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B Cell Differentiation

M1 – Immunology Sequence

Winter 2009

University of Michigan
Medical School

1. B cell activation during antigen-driven B cell differentiation.

2. What are the cellular and molecular interactions that lead to antigen-driven B cell differentiation?

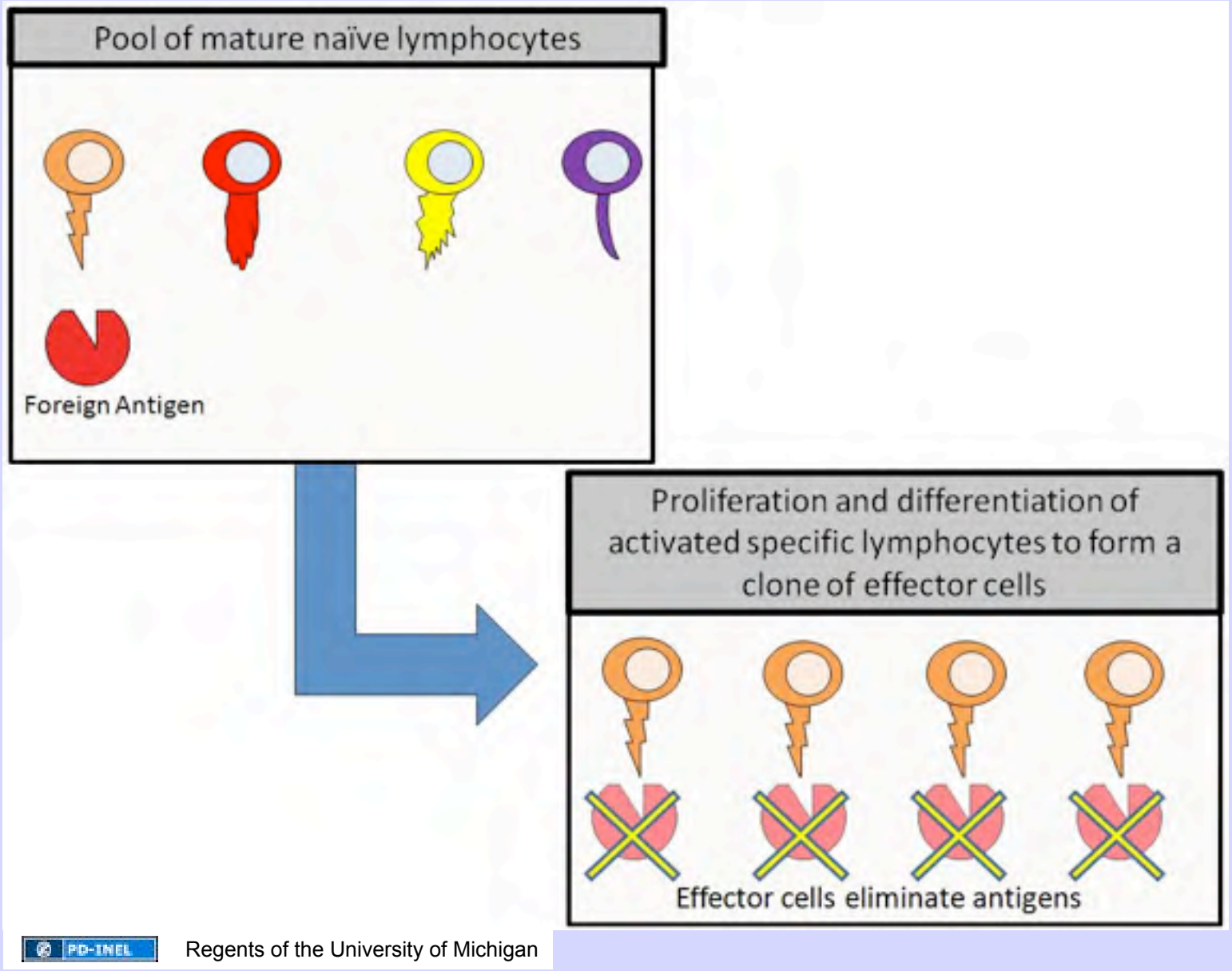
3. What is the mechanism of the heavy chain isotype switch?

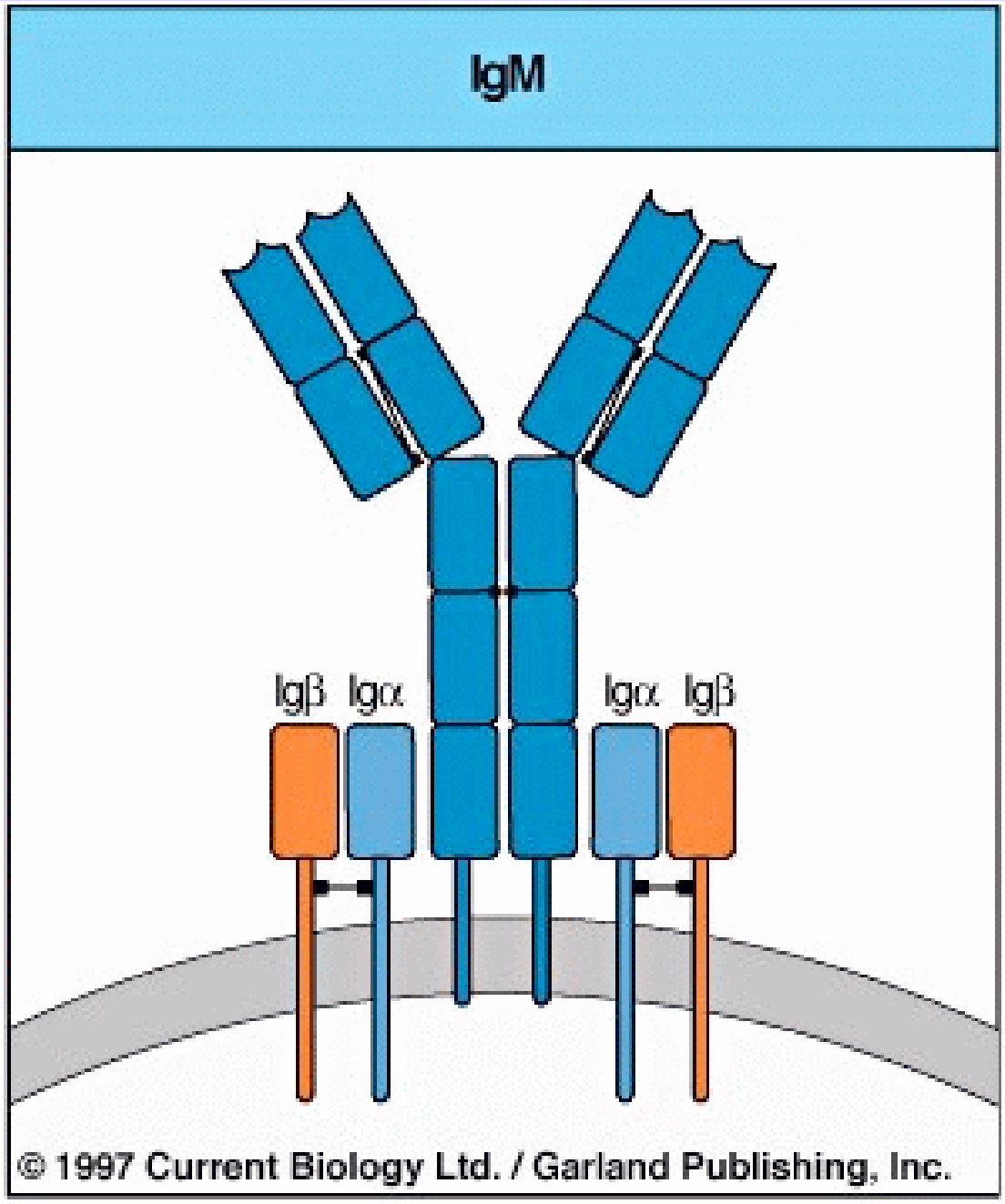
4. How can antibody variable region genes further diversify during antigen-driven B cell differentiation?

Antigen-Dependent B Cell Differentiation

In secondary lymphoid tissues, antigens on pathogens select those rare B cell clones that bind the antigen on the pathogen and causes those B cells to become activated and divide.

This is clonal selection of one in ten thousand or one in one hundred thousand B cell clones.





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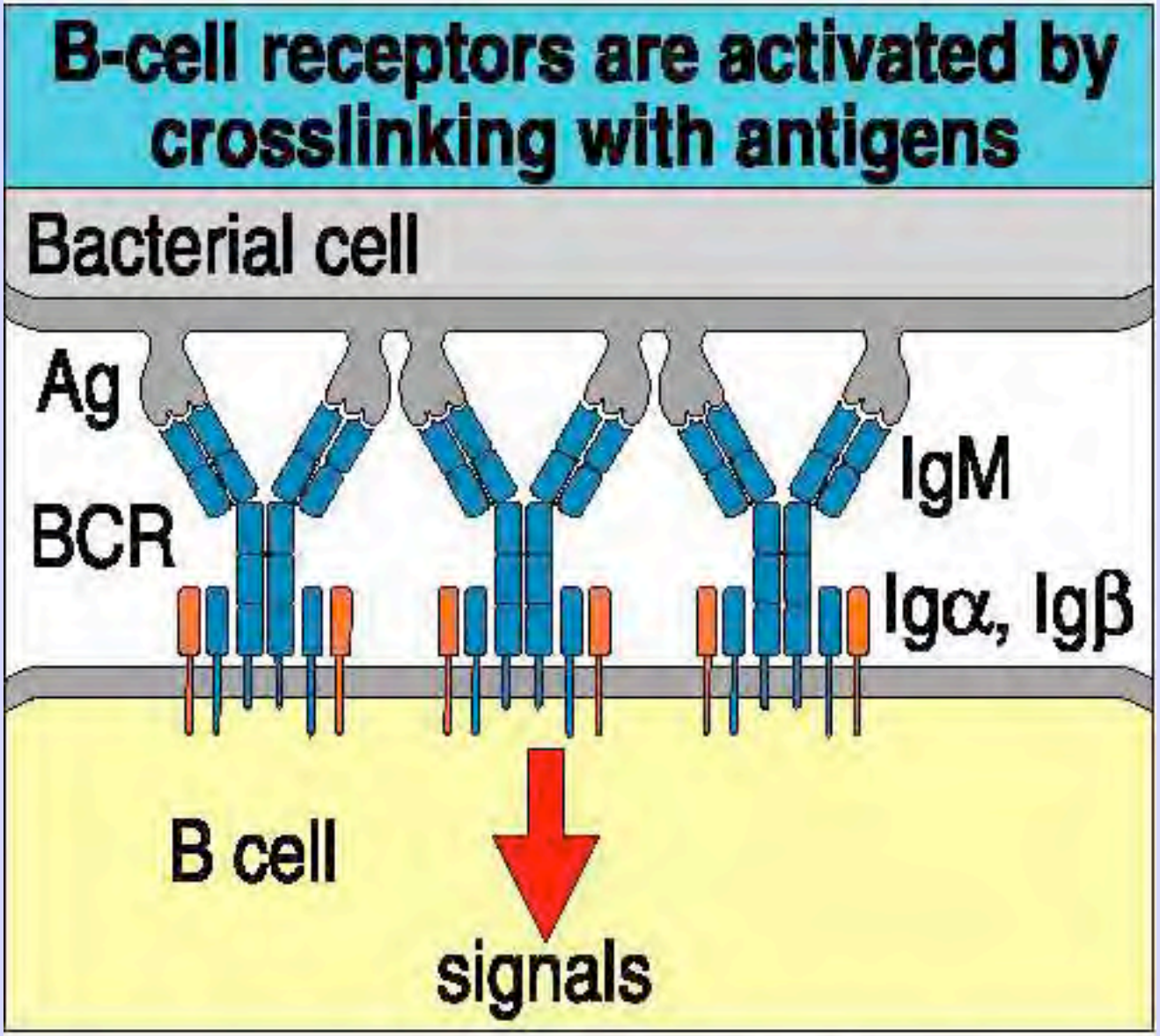
IgM and IgD on the surface of a mature B cell are associated with two chains, Igα and Igβ.

Igα and Igβ are <u>not</u> clonally distributed, because they have exactly the same sequence in all B cells.

One part of B cell activation involves phosphorylation of tyrosines on Igα and Igβ, and then activation of a series of signaling molecules (for example, btk).

Cross-linking of immunoglobulin (IgM and IgD) receptors (by binding antigen on follicular dendritic cells or on a bacterial cell wall?) on the B cell surface is required for signal transduction and for B cell activation.

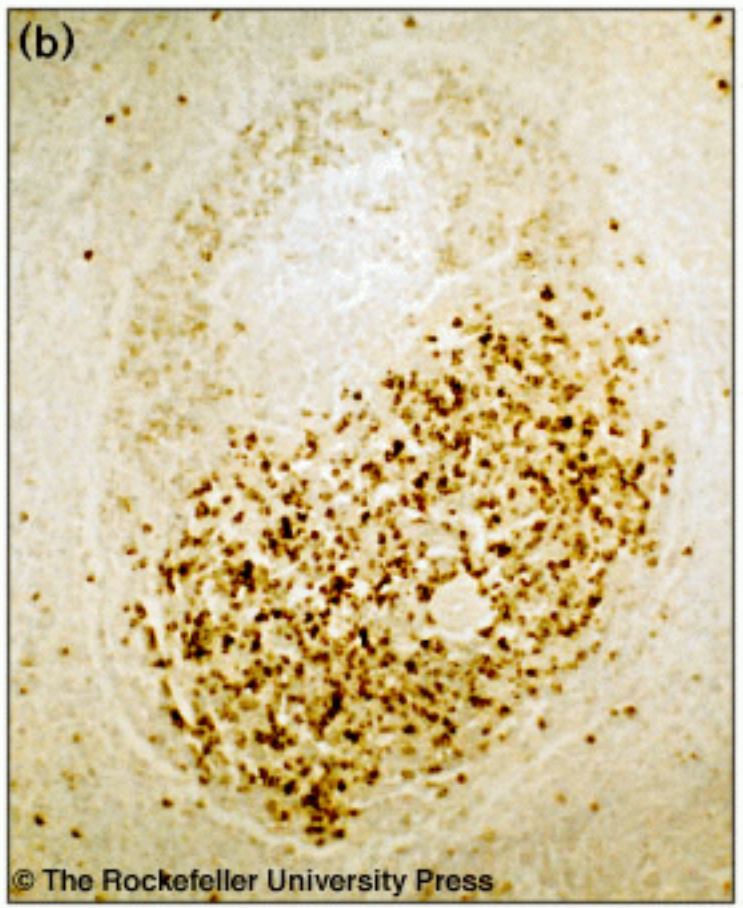
Figure 7.1



Antigen-dependent B cell differentiation requires T cell help.

B cell:T cell interaction occurs in germinal centers. These are areas of massive B cell proliferation in secondary lymphoid tissue. They arise from follicles, areas of clustered B cells.

Brown stain is anti-IgD. The clear area is due to proliferation by antigen-responsive B cells that lack IgD. Brown cells are those the follicular B cells that are not participating in the immune response.



Differentiation to plasma and memory cells

a. Cell division

b. Morphological changes--
differentiation to plasma cells

c. Secretion of antibodies

d. Affinity maturation

e. Switch to IgG, IgA, IgE

Another outcome of antigen-dependent B cell differentiation is the generation of memory B cells. These are small lymphocytes which may have IgM, IgG, IgA, or IgE on their surface. Upon a second encounter with antigen, they are activated, proliferate, and differentiate to plasma cells much faster than naïve B cells.

Some aspects of antigen-dependent B cell differentiation require T cell help, and all are enhanced by T cell help.

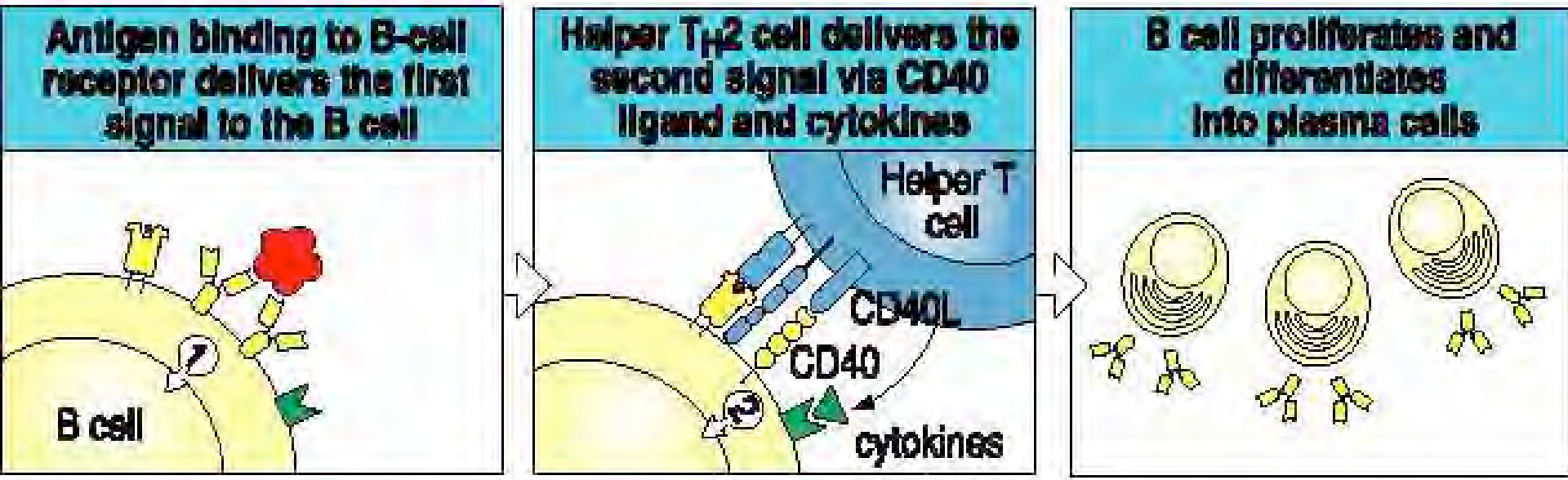
Stages in T cell help for B cells

1. A naïve B cell takes up antigen via its immunoglobulin receptors.

2. The antigen is broken down (processed) and returned to the cell surface, where antigenic fragments are bound to self proteins.

3. The T cell recognizes the antigen:self protein complex, and begins to be activated.

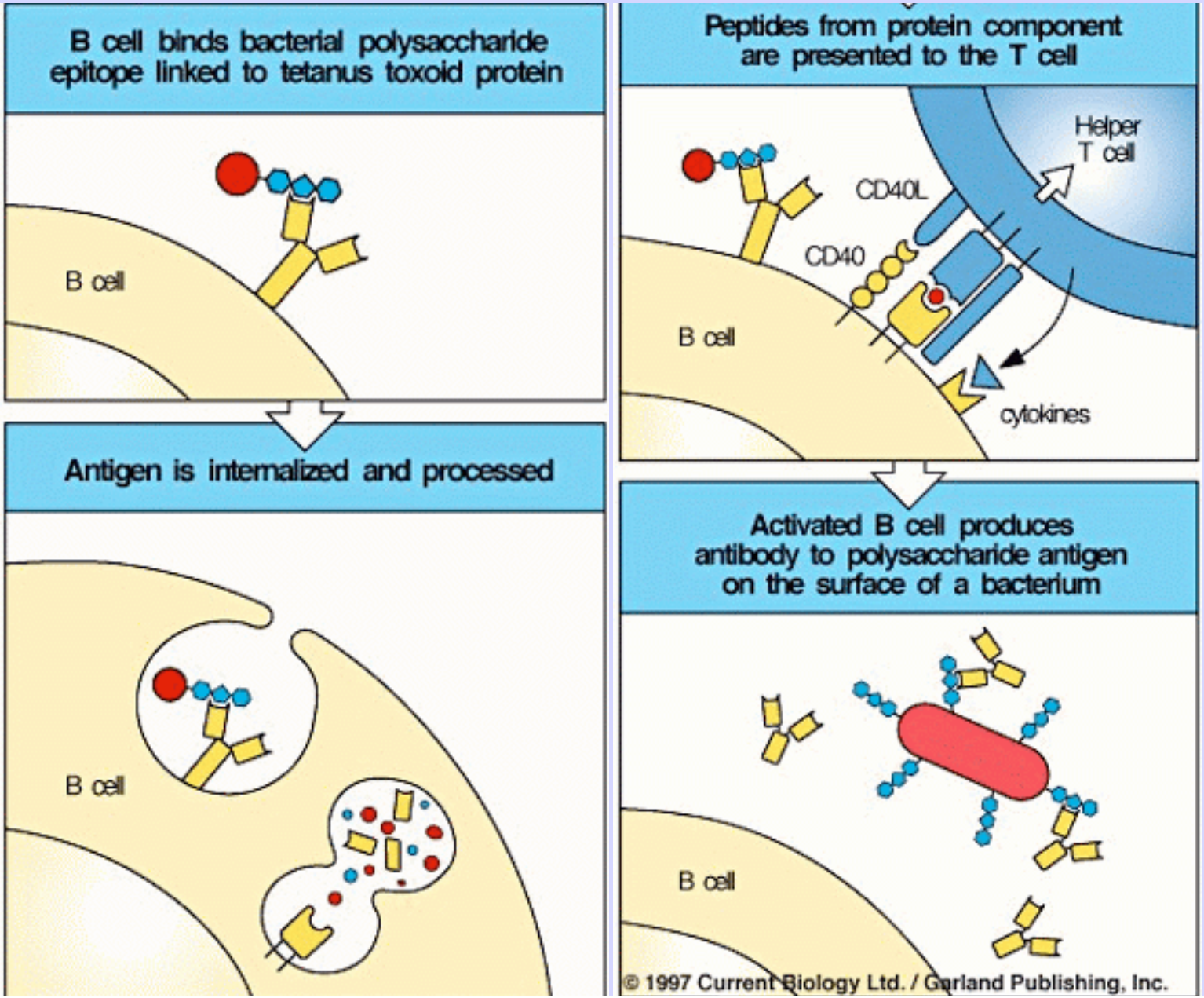
Figure 7.8



4. T cell activation includes the upregulation of CD40 ligand, a cell surface protein which is not expressed on the surface of naïve T cells.

5. The CD40 ligand on the T cell ligates the CD40 on the surface of the B cell, which leads to full B cell antigen-driven differentiation. This includes the heavy chain switch to IgG, IgA, or IgE.

6. The cell surface protein B7 (CD80, CD86) is upregulated on the activated B cell and engages CD28 on the Th cell. CD28:B7 interaction is additionally important for full activation of both cells.



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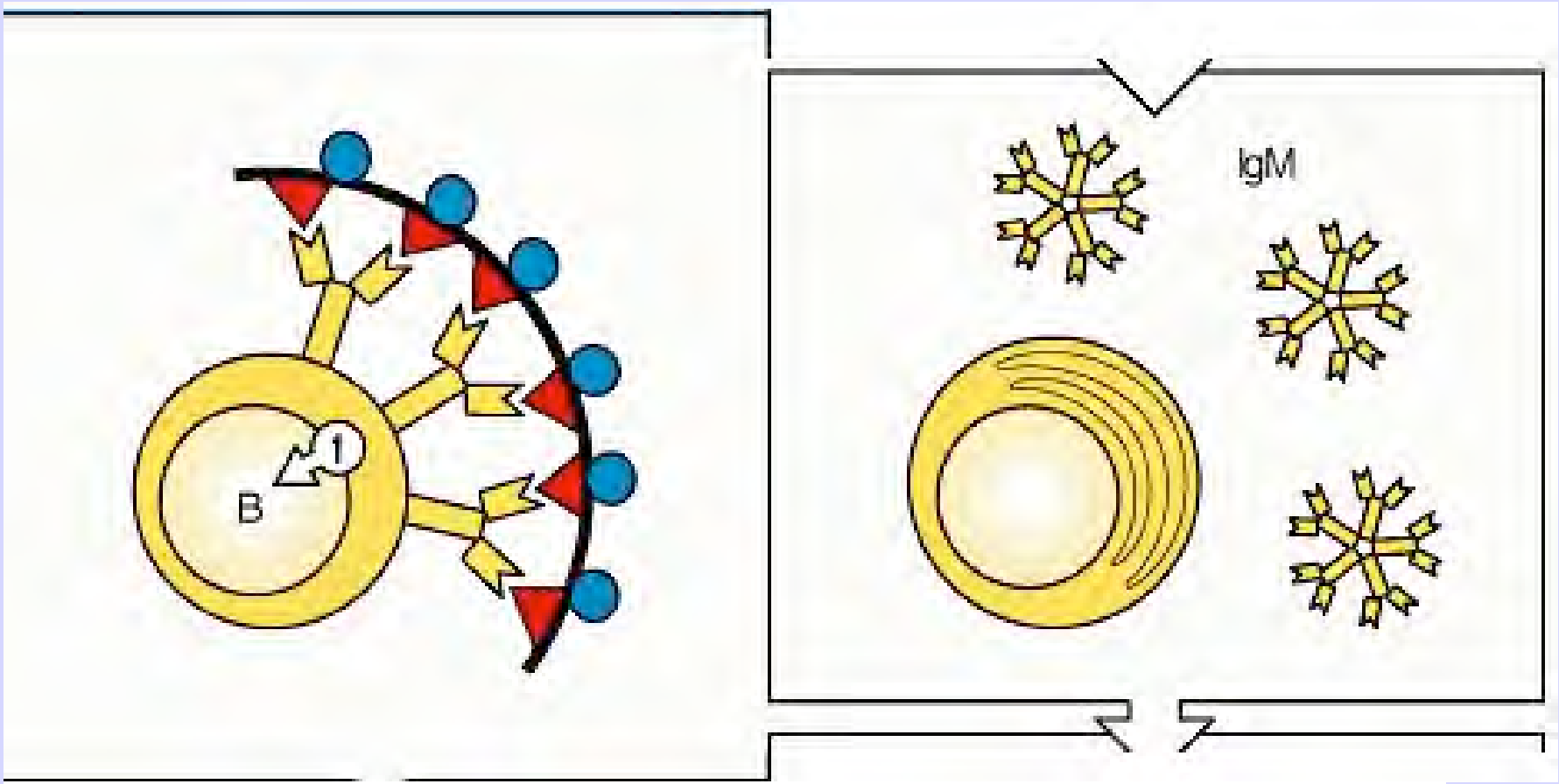
The antibody response to a small group of antigens is independent of T cells. These are antigens which extensively cross-link the immunoglobulin receptor on B cells. Proliferation is modest, and there is very little switching to non-IgM isotypes.



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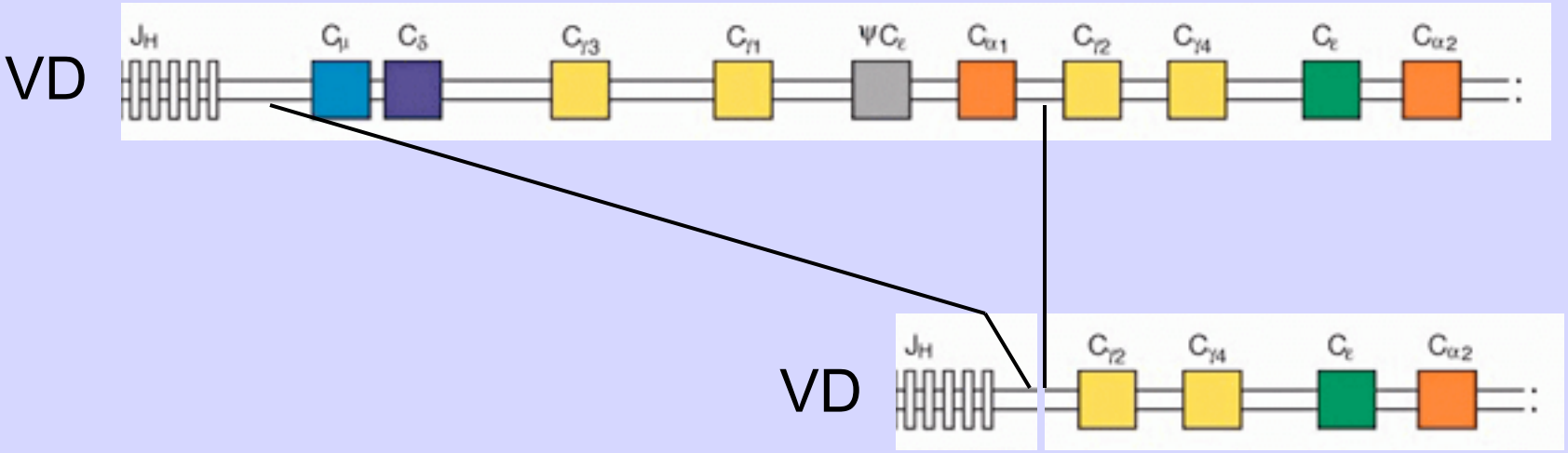
One of the results of antigen-driven B cell differentiation is secretion of antibodies. Even though mu on the B cell surface has the configuration of H_2L_2, secreted IgM has five H_2L_2 components, a total of ten light chains and ten heavy chains and therefore can bind ten epitopes.

Secreted IgA is composed of a dimer of two H_2L_2 components.

The heavy chain switch is a DNA deletion event.



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Like V(D)J recombination, the heavy chain switch is a deletion. Since DNA is lost, the heavy chain switch is not reversible. However, the deletion which mediates the heavy chain switch is different than VDJ recombination.

A. Uses signals different than VDJ--Switch regions--which are 2-8 kb regions that lie about 2 kb 5' of each heavy chain constant region gene (except Cδ). They are composed of simple sequences repeated many times in tandem.

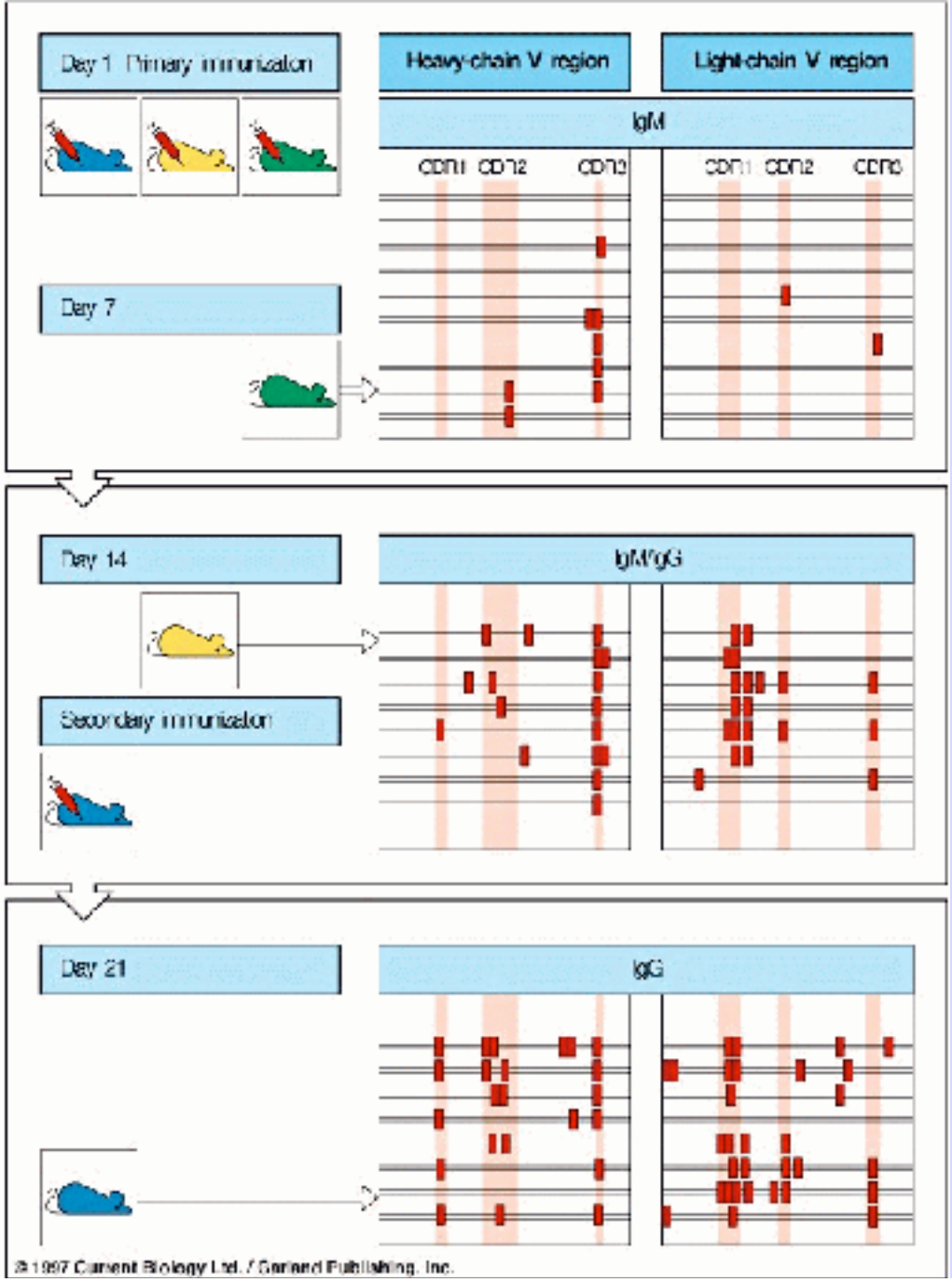
B. Different location--intron versus exon.

C. During antigen driven differentiation

One of the final stages of T cell activation is the secretion of various interleukins and other cytokines: IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, and interferon-γ.

By a partially understood mechanism, the nature of the antigenic stimulation directs Th cells to produce a specific set of interleukins, and thus direct the antibody response to specific isotypes. For example, IL-4 production by Th cells is critical to switch recombination to ε and expression of IgE by B cells.

The induced isotypes should be best suited for the pathogen (antigen) which induced them.



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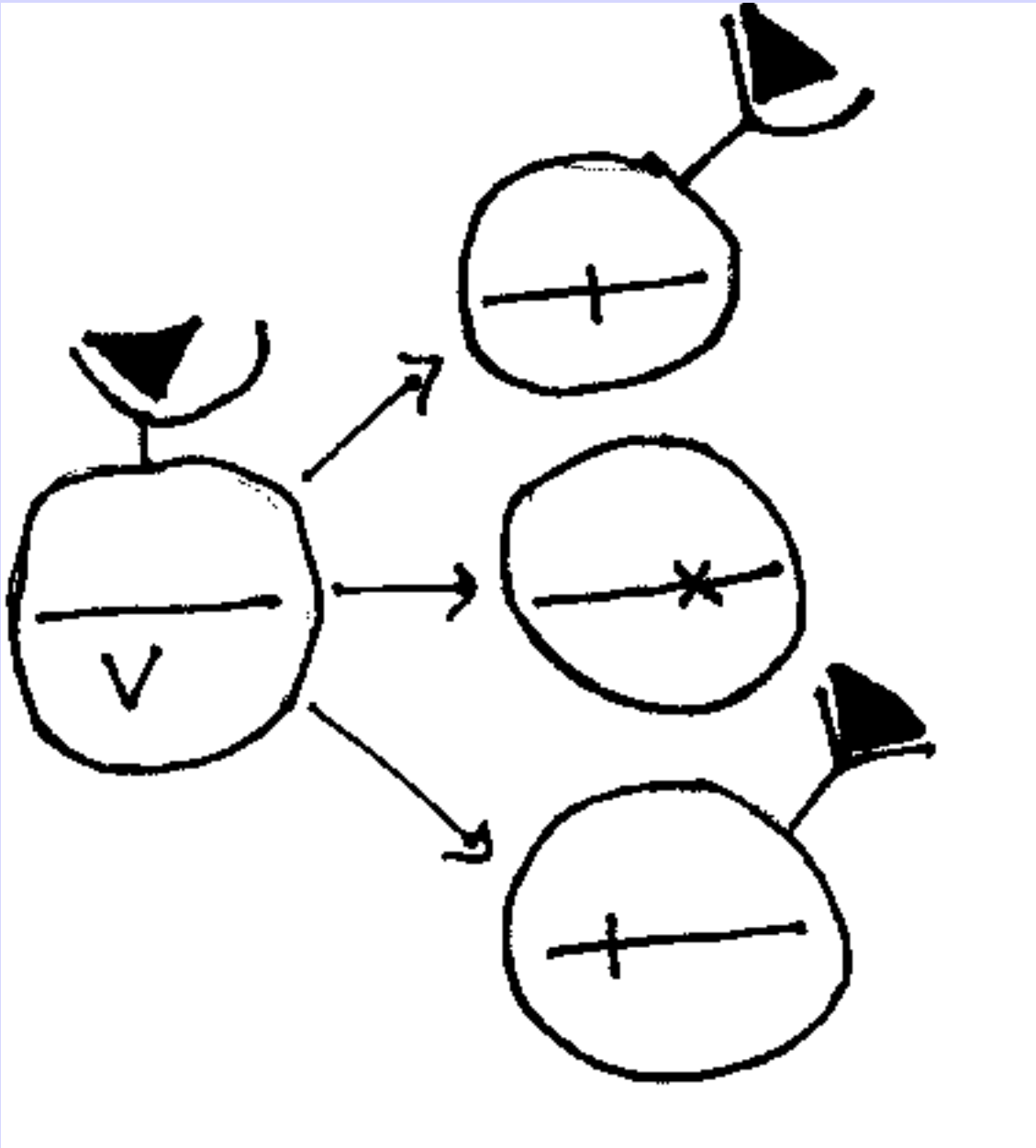
Somatic hypermutation during antigen-driven B cell differentiation.

1. Rearranged V(D)J genes only
2. During antigen-driven differentiation
3. 0.01-0.1% per nucleotide per division
4. Single nucleotide changes, not at the VDJ junction.



5. Since somatic hypermutation is random, it increases diversity and affinity, but at a significant cost.

A somatic mutation can be silent, and not change the ability of the immunoglobulin receptor to bind antigen. A B cell with this unchanged receptor continues to participate in the immune response.

A somatic mutation can introduce a stop codon, or change an invariant residue, or otherwise disrupt the immunoglobulin receptor. A B cell with a disrupted immunoglobulin gene will no longer participate in the immune response and die.

A rare somatic mutation can introduce a change in an amino acid that improves binding to the antigen. The B cell with an improved immunoglobulin receptor binds antigen better, divides more, and undergoes more somatic mutation. It will tend to dominate the immune response, compared to its sister B cells clones, in the same germinal center.

Summary

1. B cell activation during antigen driven differentiation is initiated by clustering of the immunoglobulin receptor complex.

2. This activation results in massive proliferation of a B cell clone, new gene expression, and differentiation to plasma and memory cells.

3. Antigen-dependent B cell differentiation occurs in germinal centers and requires T cell help.

4. T cell help involves several T cell:B cell interactions.

5. The heavy chain switch is mediated by a DNA deletion.

6. Somatic hypermutation of variable region genes occurs during antigen-driven differentiation and results in affinity maturation.

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