Humoral Immunity

Immunology Lecture 9

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Introduction

- Arise and mature in the red bone marrow
- Found primarily in the spleen, lymph nodes, and MALT (The **mucosa-associated lymphoid tissue** (**MALT**), also called mucosa-associated lymphatic tissue, is a diffuse system of small concentrations of lymphoid tissue found in various submucosal membrane sites of the body, such as the gastrointestinal tract, thyroid, breast, lung, salivary glands, eye, and skin).
- Small percentage of B cells circulates in the blood
- Major function is the secretion of antibodies

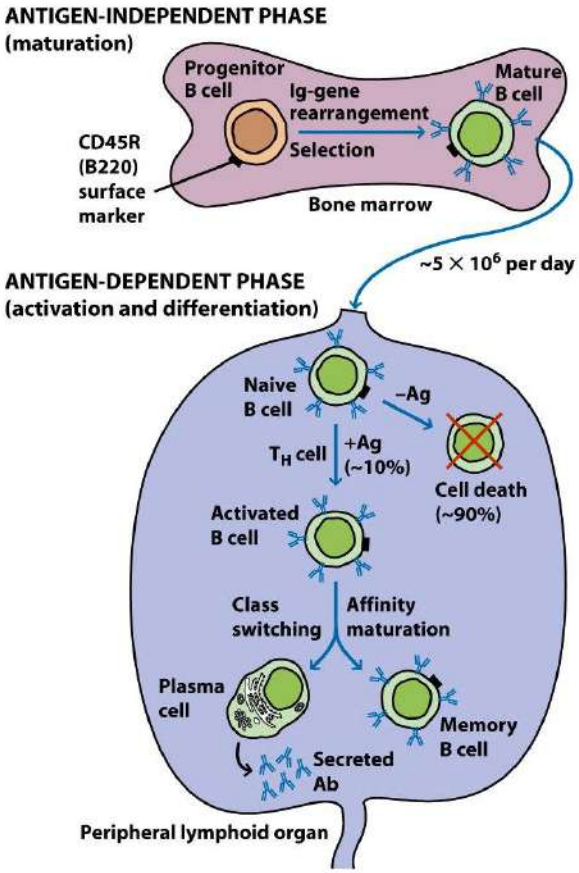
Importance

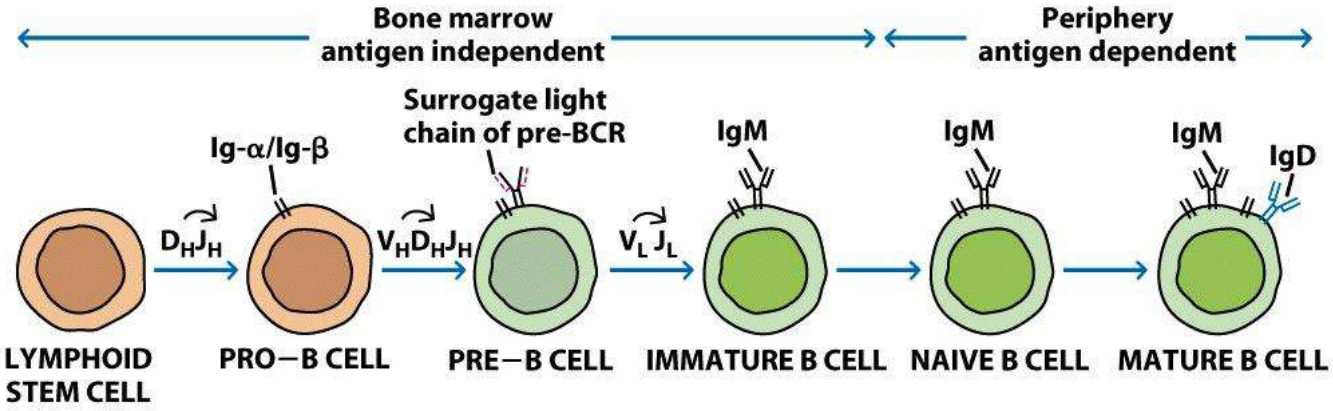
- Humoral immunity helps cellular immunity to perform action through interaction of T helper cells with B cells
- Is the arm of adaptive immunity in killing extracellular microbes and microbial toxins
- Important in defending against microbes with capsule

B Cells Maturation

- B cells matures in bone marrow independent of antigen, then continue to maturate in peripheral lymphoid organs with the presence of antigen
- Three main steps of maturation:

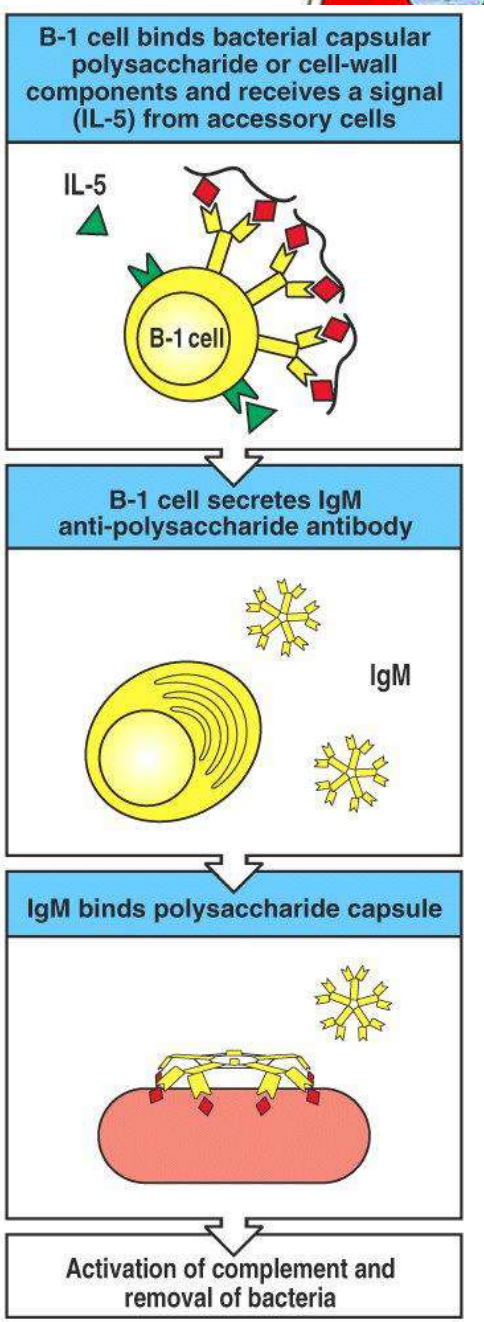
1. Progenitor- Ig alpha and beta- for signal transduction (long tails)
2. Pre-B cell- IgM heavy chain, and light chain
3. “mature”- IgD

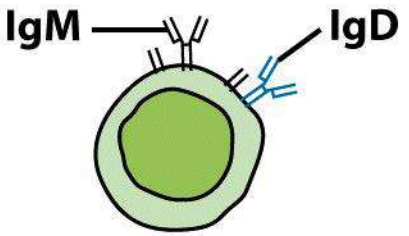

ANTIGEN-INDEPENDENT PHASE
(maturation)
Progenitor B cell
Ig-gene rearrangement
Mature B cell
CD45R (B220) surface marker
Selection
Bone marrow
~5 × 10^6 per day
ANTIGEN-DEPENDENT PHASE
(activation and differentiation)
Naive B cell
–Ag
TH cell
+Ag (~10%)
Cell death (~90%)
Activated B cell
Class switching
Affinity maturation
Plasma cell
Memory B cell
Secreted Ab
Peripheral lymphoid organ

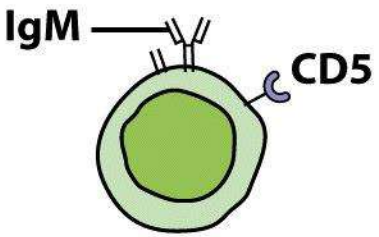

Bone marrow
antigen independent
Periphery
antigen dependent
Surrogate light chain of pre-BCR
Ig-α/Ig-β
IgM
IgM
IgM
IgD
DHJH
VHDHJH
VLJL
LYMPHOID STEM CELL
PRO–B CELL
PRE–B CELL
IMMATURE B CELL
NAIVE B CELL
MATURE B CELL

B-1 B cells

- “Innate-like” subset of B cells.
- Appear during fetal life and express IgM but little IgD and display CD5. Are also found in peritoneum and pleural space.
- Originates from stem cell in bone marrow, but also from proliferation of B-1 cells outside the BM.
- Responds poorly to protein antigen, but strongly to carbohydrate antigens.
- Antibodies produced are of low affinity.
- No memory produced







Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Figure 11-5
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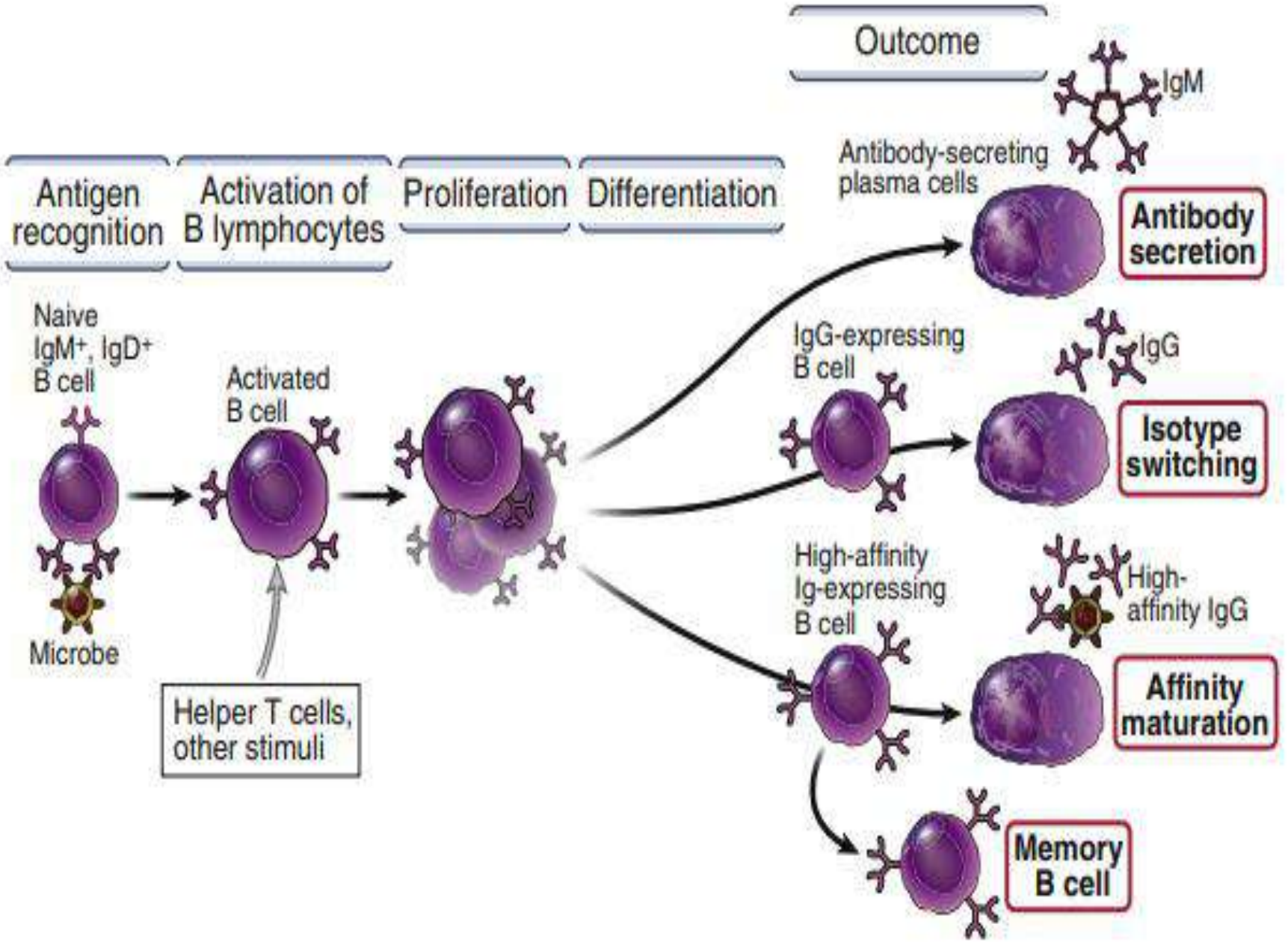
B cells Clonal Selection

- Self-reactive B cells are eliminated in bone marrow (BM).
- BM produces 5 x 10^7 B cells/day, but only 5 x 10^6 B cells/day or 10% actually enter the circulation.
- Some of this loss is due to negative selection and elimination or clonal deletion of immature B cells expressing auto antibodies to self-antigens.
- “Cross-linking” of mIgM by self Ag may lead to cell death or anergy
- The clones of lymphocytes that can be interacted with corresponding Ag will be selected and lead to activation, proliferation, produce Ab and specific memory cells.

Stages of B cells Activation

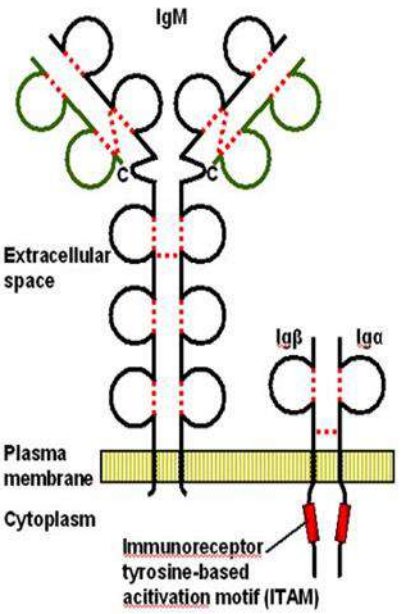
- B cells development involve three main stages

1. B cells recognition and binding
2. B cells undergo Ag-induced activation, proliferation and differentiation in the periphery
3. Activated B cells give rise to Ab-secreting plasma cells and memory cells
4. Effector B cells start to function
5. Shut down of immune response


Outcome
IgM
Antigen recognition
Activation of B lymphocytes
Proliferation
Differentiation
Antibody-secreting plasma cells
Antibody secretion
Naive IgM+, IgD+ B cell
Activated B cell
IgG-expressing B cell
IgG
Isotype switching
High-affinity Ig-expressing B cell
High-affinity IgG
Affinity maturation
Microbe
Helper T cells, other stimuli
Memory B cell

1. Antigen Recognition

- Naive B lymphocyte too express membrane bound antibodies IgM and IgD that function as antigen receptors (B cells receptors – BCR)
- Protein antigen only processed by APCs and recognized by helper T cells that play important role in B cells activation this is referred to as T dependent B cell activation
- Non protein antigen including lipids and polysaccharides activate B cells directly without involvement of helper T cells (T-independent activation). B cells in return can activate T helper cells



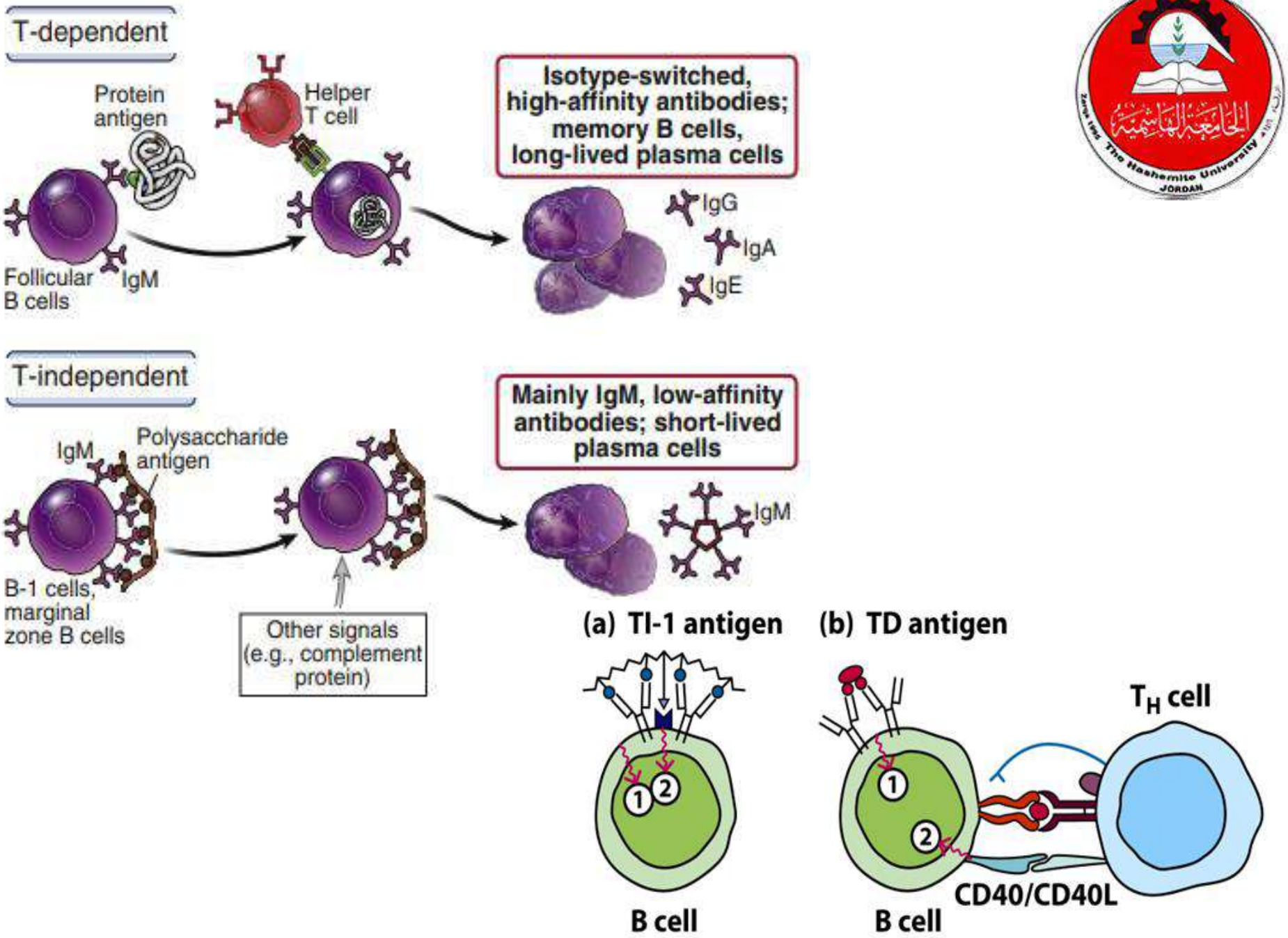


Figure 11-7
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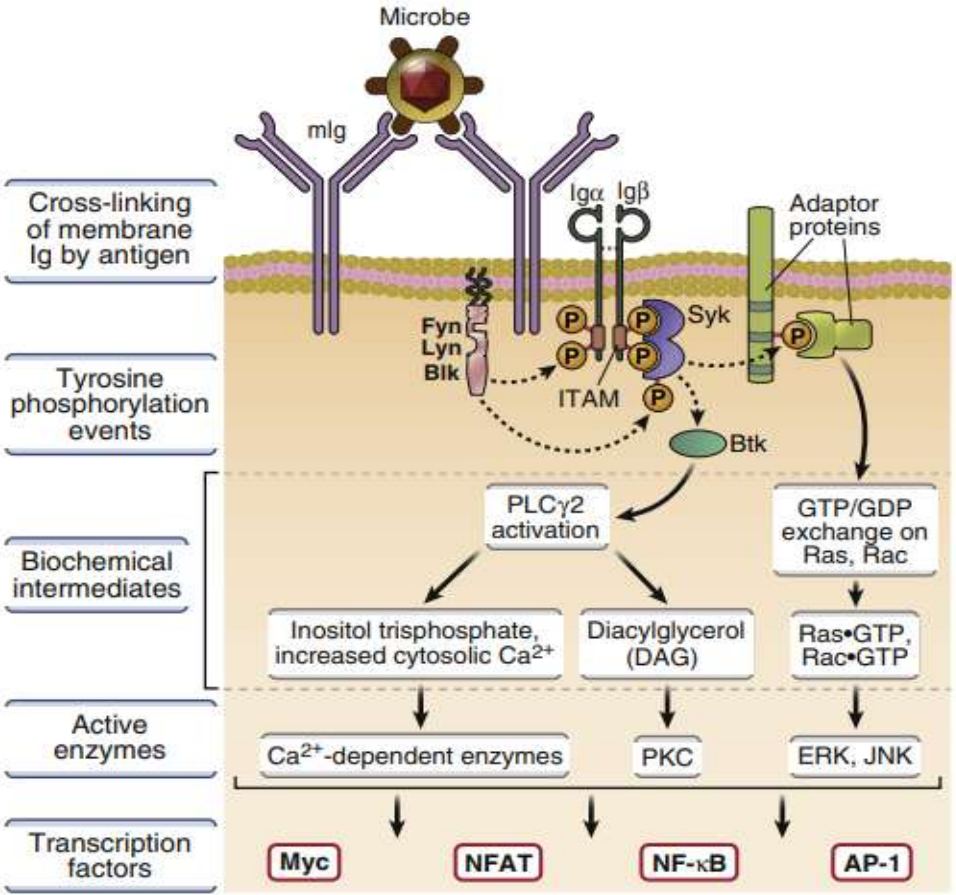
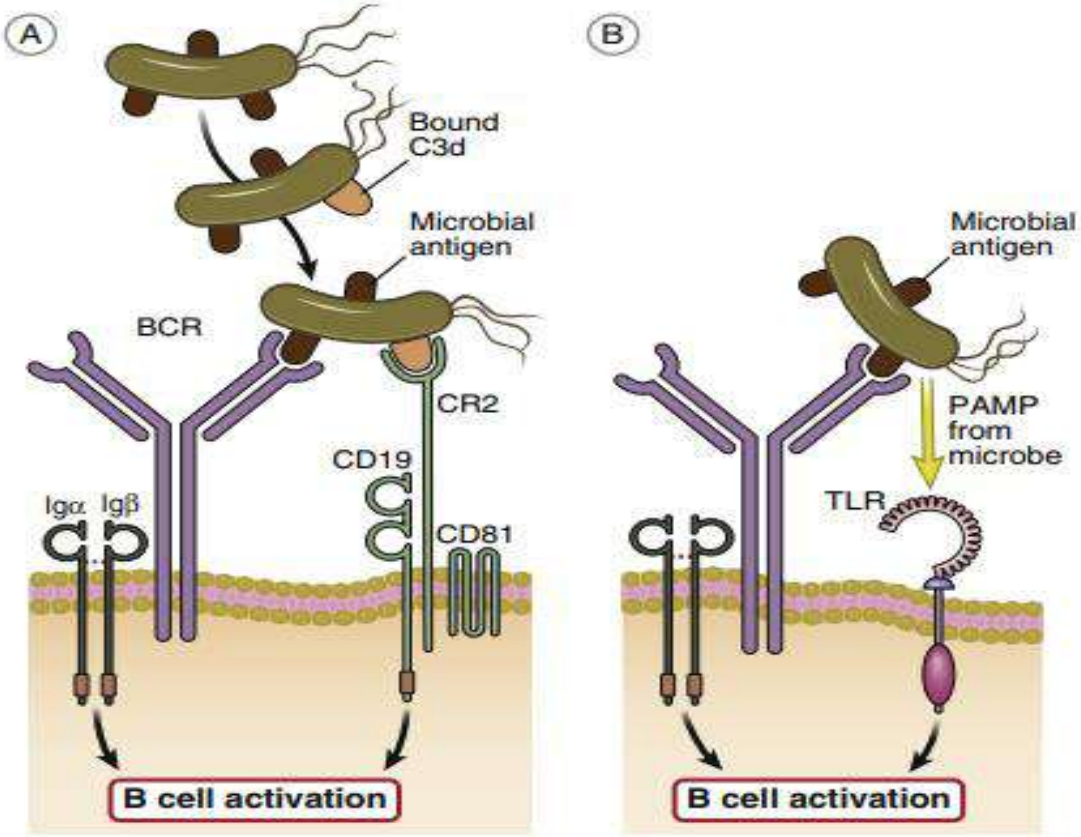
	TD Antigens	TI Antigens
Chemical nature	Proteins	Polymeric antigens, especially polysaccharides; also glycolipids, nucleic acids
Features of Response		
Primary B cell subset	Follicular B (B2) cells	MZ(/B1) B cells
Germinal center formation	Yes	No
Secondary isotypes (isotype switching)	Yes; IgG, IgE, and IgA	Little; some IgG and IgA
High affinity Ab's (affinity maturation)	Yes	No
Secondary response and memory B cells	Yes	Limited, only for some antigens
Long-lasting serum antibody titers (long-lived PCs)	Yes	No/limited

2. B Cell Activation and Signaling

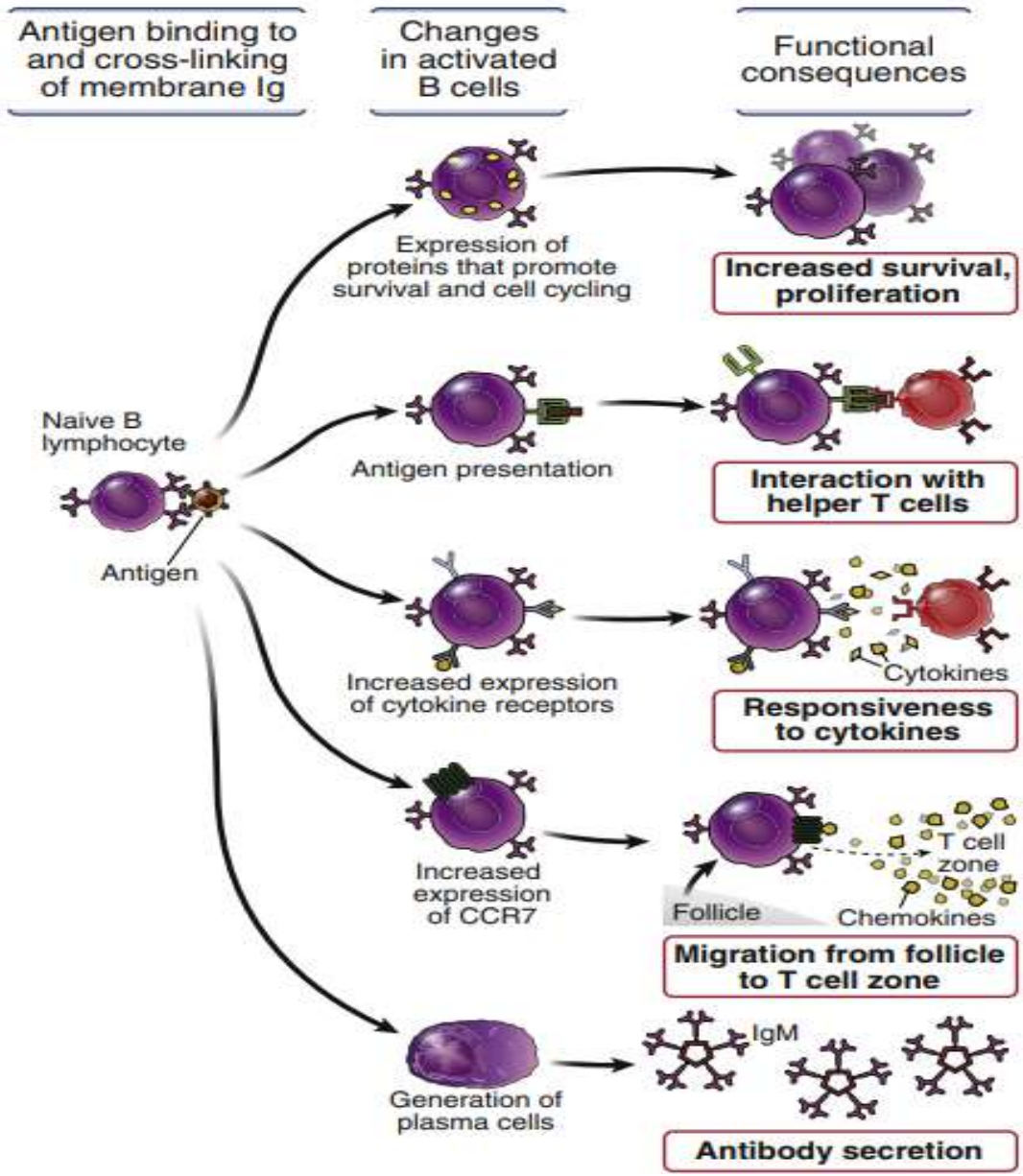
- Antigen induce clustering (cross linking- or bring together) of membrane Ig receptors. Ig clustering occurs when antigen molecules forms aggregates, or antigen have repeated epitopes molecules
- Ig clustering induce signaling through Igα and Igβ proteins in the B cell receptor complex



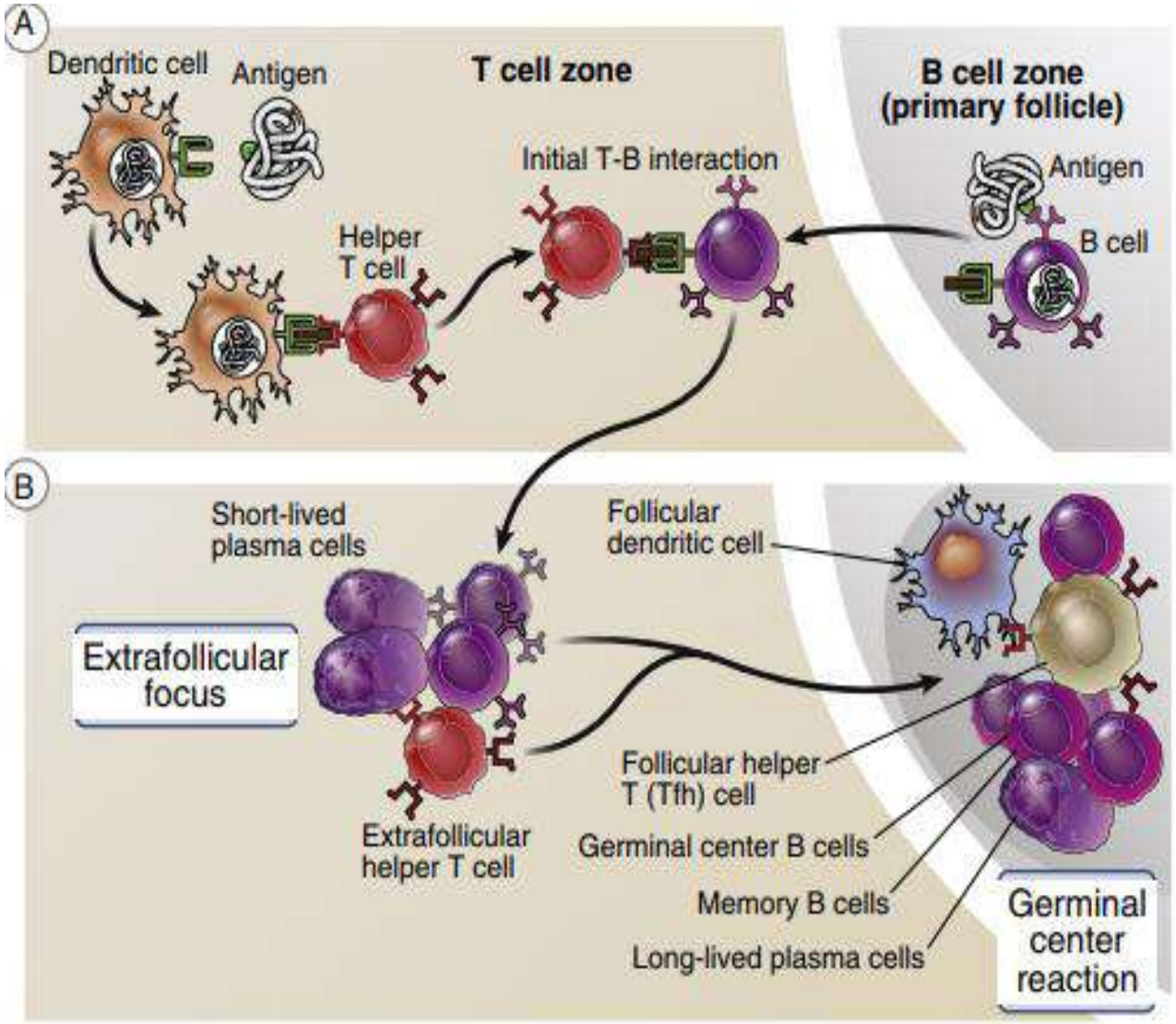
- Furthermore, microbes can activates complement system including C3 to form C3d. C3d can directly bind to B cells through CR2 and other receptors which enhance B cells activation (second signal)
- Later on signal from Ig and CR2 activates many biochemical's and enzymes that ends by formation of different transcription factors



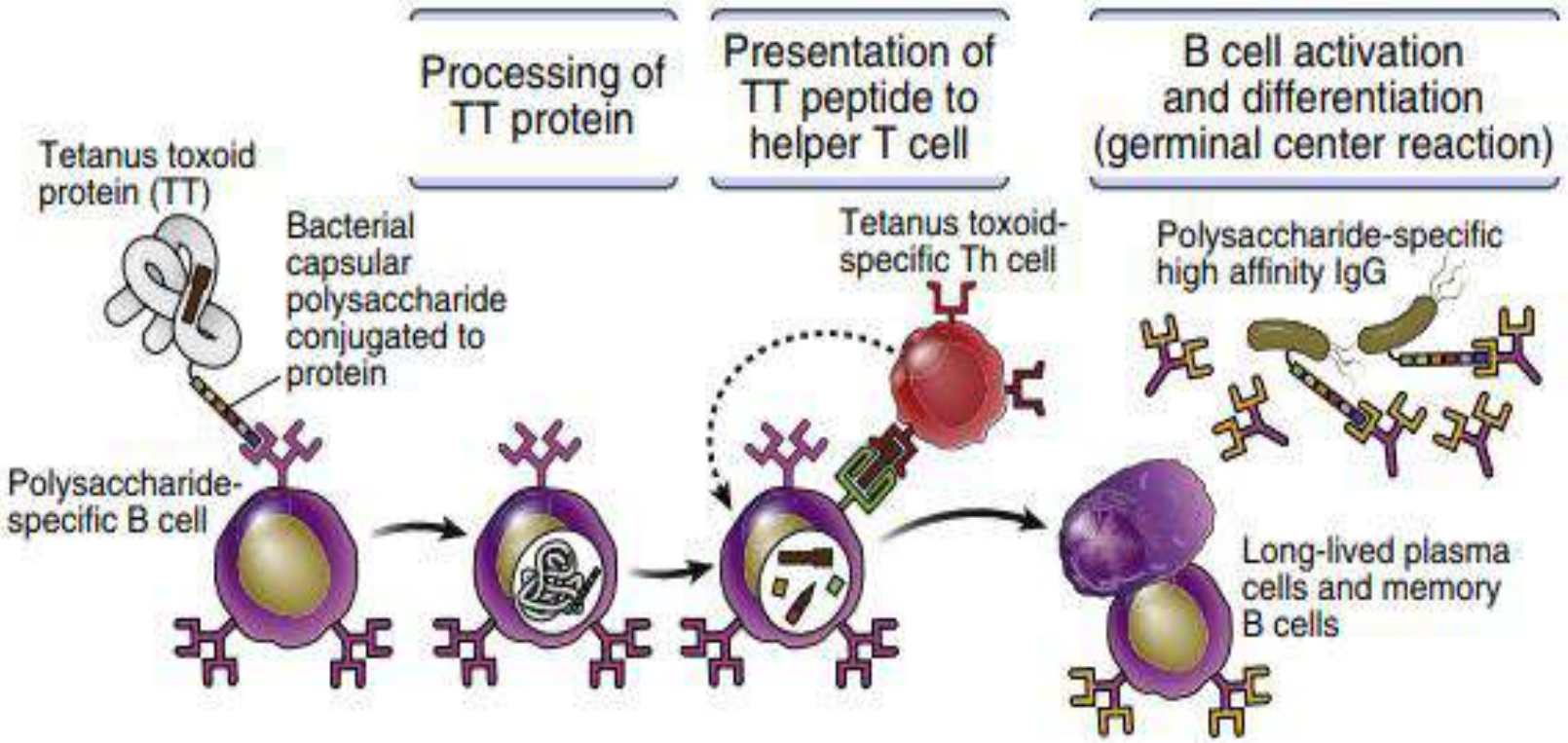
Functional consequences of B-cell signaling



Activation and migration of helper T cells and B cells



Conjugate vaccine

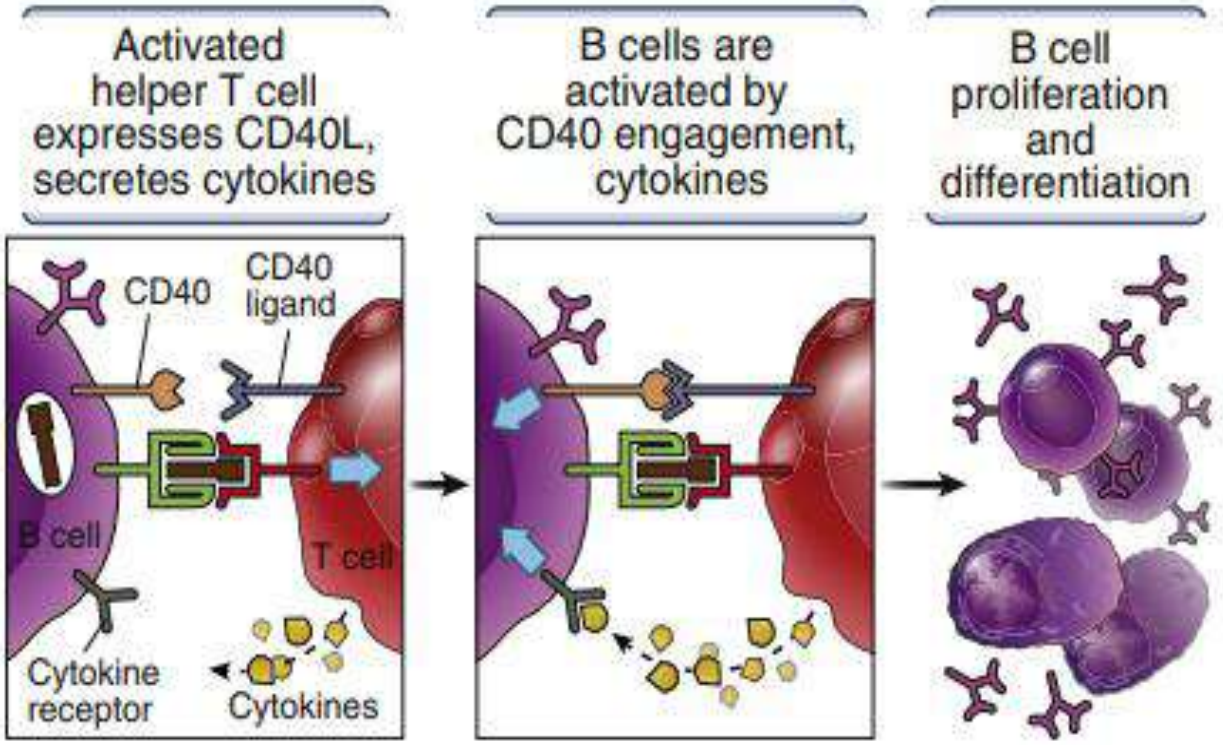


3. Clonal Expansion, proliferation and differentiation

Antigen specific B cells expand in numbers to produce specific antibodies

B cells differentiate into

1. **Antibody-producing plasma cells**
2. **Memory cells**



4. Antibodies Production (isotype switching)

- Activated B cells start to produce different classes of antibodies in large amount to eliminate infection
- Antigen stimulated B cells may differentiate into IgM producing antibodies, however, later on, under the influence of CD40L and cyokines B cells can differentiates into cells producing other classes of heavy chain antibodies (antibody switching)
- Repeated exposure to antigen leads to increase the binding abilities of antibodies through affinity maturation, where high affinity B cells are selected to produce antibodies

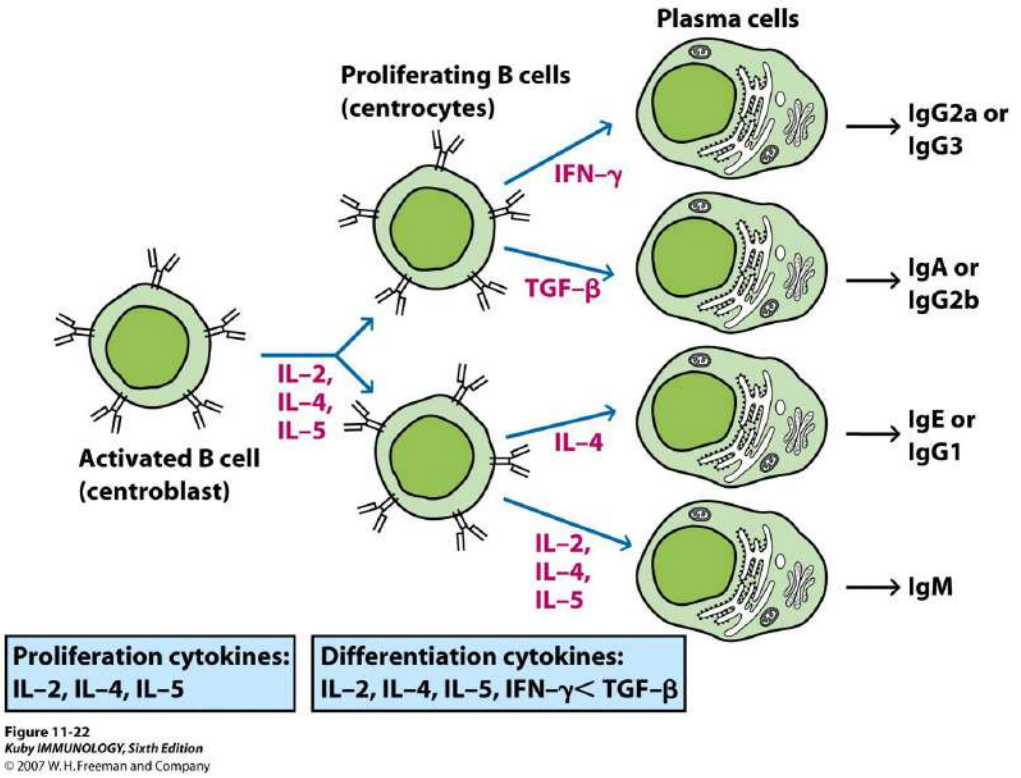


Figure 11-22
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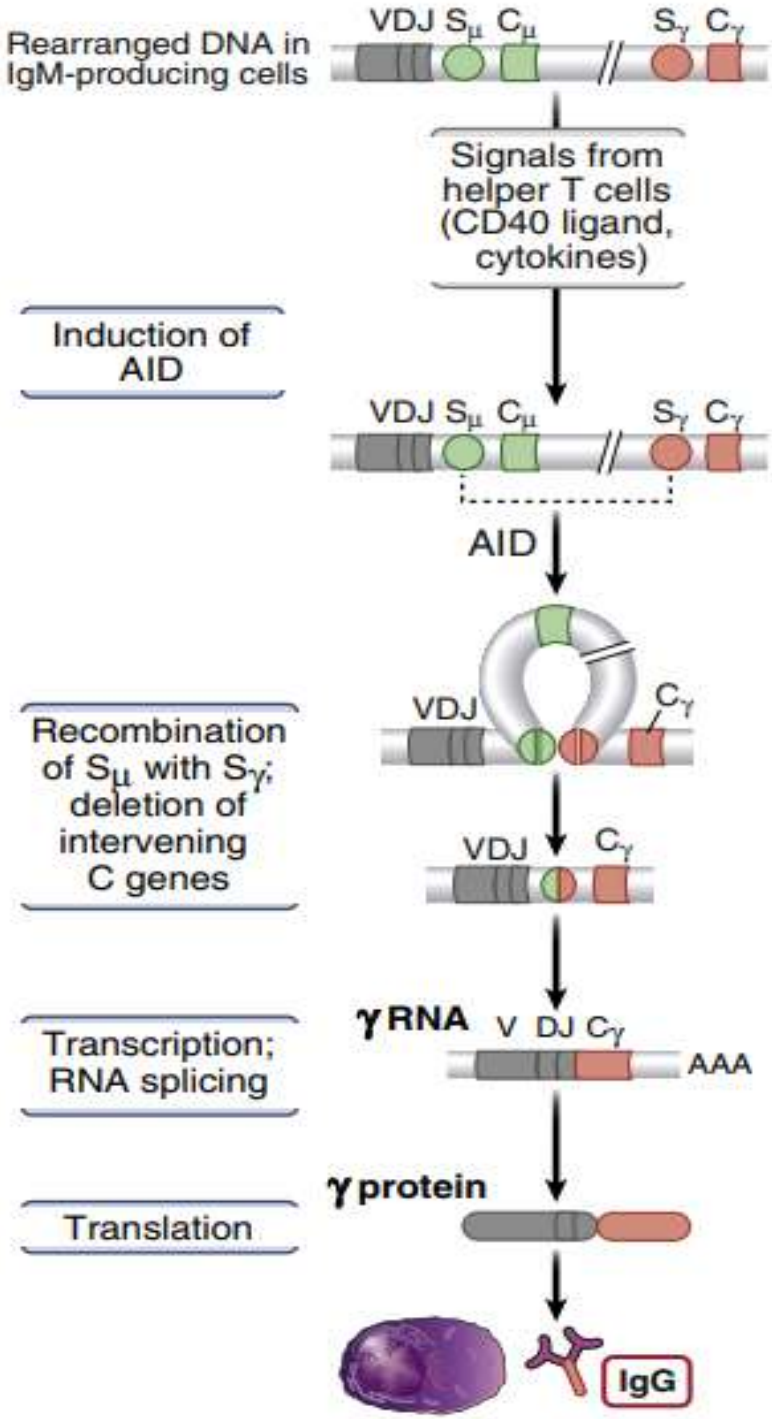
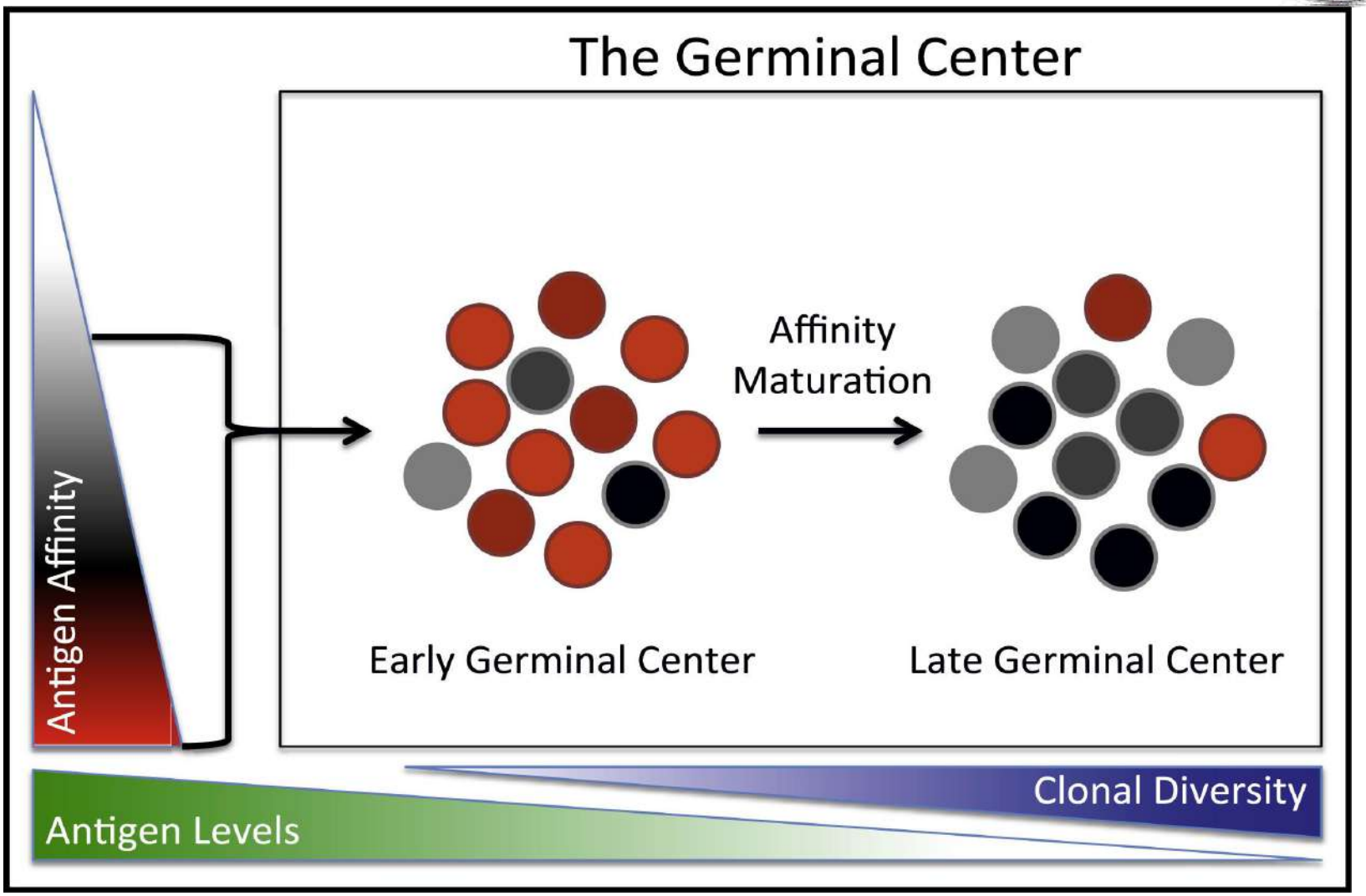

Rearranged DNA in IgM-producing cells
VDJ Sμ Cμ
Sγ Cγ
Signals from helper T cells (CD40 ligand, cytokines)
Induction of AID
AID
Recombination of Sμ with Sγ; deletion of intervening C genes
VDJ
Cγ
γ RNA
V DJ Cγ
AAA
Transcription; RNA splicing
γ protein
Translation
IgG

Affinity maturation



6. Humoral immunity shut down and formation of memory B cells

- After antibodies are capable of killing invading microorganisms, most of activated B cells die by programmed cell death
- Furthermore, circulating IgG antibodies that binds to antigen in periphery induce negative feedback mechanism to inhibit further antibody production
- Memory B cells are formed and stay for long time to facilitate faster antibodies production when the body is exposed to same antigen next time

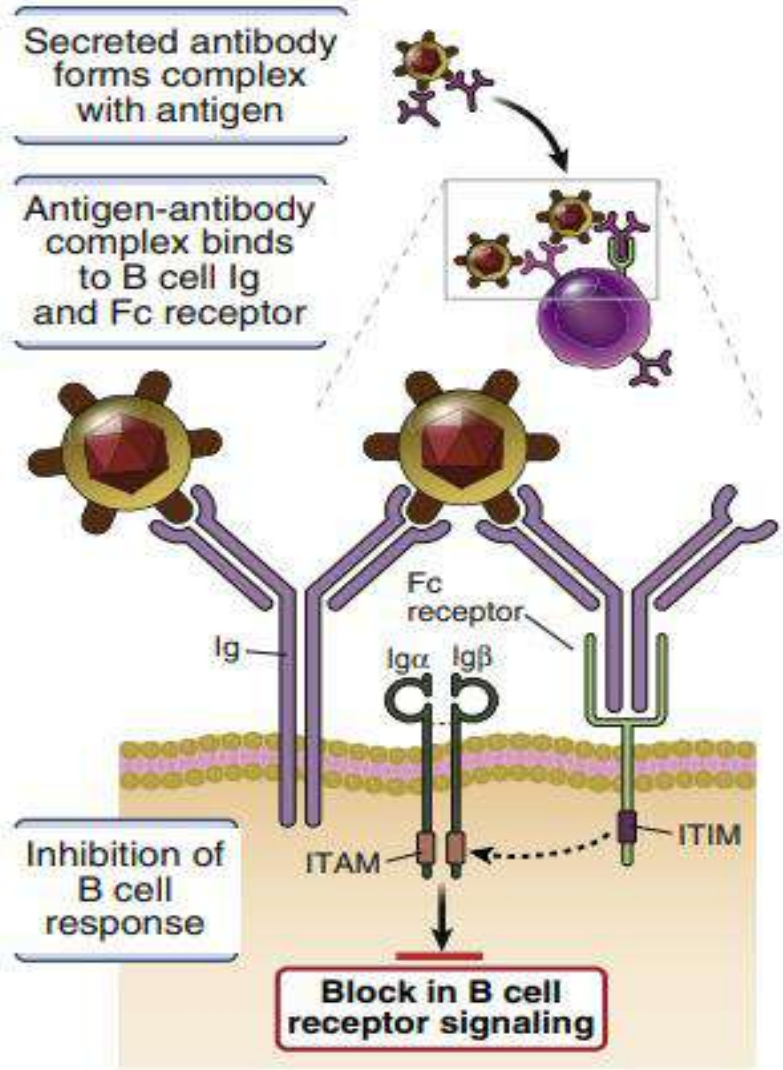


TABLE 11-6 Comparison of naive and memory B cells

Property	Naive B cell	Memory B cell
Membrane markers		
Immunoglobulin	IgM, IgD	IgM, IgD(?), IgG, IgA, IgE
Complement receptor	Low	High
Anatomic location	Spleen	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation*
Adhesion molecules	Low ICAM-1	High ICAM-1

*Affinity maturation results from somatic mutation during proliferation of centroblasts and subsequent antigen selection of centrocytes bearing high-affinity mIg.

Table 11-6
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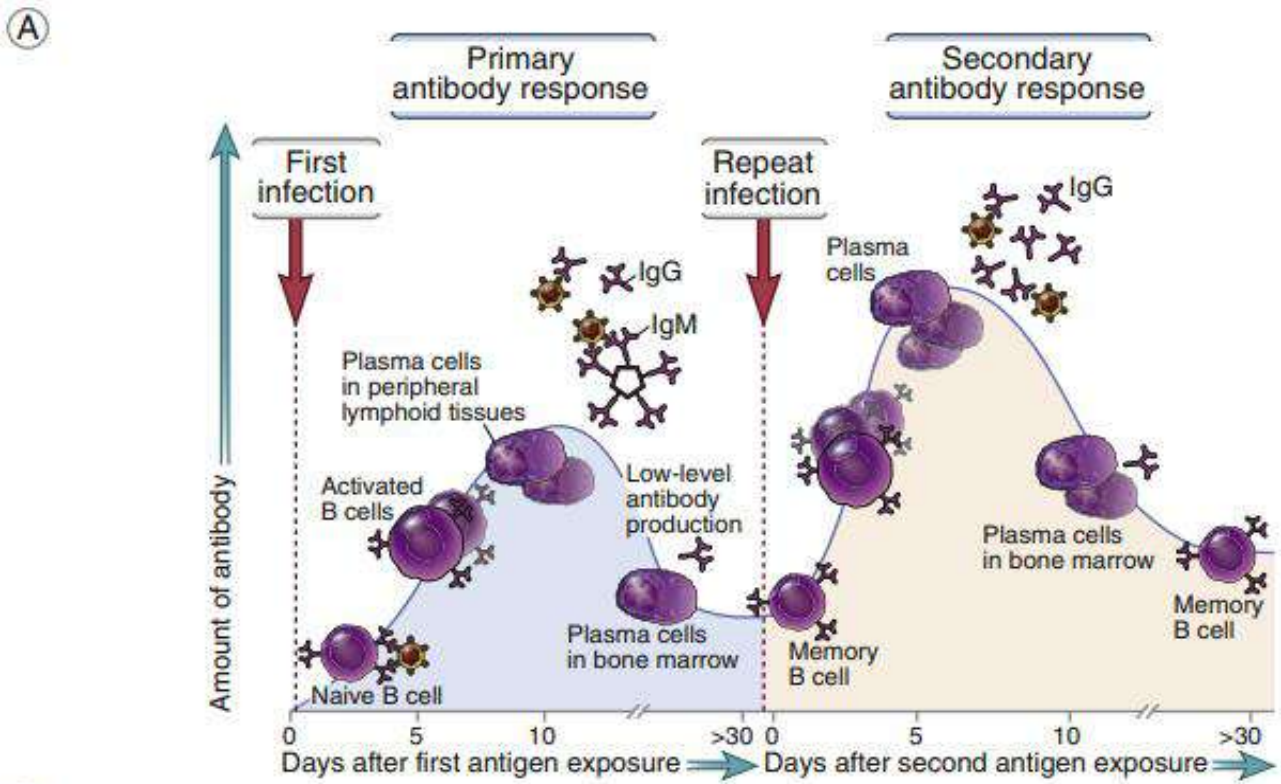
Primary and secondary humoral immunity

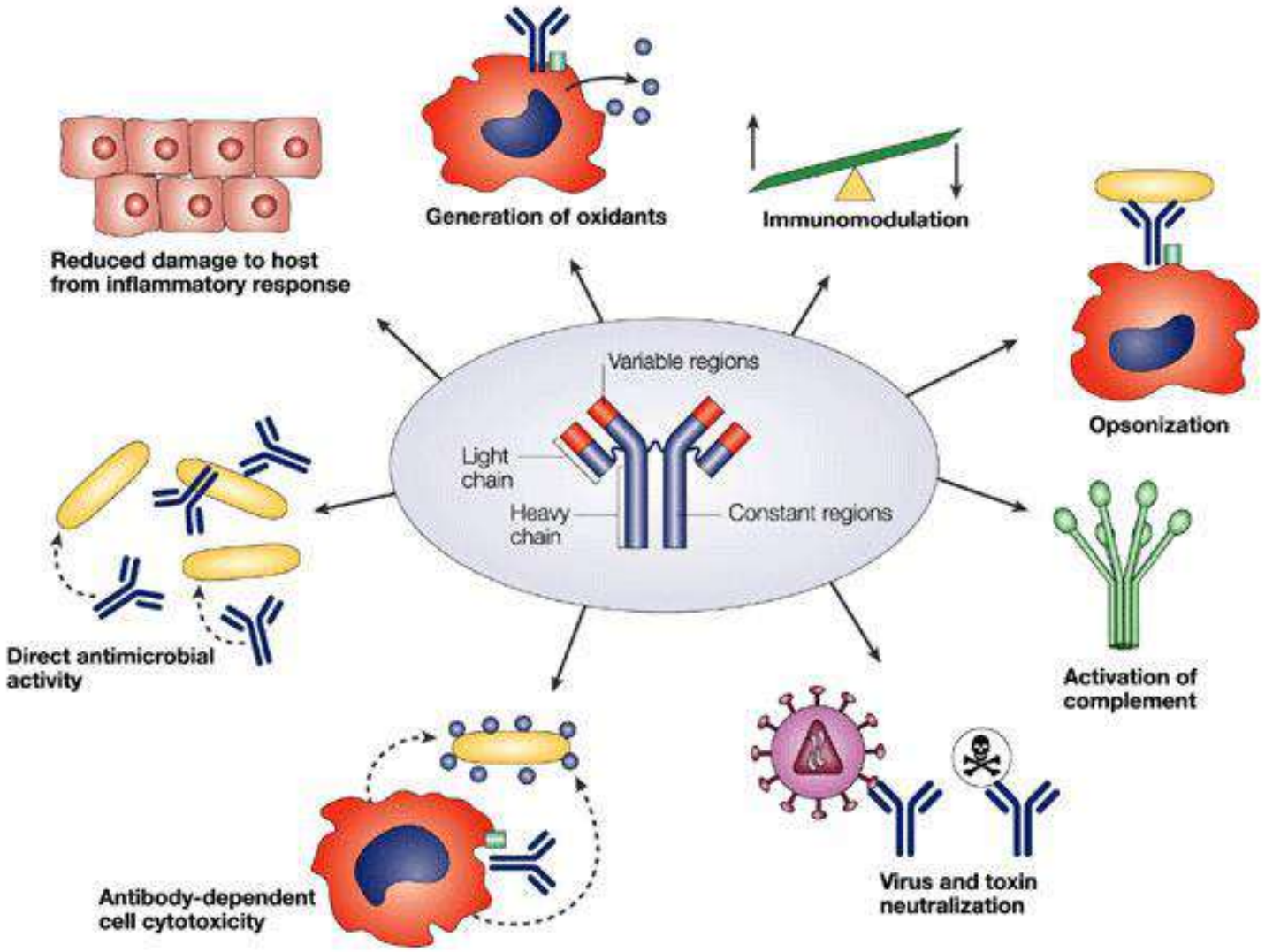


B

	Primary response	Secondary response
Lag after immunization	Usually 5–10 days	Usually 1–3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM>IgG	Relative increase in IgG and, under certain situations, in IgA or IgE (heavy-chain isotype switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

5. Effector Mechanisms

- Neutralization
- Opsonization
- Complement activation
- Antibody dependent cell mediated toxicity (ADCC)
- Transcytosis- movement across epithelial cells


Reduced damage to host from inflammatory response
Generation of oxidants
Immunomodulation
Variable regions
Light chain
Heavy chain
Constant regions
Opsonization
Direct antimicrobial activity
Activation of complement
Antibody-dependent cell cytotoxicity
Virus and toxin neutralization
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