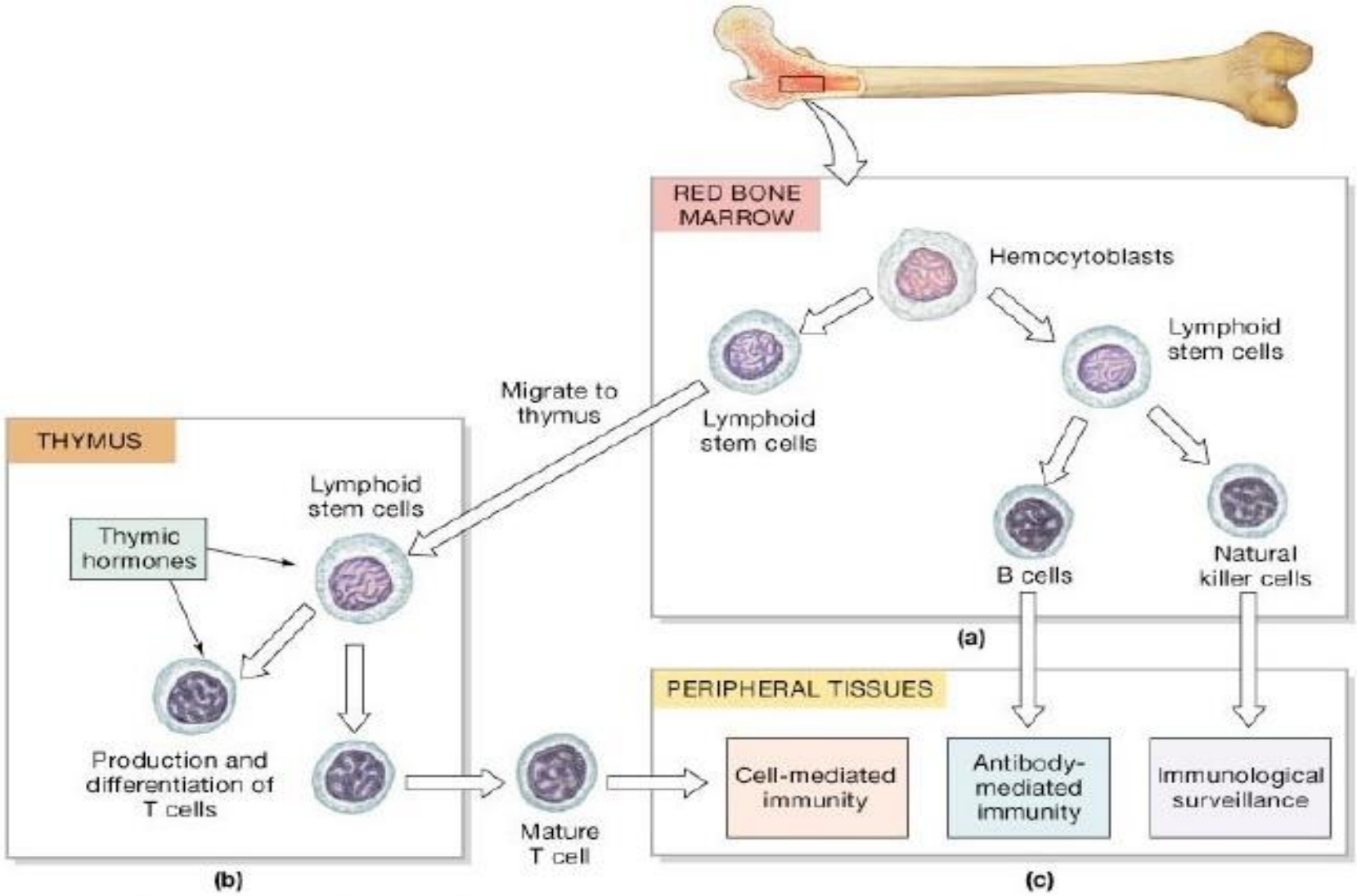
FACULTY OF ENGINEERING & TECHNOLOGY

Unit-I
Topic- T-Cell and B-Cell Activation and maturation.

Overview

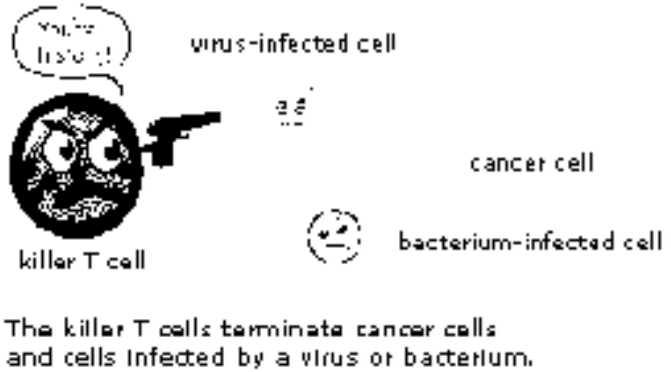

RED BONE MARROW
Hemocytoblasts
Lymphoid stem cells
Lymphoid stem cells
Migrate to thymus
B cells
Natural killer cells
(a)
THYMUS
Lymphoid stem cells
Thymic hormones
Production and differentiation of T cells
(b)
Mature T cell
PERIPHERAL TISSUES
Cell-mediated immunity
Antibody-mediated immunity
Immunological surveillance
(c)

T-Cell

arise in the bone marrow **BUT** migrate to the thymus gland to mature

cannot recognize antigen alone, T-cell receptors can recognize only antigen bound to cell-membrane proteins (MHC molecules)

CD4-TH; CD8-TC



The killer T cells terminate cancer cells and cells infected by a virus or bacterium.

TYPES:

Helper T cells, Cytotoxic T cells, Suppressor T cells

CRUCIAL STEPS:

a naive T cell encounters antigen combined with a MHC molecule on a cell

T cell proliferates

differentiates into memory T cells and various effector T cells

B-Cell

B lymphocytes mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane

Plasma cells live for only a few days, they secrete enormous amounts of antibody (2000/sec)

T-cell receptors (**TCRs**) enable the cell to bind to and, if additional signals are present, to be activated by and respond to an epitope presented by **APCs**

There are two types of T cells and thus two types of TCRs: CD8 and CD4

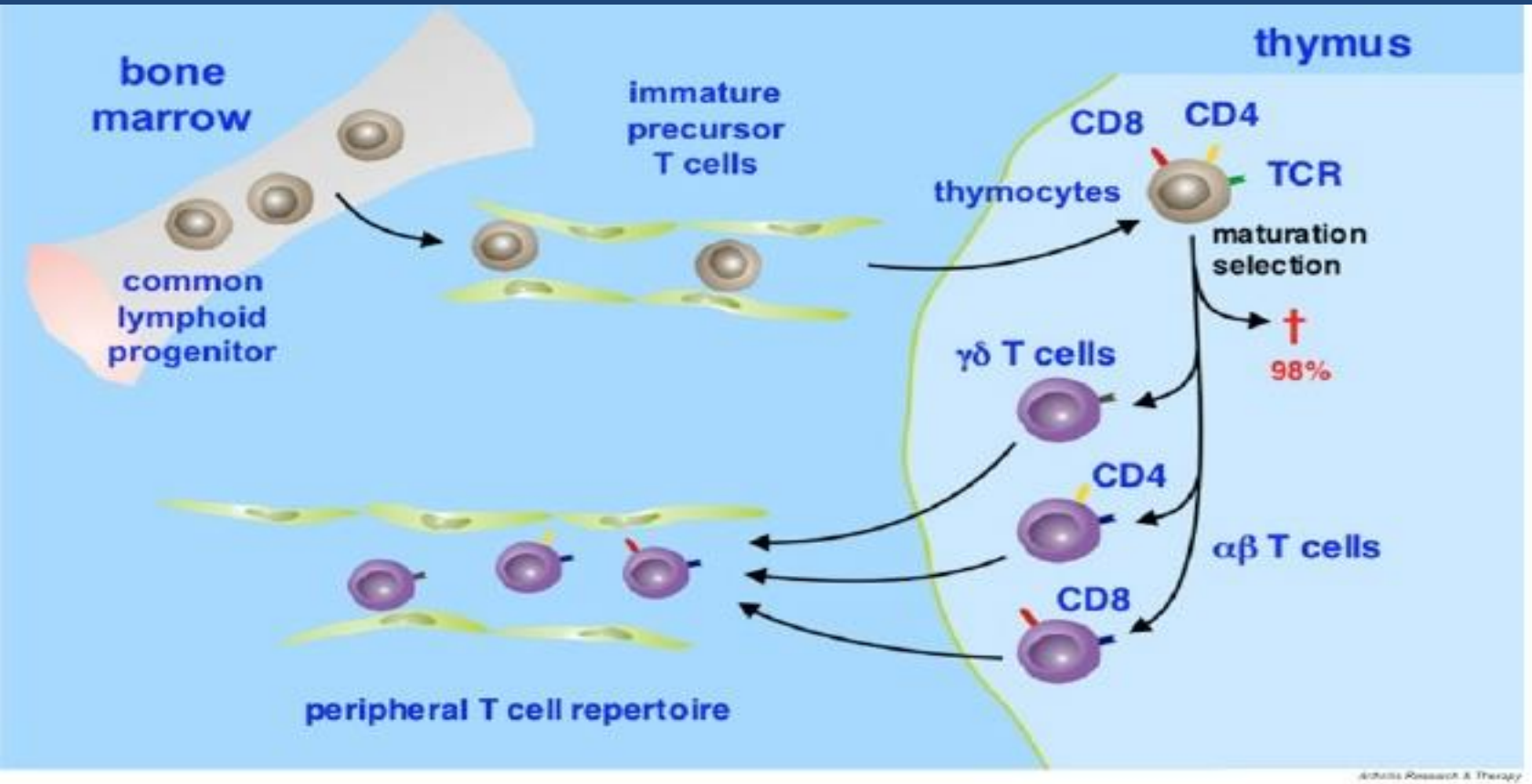
CD8 T cells destroy the cells they bind to, such as virus cells.

CD4 T cells group together to cause inflammation, which isolates an infected area so it can heal = helps build immunities

B-cell receptors (**BCRs**) enable the cell to bind to and, if additional signals are present, to be activated by and respond to an epitope on molecules of a **soluble antigen**

B cells bind to these toxins and digest them into smaller pieces

the response ends with descendants of the B cell secreting **antibodies** (via the plasma cells)



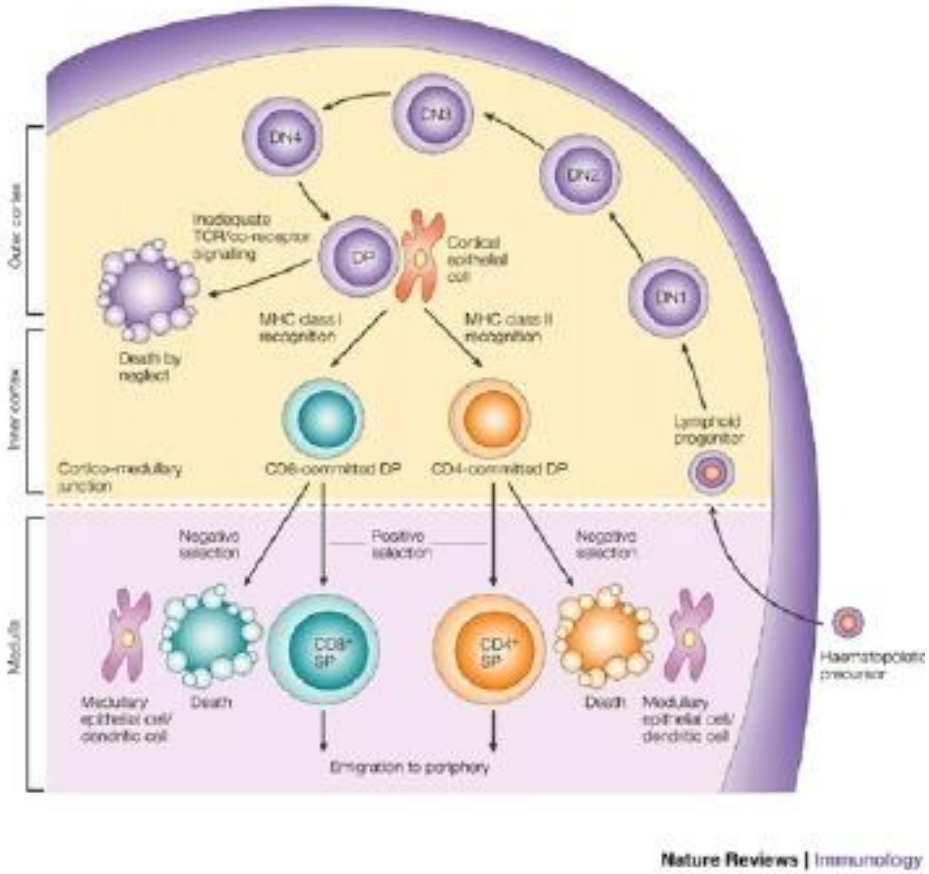
T-CELL

- In the thymus, developing T cells, known as thymocytes, proliferate and differentiate along developmental pathways that generate functionally distinct subpopulations of mature T cells
- Aside from being the main source of all T cells, it is where T cells diversify and then are shaped into an effective primary T-cell repertoire by [illegible] pair of selection processes (+ and - SELECTION)

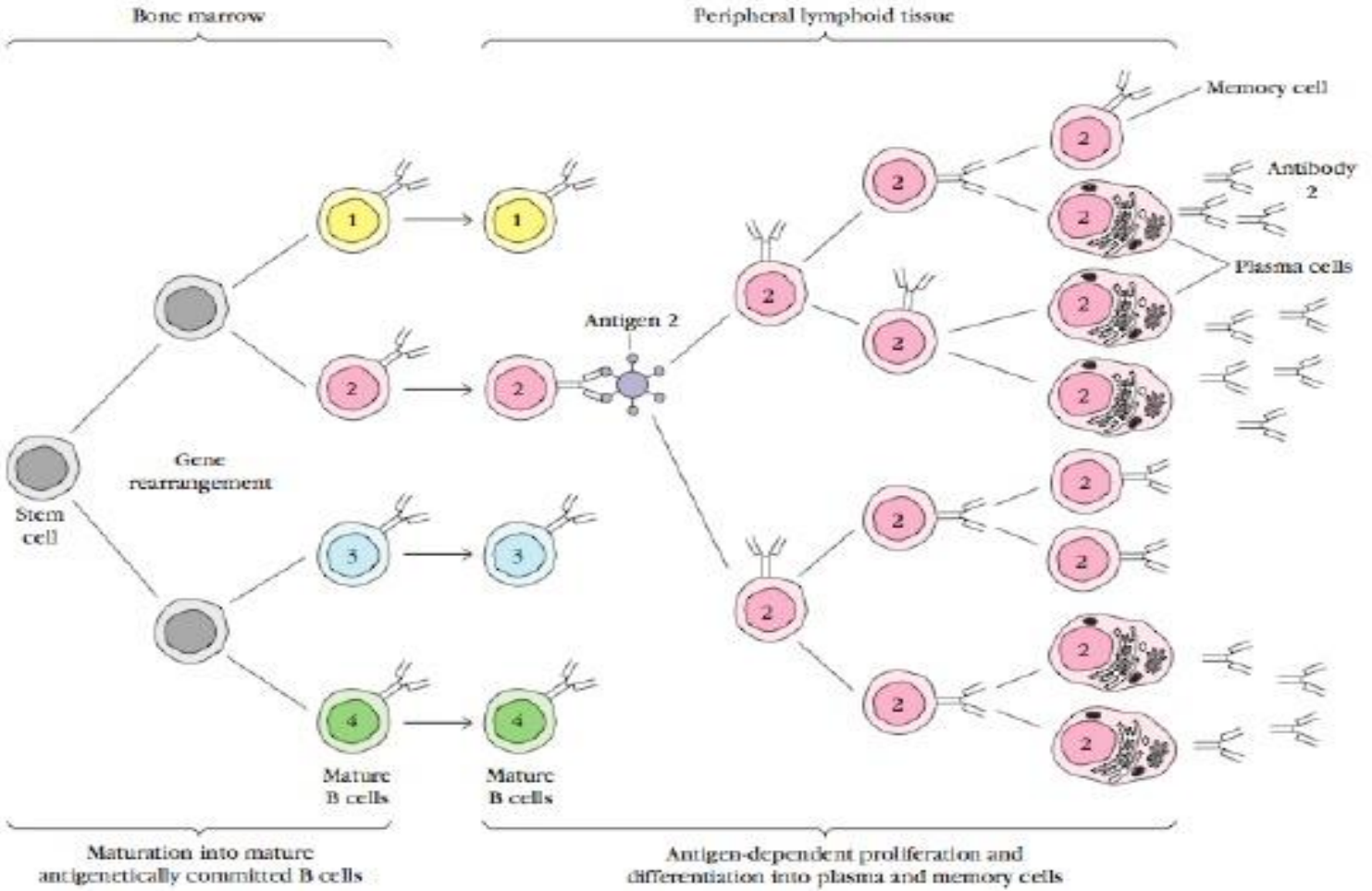
Overview

POSITIVE AND NEGATIVE SELECTION

- **positive selection**, permits the survival of only those T cells whose TCRs are capable of recognizing self-MHC molecules
  - It is thus responsible for the ***creation of a self-MHC-restricted repertoire of T cells***
    - Cells that fail positive selection are eliminated within the thymus by apoptosis
- **negative selection**, eliminates T cells that react too strongly with self-MHC or with self-MHC plus self- peptides
  - bearing high-affinity receptors for self-MHC molecules alone or self-antigen presented by self-MHC, which results in self-tolerance



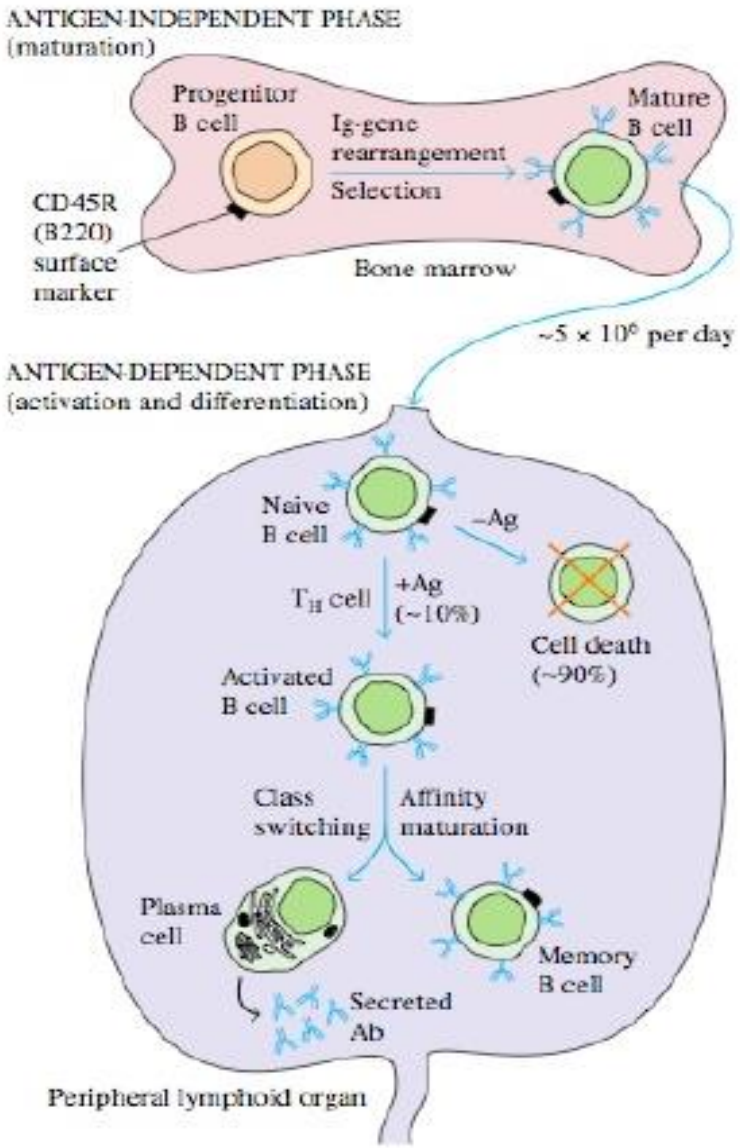
B - CELL



- B cells develop in bone marrow and undergo antigen-induced activation and differentiation in the periphery
- Activated B cells can give rise to antibody-secreting plasma

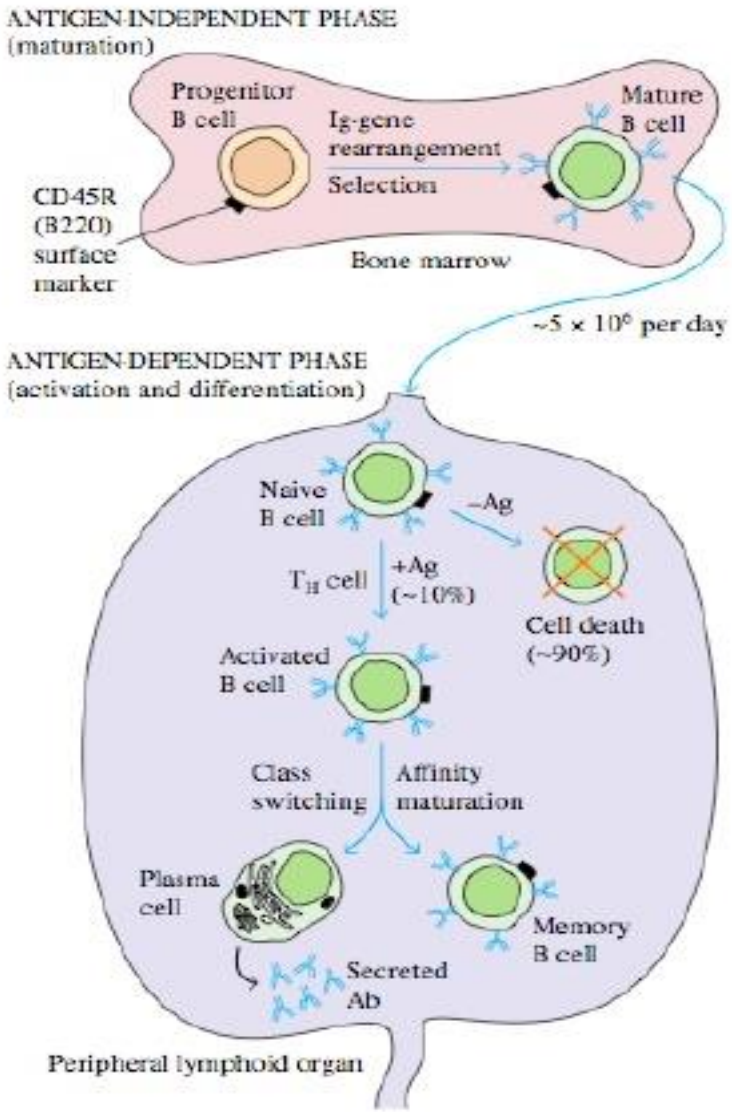
B CELL MATURATION AND DEVELOPMENT

- During B-cell development, sequential Ig-gene rearrangements transform a pro-B cell into an immature B cell expressing mIgM with a single antigenic specificity
- Further development yields mature naive B cells expressing both mIgM and mIgD



B CELL MATURATION AND DEVELOPMENT

- When a self-reactive BCR is expressed in the bone marrow, negative selection of the self-reactive immature B cells occurs
- The selected cells are deleted by apoptosis or undergo receptor editing to produce non-self-reactive mIg
- B cells reactive with self-antigens encountered in the periphery are rendered **anergic**



T cell Activation

- Initiated by TCR-CD3 complex with processed antigen on MHC molecule
  - $CD8^+$ cells with Class I
  - $CD4^+$ cells with Class II
- Initiates cascade of biochemical events
  - Inducing resting T cell to enter cell cycle, proliferate, differentiate into memory and effector T cells

T cell Activation

- Cascade of biochemical events leading to gene expression:
  - Interaction of signal and molecule (example: TCR + MHC and antigen)
  - Generation of "second messenger" that diffuses to other areas of cell
  - Protein kinases and protein phosphatases are activated or inhibitied
  - Signals are amplified by enzyme cascades

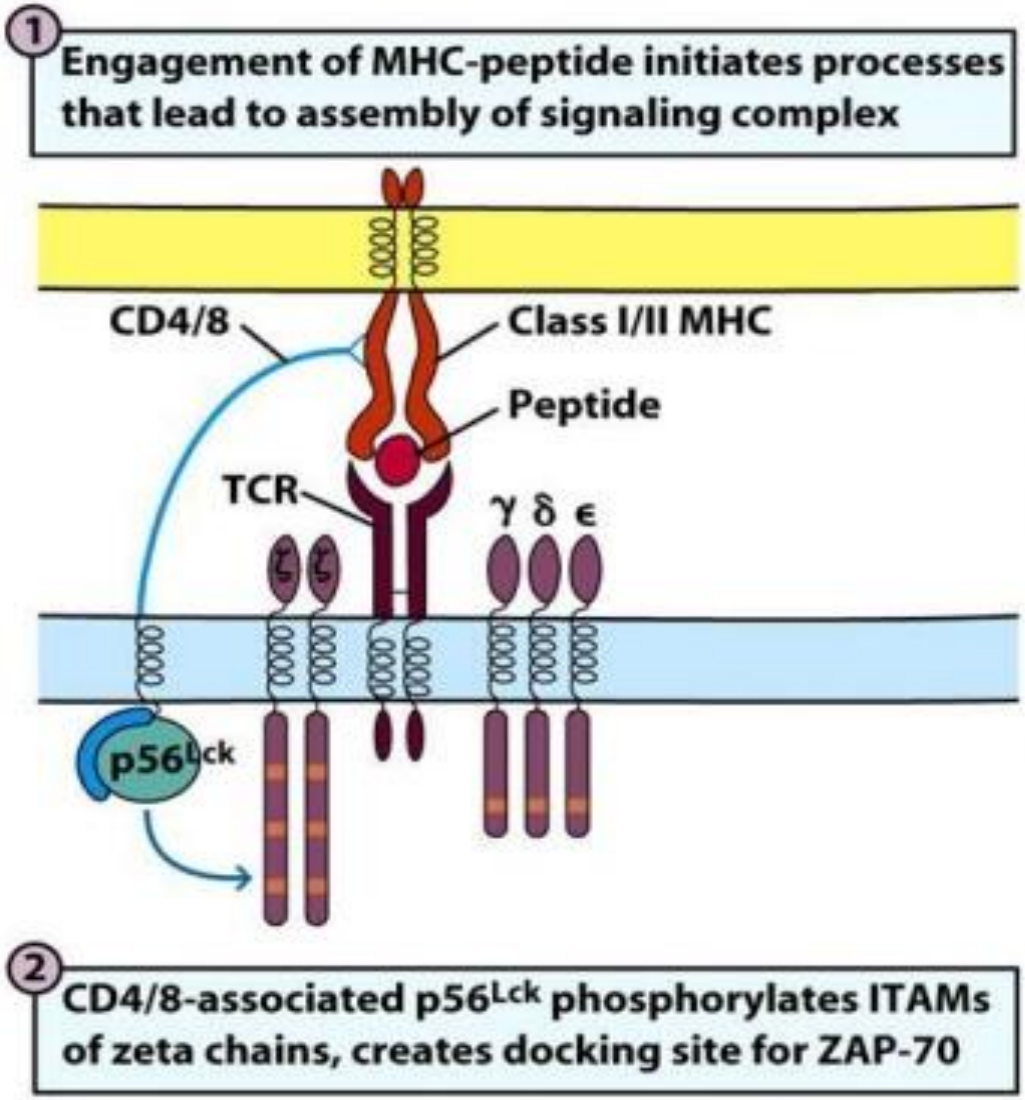


FIGURE 10-10 Overview of TCR-mediated signaling. TCR engagement by peptide-MHC complexes initiates the assembly of a signaling complex. An early step is the Lck-mediated phosphorylation of ITAMs on the zeta (ζ) chains of the TCR complex, creating docking sites to which the protein kinase ZAP-70 attaches and becomes activated by phosphorylation. A series of ZAP-70-catalyzed protein phosphorylations enable the generation of a variety of signals. (Abbreviations: DAG = diacylglycerol; GADS = Grb2-like adaptor downstream of Shc; GEF = guanine nucleotide exchange factor; ITAM = immunoreceptor tyrosine-based activation motif; Itk = inducible T cell kinase; IP3 = inositol 1,4,5 triphosphate; LAT = linker of activated T cells; PIP_2 = phosphoinositol biphosphage; PLCγ = phospholipase C gamma; Lck = lymphocyte kinase; SLP-76 = SH2-containing leukocyte-specific protein of 76 kDa; ZAP-70 = zeta associated protein of 70 kDa.)

Phosphorylation = addition of P

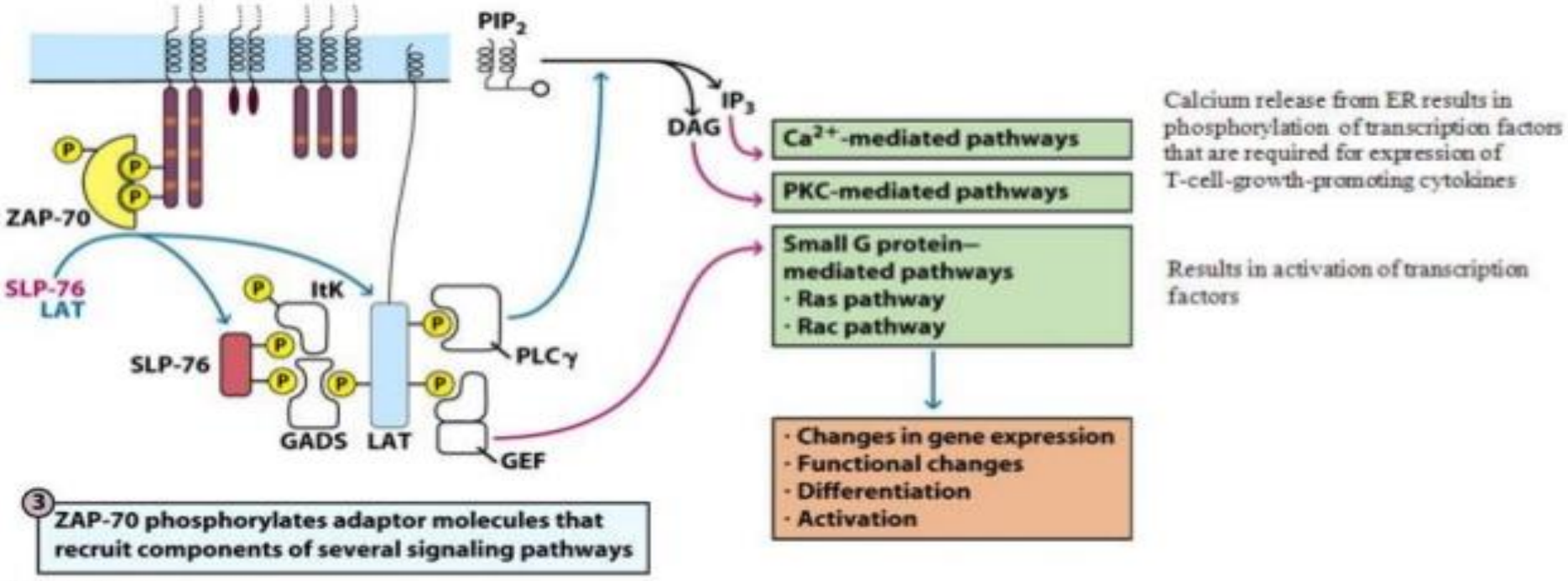


Figure 10-11 part 2
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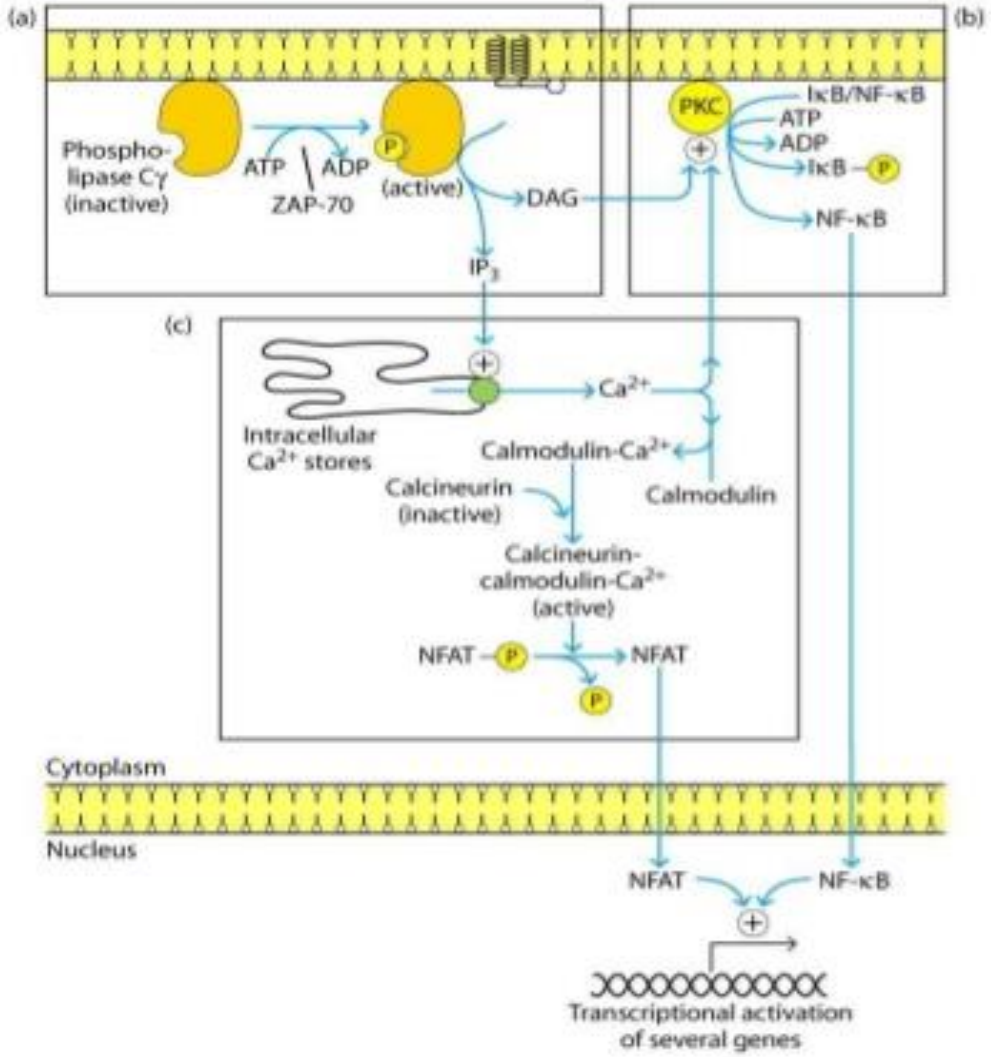
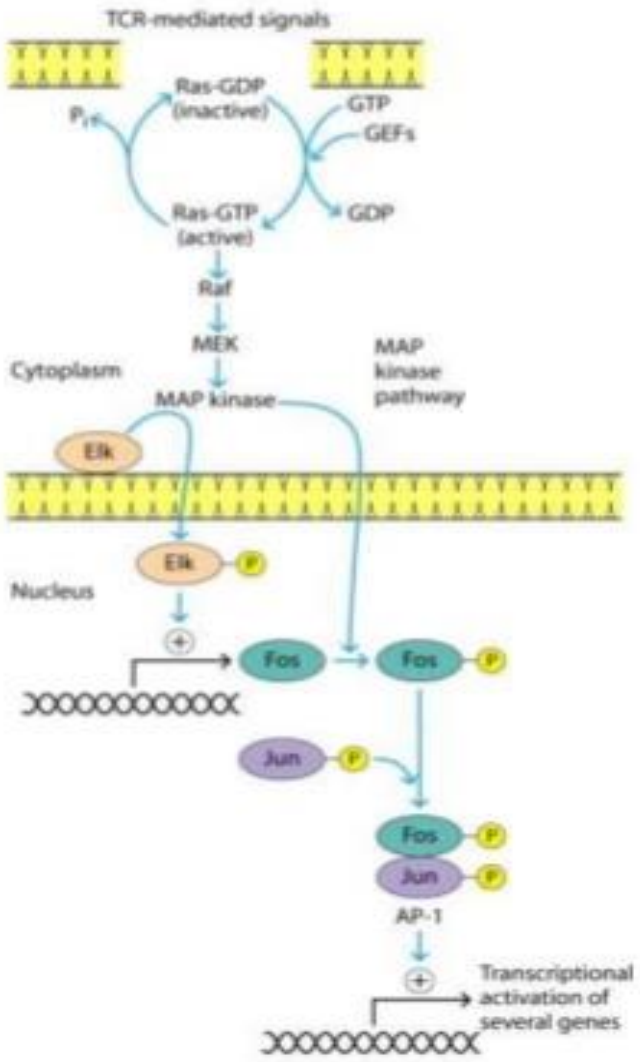
FIGURE 10-10 Overview of TCR-mediated signaling. TCR engagement by peptide-MHC complexes initiates the assembly of a signaling complex. An early step is the Lck-mediated phosphorylation of ITAMs on the zeta (ζ) chains of the TCR complex, creating docking sites to which the protein kinase ZAP-70 attaches and becomes activated by phosphorylation. A series of ZAP-70-catalyzed protein phosphorylations enable the generation of a variety of signals. (Abbreviations: DAG = diacylglycerol; GADS = Grb2-like adaptor downstream of Shc; GEF = guanine nucleotide exchange factor; ITAM = immunoreceptor tyrosine-based activation motif; Itk = inducible T cell kinase; IP3 = inositol 1,4,5 triphosphate; LAT = linker of activated T cells; PIP_2 = phosphoinositol biphosphage; PLCγ = phospholipase C gamma; Lck = lymphocyte kinase; SLP-76 = SH2-containing leukocyte-specific protein of 76 kDa; ZAP-70 = zeta associated protein of 70 kDa.)



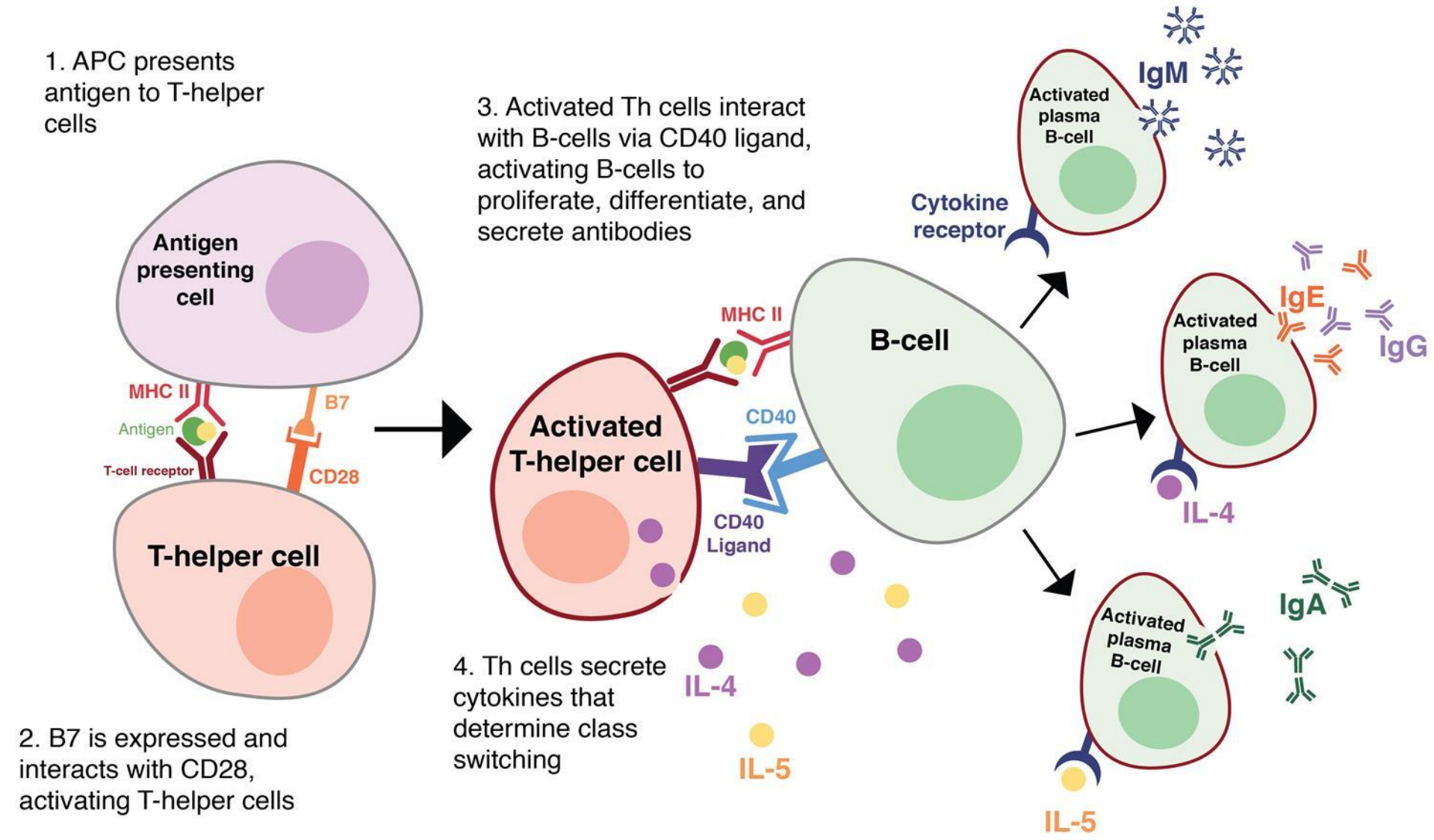
Signal-transduction pathways associated with T-cell activation.
(a) Phospholipase C (PLC) is activated by phosphorylation. Active PLC hydrolyzes a phospholipid component of the plasma membrane to generate the second messengers, DAG and IP_3.
(b) Protein kinase C (PKC) is activated by DAG and Ca_2. Among the numerous effects of PKC is phosphorylation of IkB, a cytoplasmic protein that binds the transcription factor NF-kB and prevents it from entering the nucleus. Phosphorylation of IkB releases NF-kB, which then translocates into the nucleus.
(c) Ca_2-dependent activation of calcineurin. Calcineurin is a Ca_2/calmodulin dependent phosphatase. IP_3 mediates the release of Ca_2 from the endoplasmic reticulum. Ca_2 binds the protein calmodulin, which then associates with and activates the Ca_2/calmodulin-dependent phosphatase calcineurin. Active calcineurin removes a phosphate group from NFAT, which allows this transcription factor to translocate into the nucleus.



Activation of the small G protein, Ras. Signals from the T-cell receptor result in activation of Ras via the action of specific guanine nucleotide exchange factors (GEFs) that catalyze the exchange of GDP for GTP. Active Ras causes a cascade of reactions that result in the increased production of the transcription factor Fos.

Following their phosphorylation, Fos and Jun dimerize to yield the transcription factor AP-1. Note that all these pathways have important effects other than the specific examples shown in the figure.

Activation and Class-switching of B-cells



T-Cell Differentiation

- CD4+ and CD8+ cells leave thymus and enter circulation in G_0 phase
    - Naïve cells (condensed chromatin, little cytoplasm)
    - About twice as many CD4+
- Naïve cell recognized MHC-antigen complex
    - Initiated primary response
    - After 48 hours, enlarges into blast cell and undergoes repeated rounds of cell division
    - Differentiate into:
        - » Effector cells – cytokine secretion, B-cell help
        - » Memory cells – long lived, respond with heightened activity (secondary response)

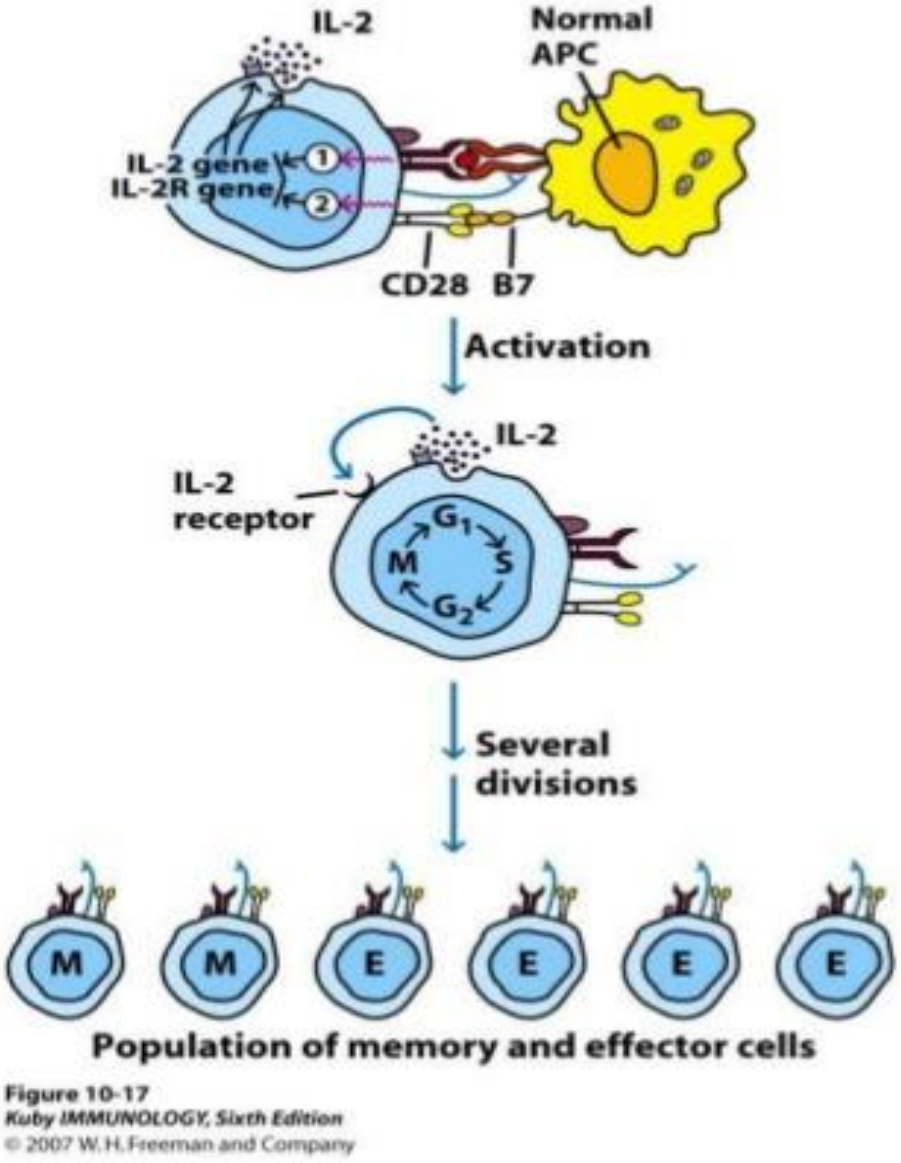


Figure 10-17
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