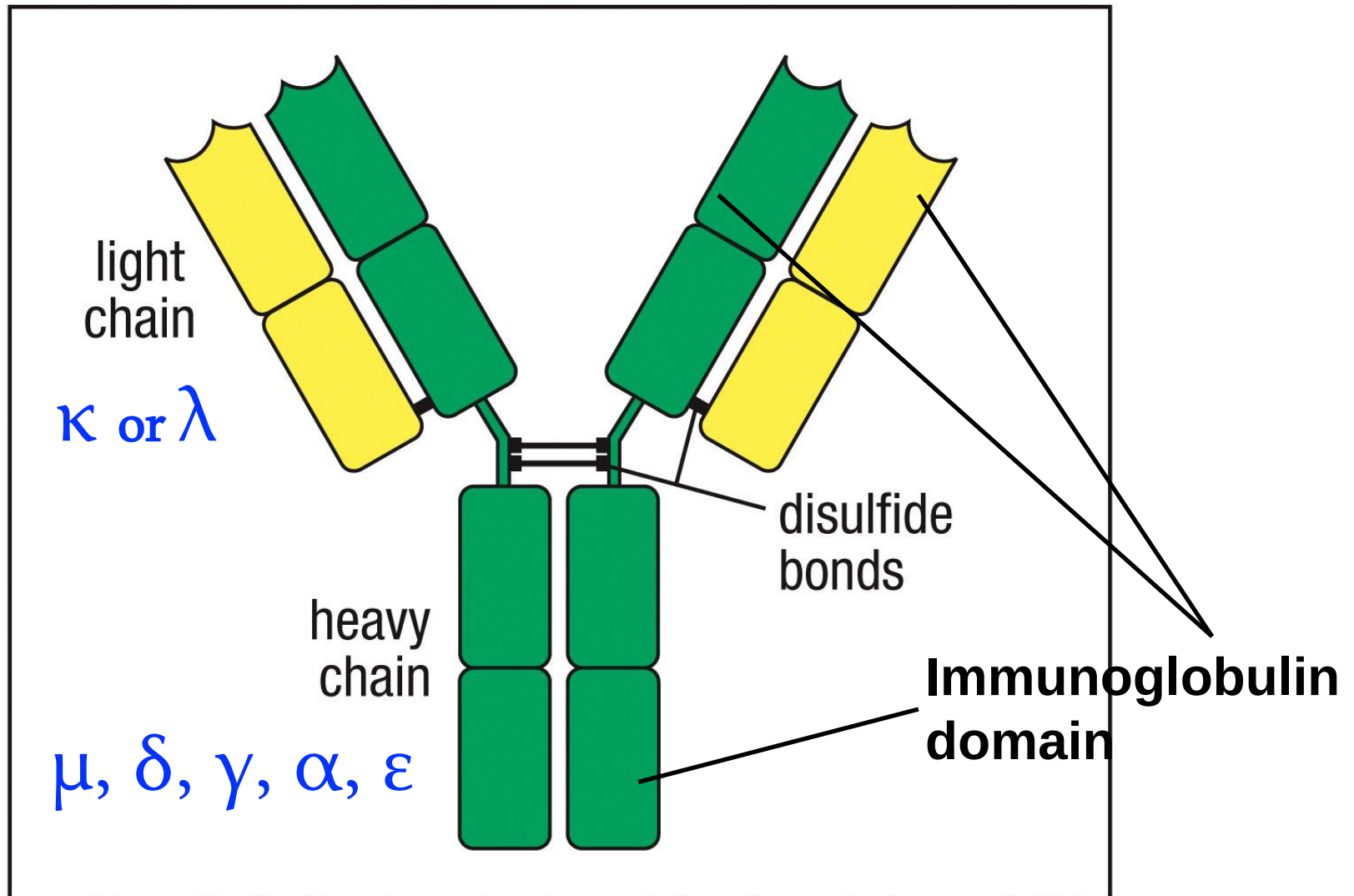
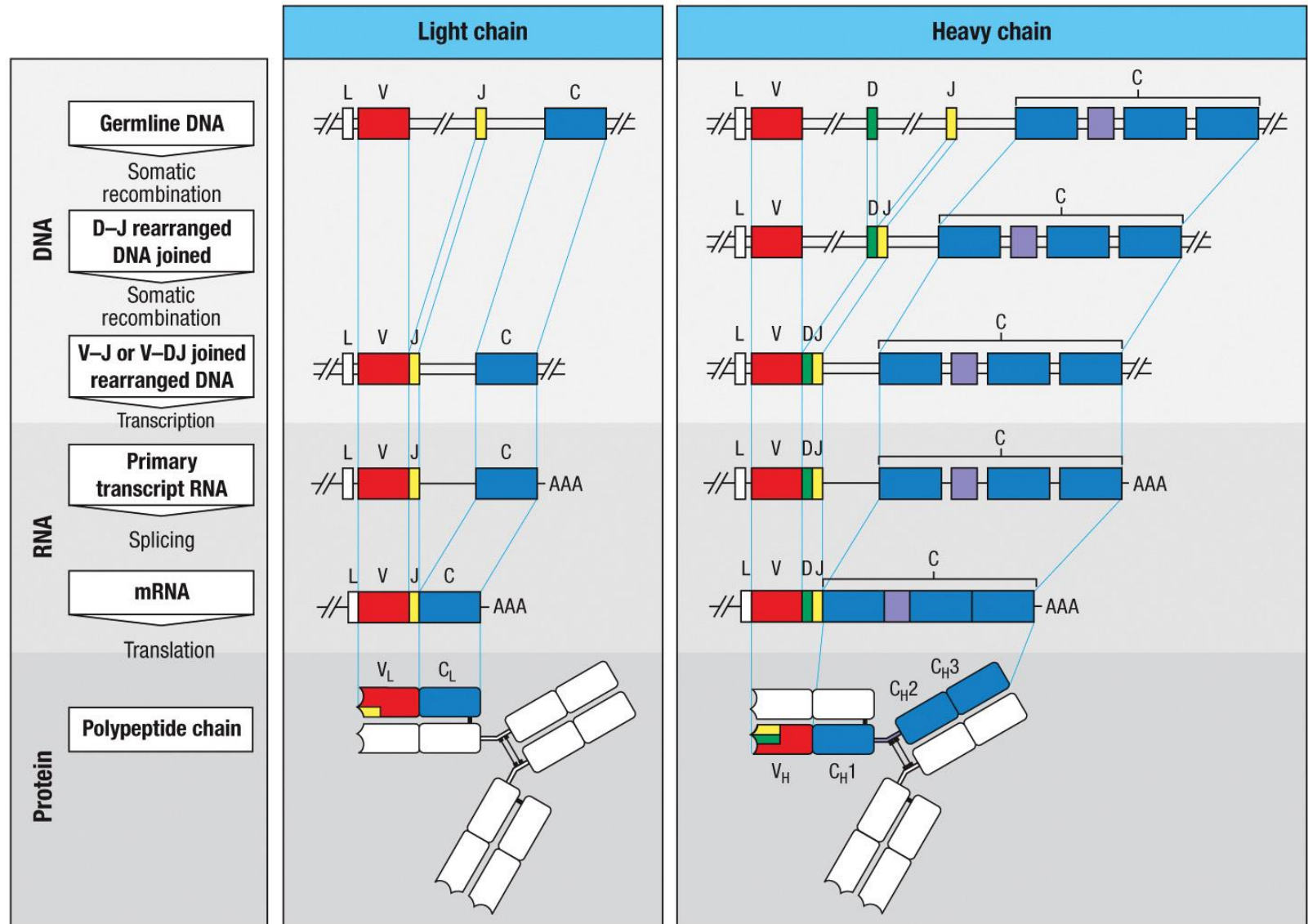


# Antibody Structure



# Construction of the Variable Region

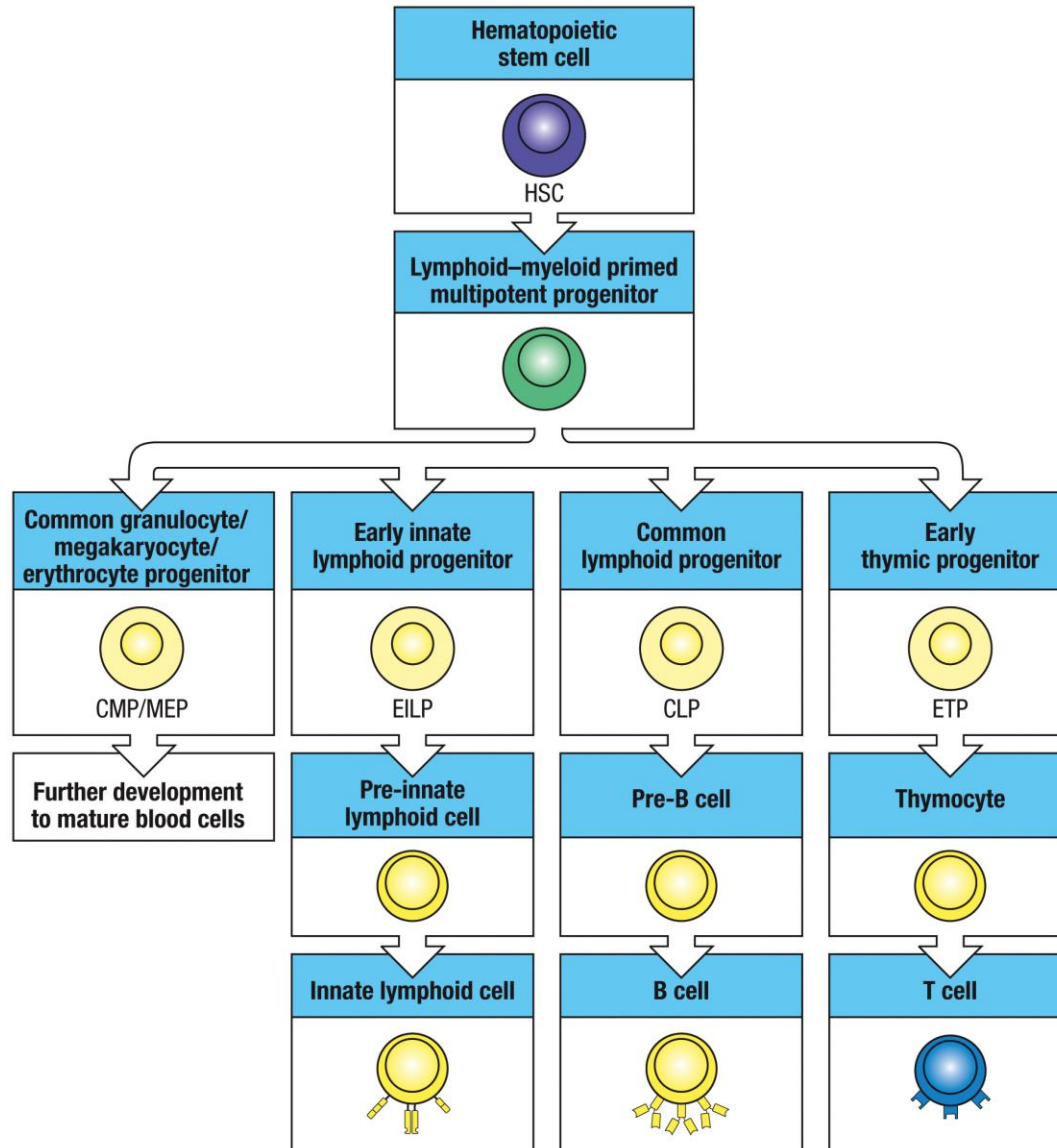


# Outline

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- B-cell development
- Selection of non-self reacting B-cells
- Signaling through B-cell receptor

# Differentiation of Hematopoietic Cells



# Life-Cycle of B Cells: Bone Marrow to Lymphoid Tissues

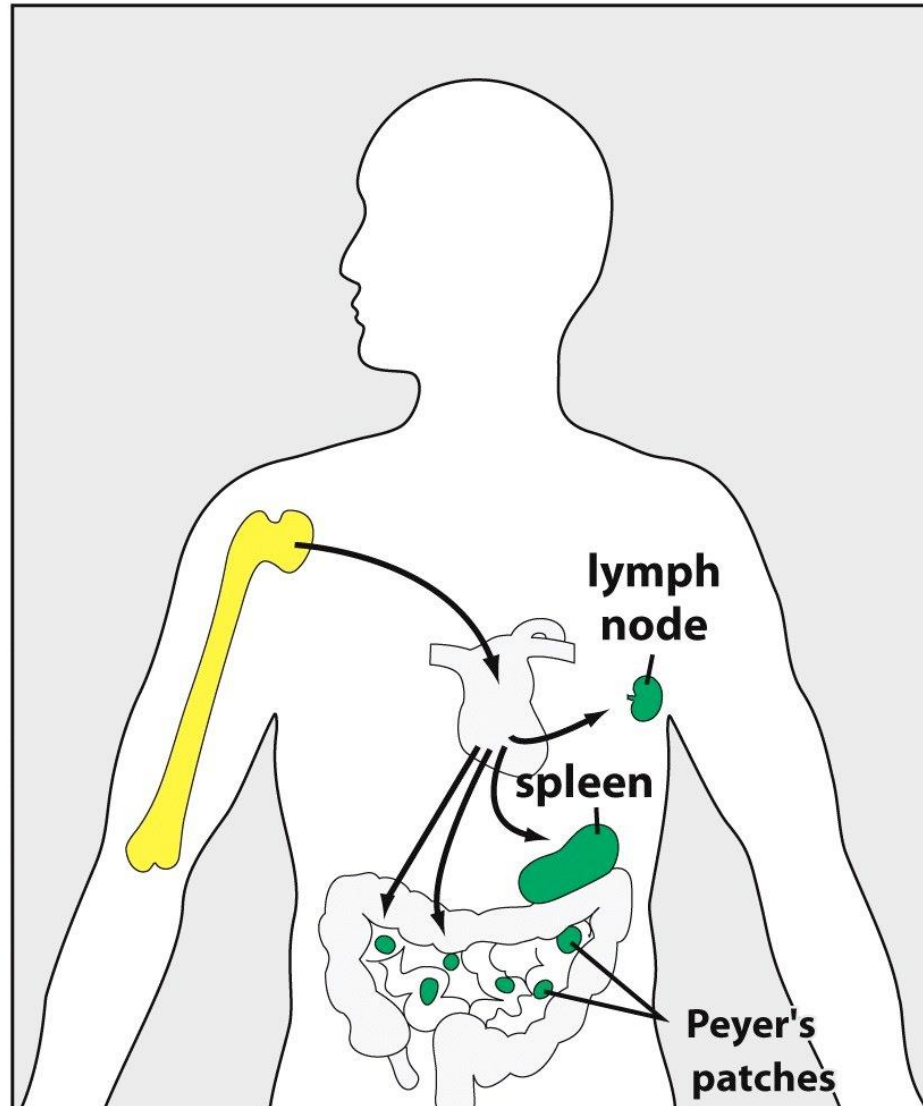


Figure 6.2 The Immune System, 3ed. (© Garland Science 2009)

# Phases of B Cell Development

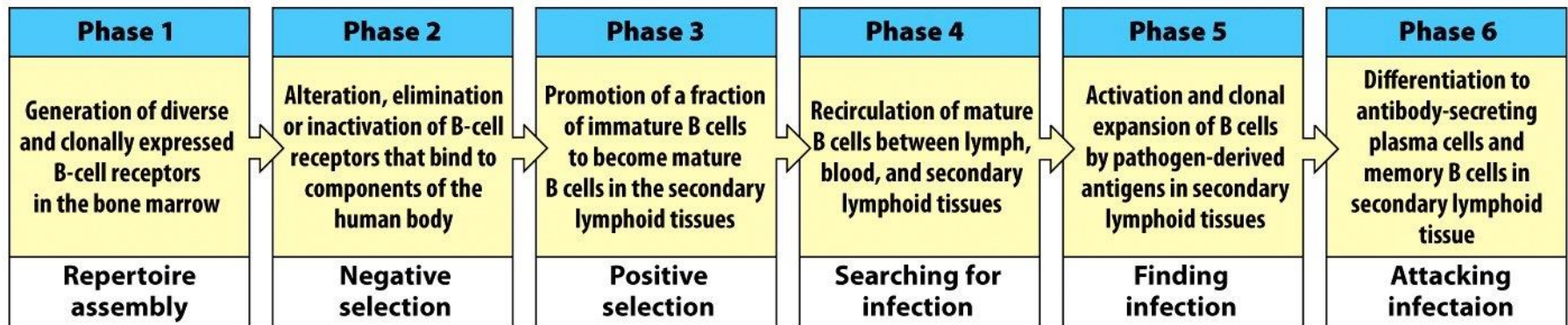
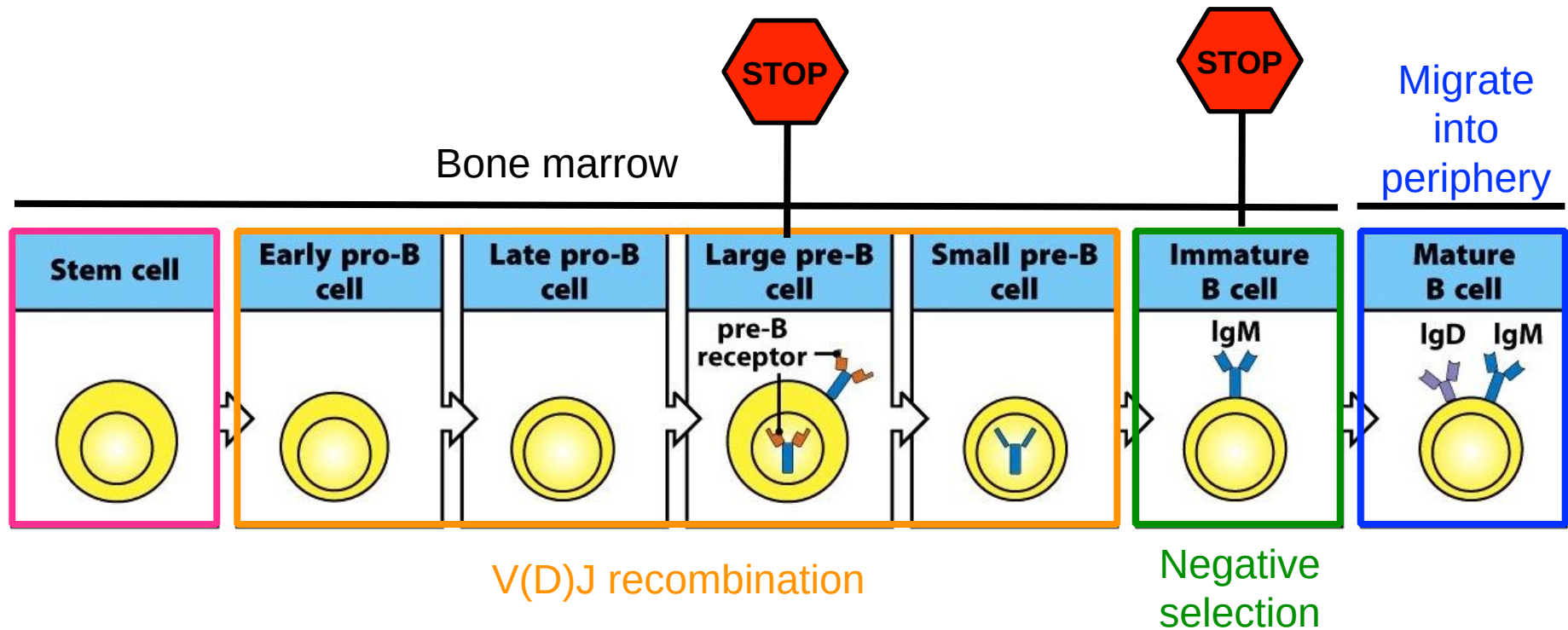


Figure 6.1 The Immune System, 3ed. (© Garland Science 2009)

Bone marrow

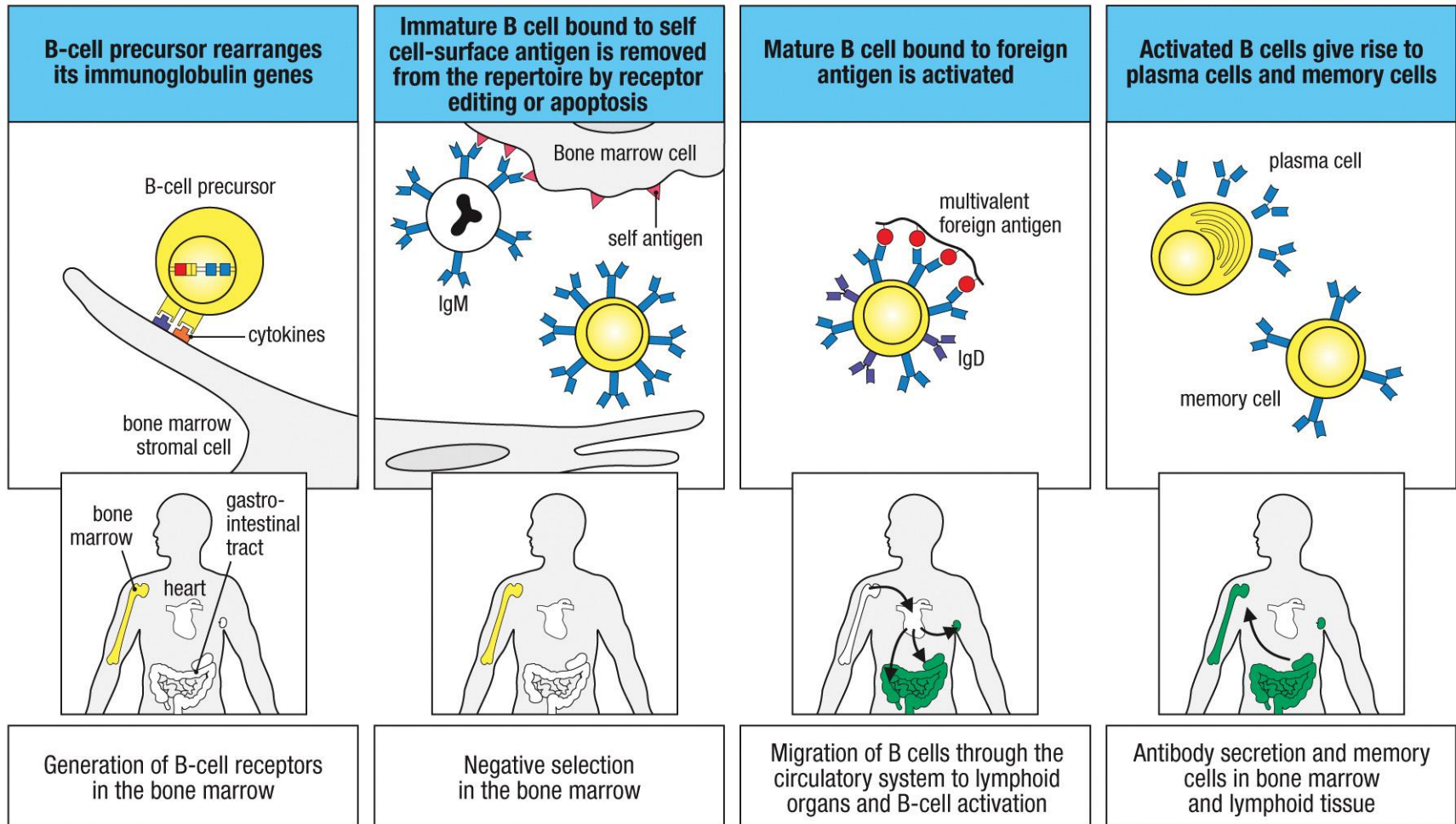
Periphery (secondary lymphoid tissues)

# Stages of B-Cell Development





# Life-Cycle of B Cells: Bone Marrow to Lymphoid Tissues





# Stages of Lymphocyte Development

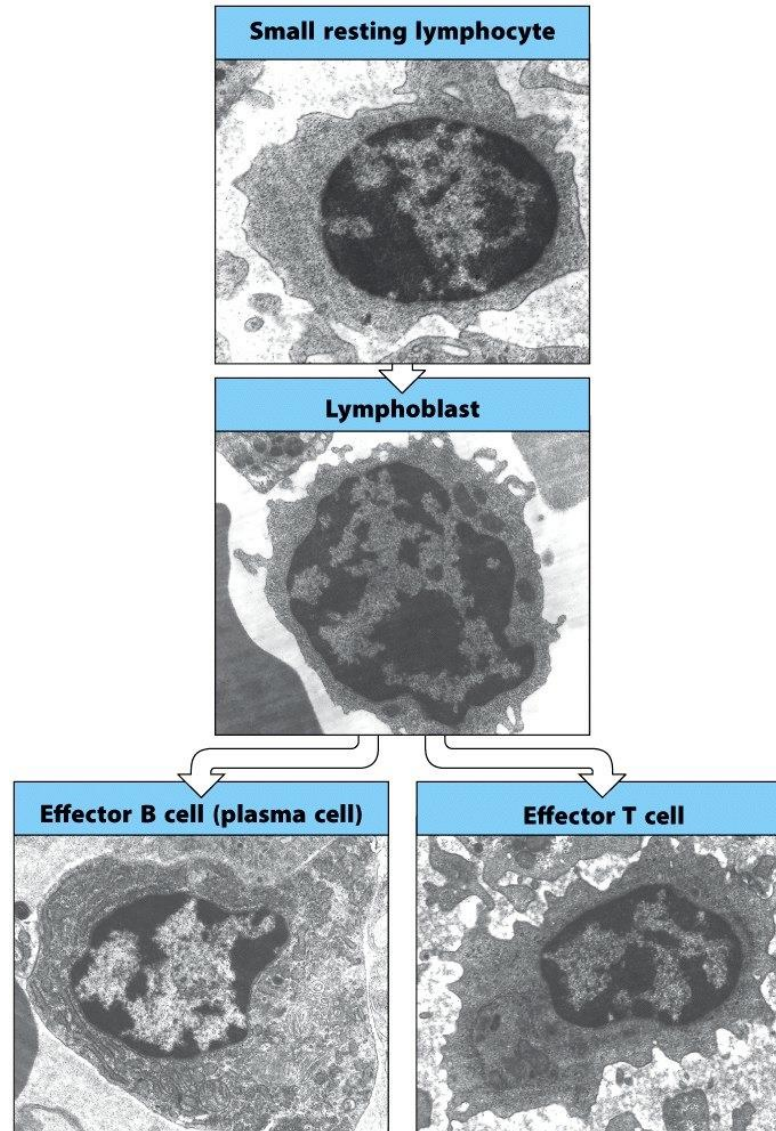
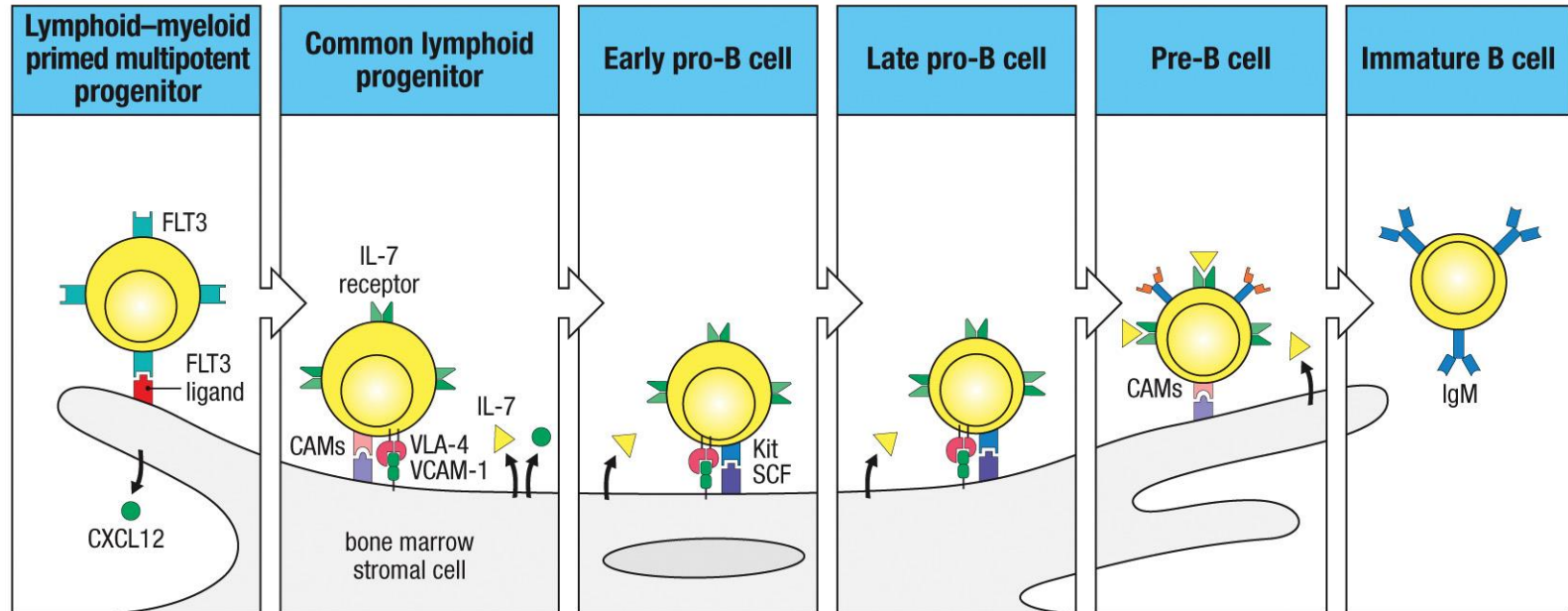


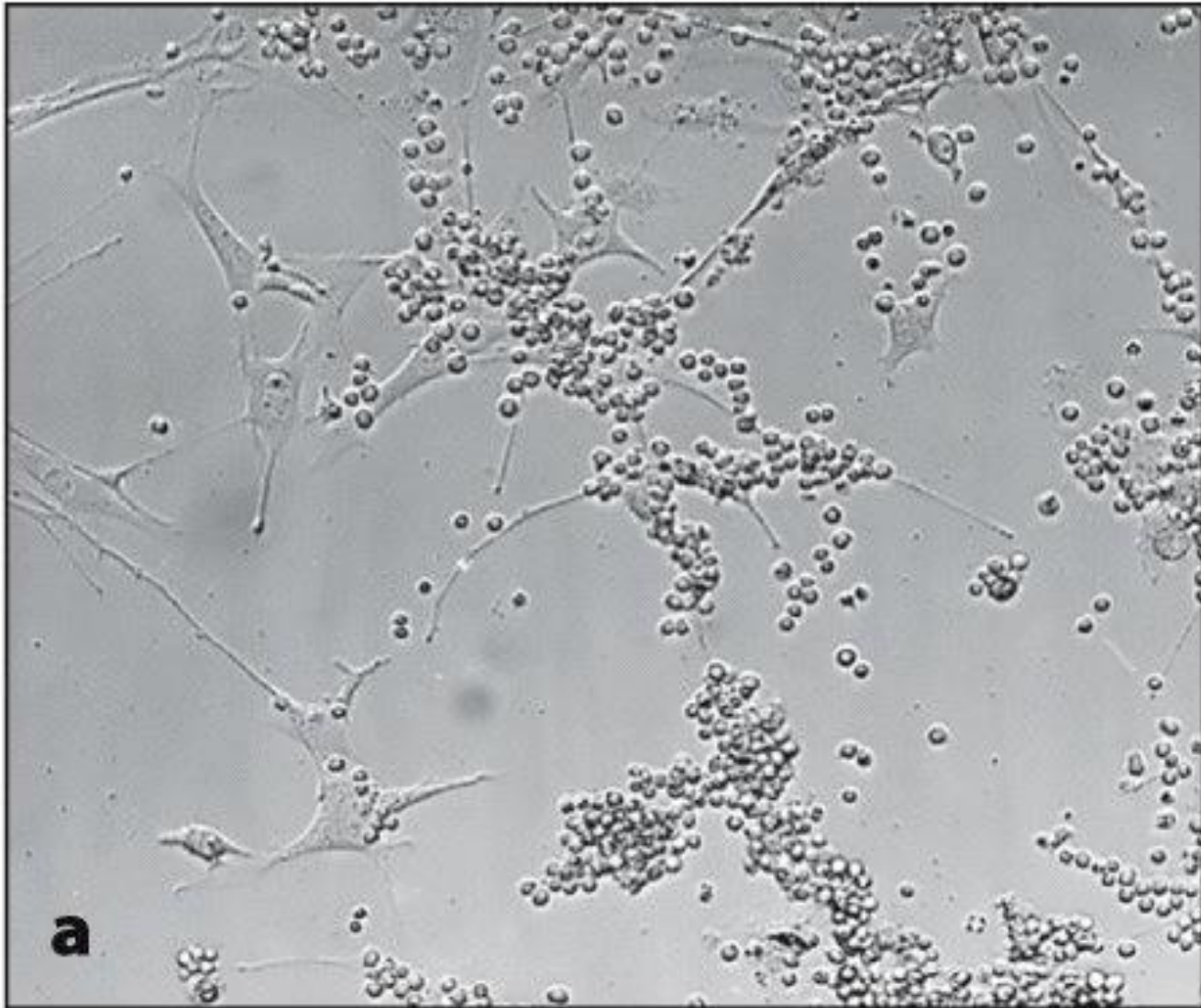
Figure 1-23 Immunobiology, 7ed. (© Garland Science 2008)

# Early Stages of B-Cell Development Are Dependent on Stromal Cells

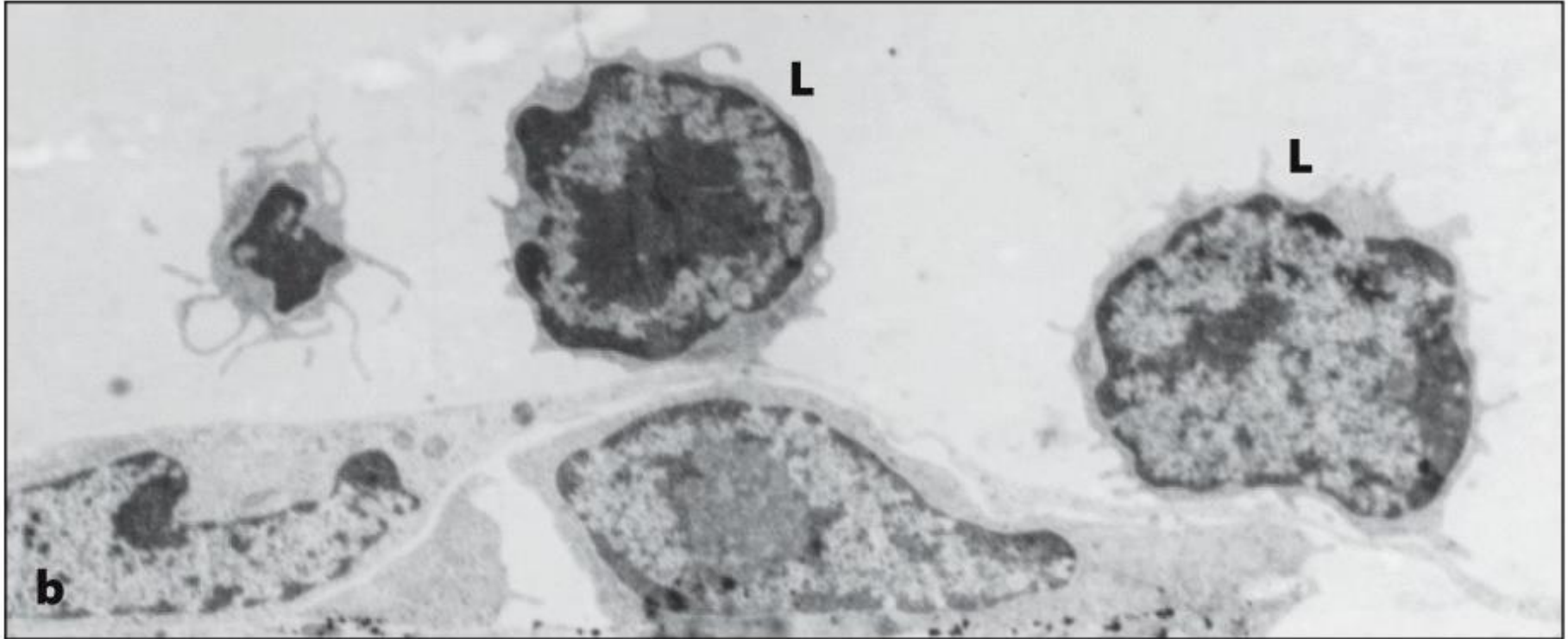


|              |  |
|--------------|--|
| Ikaros, PU.1 |  |
| E2A          |  |
| FOXO1, EBF   |  |
| PAX5/BSAP    |  |

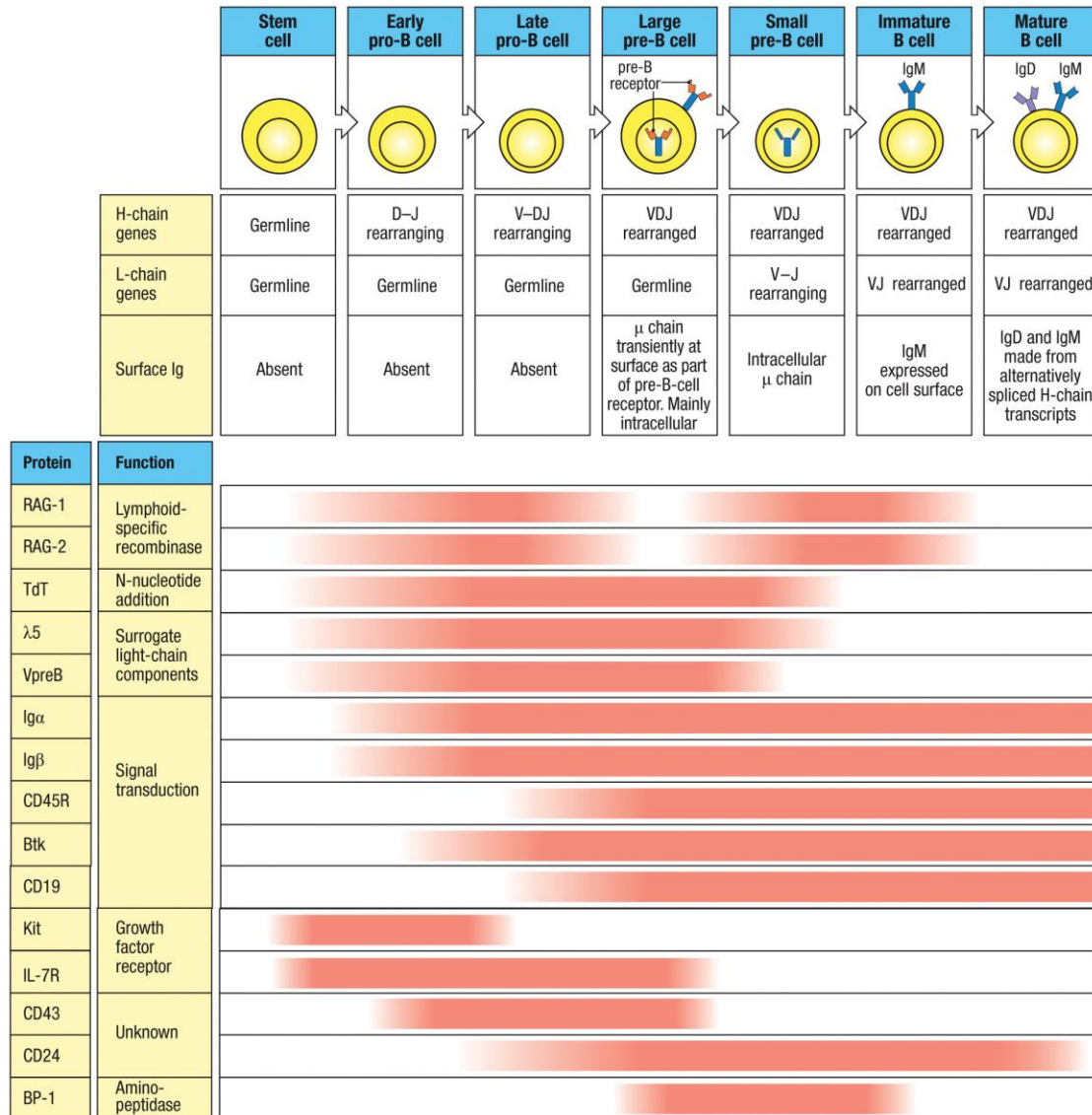
# B-Cells Interact With Stromal Cells During Development



# B-Cells Interact With Stromal Cells During Development

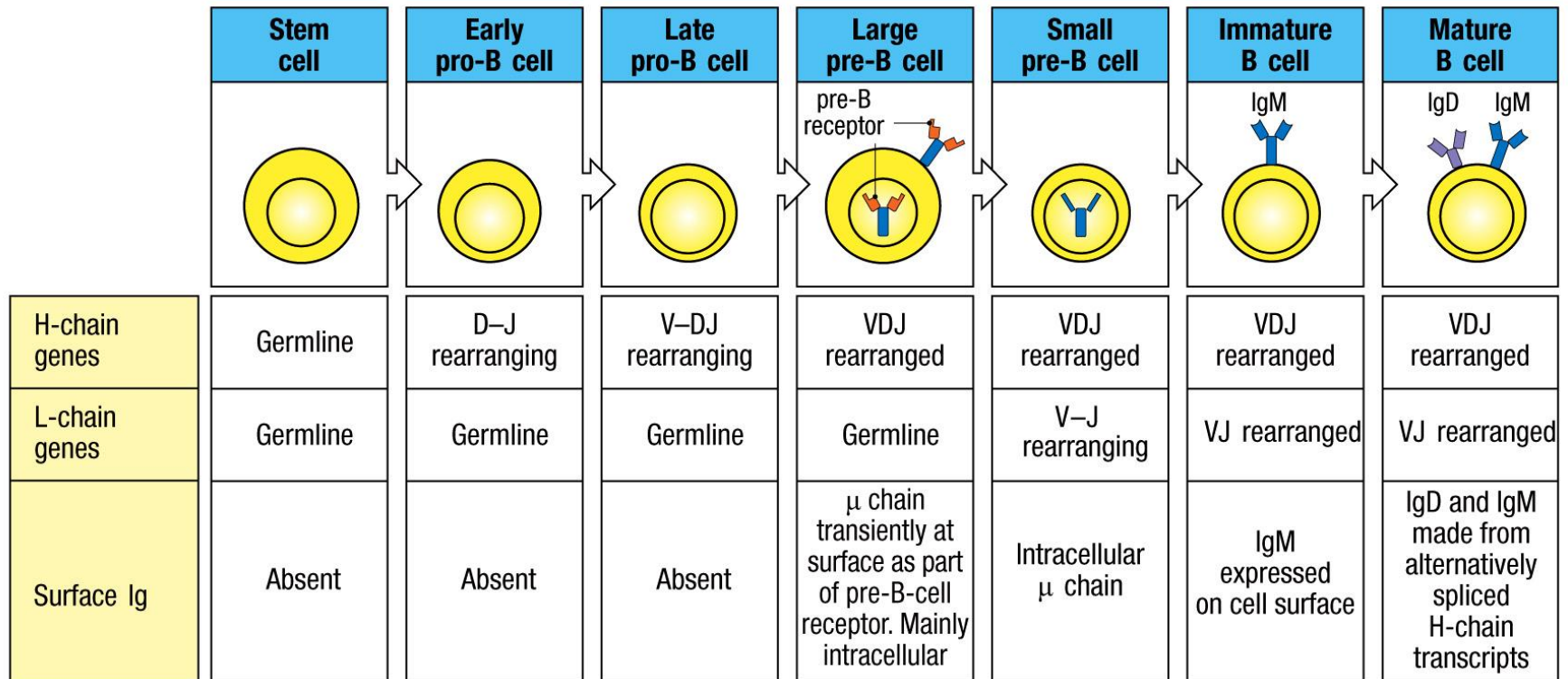


# Protein Expression During B-Cell Development

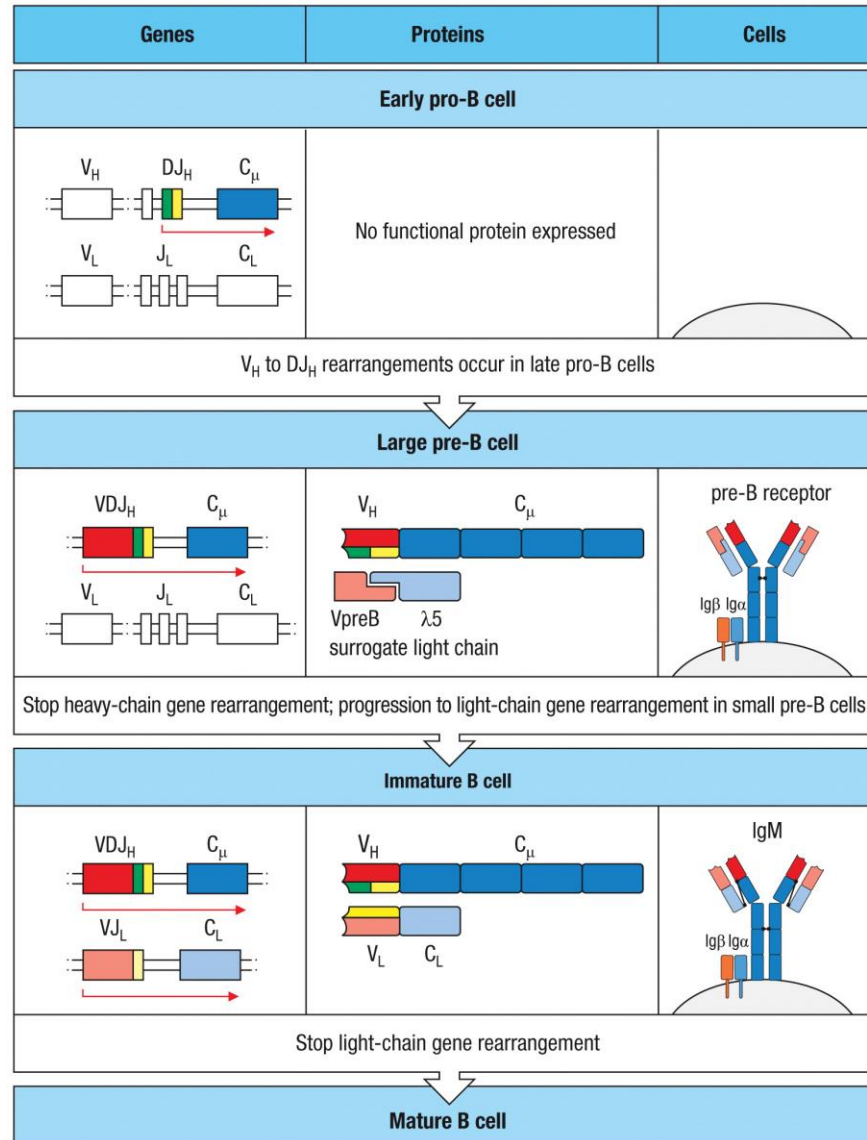




# B-Lineage Development



# Pre-B-Cell Receptor Assembly

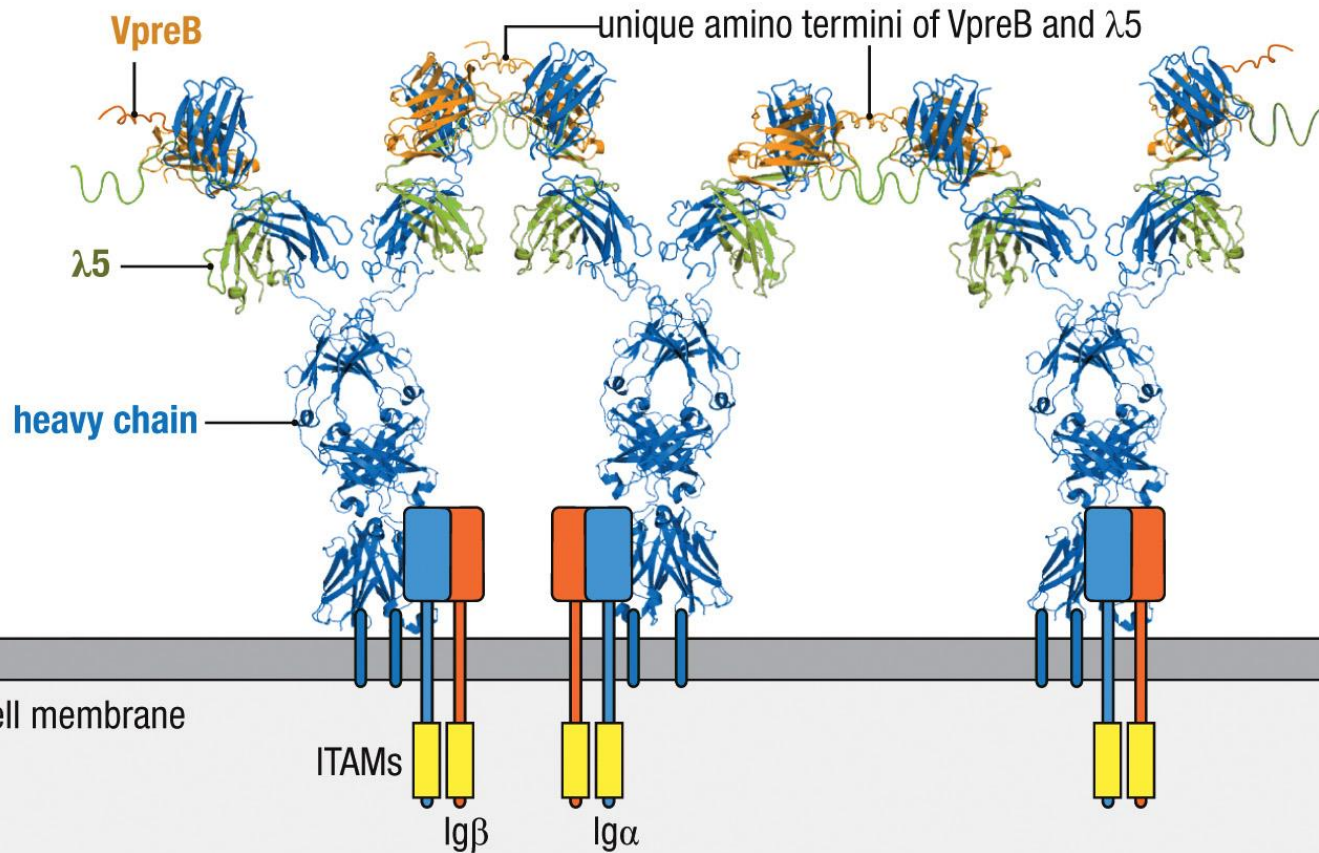


Courtesy of K. Christopher Garcia



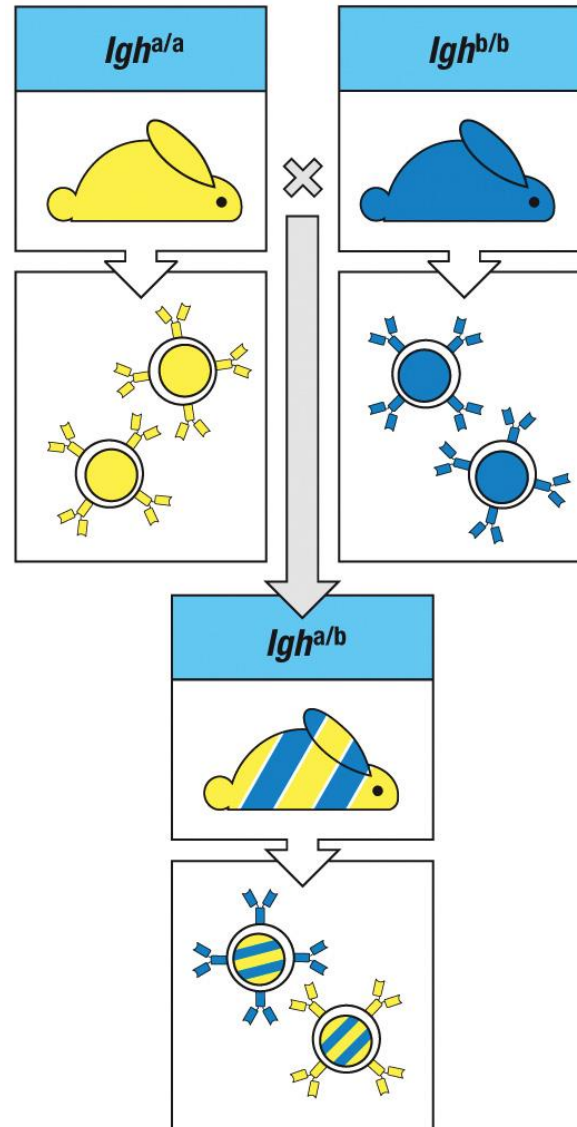
# Pre-B-Cell Receptor

Amino-terminal tails on VpreB and  $\lambda 5$  in adjacent pre-B-cell receptor molecules bind each other and cross-link the receptors, inducing clustering and signaling



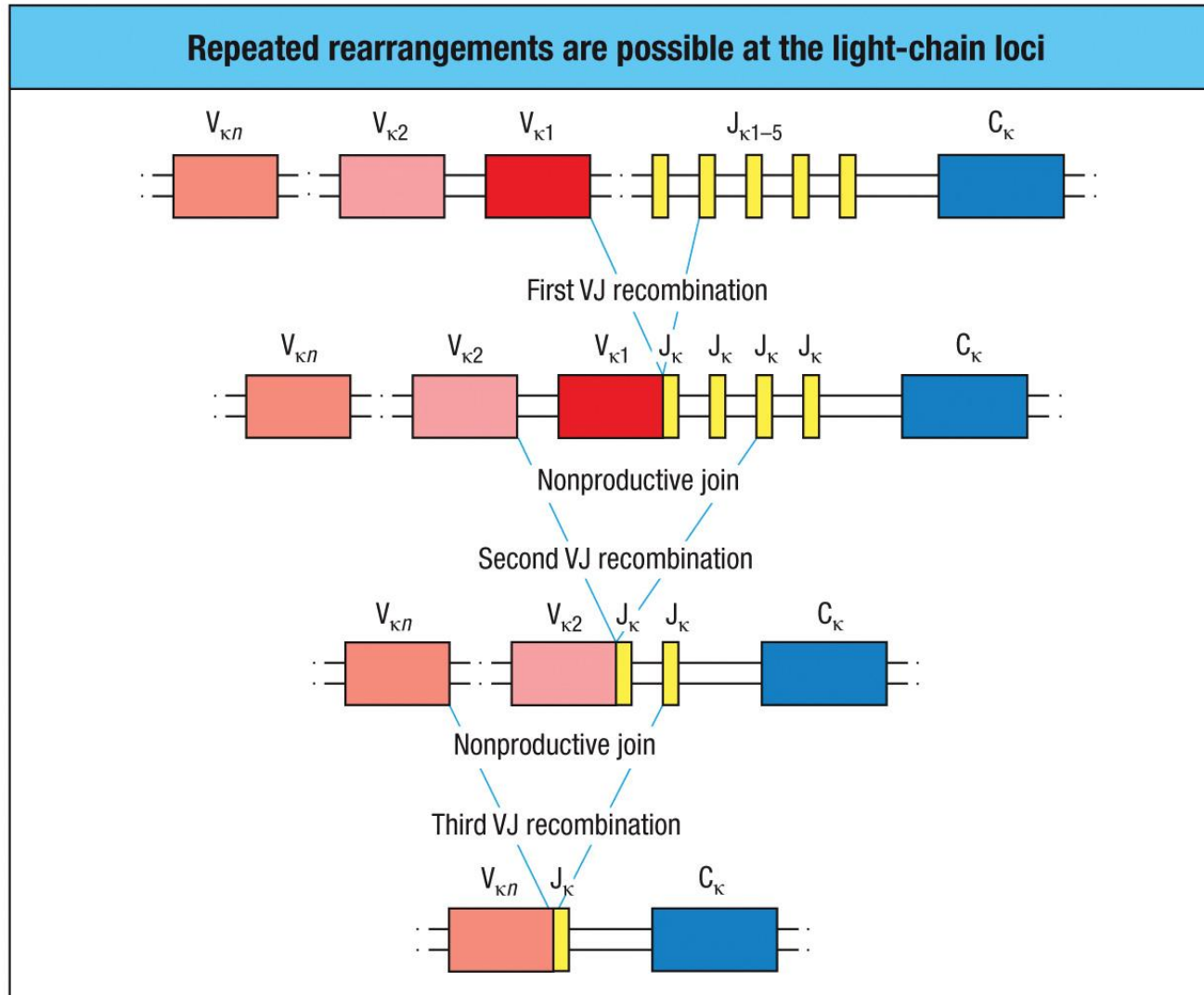
Courtesy of K. Christopher Garcia

# Allelic Exclusion in B-Cells



# Generation of Productive V(D)J Rearrangement

Rearrangement of light chain is usually successful



# Steps of Immunoglobulin Gene Rearrangement

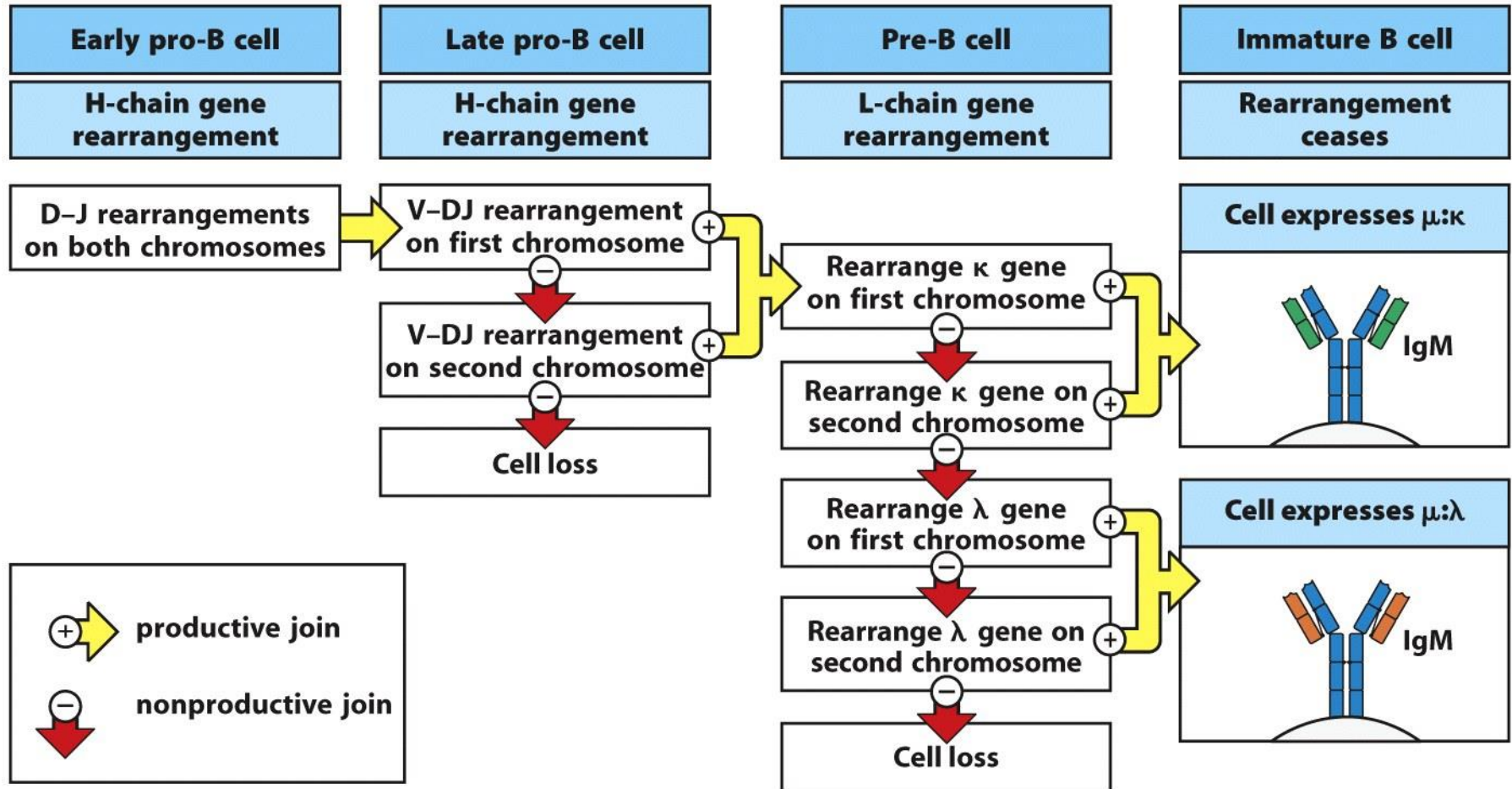


Figure 8.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# Question

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- What is the function of the pre-B receptor?

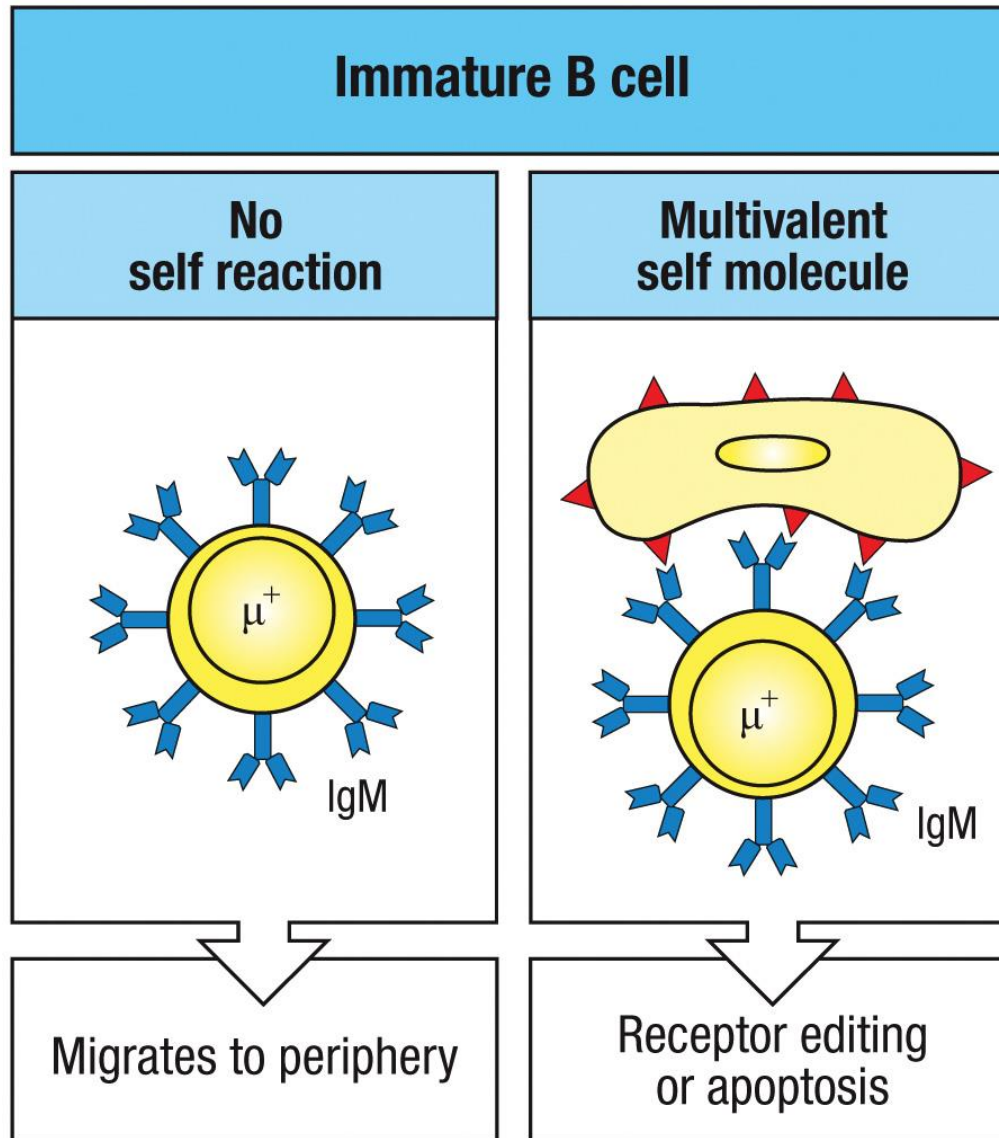
# Outline

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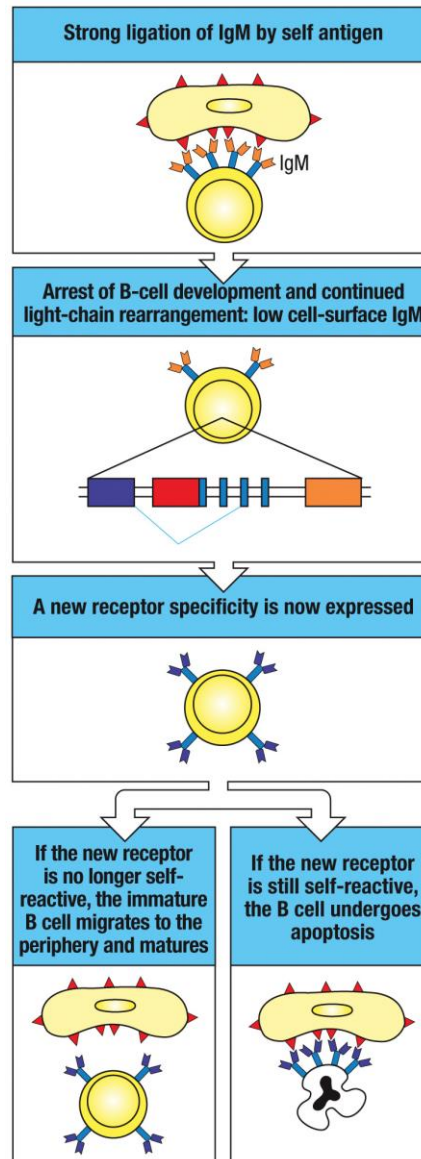
- B-cell development
- Selection of non-self reacting B-cells
- Signaling through B-cell receptor



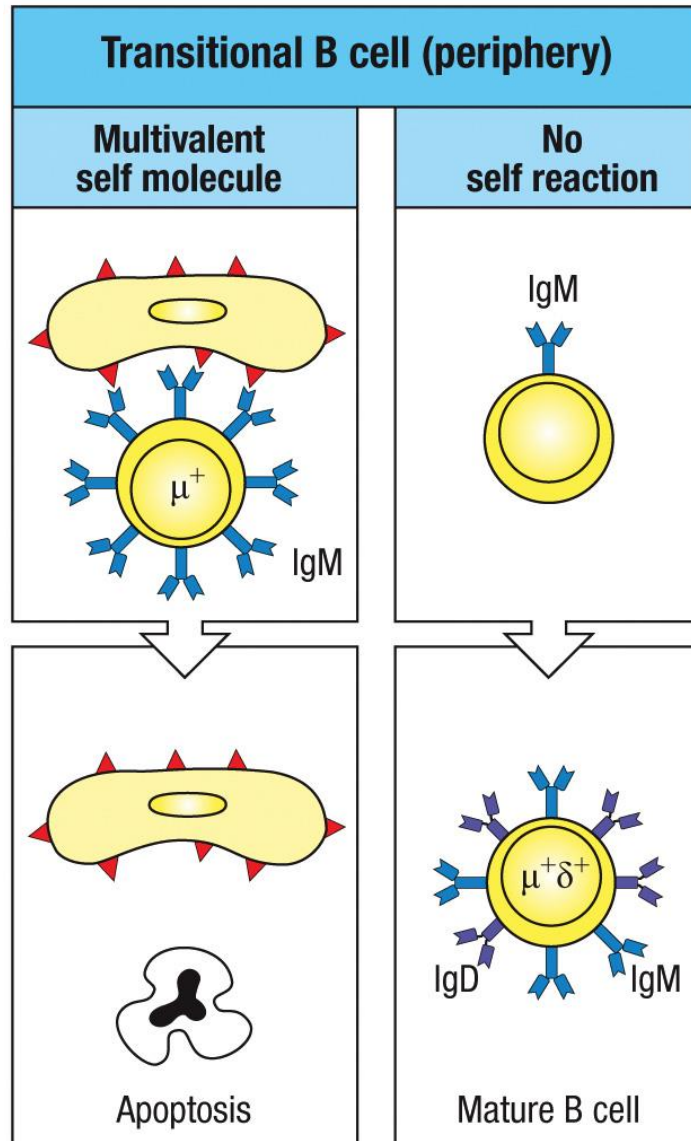
# Self-Reacting B-Cells Are Deleted During Development



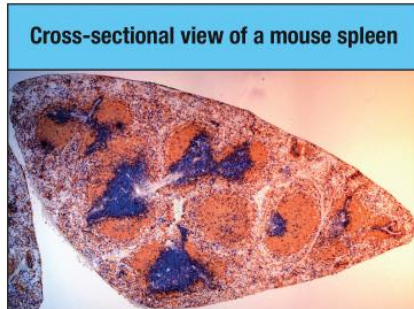
# Receptor Editing Can Rescue Self-Reacting B-Cells



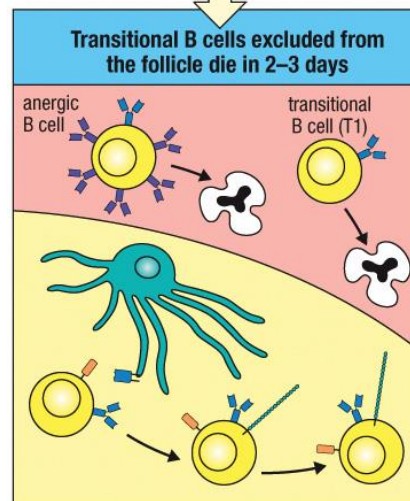
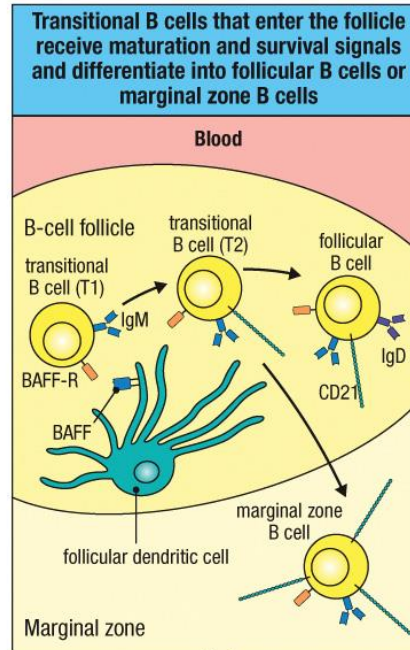
# Transitional B cells



# Transitional B cells complete their maturation in B-cell follicles in the spleen



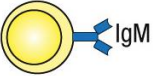
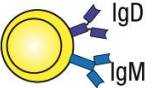
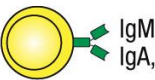
Micrograph courtesy of Xiaoming Wang and Jason Cyster. Howard Hughes Medical Institute and Department of Microbiology and Immunology, UCSF



# B-Cell Development

|                     | B cells                                                                                                              | Heavy-chain genes                                       | Light-chain genes | Intra-cellular proteins    | Surface marker proteins                                                           |             |
|---------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------------------|----------------------------|-----------------------------------------------------------------------------------|-------------|
| ANTIGEN INDEPENDENT | Common lymphoid progenitor<br>      | Germline                                                | Germline          | RAG-1 λ5, RAG-2 VpreB, TdT | CD34, CD45, CD93                                                                  | BONE MARROW |
|                     | Early pro-B cell<br>                | D–J rearranged                                          | Germline          | TdT λ5, VpreB              | CD34, CD45R, CD93, IL-7R, MHC class II, CD10, CD19, CD38                          |             |
|                     | Late pro-B cell<br>                 | V–DJ rearranged                                         | Germline          | λ5, VpreB                  | CD45R, CD93, IL-7R, MHC class II, CD10, CD19, CD38, CD20                          |             |
|                     | Large pre-B cell<br> pre-B receptor | VDJ rearranged                                          | Germline          | μ RAG-1 RAG-2              | CD45R, CD93, IL-7R, MHC class II, pre-BCR, CD19, CD38, CD20                       |             |
|                     | Small pre-B cell<br> cytoplasmic μ | VDJ rearranged                                          | V–J rearrangement |                            | CD45R, CD93, MHC class II, CD19, CD38, CD20                                       |             |
|                     | Immature B cell<br> IgM           | VDJ rearranged. μ heavy chain produced in membrane form | VJ rearranged     |                            | CD45R, MHC class II, IgM, CD19, CD20, CD24, CD93, CD21, CD38, CD23 <sup>+/+</sup> |             |

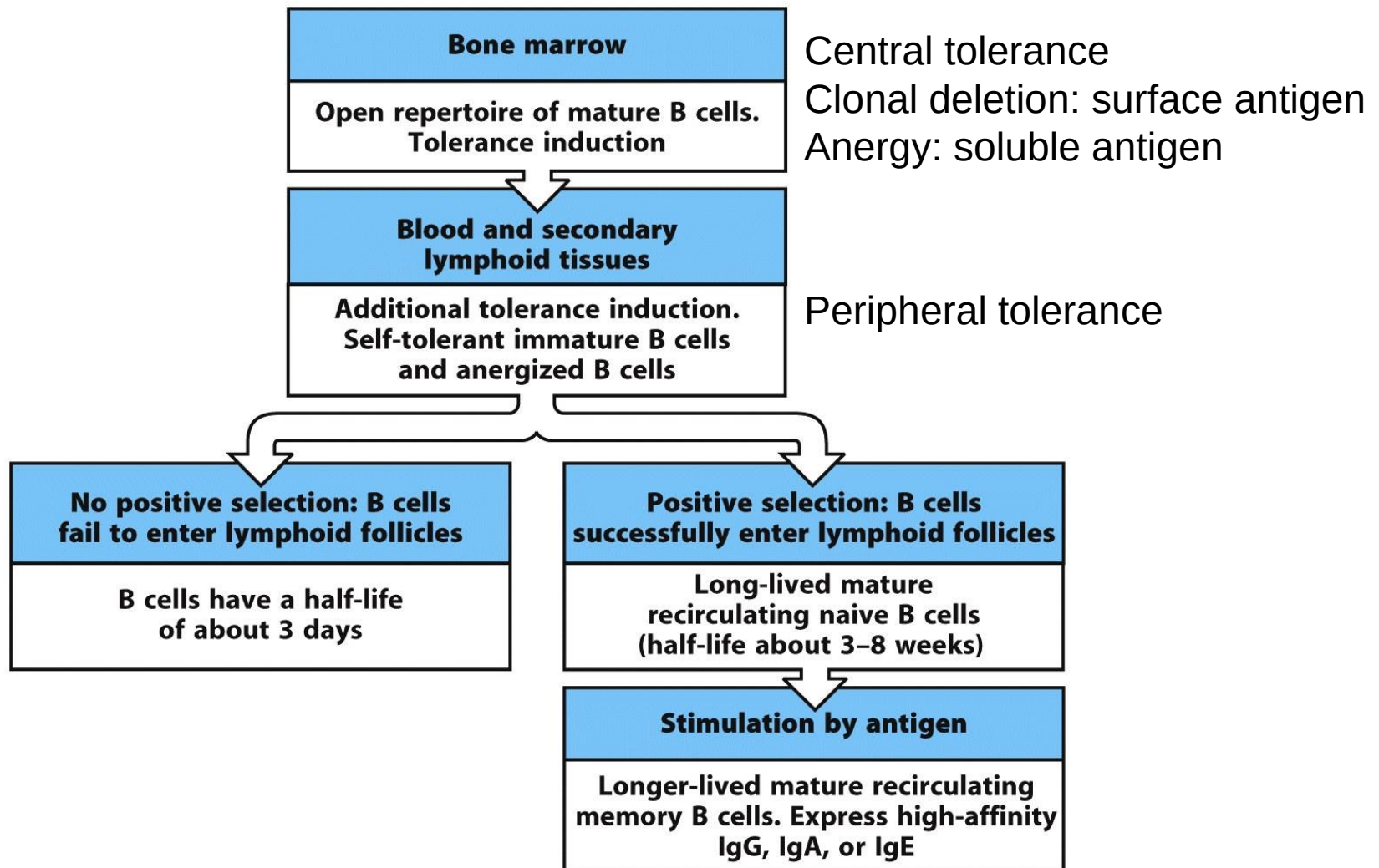
# B-Cell Development

|                             |                                   |                                                                                     |                                                                                                                     |                          |    |                                                                                                                      |           |
|-----------------------------|-----------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------|----|----------------------------------------------------------------------------------------------------------------------|-----------|
| ANTIGEN<br>DEPENDENT        | Transitional<br>B cell            |    |                                                                                                                     |                          |    | CD45R, MHC class II, IgM,<br>CD19, CD20, CD24, CD93,<br>CD21, CD38, CD23 <sup>+/+</sup>                              | PERIPHERY |
|                             | Marginal<br>zone<br>B cell        |    | VDJ rearranged.<br>Alternative splicing yields $\mu + \delta$<br>mRNA that encodes IgM and IgD.<br>IgM predominates |                          |    | CD45R, MHC class II, IgM <sup>hi</sup> ,<br>IgD <sup>lo</sup> , CD19, CD20, CD1,<br>CD9, CD21, CD22, CD35            |           |
|                             | Mature<br>follicular<br>B cell    |    | VDJ rearranged.<br>Alternative splicing yields $\mu + \delta$<br>mRNA that encodes IgM and IgD.<br>IgD predominates |                          |    | CD45R, CD93, MHC class II,<br>IgM <sup>lo</sup> , IgD <sup>hi</sup> , CD19, CD20,<br>CD21, CD22, CD23, CD24,<br>CD38 |           |
|                             | Lymphoblast                       |    | Alternative splicing yields<br>secreted $\mu$ chains                                                                |                          | Ig | CD45R, MHC class II,<br>CD19, CD20, CD21                                                                             |           |
|                             | Memory<br>B cell                  |   | Often isotype switched to $C\gamma$ ,<br>$C\alpha$ , or $C\epsilon$ . Somatic<br>hypermutation                      | Somatic<br>hypermutation |    | CD45R, MHC class II,<br>IgM, IgG, IgA, IgD <sup>neg</sup> ,<br>CD19, CD20, CD38, CD80                                |           |
| TERMINAL<br>DIFFERENTIATION | Plasmablast<br>and<br>plasma cell |  | Alternative splicing yields both<br>membrane and secreted Ig.<br>In plasma cells, Ig is<br>predominantly secreted   | VJ<br>rearranged         | Ig | CD138, plasma cell<br>antigen-1, CD38                                                                                |           |



# B-Cell Population Dynamics

B cells are produced throughout the life time.



# B Cell Subtypes

| Property                                 | B-1 B cells                         | Follicular B cells         | Marginal zone B cells |
|------------------------------------------|-------------------------------------|----------------------------|-----------------------|
| When first produced                      | Fetus                               | After birth                | After birth           |
| N-regions in VDJ junctions               | Few                                 | Extensive                  | Yes                   |
| V-region repertoire                      | Restricted                          | Diverse                    | Partly restricted     |
| Primary location                         | Body cavities (peritoneal, pleural) | Peripheral lymphoid organs | Spleen                |
| Dependence on BAFF                       | No                                  | Yes                        | Yes                   |
| Dependence on IL-7                       | No                                  | Yes                        | Yes                   |
| Mode of renewal                          | Self-renewing                       | Replaced from bone marrow  | Long-lived            |
| Spontaneous production of immunoglobulin | High                                | Low                        | Low                   |
| Isotypes secreted                        | IgM >> IgG                          | IgG > IgM                  | IgM > IgG             |
| Response to carbohydrate antigen         | Yes                                 | Maybe                      | Yes                   |
| Response to protein antigen              | Maybe                               | Yes                        | Yes                   |
| Requirement for T-cell help              | No                                  | Yes                        | Sometimes             |
| Somatic hypermutation                    | Low to none                         | High                       | ?                     |
| Memory development                       | Little or none                      | Yes                        | ?                     |

# Question

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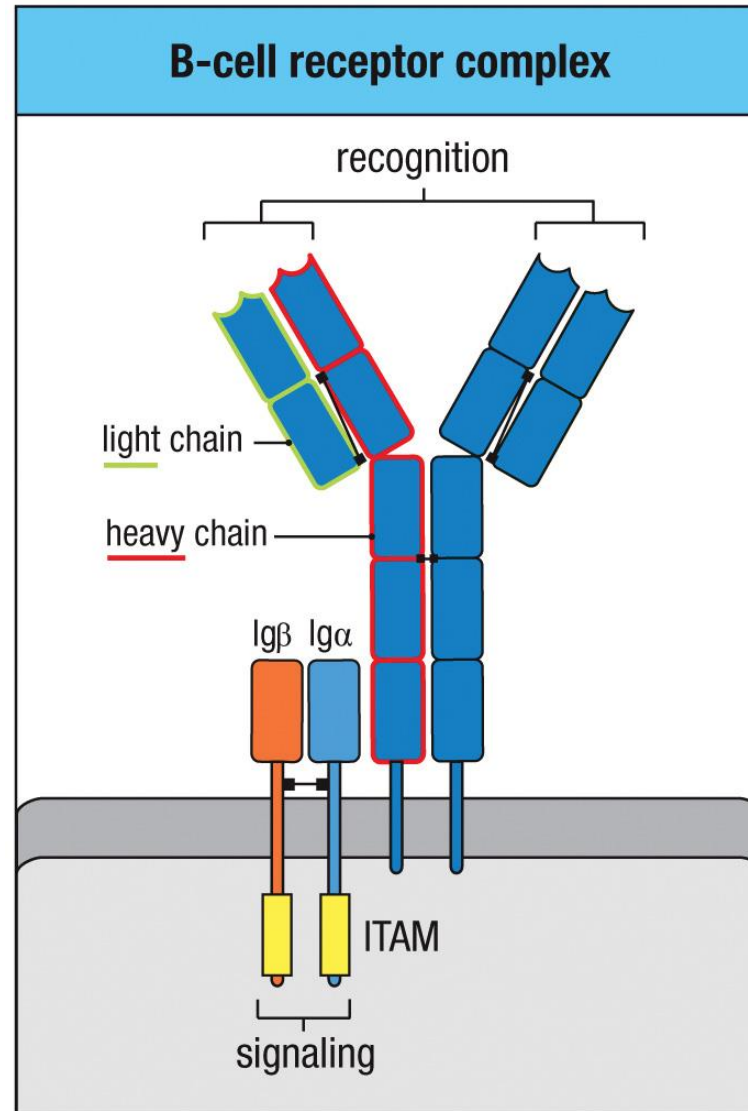
- Where does B cell positive selection occur?
- A) central lymphatic organ
- B) peripheral lymphatic organ
- C) both
- D) neither

# Outline

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- B-cell development
- Selection of non-self reacting B-cells
- Signaling through B-cell receptor

# B-Cell Receptor Complex



# Cross-linking of BCR Is Required for B-Cell Activation

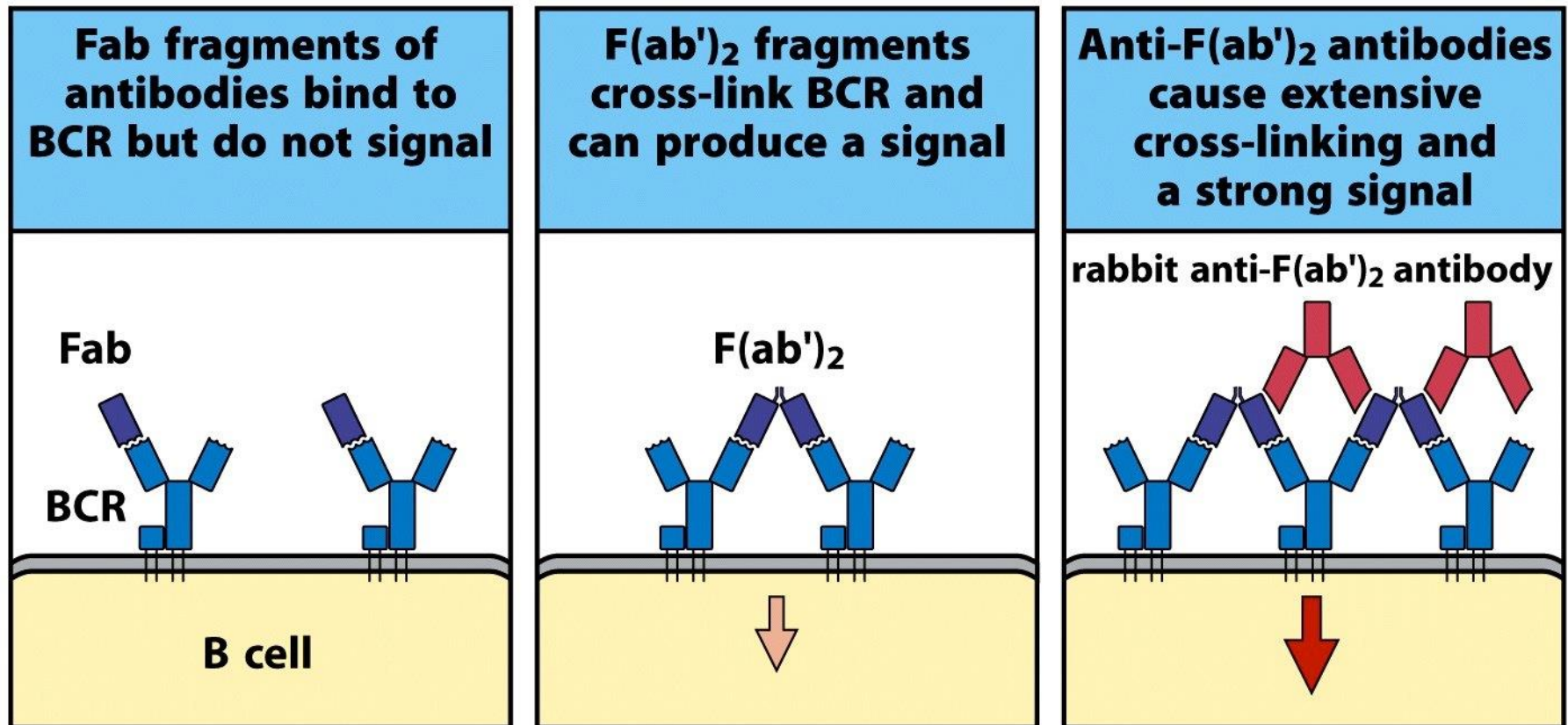
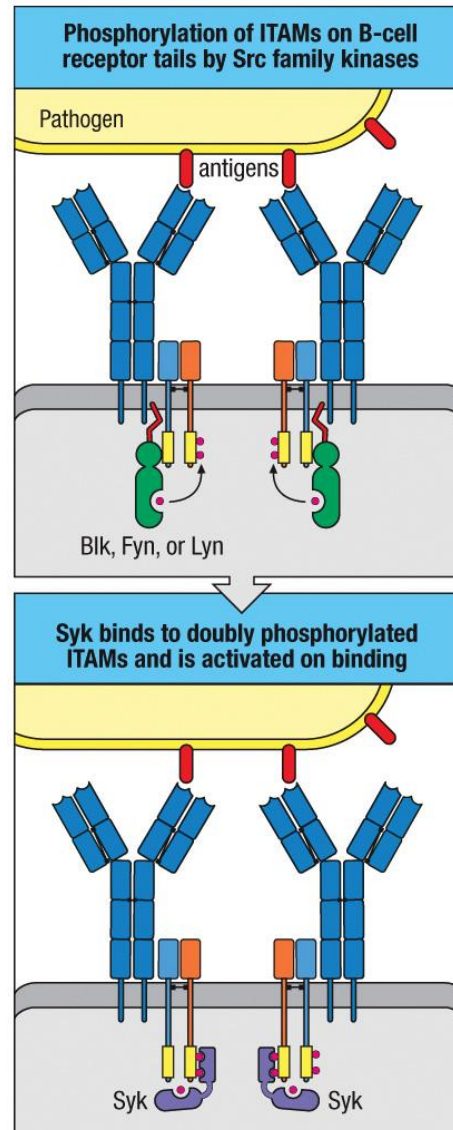


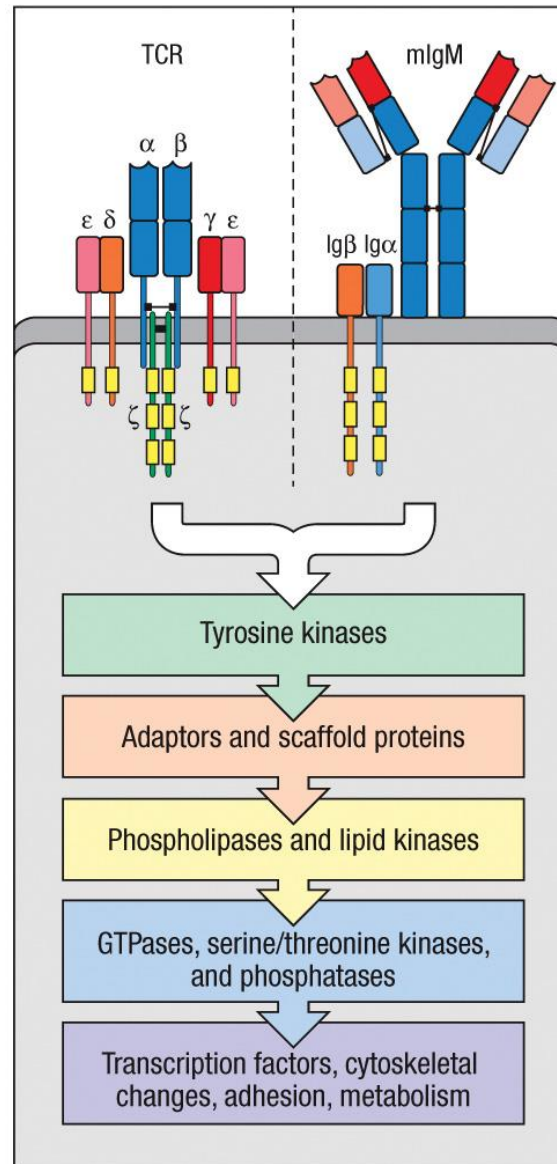
Figure 6-11 Immunobiology, 7ed. (© Garland Science 2008)



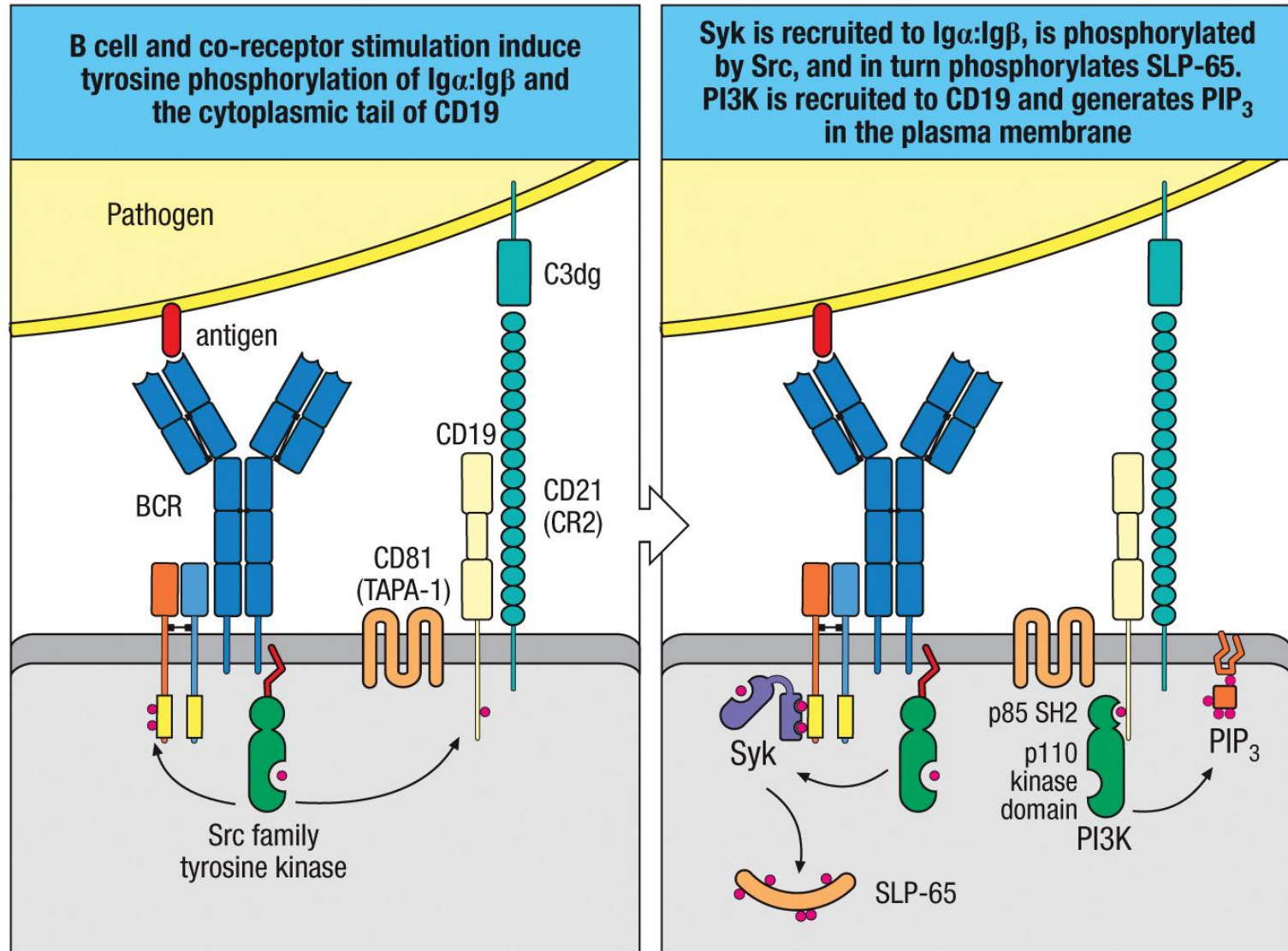
# Signaling Through BCR



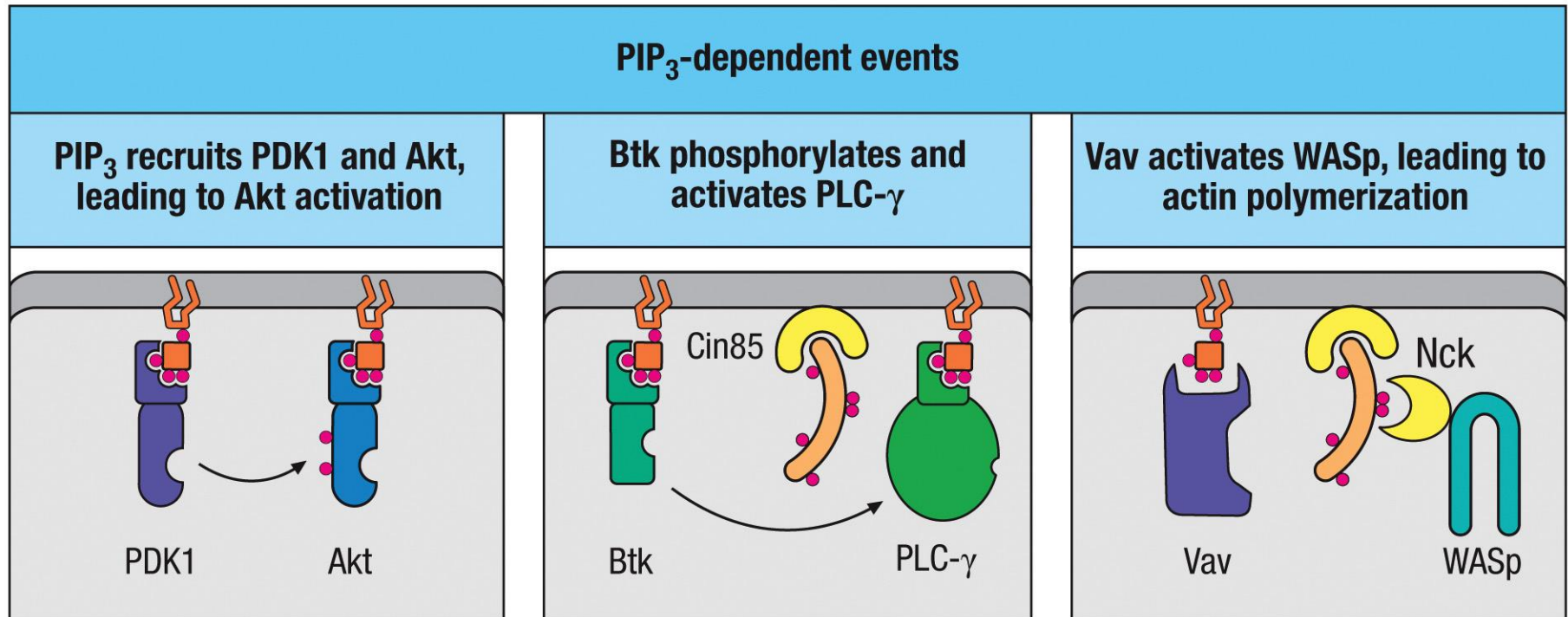
# Signaling Through BCR



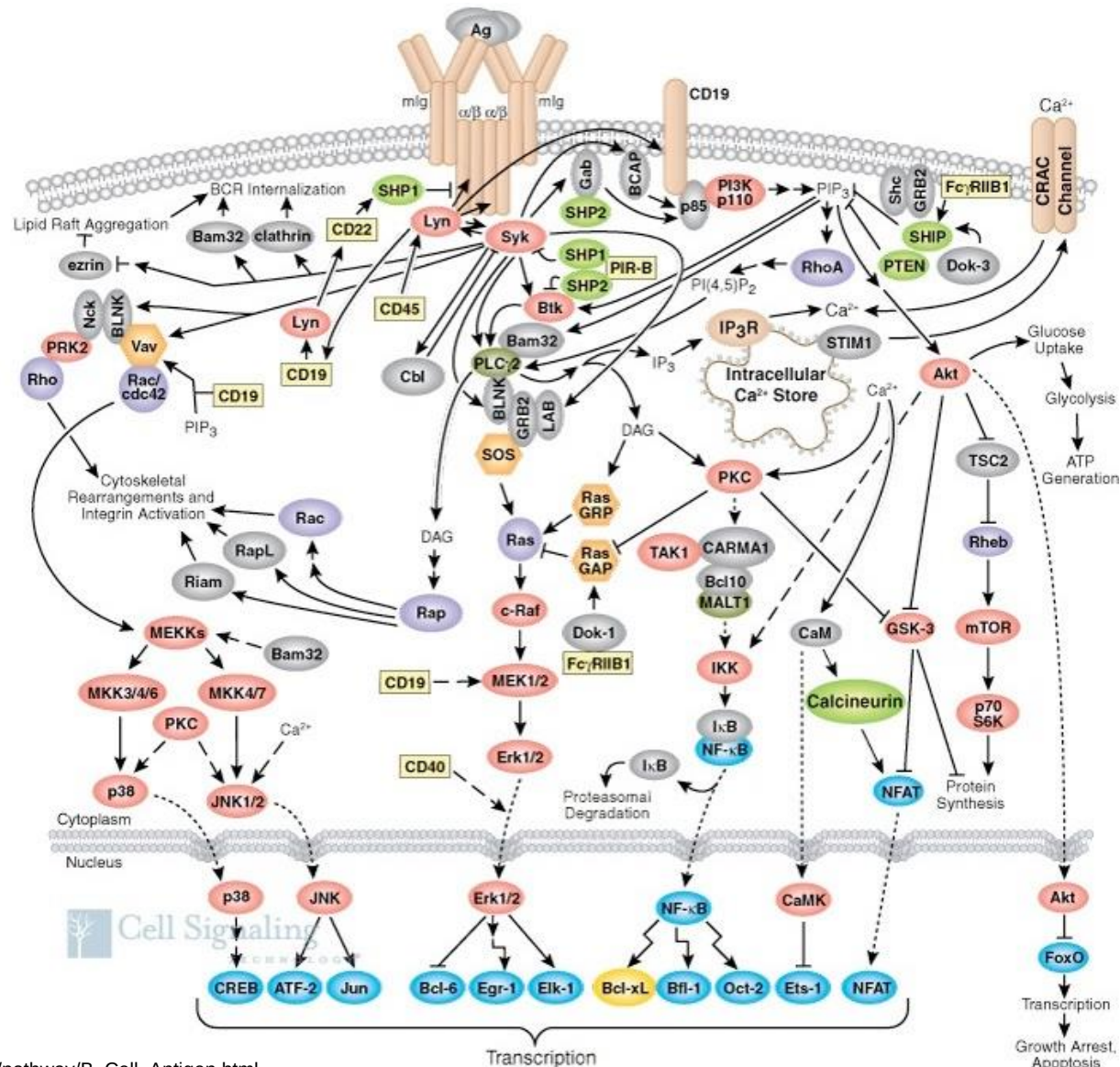
# B Cell Co-receptor Signaling



# B Cell Co-receptor Signaling



# Signaling Through BCR



# Question

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- How is the BCR activated?

# Outline

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- B-cell development
- Selection of non-self reacting B-cells
- B-cell maturation
- Signaling through B-cell receptor



# Case Study: X-linked Agammaglobulinemia

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- Patient:
  - Male
  - Repeated infection since infancy
  - Extracellular pyogenic (pus-forming) bacteria
- Diagnosis:
  - Absence of B cells
- Treatment:
  - Weekly infusion with gamma globulin

# Absent of B Cells

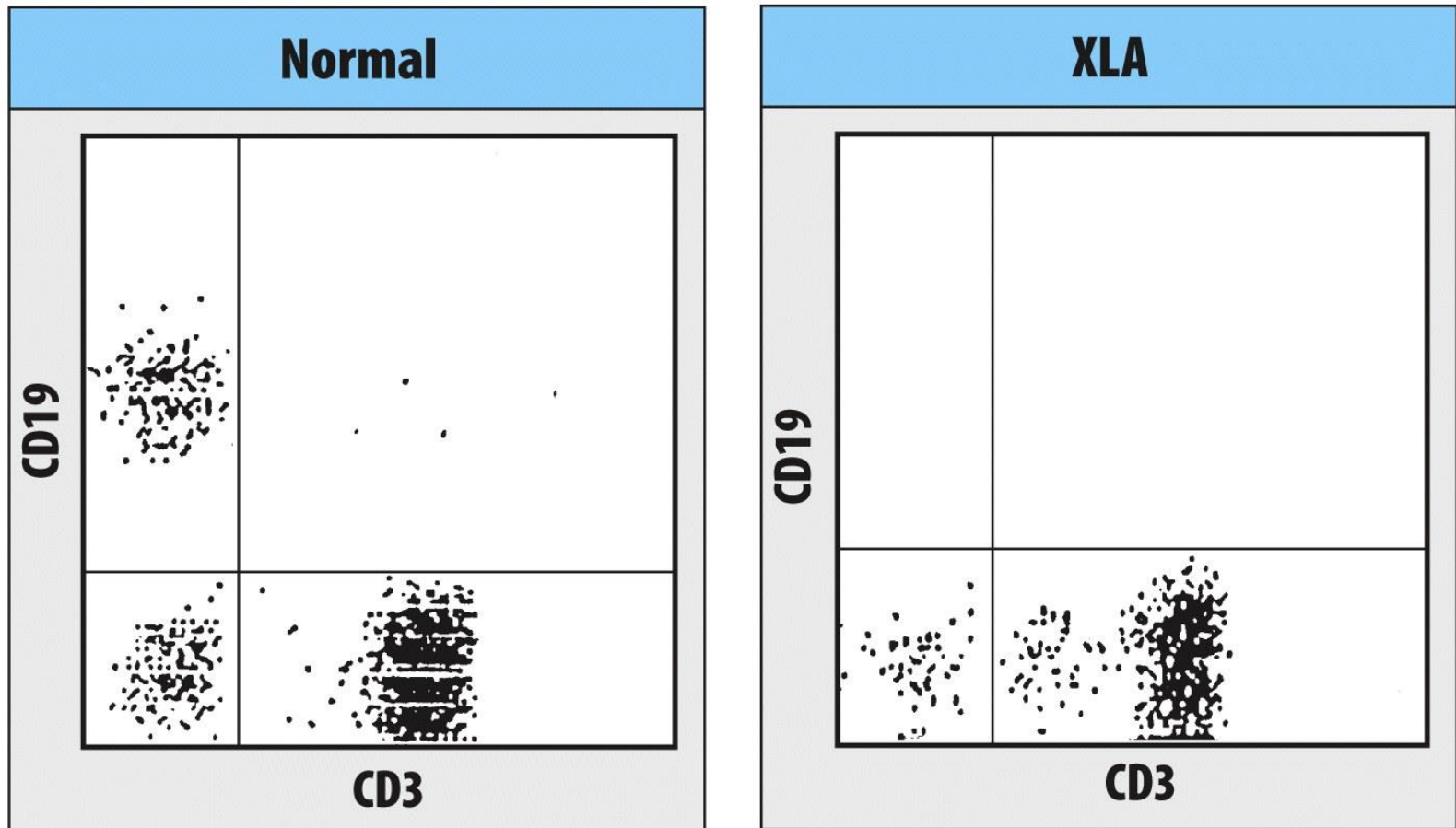


Figure 1.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

# X-linked Recessive Disease

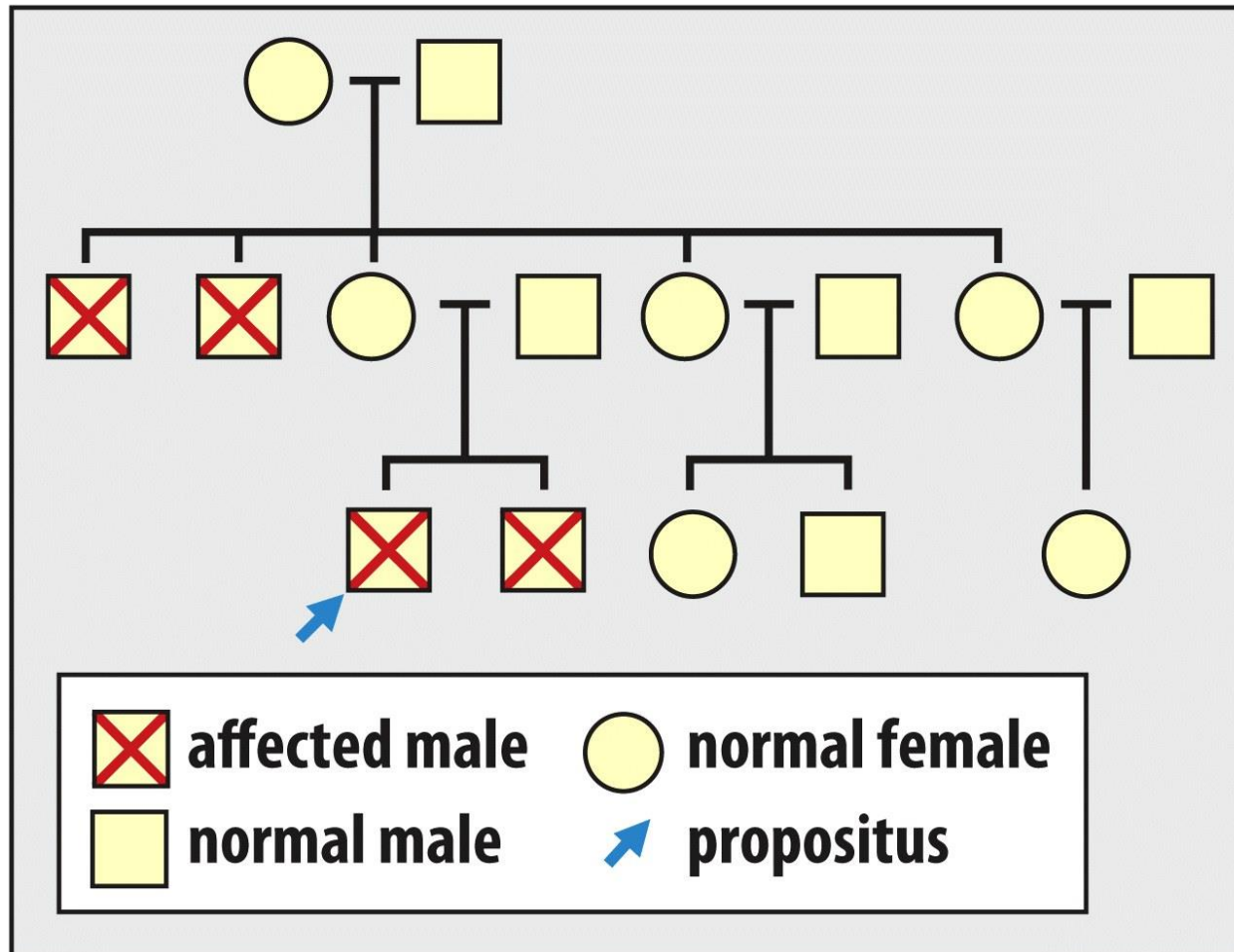
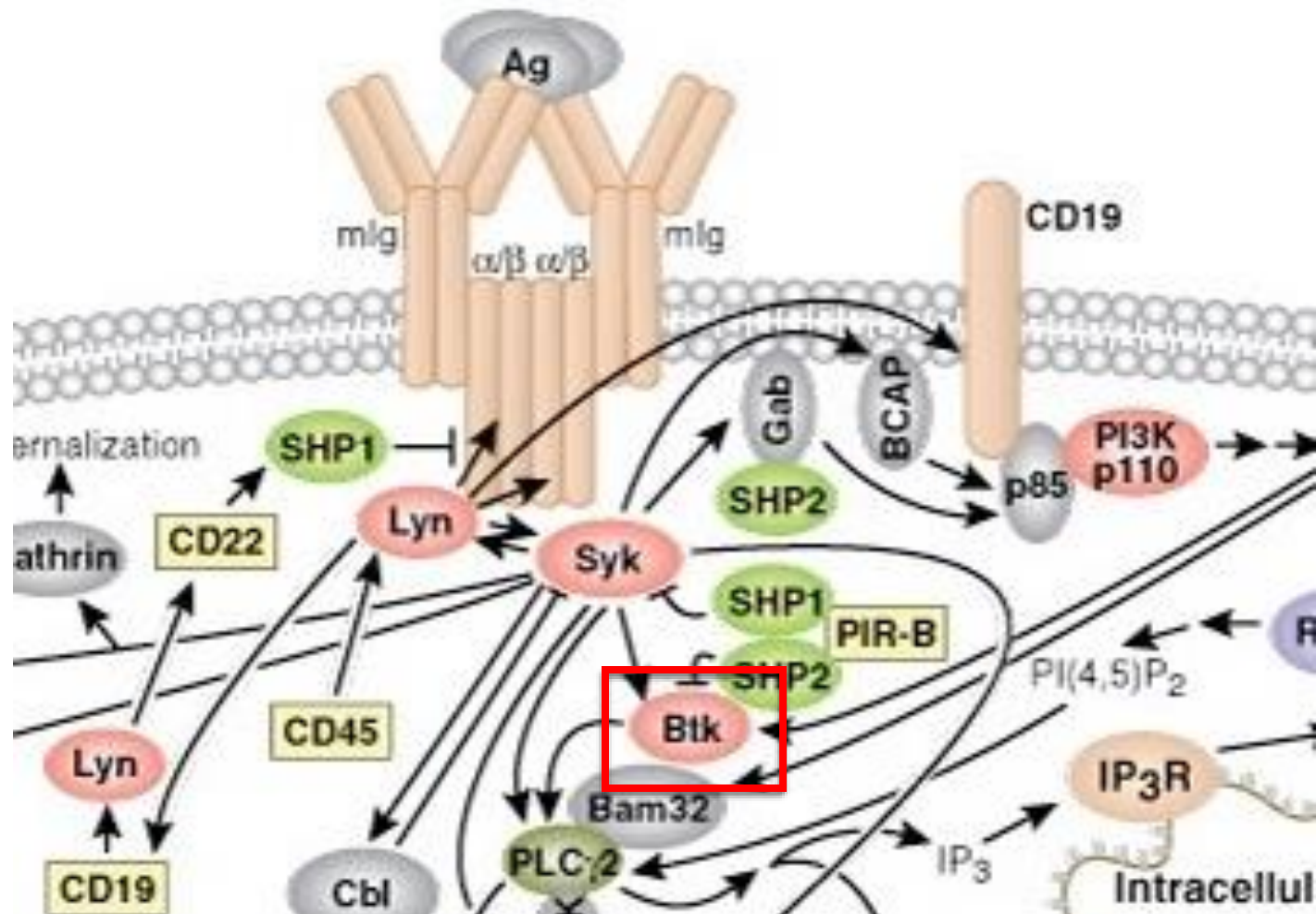


Figure 1.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

# Defect in Btk



# What's Wrong with the Patient?

Absent of B cells and antibodies  
Susceptible to extracellular bacteria

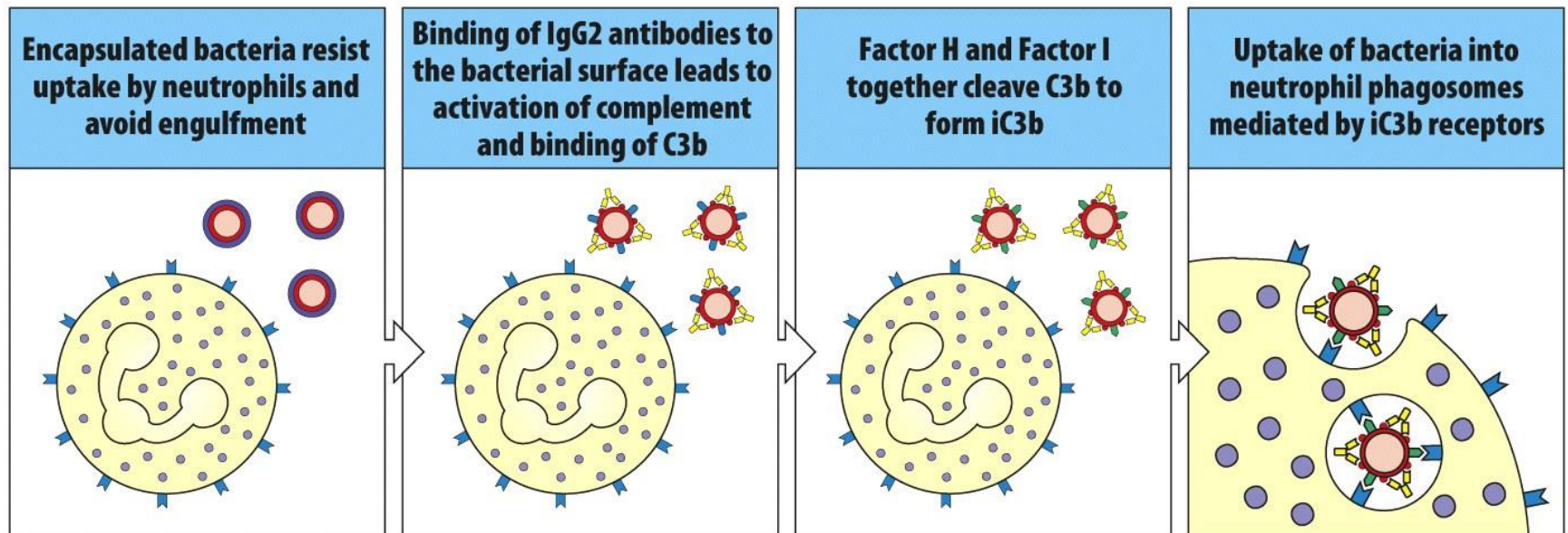


Figure 1.6 Case Studies in Immunology, 6ed. (© Garland Science 2012)