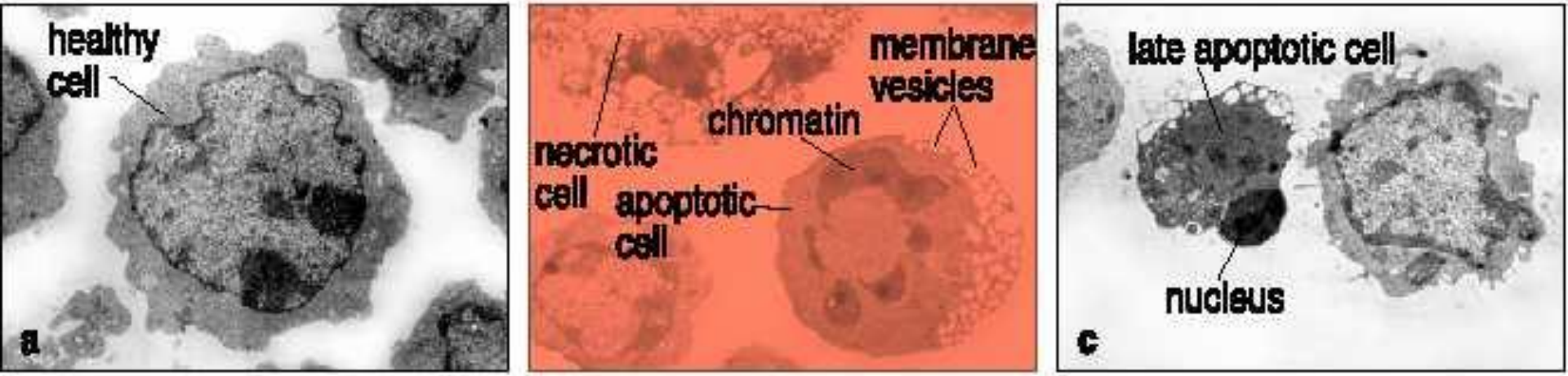
- CD8+
- Foreign antigens are recognized in complex with HLA-I class antigens.
- Mechanism of cytotoxicity: perforin (induction of membrane pores), various mechanism inducing apopsosis of the target cell (granzymes, FasL, lymfotoxin).
- Produce various cytokines (Tc1 and Tc2 cells)

Cytotoxic effect of CD8+ cells

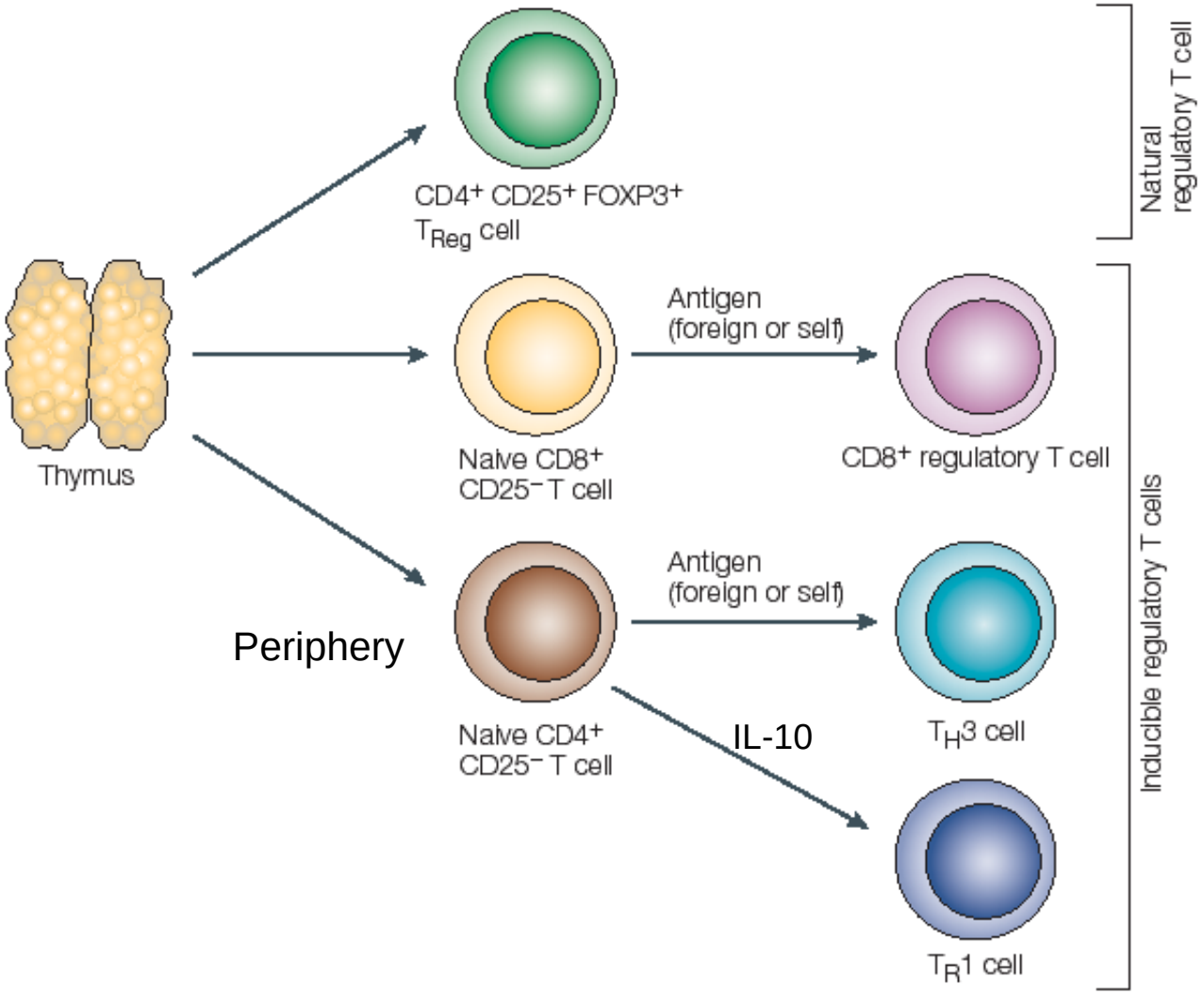


CD8 lymphocytes induce apoptosis of target cells

Figure 6.25



Types of regulatory T-lymphocytes



From: Nature Immunology

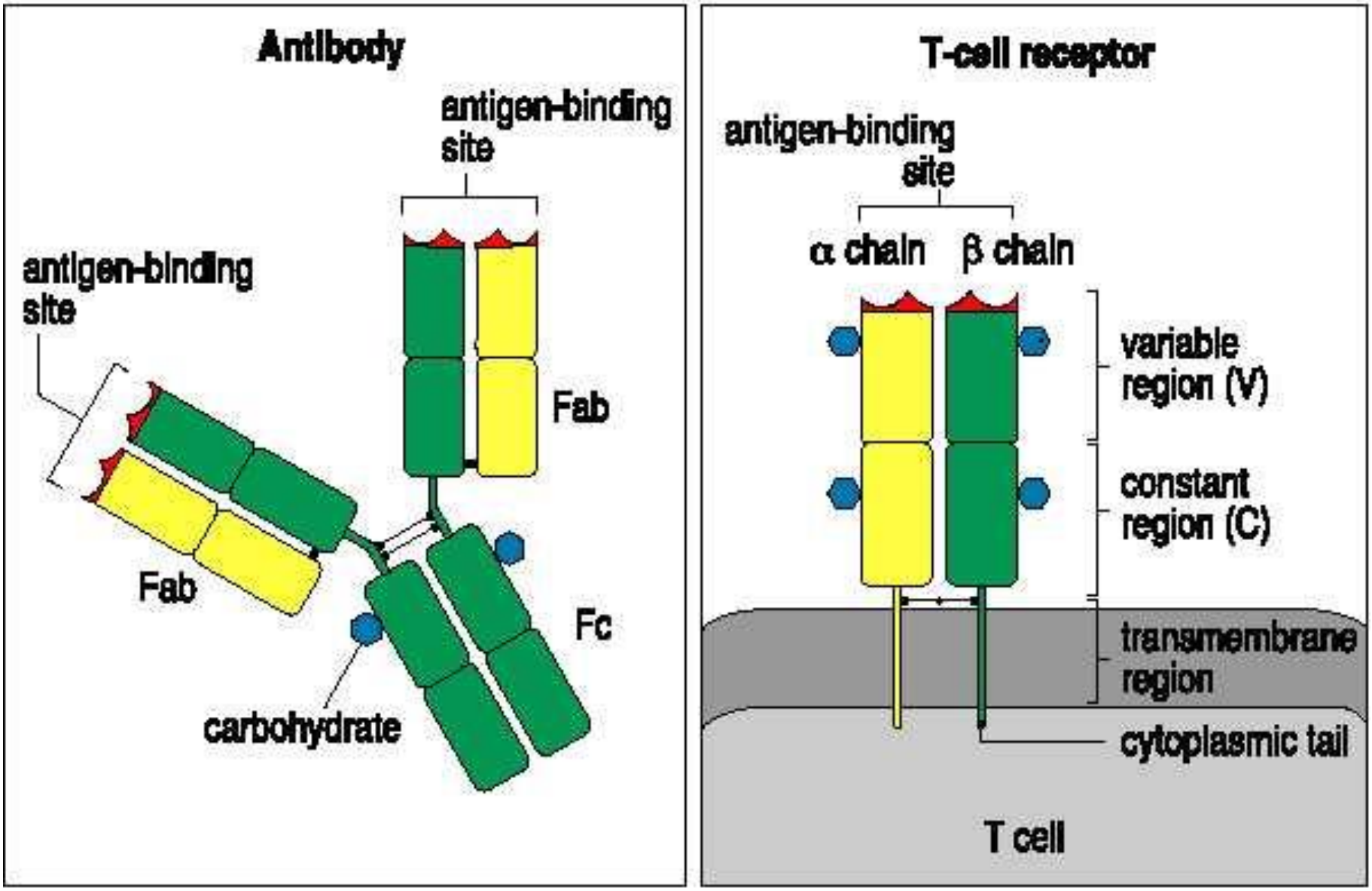
T_{reg} lymphocytes

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

TR-1 Lymphocytes

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

Figure 3.1 T- and B-cells antigen-speciphic receptors



γδ-T-lymphocytes

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

Intraepitelial 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+