B-Cell Maturation, Activation and Differentiation

Molecular and Human Genetics (203)

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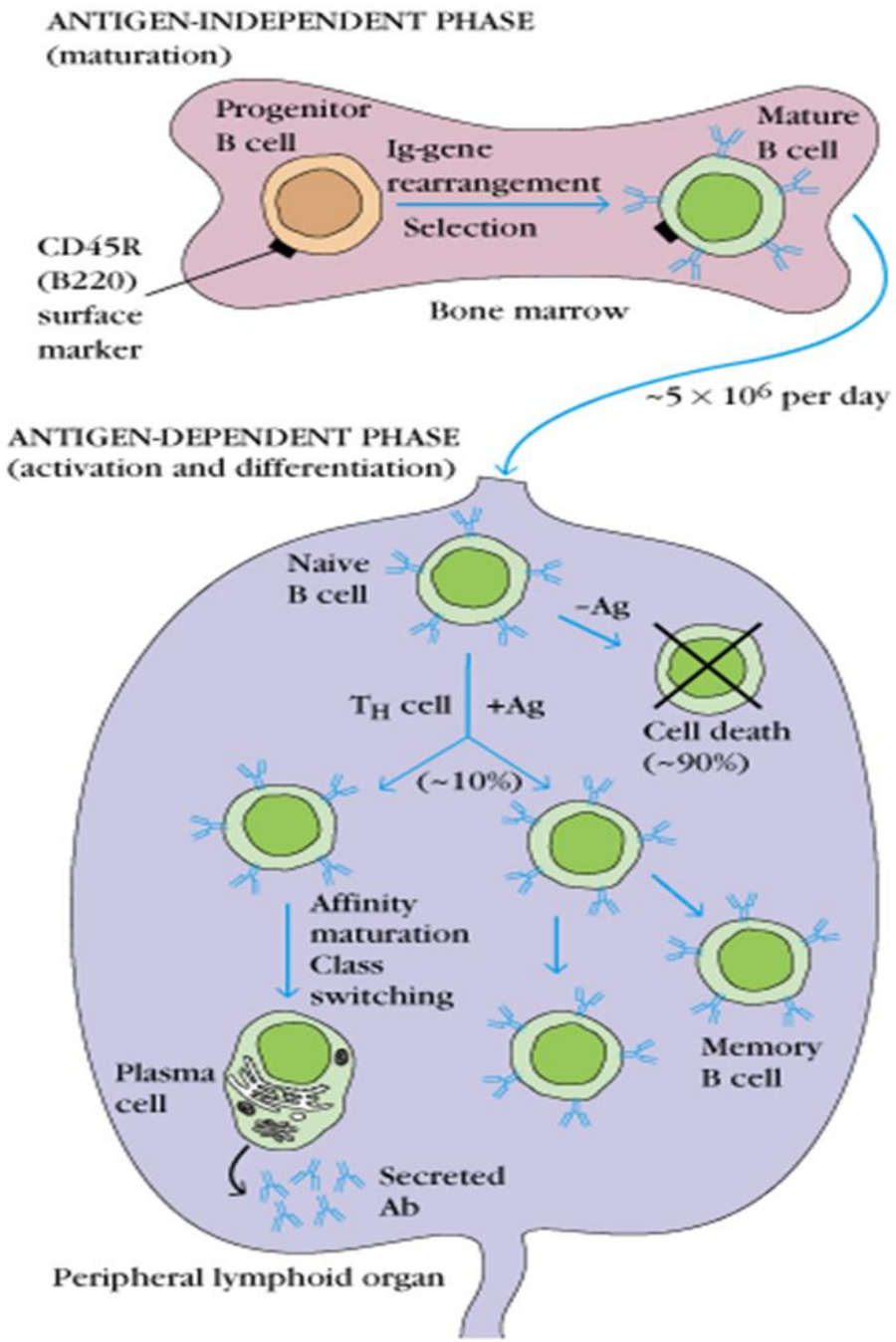


Overview of B-Cell Maturation, Activation, Differentiation

B-Cell Development

Antigen-Independent (Maturation)

1) Pro-B stages

B-cell markers

2) Pre B-stages

H- an L- chain loci rearrangements
surrogate light chain

3) Naïve B-cell

functional BCR

- B cells are generated in the bone marrow.
- Takes 1-2 weeks to develop from hematopoietic stem (HSC) cells to mature B cells.
- Sequence of expression of cell surface receptor and adhesion molecules which allows for differentiation of B cells, proliferation at various stages, and movement within the bone marrow microenvironment.

Begins in the Bone Marrow and Is Completed in the Periphery

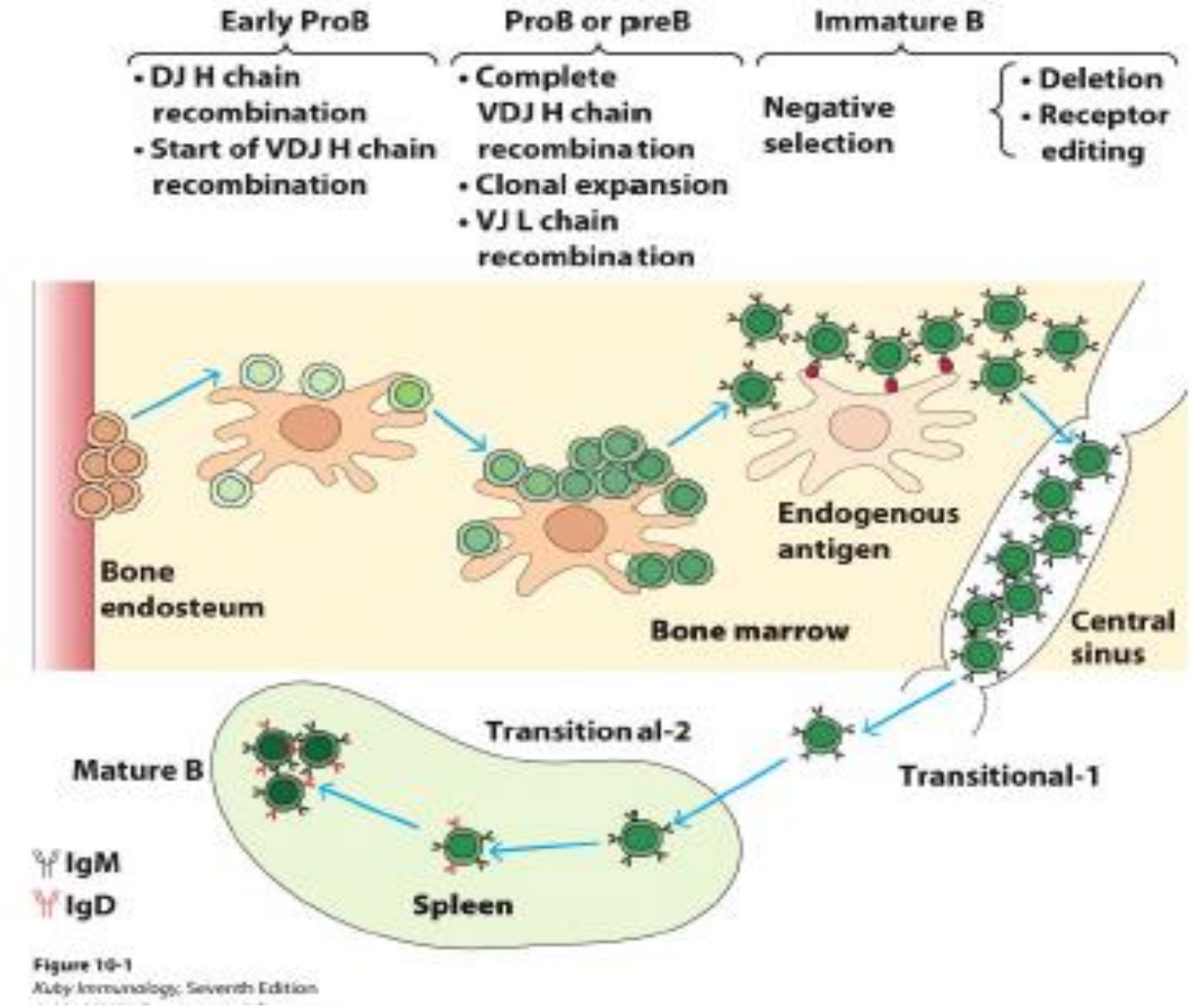


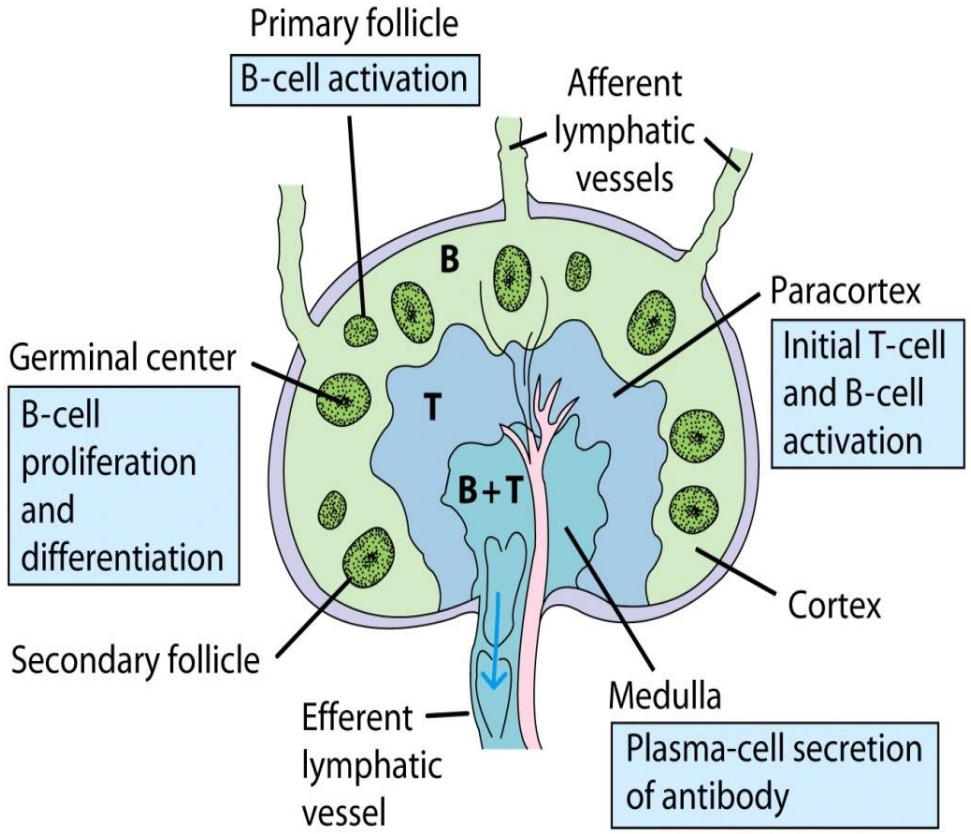
Figure 10-1
Kuby Immunology, Seventh Edition

HSC passes through progressively more delimited progenitor-cell stages until it reaches the pro-B cell stage.

Pre-B cell is irreversibly committed to the B-cell lineage and the recombination of the immunoglobulin genes expressed on the cell surface

Immature B cell (transitional B cell) leaves the bone marrow to complete its maturation in the spleen through further differentiation.

Immune system must create a repertoire of receptors capable of recognizing a large array of antigens while at the same time eliminating self-reactive B cells.



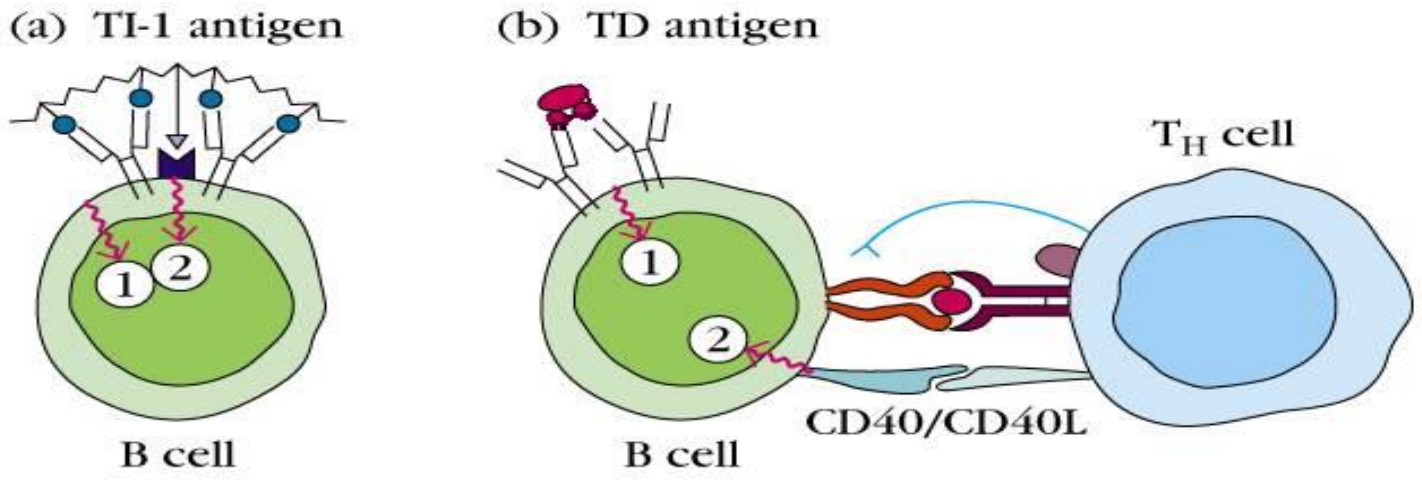
Source: Internet

B-Cell Activation and Differentiation

- Exposure to antigen or various polyclonal mitogens activates resting B cells and stimulates their proliferation.
- Activated B cells lose expression of sIgD and CD21 and acquire expression of activation antigens.
  - ❖ Growth factor receptors, structures involved in cell-cell interaction, molecules that play a role in the localization and binding of activated B cells

Two major types:

- ➢ **T cell dependent (TD)**
- ➢ **T cell independent (TI)**



B-Cell Activation by Thymus-Independent and Dependent Antigens

Source: Kuby

T cell dependent: Involves protein antigens and CD4+ helper T cells.

- ✓ Multivalent antigen binds and crosslinks membrane Ig receptors.
- ✓ Activated T cell binds B cell thru antigen receptor and via CD40L (T)/CD40 (B) interaction.

T cell independent: Most TI antigens are polyvalent and induce maximal Crosslinking of membrane Ig on B cells, without a Need for T cell help.

- ✓ TI-1: e.g., LPS. Mitogenic at high concentrations to most B cells because of binding to pattern recognition receptors (PRRs) on B cell surface. At low concentrations, only activates those B cells that bind the antigen via the Ig receptor.
- ✓ TI-2: e.g., bacterial capsular polysaccharide. Highly repetitive antigens. Not mitogenic but can crosslink Ig receptors. Many are bound by C3d.

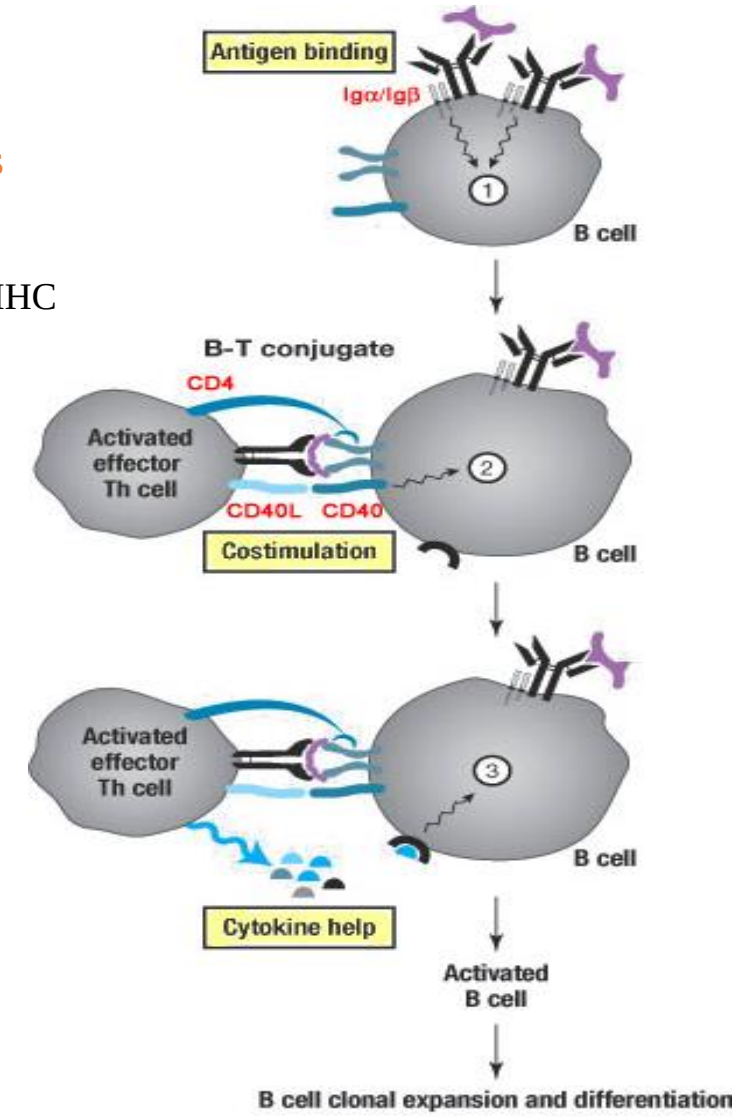
- ❑ TD antigen activation, some activated B cells differentiate into plasma cells in primary foci that are outside of the follicles, then migrate to the medullary cords of the lymph node or to the bone marrow. Secrete IgM within 4 days.
- ❑ Other activated B cells enter the follicle, divide and differentiate; germinal centers form.
- ❑ Within the germinal center, Ig genes undergo class switching: the μ constant regions replaced by other constant regions and the variable region is subject to somatic hypermutation.
- ❑ Mutated variable region subject to antigen-mediated selection.
- ❑ Low affinity and autoreactive B cells die while those with improved affinity leave the germinal centers.
- ❑ Antibodies with mutations in the variable region appear in the circulation within 6-10 days.

B Cell Responses to Thymus-Dependent Antigens (T Cell-Dependent Antibody Responses)

1) Antigen crosslinking of antibodies
   - antigen engagement
   - Igα/Igβ signaling
   - up-regulation of CD40 & MHC

2) T_H cell engagement
   - Cell/cell interactions
   - MHC presentation
   - TCR recognition
   - CD40/CD40L coupling

3) Cytokine stimulation
   - IL4, IL2, etc.
   - class switching to IgG
   - memory cell formation



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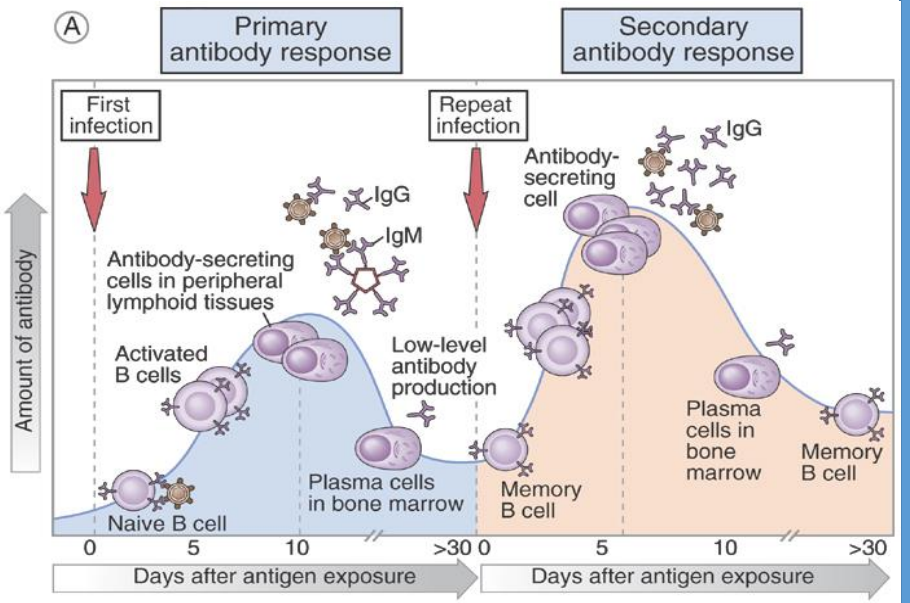


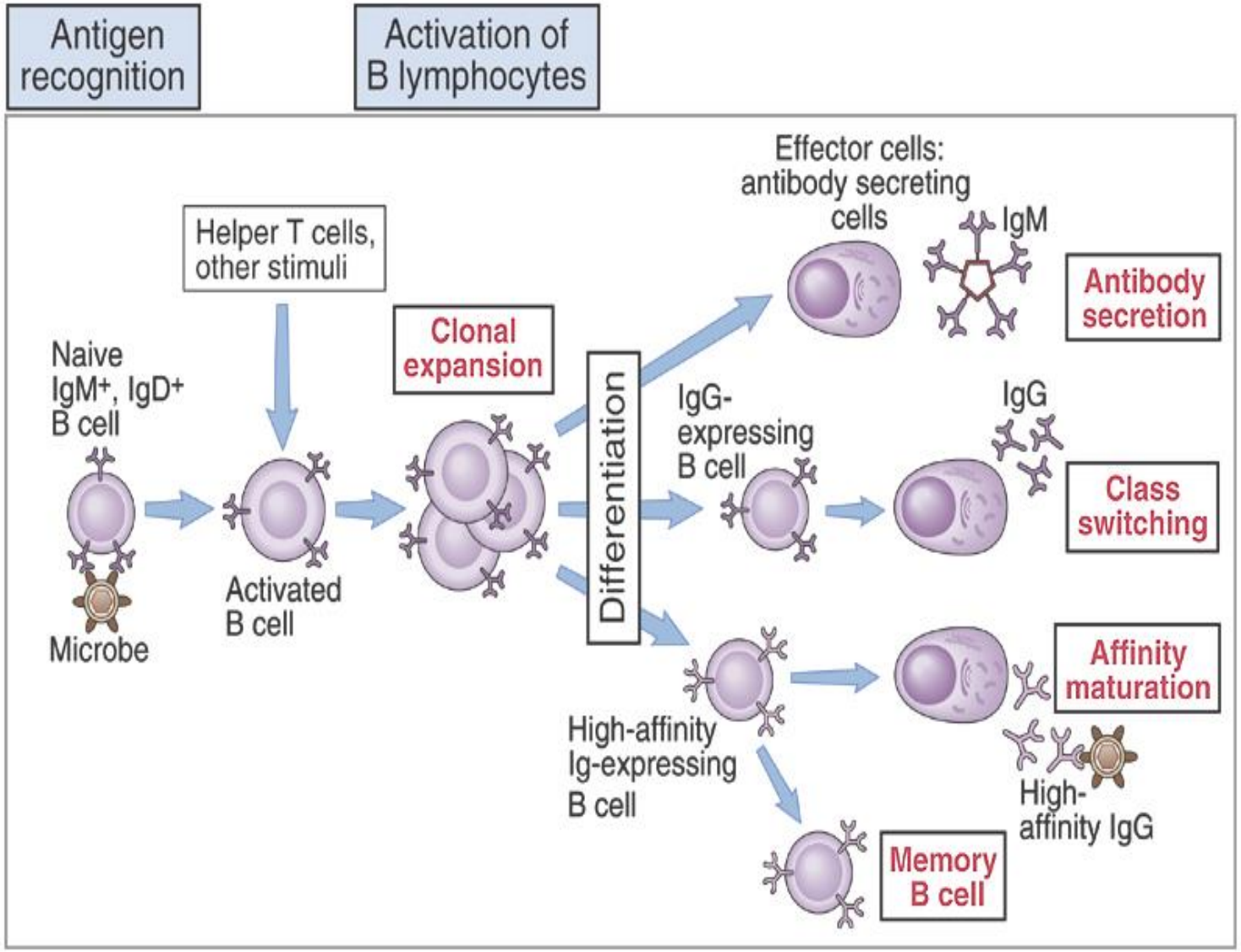
B

	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 class switching)
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)

Primary and Secondary Antibody Responses

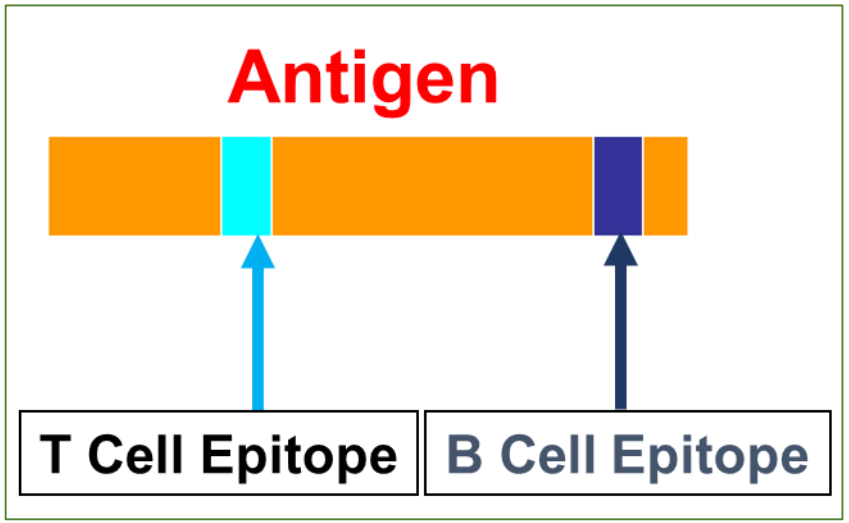
Source: Abbas et al, 2011

Phases of the Humoral Immune Response

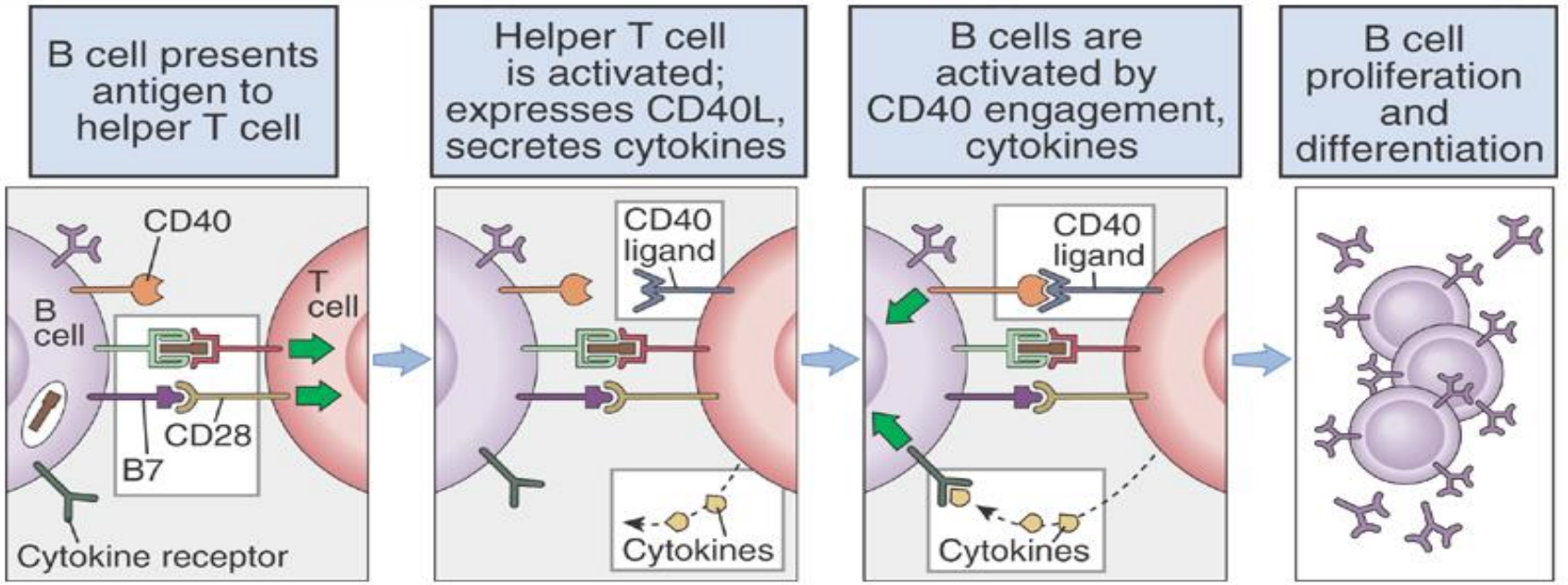


Source: Abbas et al, 2011

A T-Dependent Antigen Must Contain Both B and T Cell Epitopes



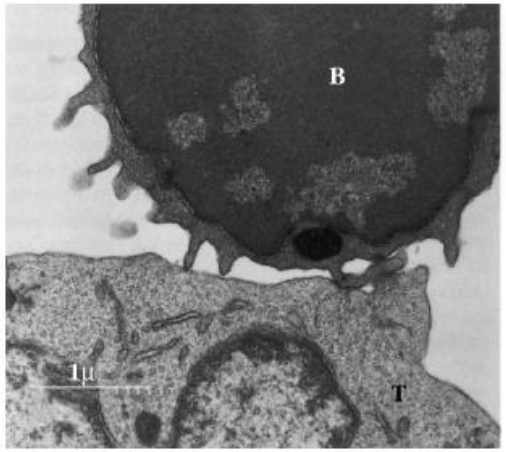
Helper T Cell-Dependent Activation of B Lymphocytes



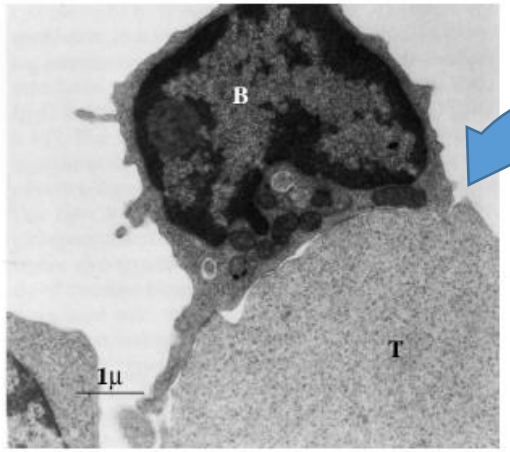
Source: Abbas et al, 2011

TEM Picture

Initial Contact

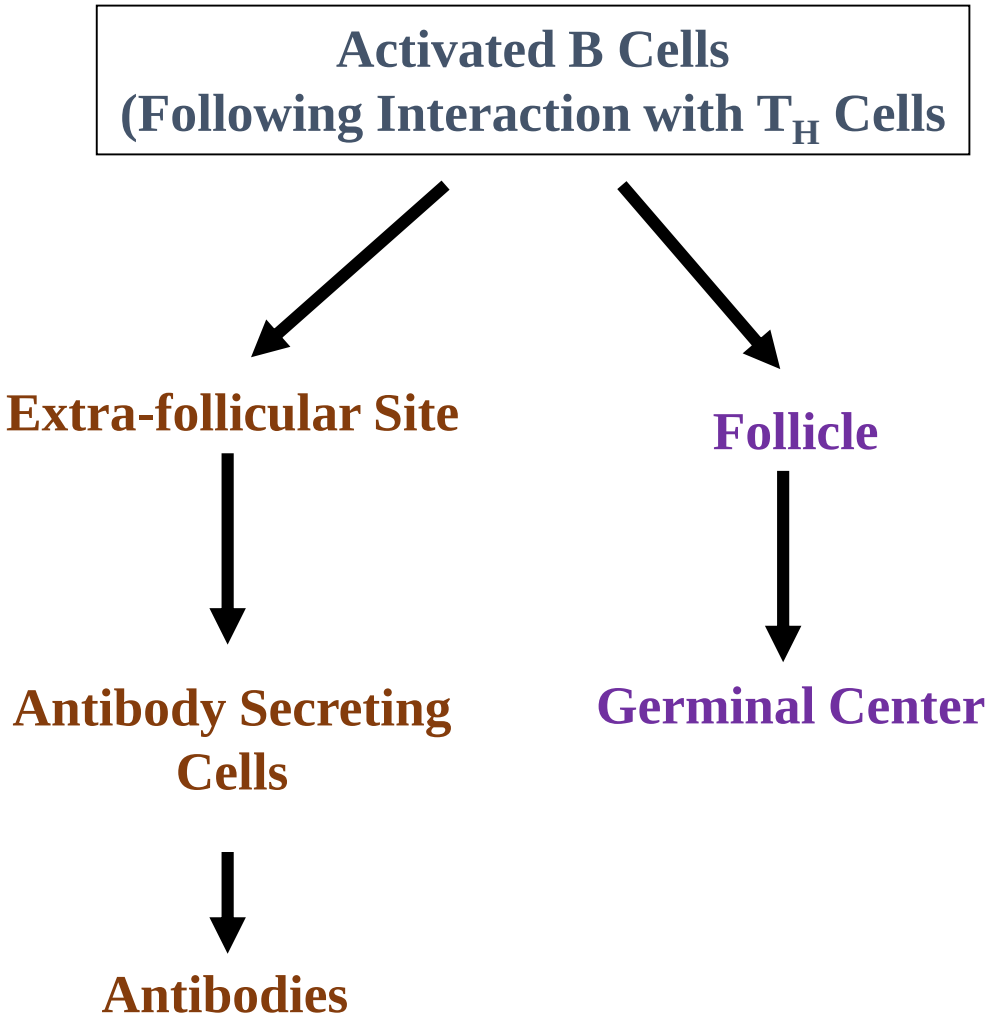


T-B Conjugate



Source: Kuby

Note the broad area of membrane contact between B and T Cells.



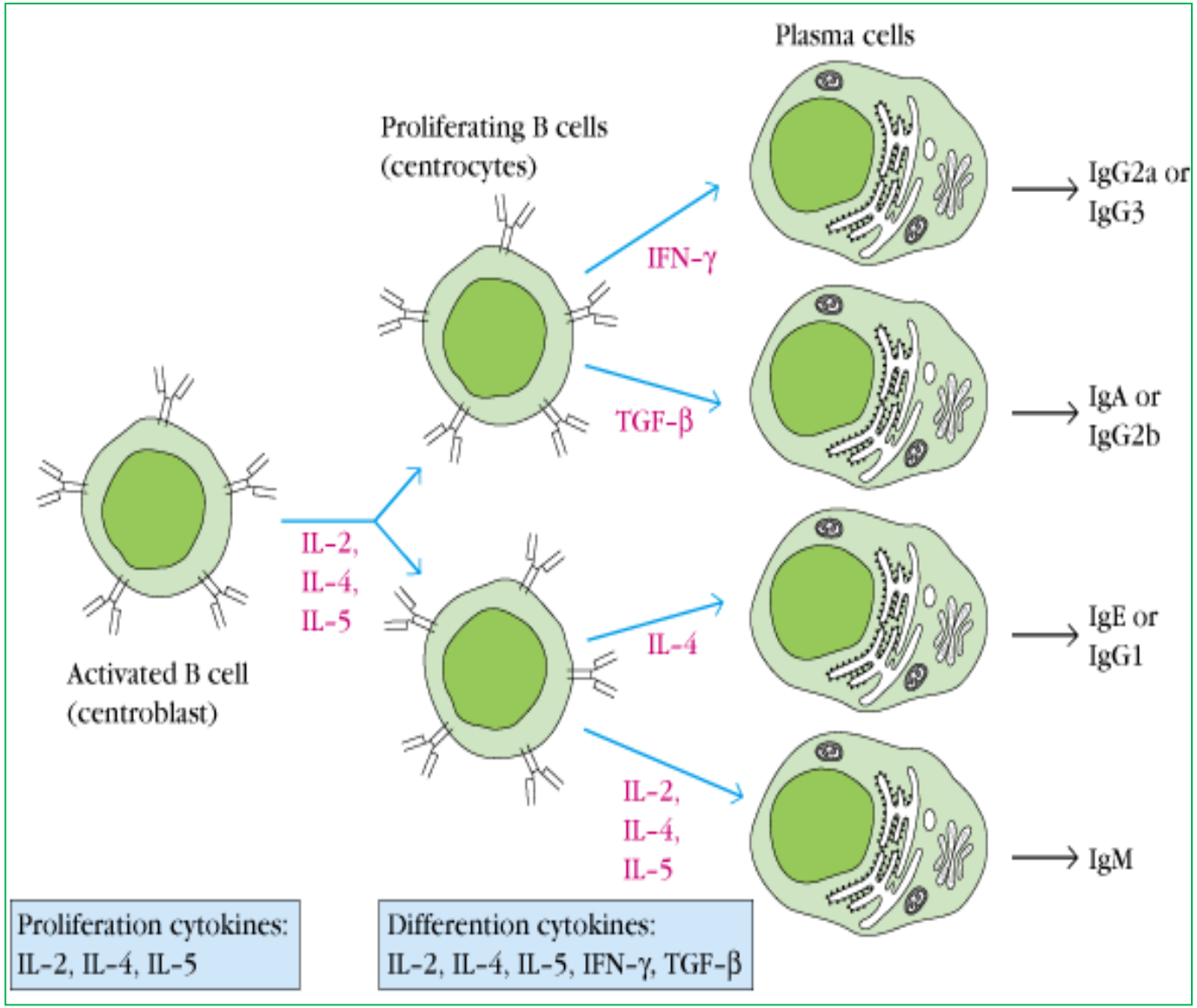
Late Events in T Cell-Dependent Antibody Responses- Germinal Center Reaction

- Affinity Maturation
- Somatic Hypermutation
- Generation of Memory B Cells

Somatic Hypermutation and Affinity Maturation of Antibodies →

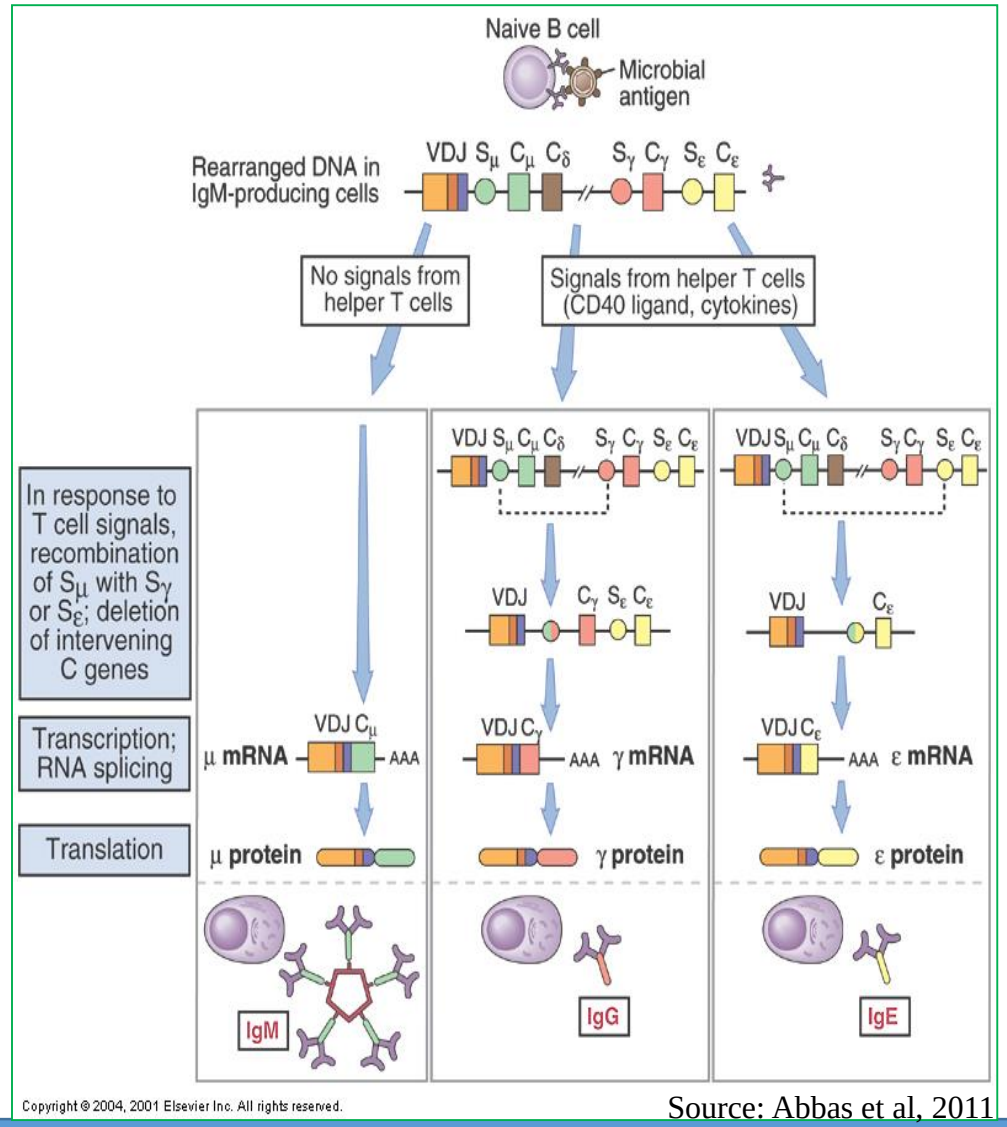
Affinity maturation is the process that leads to increased affinity of antibodies for a particular antigen as a result of somatic mutation in the Ig genes followed by selective survival of B cells producing the antibodies with the highest affinity.

Isotype Switching Under the Influence of Helper T Cell-Derived Cytokines



Source: Kuby

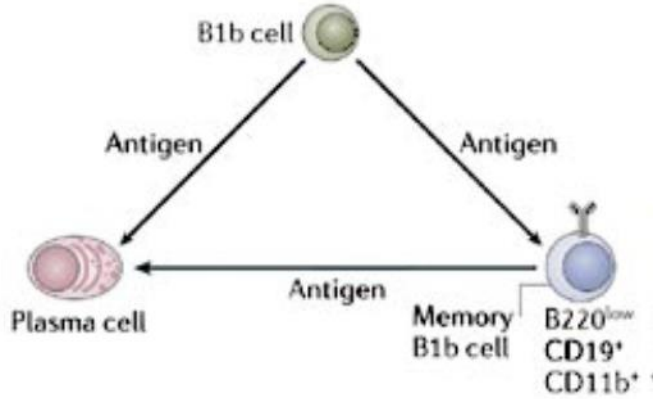
Mechanism of Ig Isotype Switching



Source: Abbas et al, 2011

B Cell activation can occur without T-cell help

- Rapidly mature into short-lived plasma cells without undergoing somatic hypermutation or class switching.
- Secrete IgM antibodies of low affinity.
- Do not contribute to memory B cell pools.
- B-1 cells may preferentially follow this non-follicular differentiation pathway as they appear to be much less dependent on T cell help for antibody production.

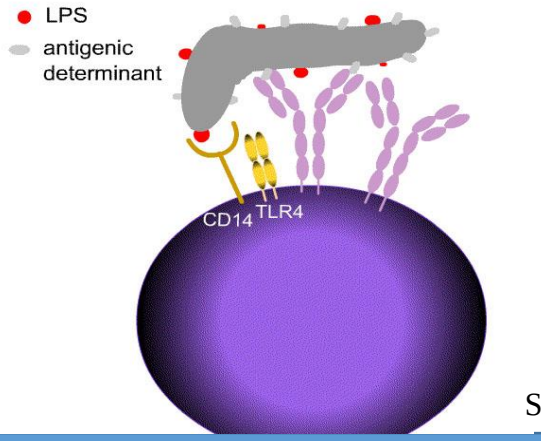


Two types

Ti type-1 – e.g., LPS
- **many are mitogens**
- **signal through TLRs**
- **CD14 is LPS receptor**

✓ Sometimes coupled with BCR engagement
✓ Some can activate without BCR engagement

Ti type-2 – e.g. capsule polysaccharides
bacterial flagellin
- **crosslink Abs**
- **AGs have repetitive, polymeric structure**

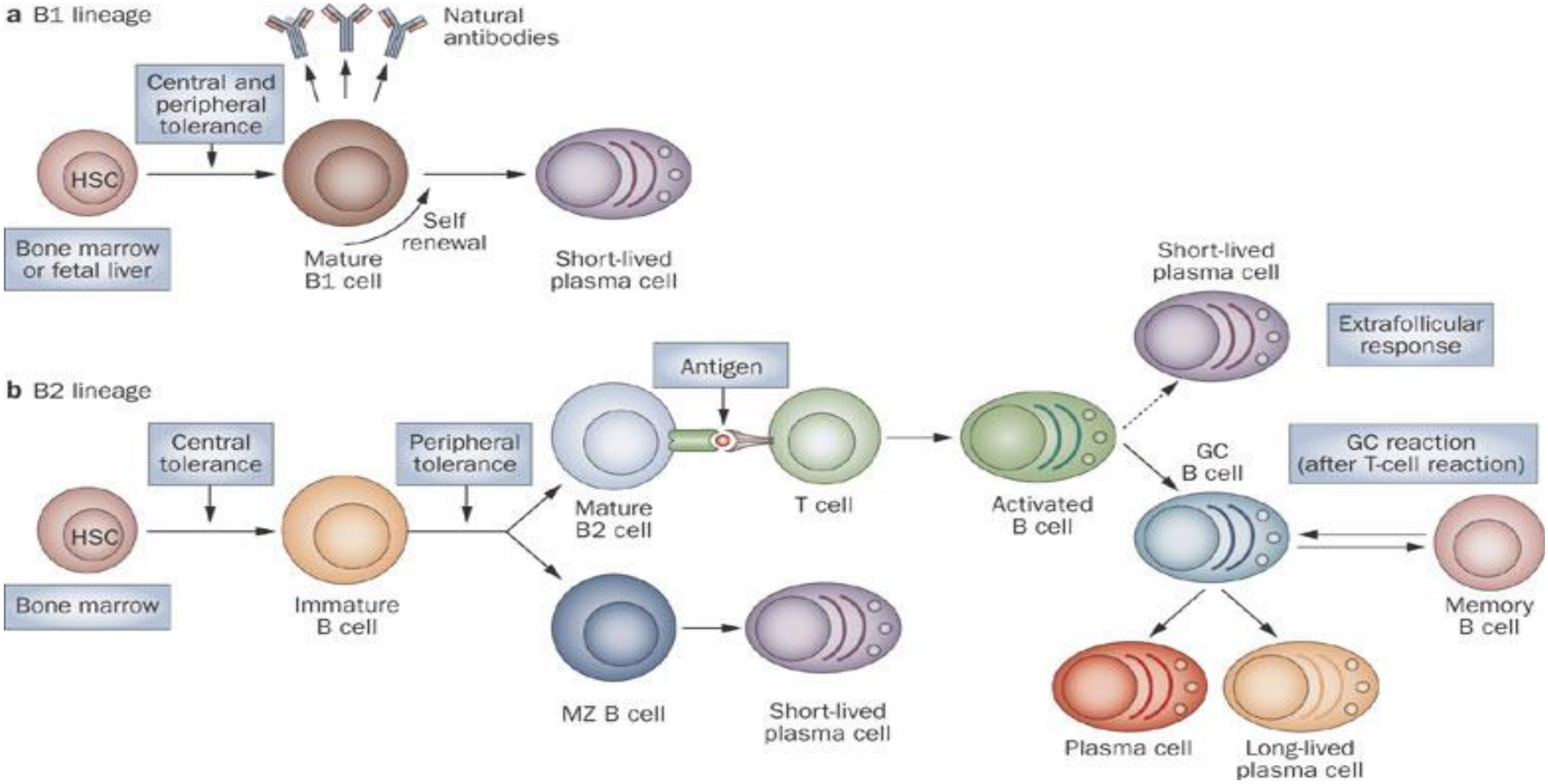


Source: Internet

Summary of thymus-dependent vs thymus-independent antigens and B-cell differentiation

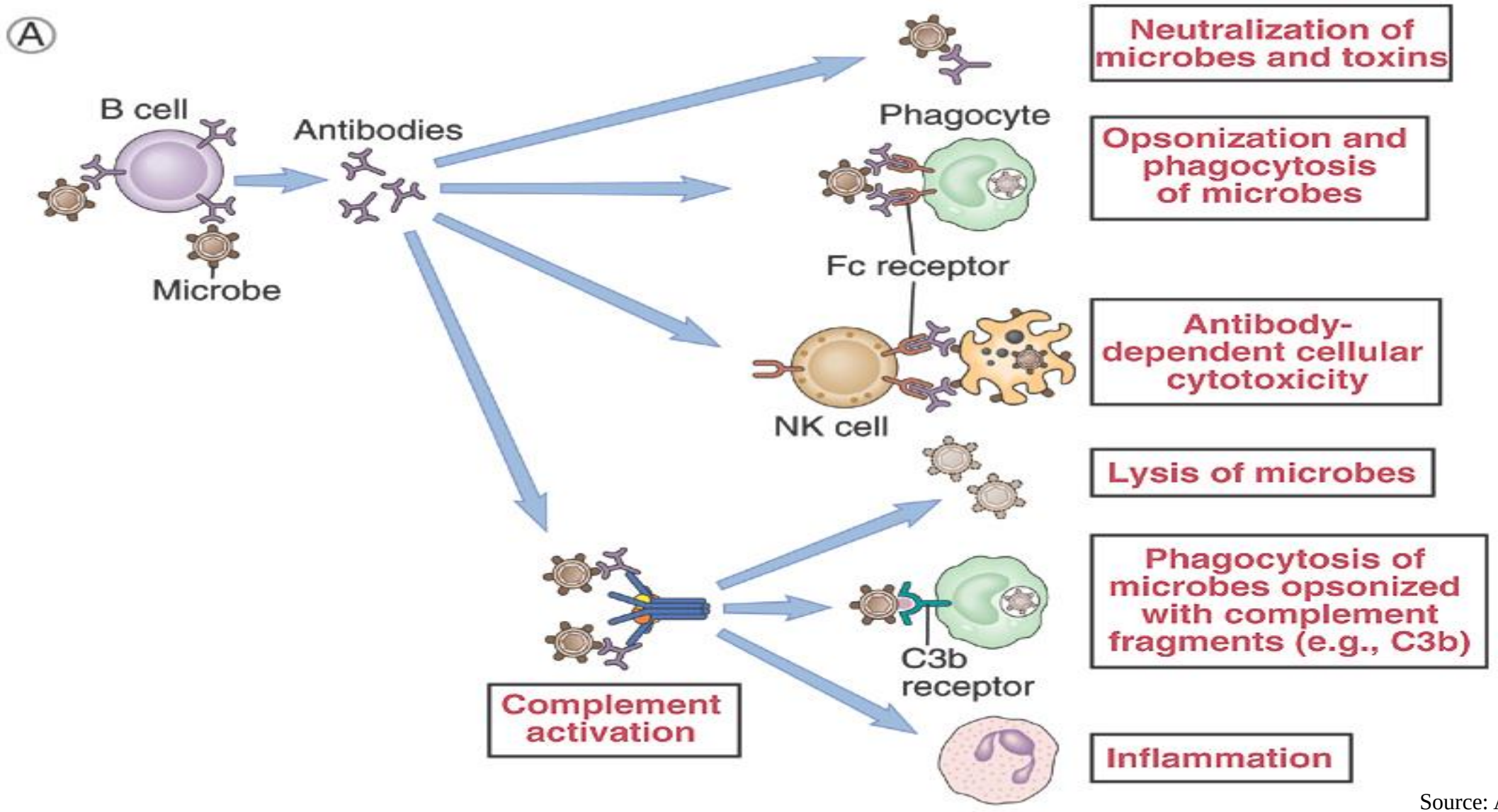
	TD antigens	TI type I antigens	TI type 2 antigens
Antigen type	Soluble protein	Bacterial cell wall components (e.g., LPS)	Polymeric protein antigens, capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No*
Polyclonal activation	No	Yes (high doses)	No

*Some antigen can produce memory cell.



Dörner, T. *et al.* (2009) B-cell-directed therapies for autoimmune disease *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2009.141

Effector Functions of Antibodies



Source: Abbas et al, 2011

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Thank You!