T-cell-mediated response

Dr.Fawzia Ali Abdullah

3rd class

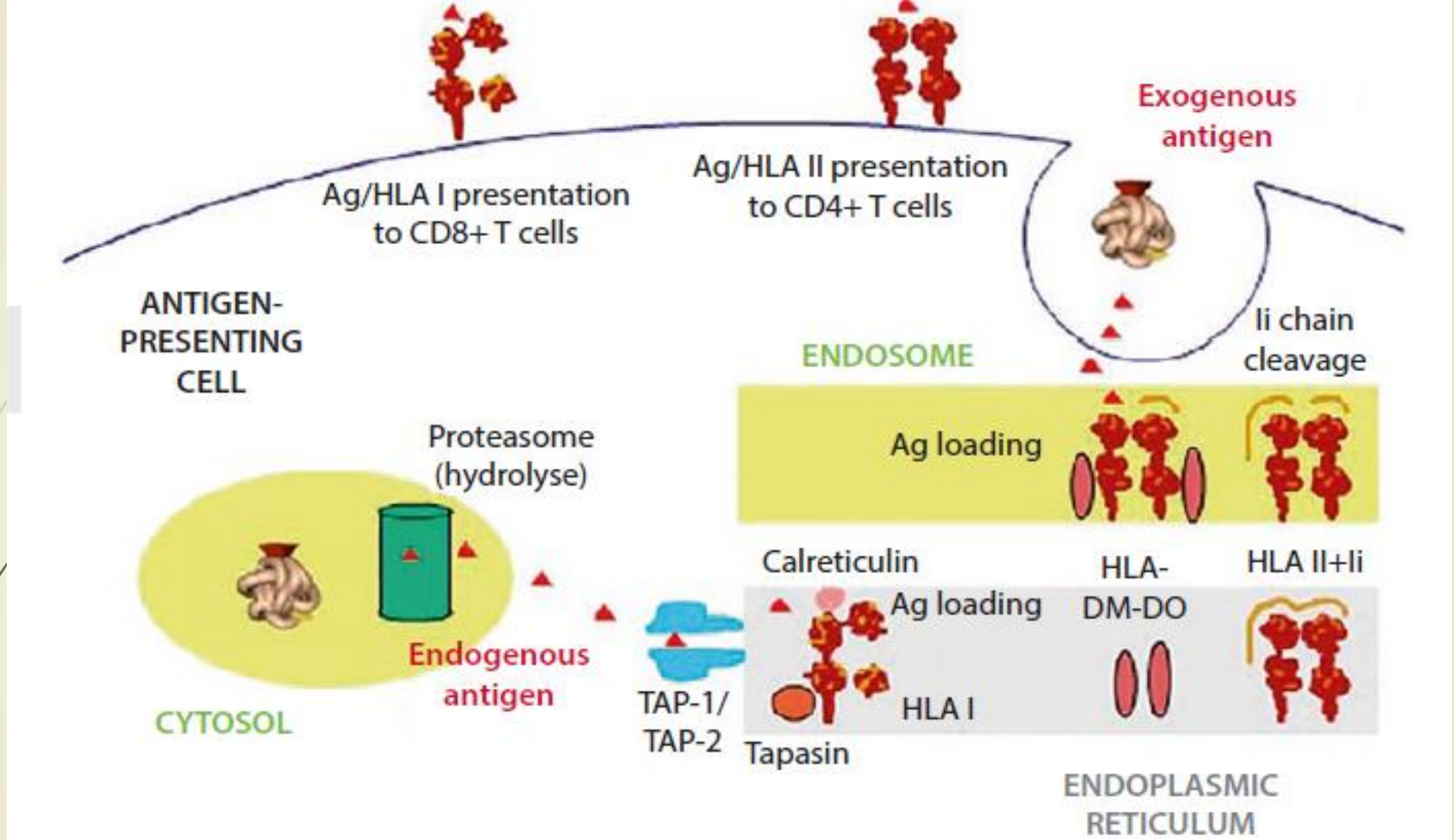


Fig. 4.1 Antigen processing

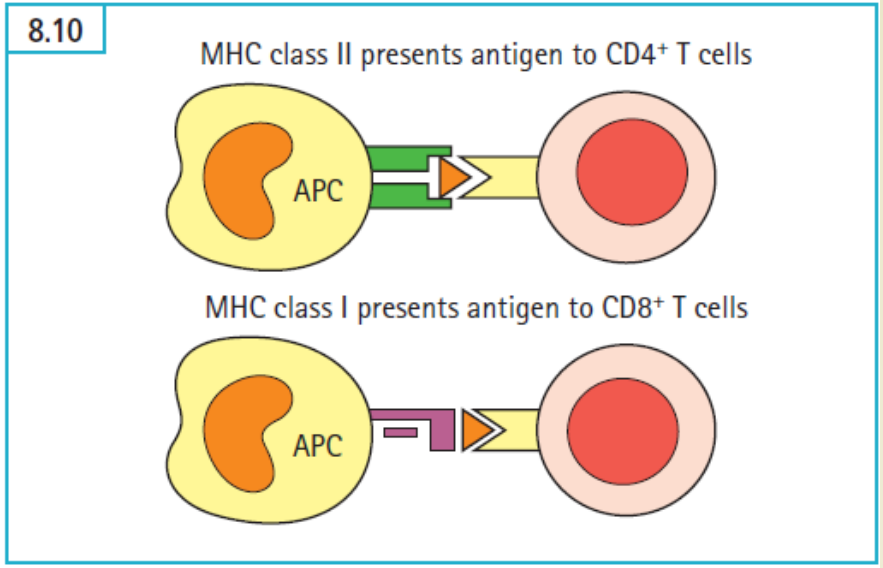
THE T-CELL RECEPTOR

- T lymphocytes are distinguished by the expression of the CD4 molecule (the helper T cells; Th) or the CD8 molecule (the cytotoxic T cells; Tc). all of these molecules are further members of the immunoglobulin superfamily
- The TCR of most T cells comprises an a and β chain, each of which has outermost variable domains and constant region domains bind to the cell membrane.

- In accordance with Burnett's clonal selection theory the extremely large. number of T cells within the immune system must have almost unique antigen specificity in order to provide protection from the very large number of foreign antigens.
- Each individual must therefore have an enormous 'repertoire' of different TCRs to make this possible. This extraordinary repertoire is created at the molecular level by rearranging the series of genes that encode different areas of the complete TCR a and β chains.

T-CELL ACTIVATION

- Peptides presented by MHC class II molecules stimulate only CD4+ T cells, whereas peptides presented by MHC class I are the signal for activation for CD8+ T cells (Figure 8.10).
- The TCR interacts both with contact residues on the peptide and also with residues on the surrounding MHC molecule, a phenomenon known as 'MHC-restriction'.
- T-cell activation. requires three signalling events: the recognition of peptide–MHC by the TCR(signal 1), the interaction of APC and T-cell surface molecules that form the 'immunological synapse' (signal 2), and the binding of an APC-derived co-stimulatory cytokine to a T-cell cytokine receptor (signal 3).(Figure 8.11).



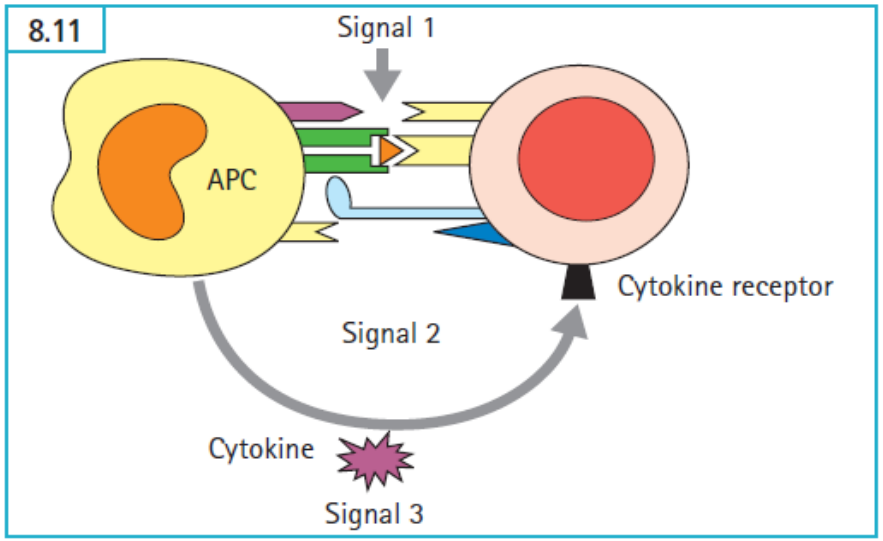
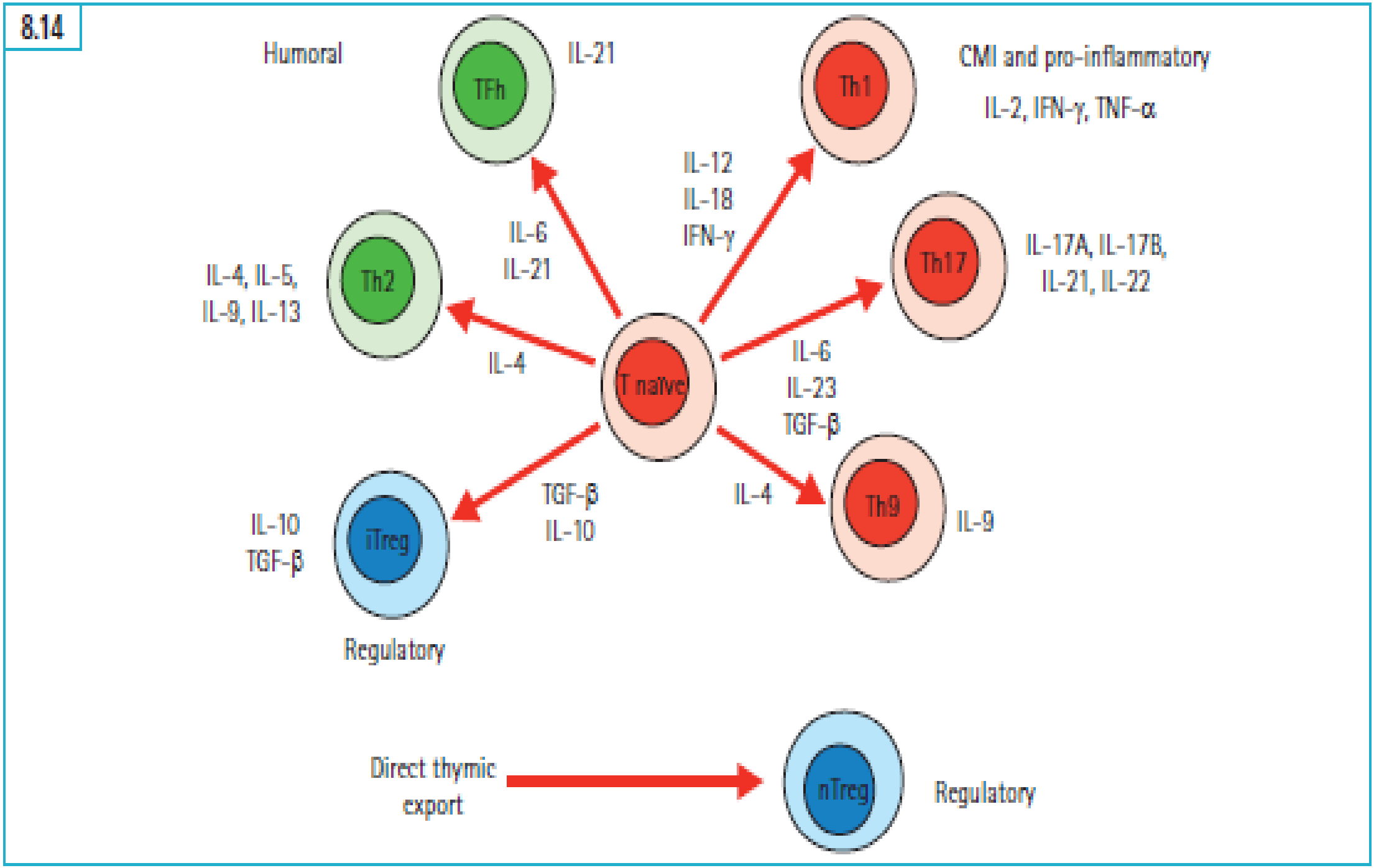


Fig. 8.11 T-cell activation. T-cell activation requires three signalling events: the recognition of peptide–MHC by the TCR (signal 1), the interaction of an array of APC and T-cell surface molecules that form the 'immunological synapse' (signal 2), and the binding of an APC-derived co-stimulatory cytokine to a T-cell cytokine receptor (signal 3).

THE ROLE OF CD4+ T LYMPHOCYTES

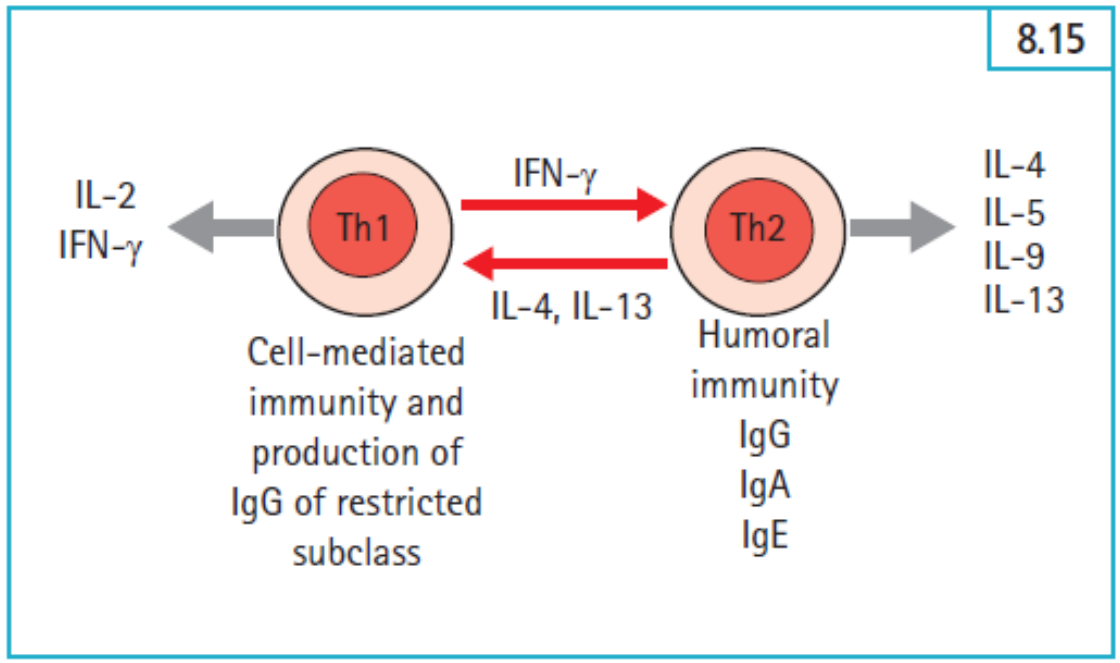
- CD4+ T cells are also termed ‘helper’ T cells (Th) and their major function is in providing such help for the generation of antibody production (humoral immunity) or cytotoxicity (cell-mediated immunity;CMI). these cells also have a key role in suppression or down-regulation of the immune response.
- Subsets of CD4+ T cells. Naïve CD4+ T cells may differentiate to become one of a number of effector T cells when activated by signals 1–3. The nature of signal 3 (i.e. the type of co-stimulatory cytokine indicated in the link between naïve and effector cell) is an important factor in this process.
- Effector T cell subsets are characterized by a specific cytokine signature (indicated adjacent to each cell type) and may function in cell-mediated/pro-inflammatory, humoral or regulatory roles. For example, Th17 cells are generated in the presence of IL-6, IL-23 and TGF-b signalling, and themselves produce the cytokines IL-17A, IL-17F, IL-21 and IL-22.
- Induced T regulatory (iTreg) cells are also generated from naïve CD4+ T cell precursors, while natural T regulatory (nTreg) cells are exported directly from the thymus.

8.14


Humoral
IL-21
TFh
CMI and pro-inflammatory
IL-2, IFN-γ, TNF-α
Th1
IL-12
IL-18
IFN-γ
IL-6
IL-21
IL-4, IL-5,
IL-9, IL-13
Th2
Th17
IL-17A, IL-17B,
IL-21, IL-22
IL-4
T naïve
IL-6
IL-23
TGF-β
TGF-β
IL-10
IL-10
TGF-β
iTreg
IL-4
Th9
IL-9
Regulatory
Direct thymic
export
nTreg
Regulatory

THE ROLE OF CD4+ T LYMPHOCYTES

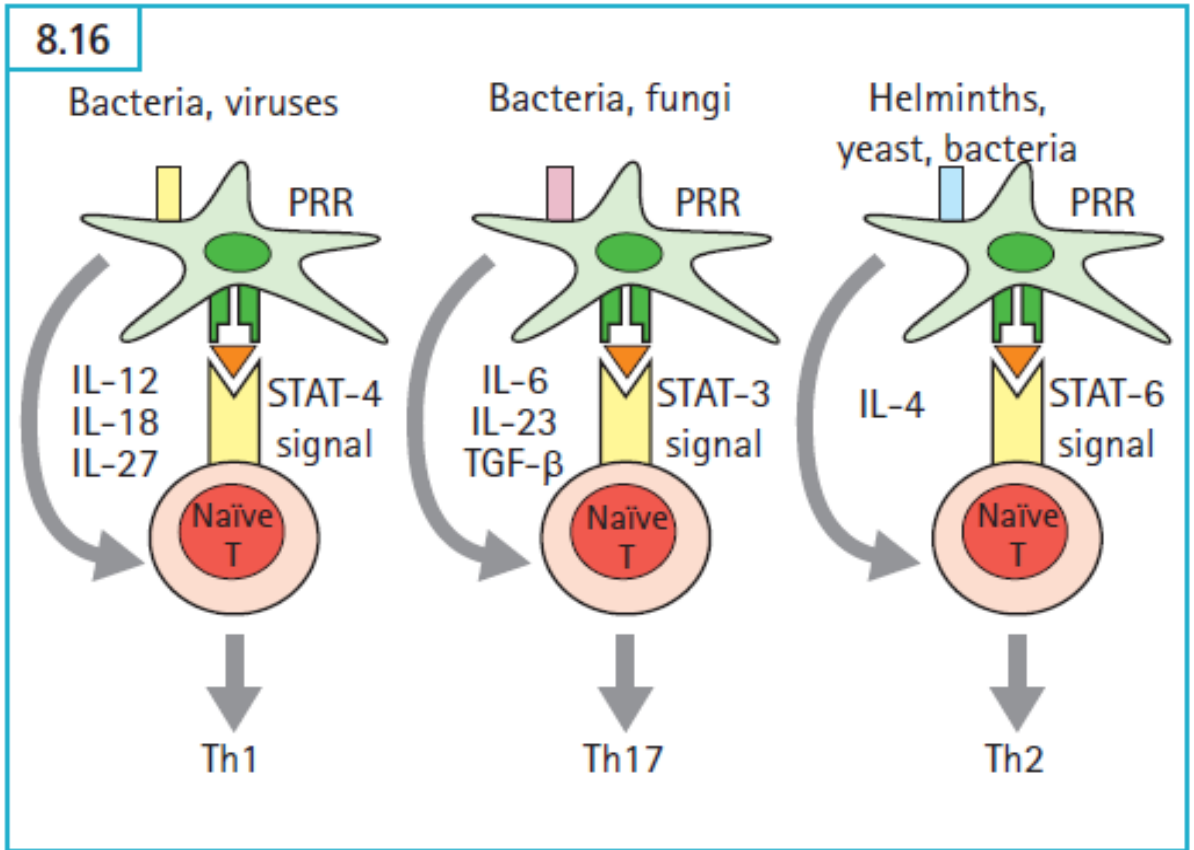
- The first of these subsets to be recognized were the T helper 1 (Th1) and T helper 2 (Th2) cells (Figure 8.15). These are both CD4+ T cells that carry an αβ TCR that responds to antigenic peptide–MHC class II on the surface of an APC.



- Th1 and Th2 CD4+ T lymphocytes. These two subsets of CD4+ T cells are characterized functionally on the basis of the cytokines that each produces.
- Th1 cells produce IL-2 and IFN-γ and stimulate cytotoxic cell-mediated immune responses. These cells provide limited help for those B cells that will eventually produce one IgG subclass involved in cytotoxic responses.
- Th2 cells produce IL-4, IL-5, IL-9 and IL-13 and preferentially provide help for B-cell differentiation and humoral immunity, leading to the production of IgG, IgA or IgE. The subsets are mutually antagonistic as IFN-γ is inhibitory of Th2 cells, and IL-4 and IL-13 are inhibitory of Th1 cell function.

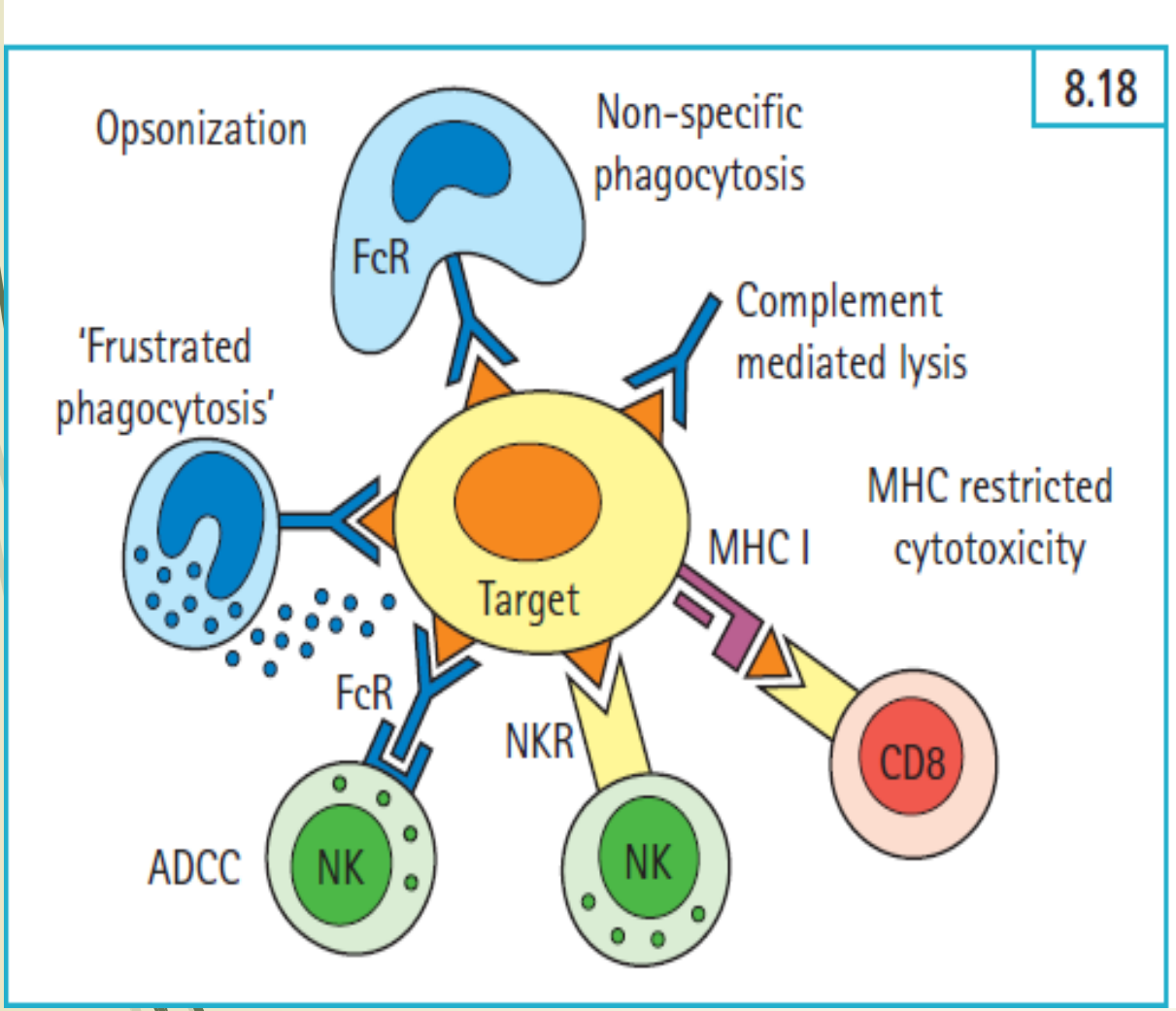
THE ROLE OF CD4+ T LYMPHOCYTES

- Th0 decision making. The decision of the naïve CD4+ T-cell precursor to differentiate to become a Th1, Th2 or Th17 effector is determined by the signals that the cell receives from the APC.



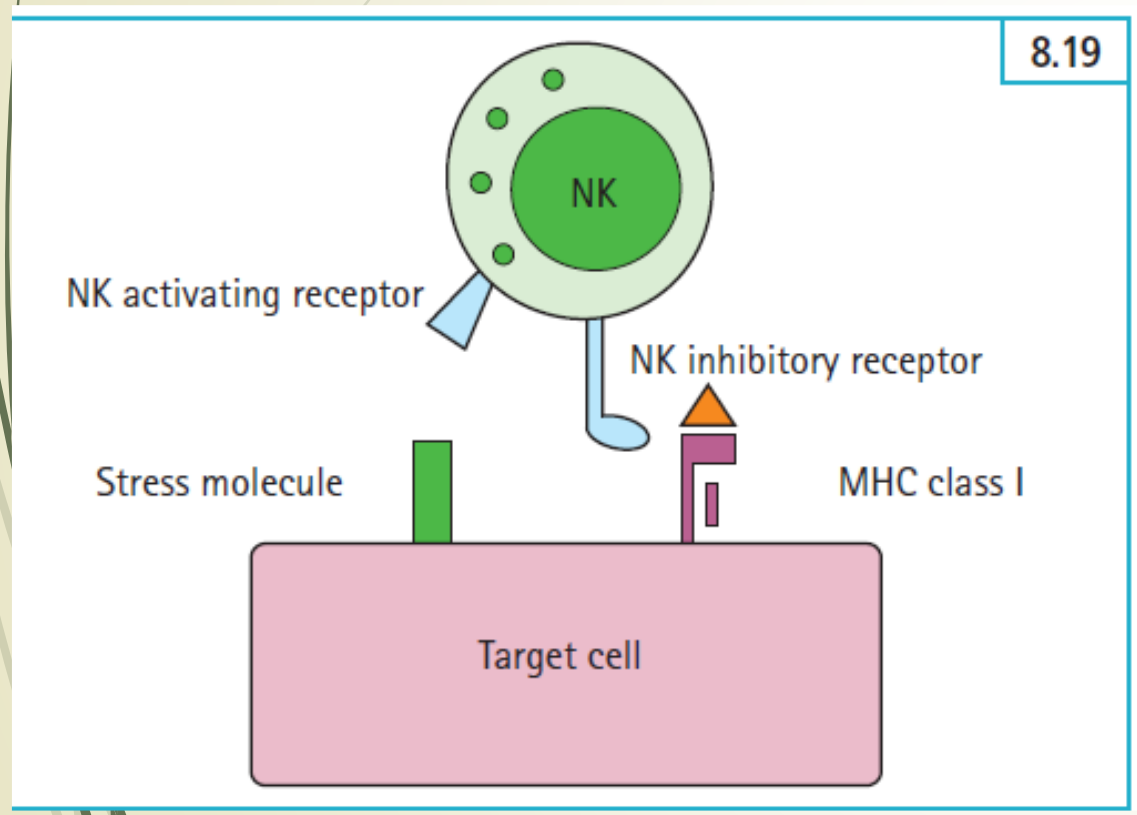
- These in turn are determined by the nature of the antigen and the combination of Pattern recognition receptors PRRs that are engaged by Pathogen-associated molecular patterns(PAMPs) expressed by that antigen.
- Differentiation to a Th1 cell requires IL-12, IL-18 or IL-27 co-stimulation and signalling through STAT-4.
- Differentiation to a Th2 cell requires IL-4 co-stimulation and signaling through STAT-6.
- Differentiation to a Th17 cell requires IL-6, IL-23 and TGF-β co-stimulation and signalling through STAT-3.
- STAT belongs to the Signal Transducer and Activator of Transcription family of proteins. These proteins transmit signals from a receptor complex to the nucleus and activate gene expression. The seven members of the STAT family are predominantly activated by growth factors and cytokines.

CYTOTOXICITY



- Cytotoxicity proceeds through several stages: recognition, adhesion, cytolysis and detachment
- The cytotoxic destruction of a target cell may arise in a number of different ways.
- The target cell may be opsonized and phagocytosed by a macrophage,
- It may be damaged by extracellular degranulation of neutrophils or eosinophils,
- antibody binding may activate the classical pathway of complement leading to formation of the MAC and osmotic lysis.

CYTOTOXICITY

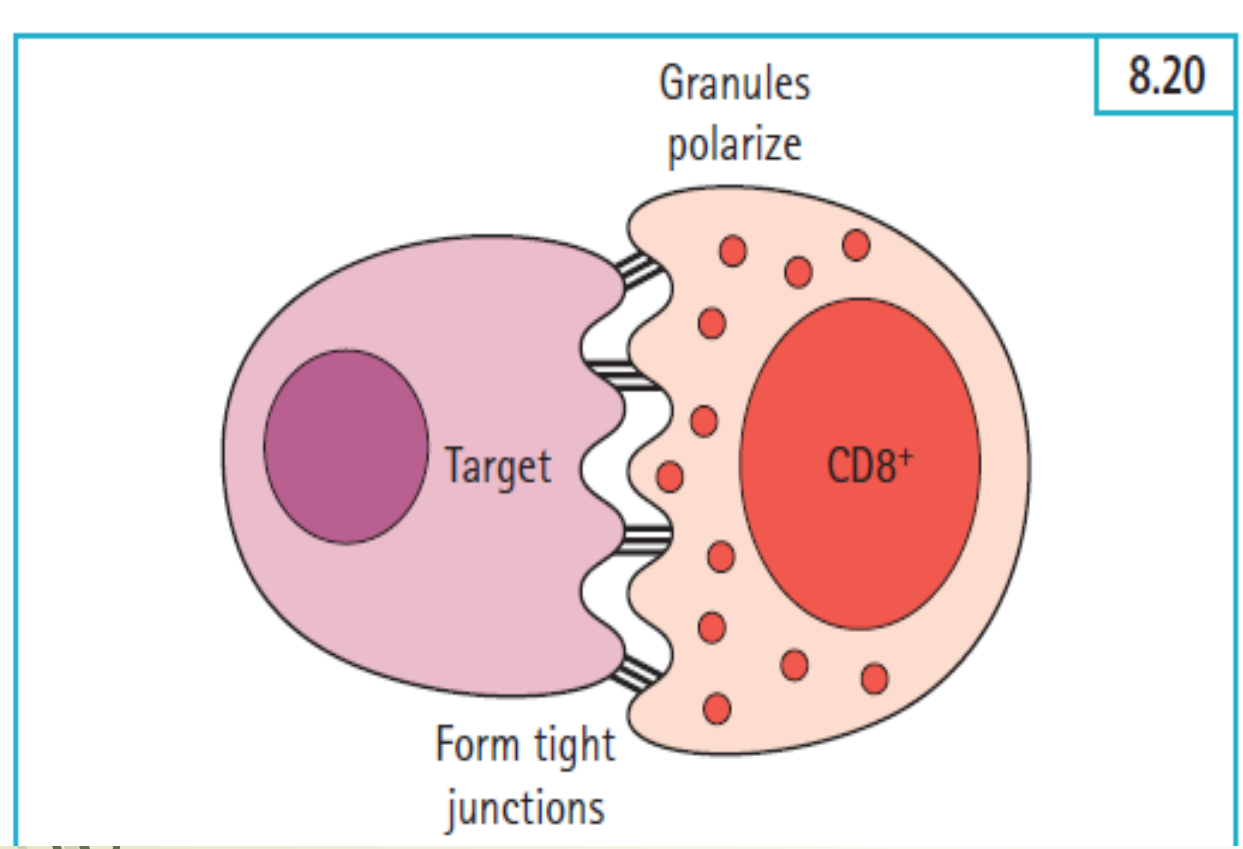


- The innate NK cells may recognize the target

through an activating receptor (NKR) or, alternatively, by binding antibody through the FcR in the process of ADCC.

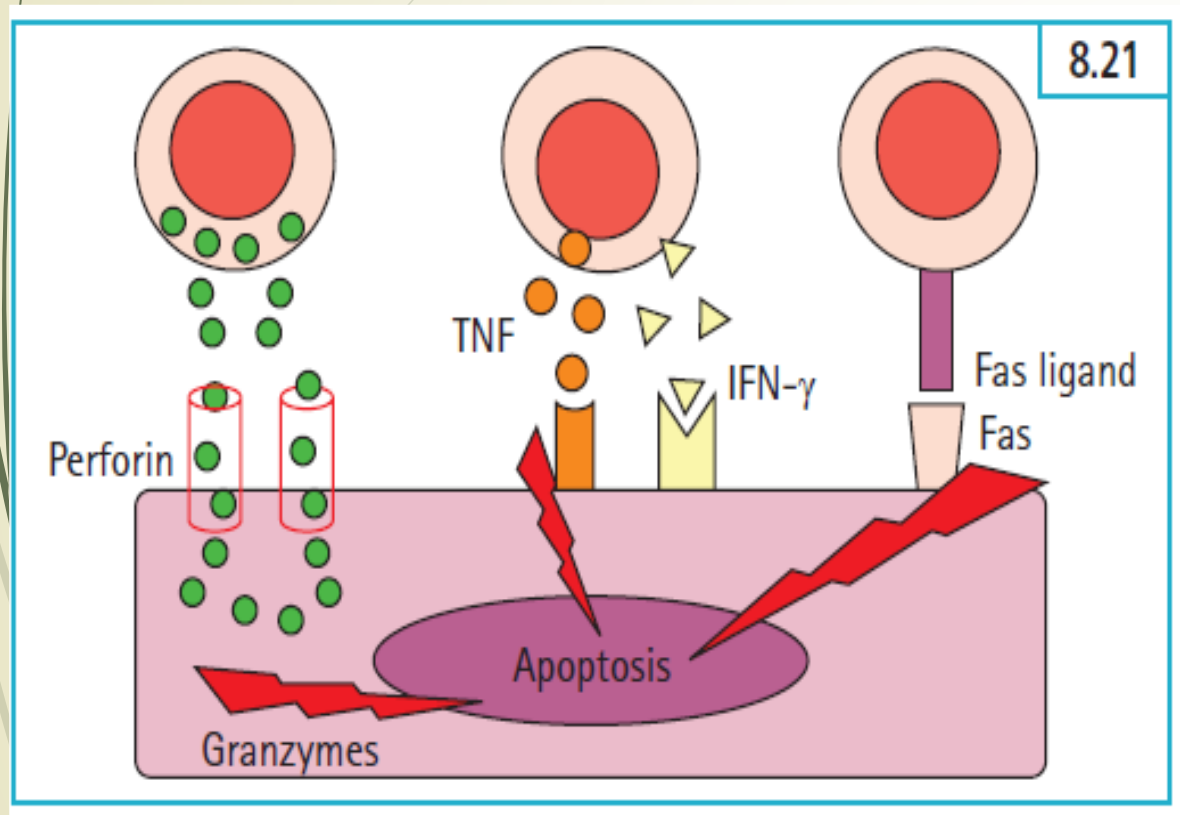
- NK cell activating receptors are members of the KIR, Ly49 or NKG2receptor families. which recognize cell surface molecules expressed by stressed cells directly.
- The NK cell can only be cytotoxic if that target cell fails to express MHC class I. Where class I is present (i.e. on a normal cell) this is bound by an inhibitory member of one of the receptor families, which prevents activation of the NK cell.

CYTOTOXICITY



- The adaptive CD8+ T cell recognizes the target in MHC-restricted fashion when that target expresses peptide
- Adhesion. After recognition, the cytotoxic cell forms close adhesion to the target cell.
- This involves interdigitation of the cell surface and the formation of tight junctions between the cells in order to create a contained microenvironment.
- The cytotoxic cell cytoplasmic granules polarize to the surface of the cell in apposition to the target.

CYTOTOXICITY



- Cytolysis. Several mechanisms are used by the cytotoxic cell to destroy the target.
- The cytoplasmic granule contents are released into the space between the two cells.
- One of these molecules (perforin) polymerizes and inserts into the target cell membrane to form a channel that has homology to the MAC of complement.
- Enzymes (granzymes) enter the target cell through this channel and cause direct damage in addition to activating the apoptotic pathway in the target.
- Apoptosis is also induced in the target following signalling through the TNF-γ receptor and the molecule Fas. The effects are amplified by cytokines such as IFN-γ.