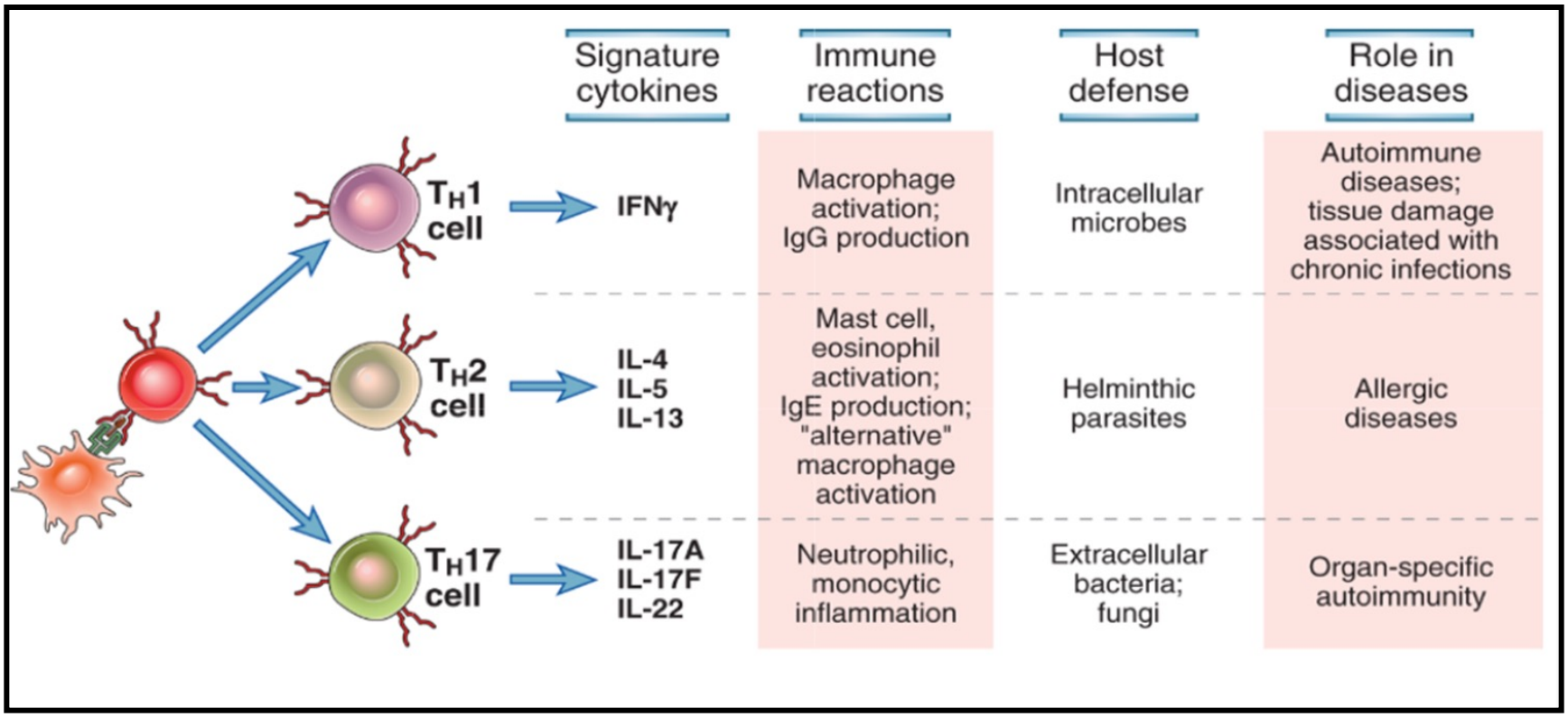
Lecture 22
3 Oct 2023

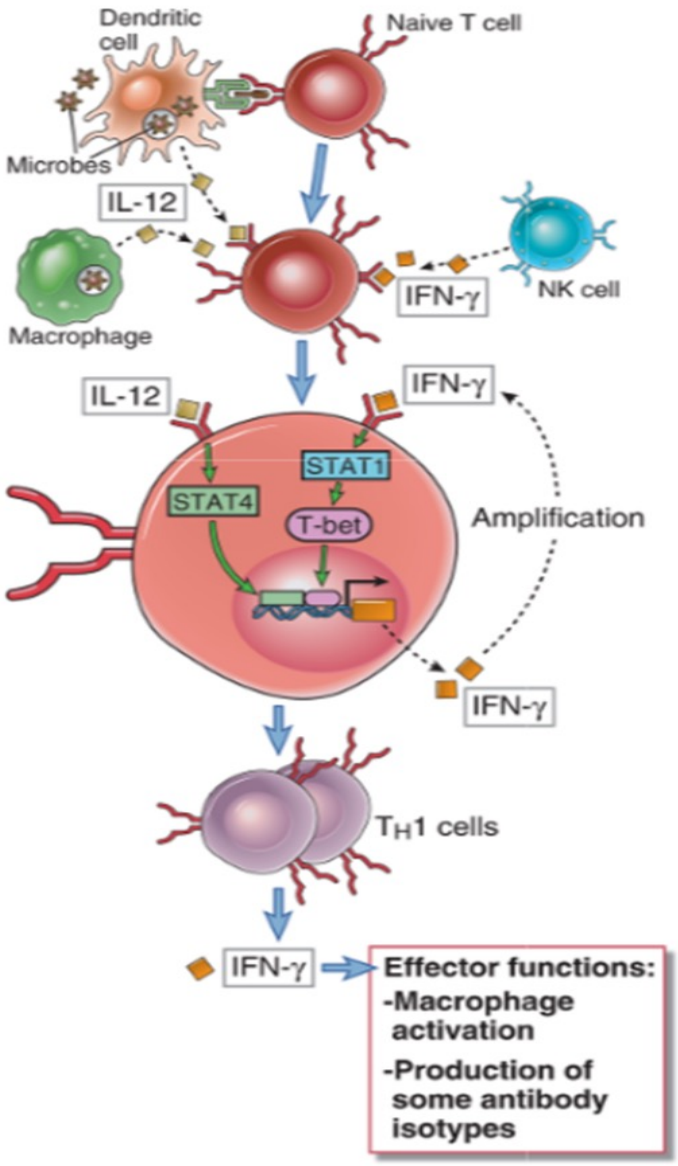
Different subsets of effector CD4+ T cells



Naive CD4+ T cells may differentiate into distinct subsets of effector cells in response to antigen, costimulators, and cytokines. The columns to the right list the major differences between the best-defined subsets.

T_H1 subsets of effector CD4+ T cells

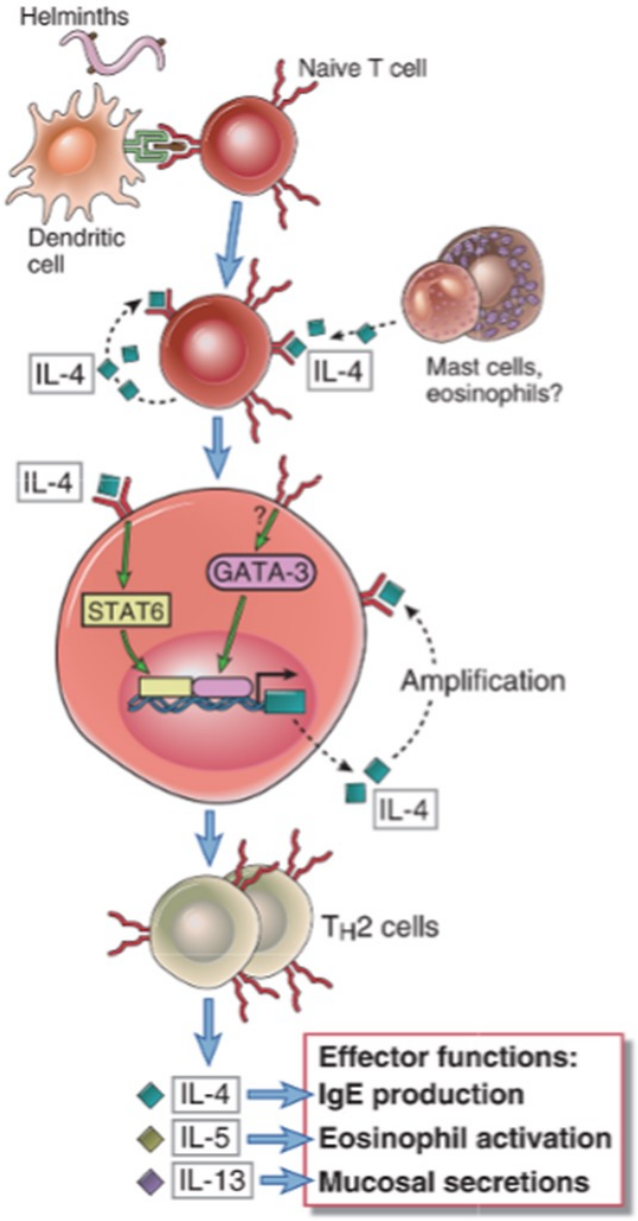
- IL-12 produced by dendritic cells and macrophages in response to microbes, including intracellular microbes, and
- IFN-γ produced by NK cells (all part of the early innate immune response to the microbes) activate the transcription factors T-bet, STAT1, and STAT4, which stimulate the differentiation of naive CD4+ T cells to the T_H1 subset.
- IFN-γ produced by the T_H1 cells amplifies this response and inhibits the development of T_H2 and T_H17 cells.



T_H2 subsets of effector CD4+ T cells

- IL-4 produced by activated T cells themselves or by mast cells and eosinophils, especially in response to helminths, activates the transcription factors GATA-3 and STAT6, which stimulate the differentiation of naive CD4+ T cells to the T_H2 subset.

- IL-4 produced by the T_H2 cells amplifies this response and inhibits the development of T_H1 and T_H17 cells.

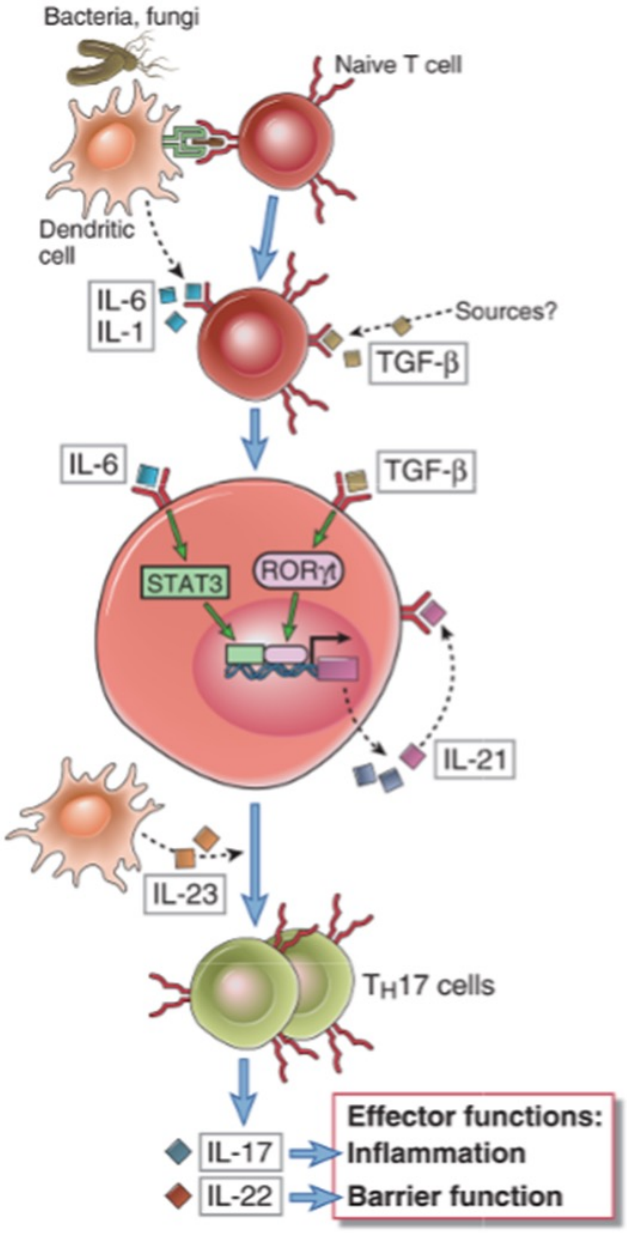


T_H17 subsets of effector CD4+ T cells

- IL-1 and IL-6 produced by APCs and transforming growth factor-β (TGF-β) produced by various cells activate the transcription factors RORγt and STAT3, which stimulate the differentiation of naive CD4+ T cells to the T_H17 subset.

- IL-23, which is also produced by APCs, especially in response to fungi, stabilizes the T_H17 cells. TGF-β may promote T_H17 responses indirectly by suppressing T_H1 and T_H2 cells, both of which inhibit T_H17 differentiation (not shown in the figure).

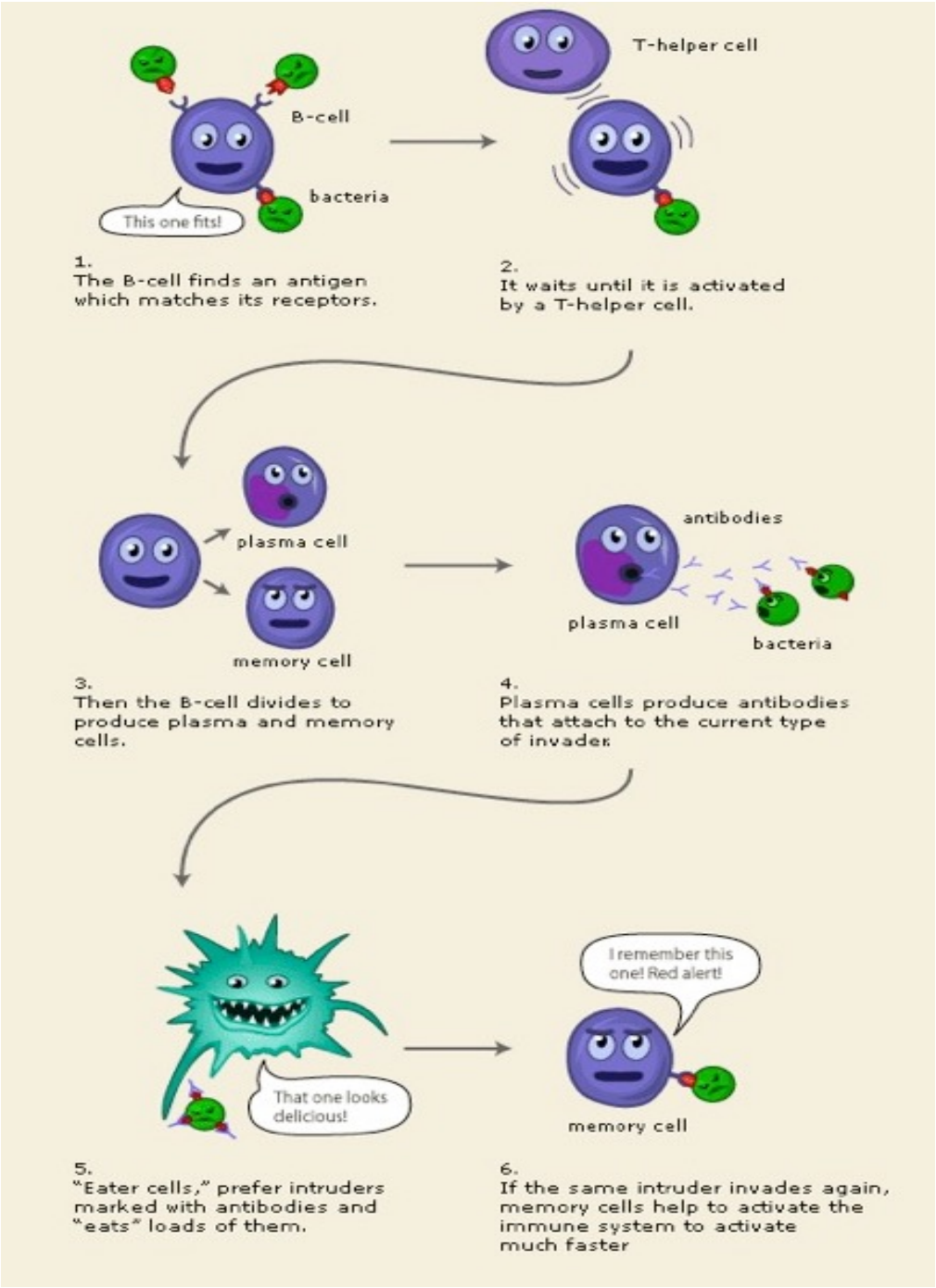
- IL-21 produced by the T_H17 cells amplifies this response.



B-Cell Development, Activation, and Differentiation

B Cells

- Provides antibody mediated immunity constitute 10-15% of blood lymphocytes.
- 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)



B-cell generation and development

- In many vertebrates, including humans and mice, B cells generation occurs in bone marrow
  - Antigen-independent phase
  - Ig-gene rearrangement to create antigen-specificity

- **Bone marrow**
  - Pro-B cell → precursor B cell →Stromal cell in bone marrow secrete IL-7 that help development into immature B cells

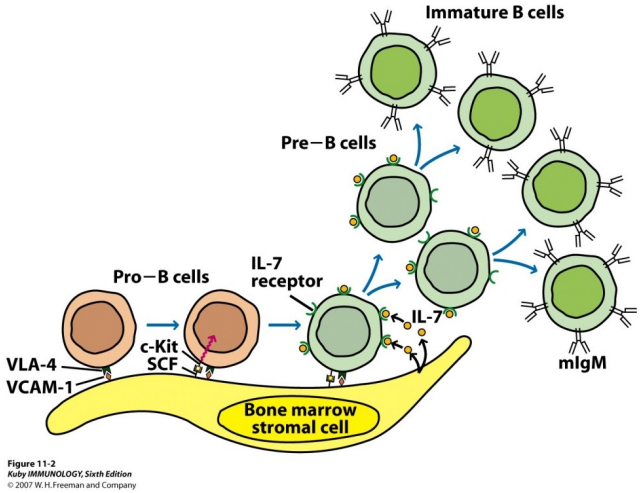
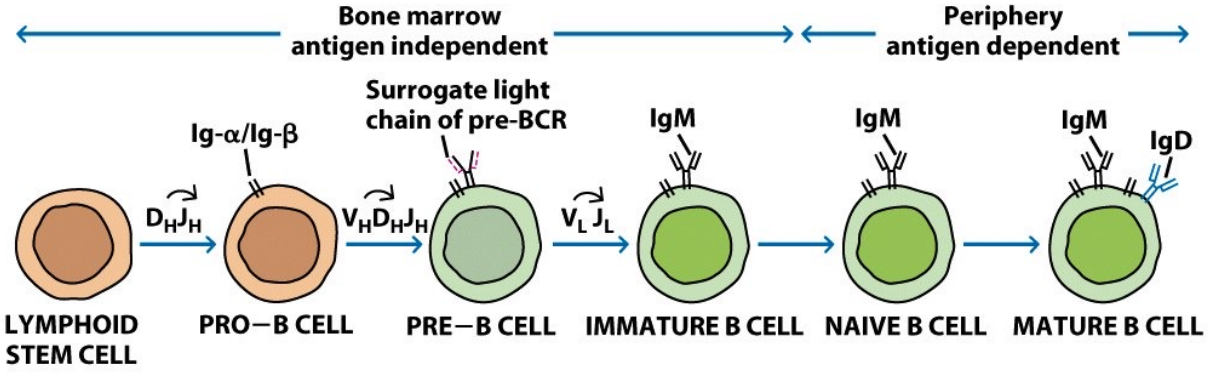


Figure 11-2
Kuby IMMUNOLOGY, Sixth Edition

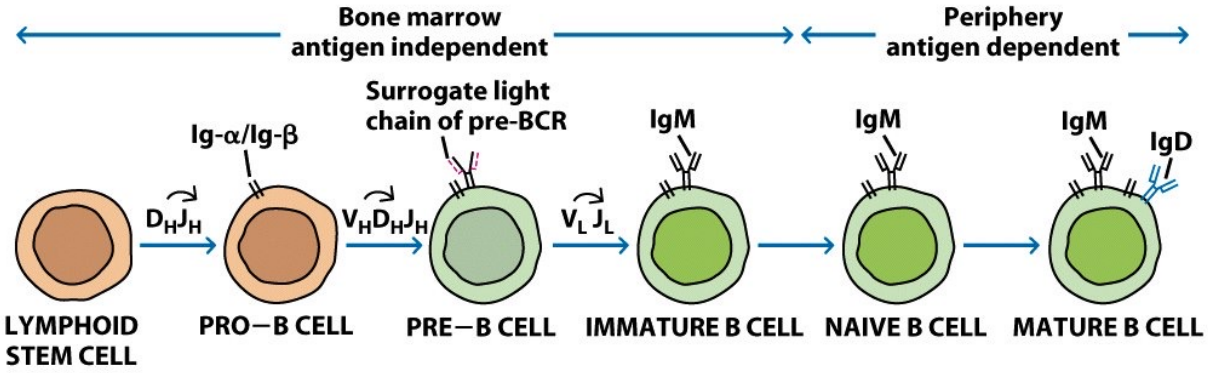
B-cell generation and development

- **Pro-B Cell**
  - Undergo Ig Heavy chain rearrangement (express Ig α/ Igβ that forms BCR)
- **Pre-B cell**
  - Translation of heavy chain genes, Light chain rearrangement
- **Immature B cell**
  - Is now committed to antigenic specificity and produces IgM
  - B cell not fully functional, must first express both IgM and IgD on membrane
  - Recognize self antigens and develops **tolerance** to self antigens.



B-cell generation and development

- 90% of B cells produced everyday die without ever leaving bone marrow
  - Negative selection due to cells that express auto-antibodies against self antigen in the marrow



Lecture 23
5 Oct 2023

Development of B cells

- **Immature B cell bearing IgD/M on membrane leaves bone marrow to peripheral lymphoid organs**
  - NAÏVE B cells – have not encountered antigen
  - Matures to express both IgM and IgD with single antigen specificity

- **Encounter antigen in secondary lymphoid tissue**
  - Differentiate into plasma cells and memory cells
  - Class switching

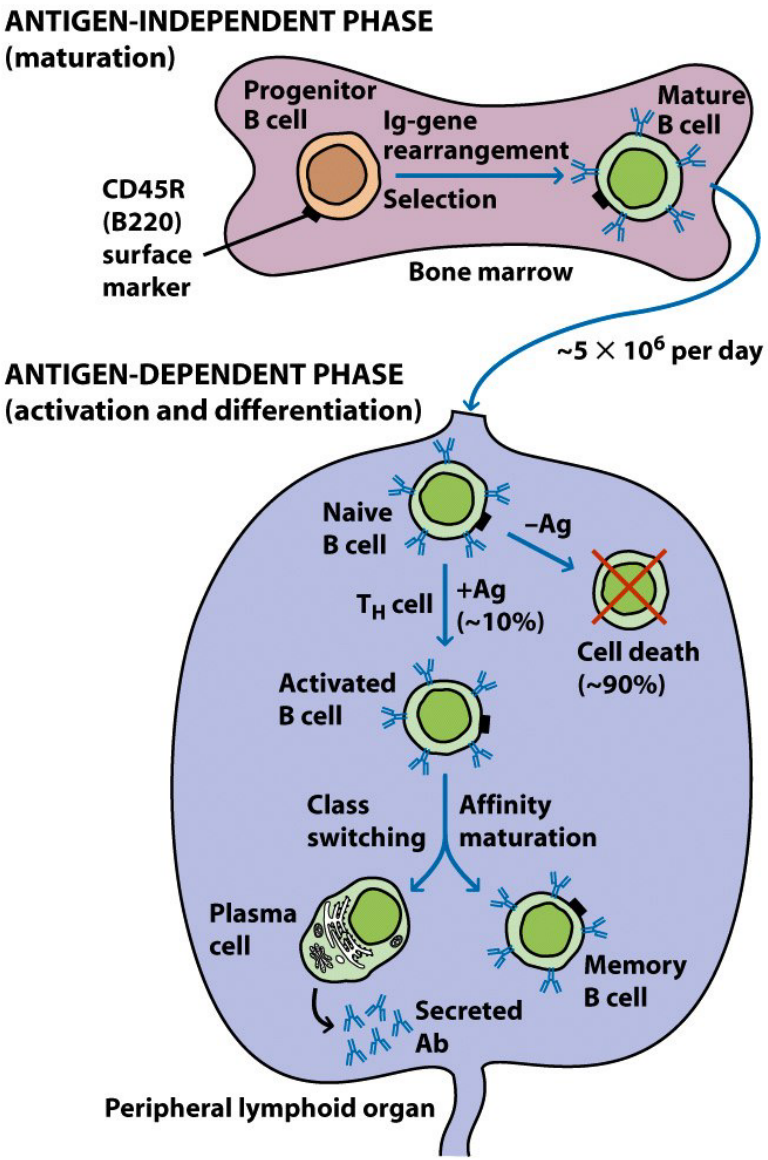


Figure 11-1
Kuby IMMUNOLOGY, Sixth Edition

B cell Activation

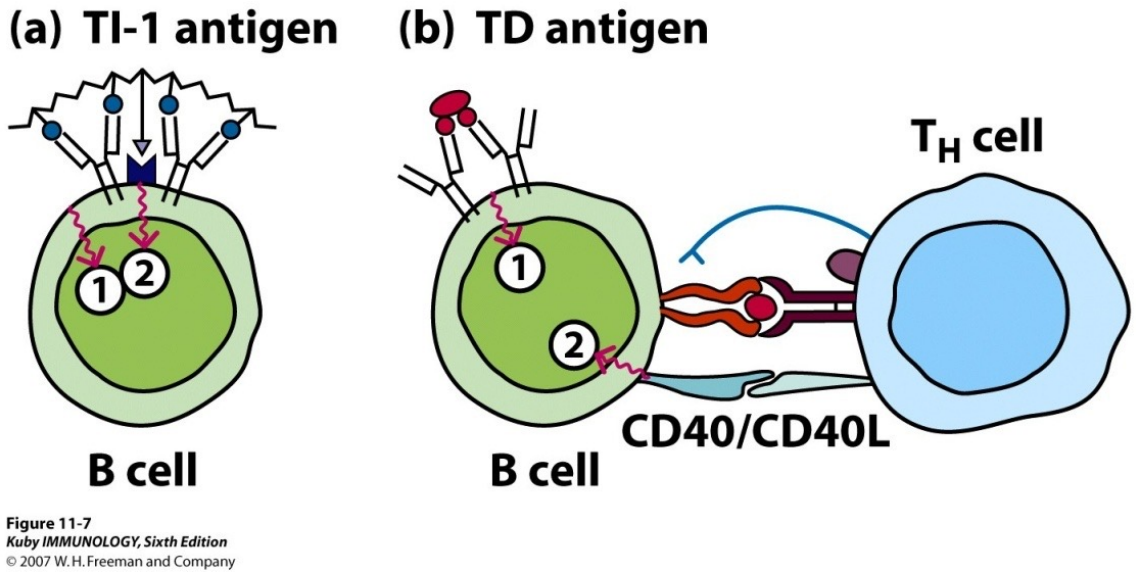


Figure 11-7
Kuby IMMUNOLOGY, Sixth Edition

- **Antigens that activate B cells fall into two categories:**

✓Thymus-independent antigens (TI)

- These antigens activate B cells by T independent means
  - Type I (TI-1) – lipopolysaccharide
  - Type 2 (TI-2) – highly repetitious molecules (bacterial flagella)

✓Thymus-dependent (TD) antigens

- B cell required direct contact with T_H cell

- T_H cells play essential role in B cell responses

(a) Antigen cross-links mIg, generating signal ①, which leads to increased expression of class II MHC and co-stimulatory B7. Antigen-antibody complexes are internalized by receptor-mediated endocytosis and degraded to peptides, some of which are bound by class II MHC and presented on the membrane as peptide–MHC complexes.

(b) T_H cell recognizes antigen–class II MHC on B-cell membrane. This plus costimulatory signal activates T_H cell.

(c) 1. T_H cell begins to express CD40L.
2. Interaction of CD40 and CD40L provides signal ②.
3. B7-CD28 interactions provide costimulation to the T_H cell.

(d) 1. B cell begins to express receptors for various cytokines.
2. Binding of cytokines released from T_H cell in a directed fashion sends signals that support the progression of the B cell to DNA synthesis and to differentiation.

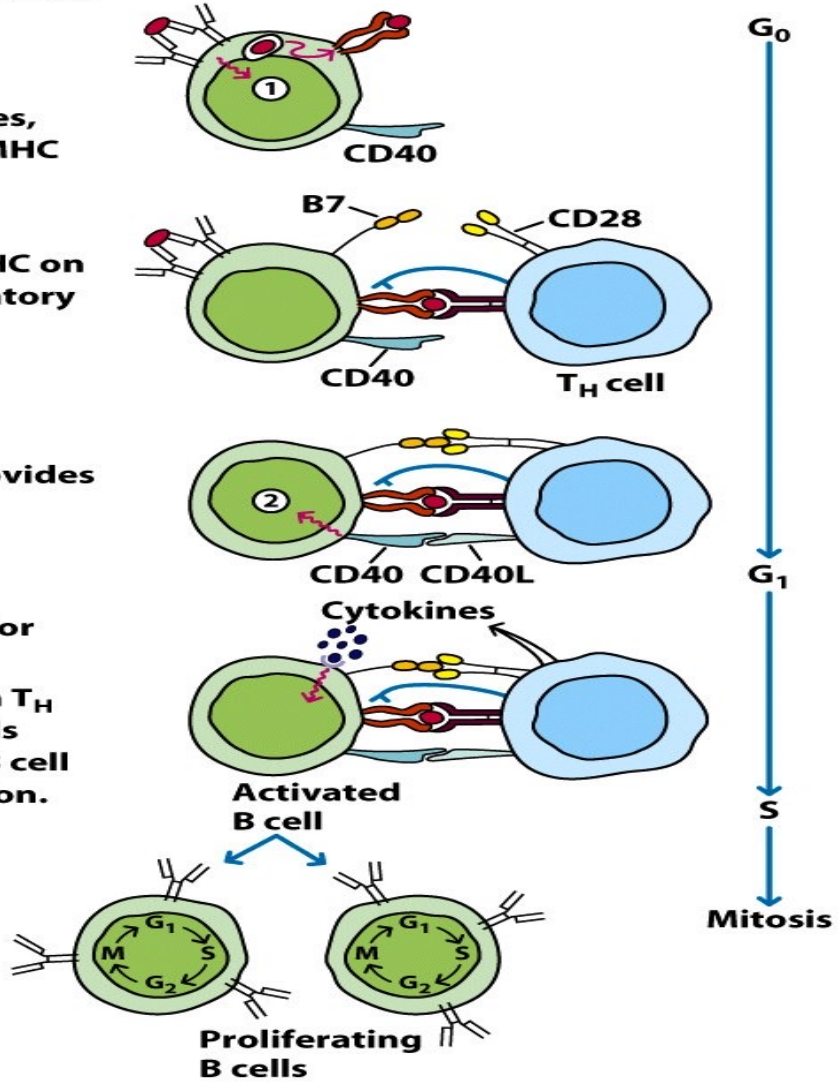


Figure 11-12
Kuby IMMUNOLOGY, Sixth Edition

B cell proliferation and differentiation

- After B cell activation by TD and TI mechanisms, they undergo proliferation and differentiation at the germinal centers into centroblasts and then to centrocytes.

3 events in germinal centers

- Affinity maturation
  - Result of somatic hypermutation
- Class switching
- Formation of plasma and memory B cells

- This centrocytes will later differentiate into plasma cells and memory cells.

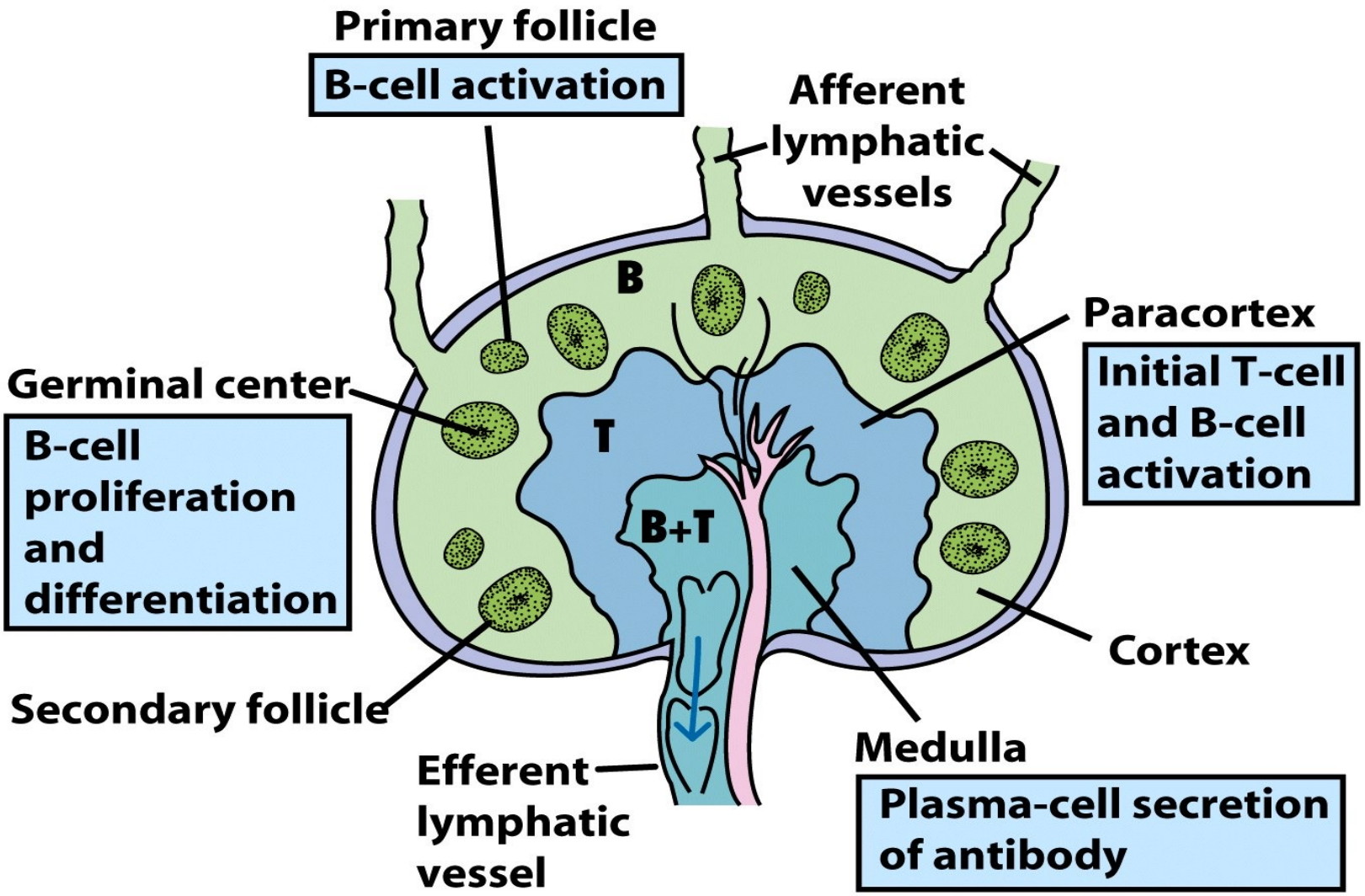
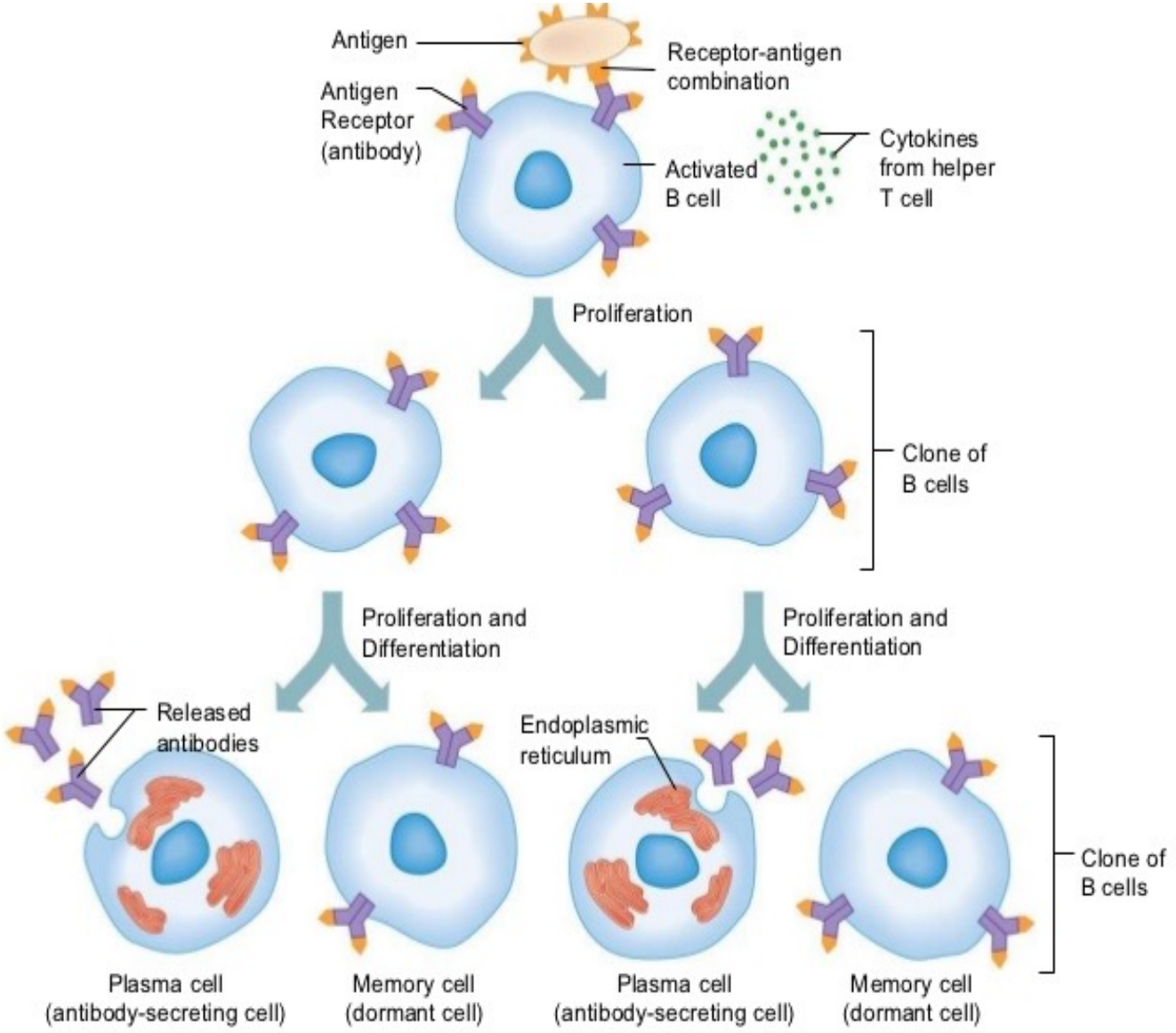


Figure 11-18
Kuby IMMUNOLOGY, Sixth Edition



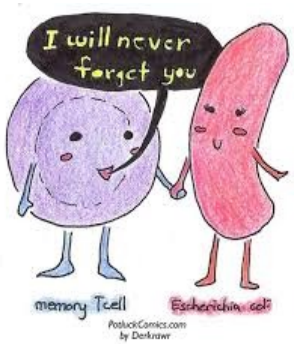
- B cells develop in bone marrow and undergo antigen induced activation and differentiation in the periphery
- Activated B cells can give rise to antibody-secreting plasma cells or memory B cells

PLASMA CELL

- Antibody secreting cell, oval, eccentrically placed oval nucleus, large block of chromatin – peripherally.
- Structurally - immunoglobulin production
- End cells
- Short life span

MEMORY CELL

- Keeps immunological memory
- Non antibody producing
- Long life span
- Helps in faster secondary response.



Class Switching

- Dependent on cytokines to switch from IgM to other isotypes
  - Thymus-dependent antigens
  - Interaction of CD40 on B cell and CD40L on T cell
  - X-linked hyper-M syndrome
    - T_H cells don't express CD40L, patients only produce IgM
      - No memory cell populations, no germinal centers

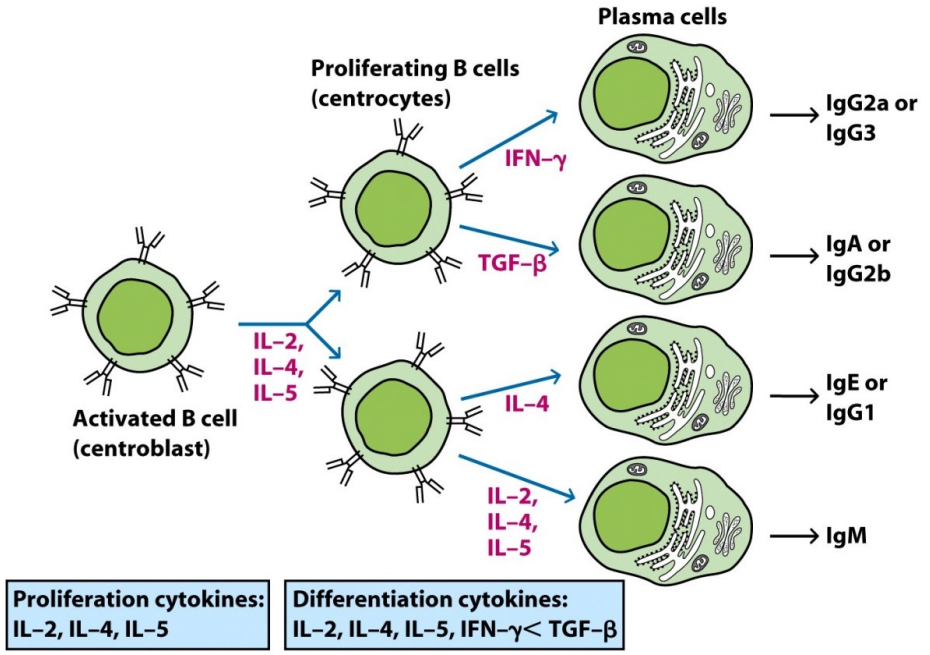


Figure 11-22
Kuby IMMUNOLOGY, Sixth Edition

Humoral Response – Primary vs Secondary

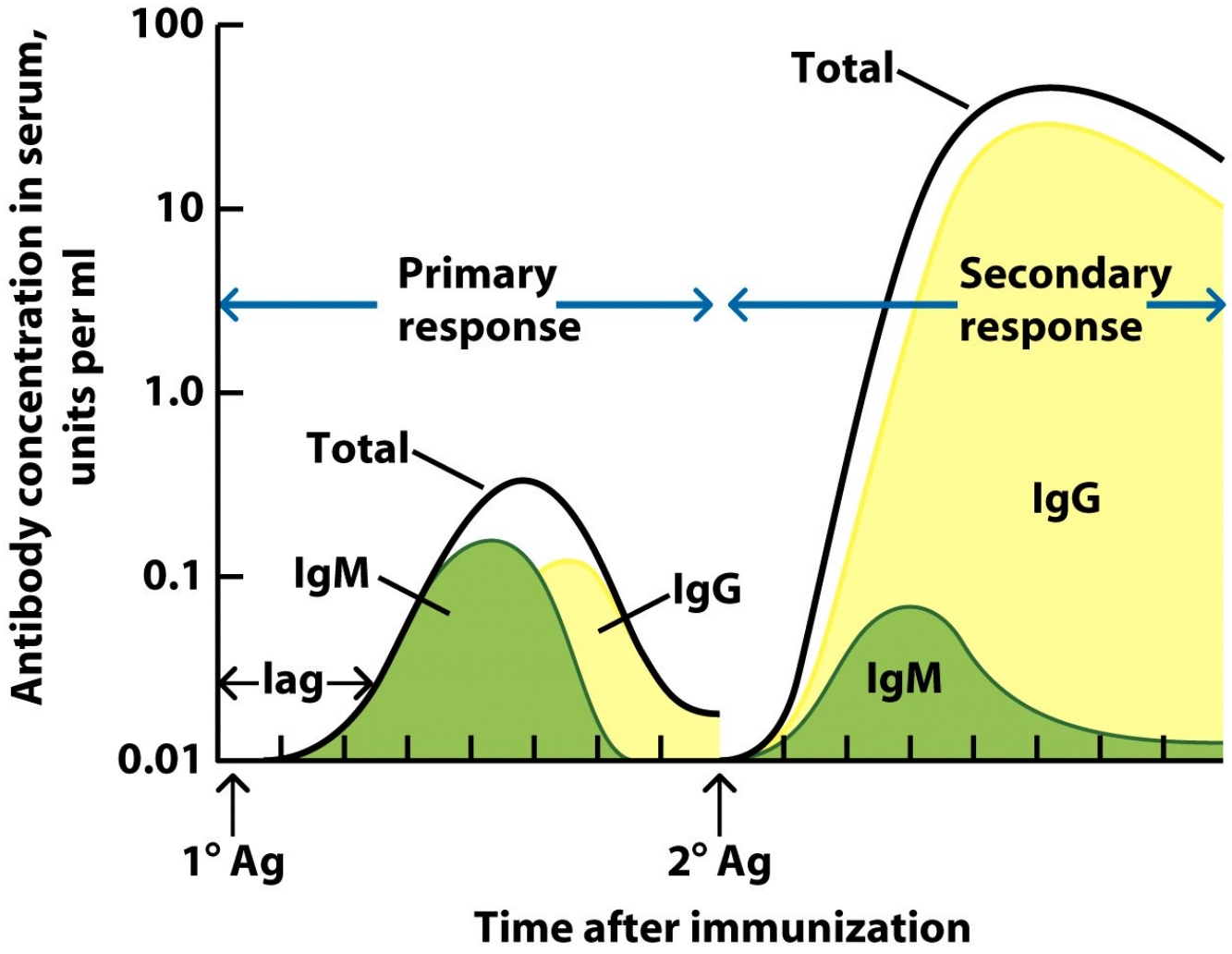


Figure 11-16
Kuby IMMUNOLOGY, Sixth Edition

Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher than primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher

Regulation of B-cell

- Humoral and cell-mediated branches must be heavily regulated

- Cytokines play an important role
- This is important to save over acting immune system.
- Antigenic competition

  Previous encounter with antigen can render animal tolerant or may result in formation of memory cells
- Presence of antibody can suppress response to antigen

T cells versus B cells