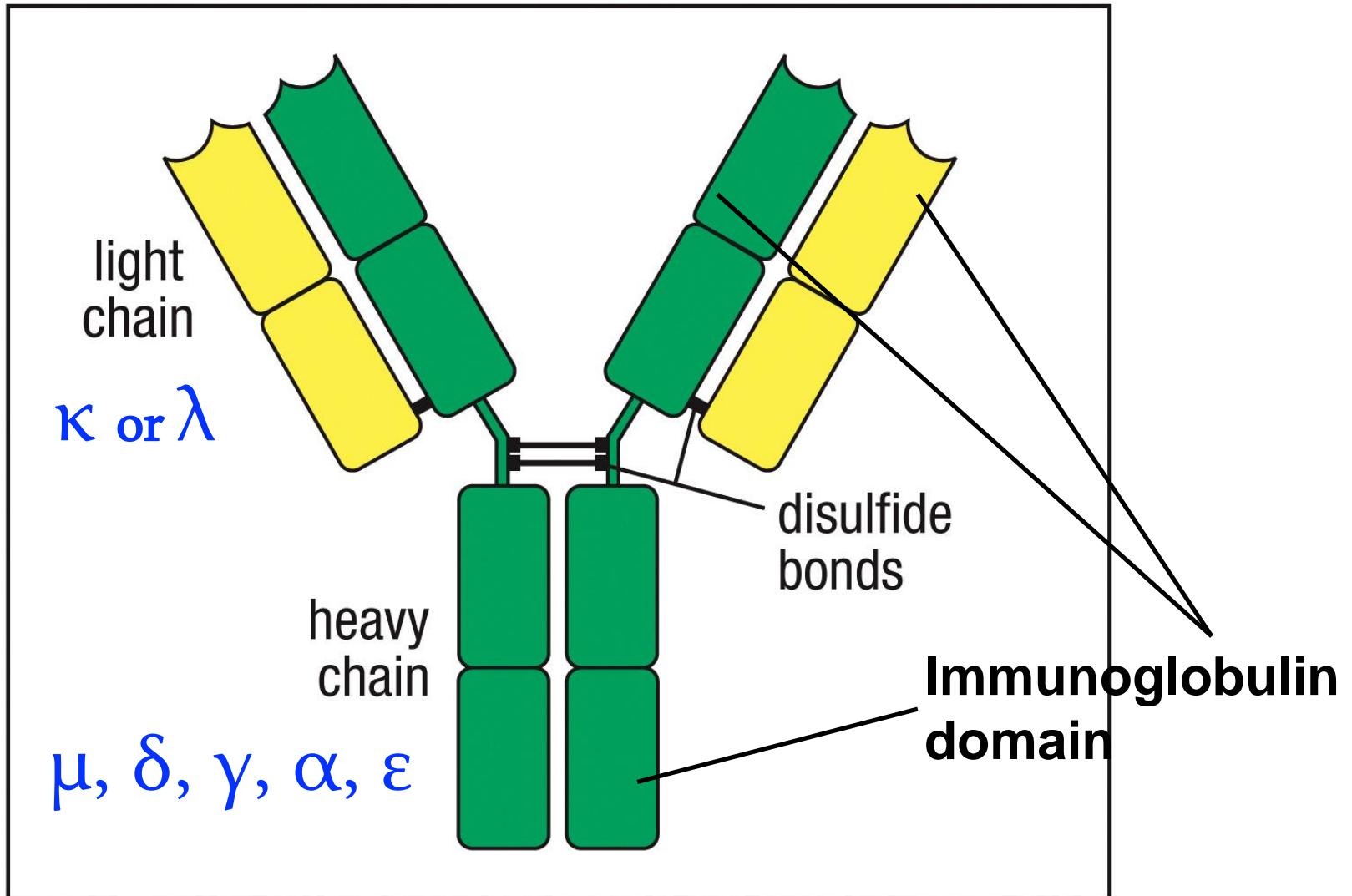
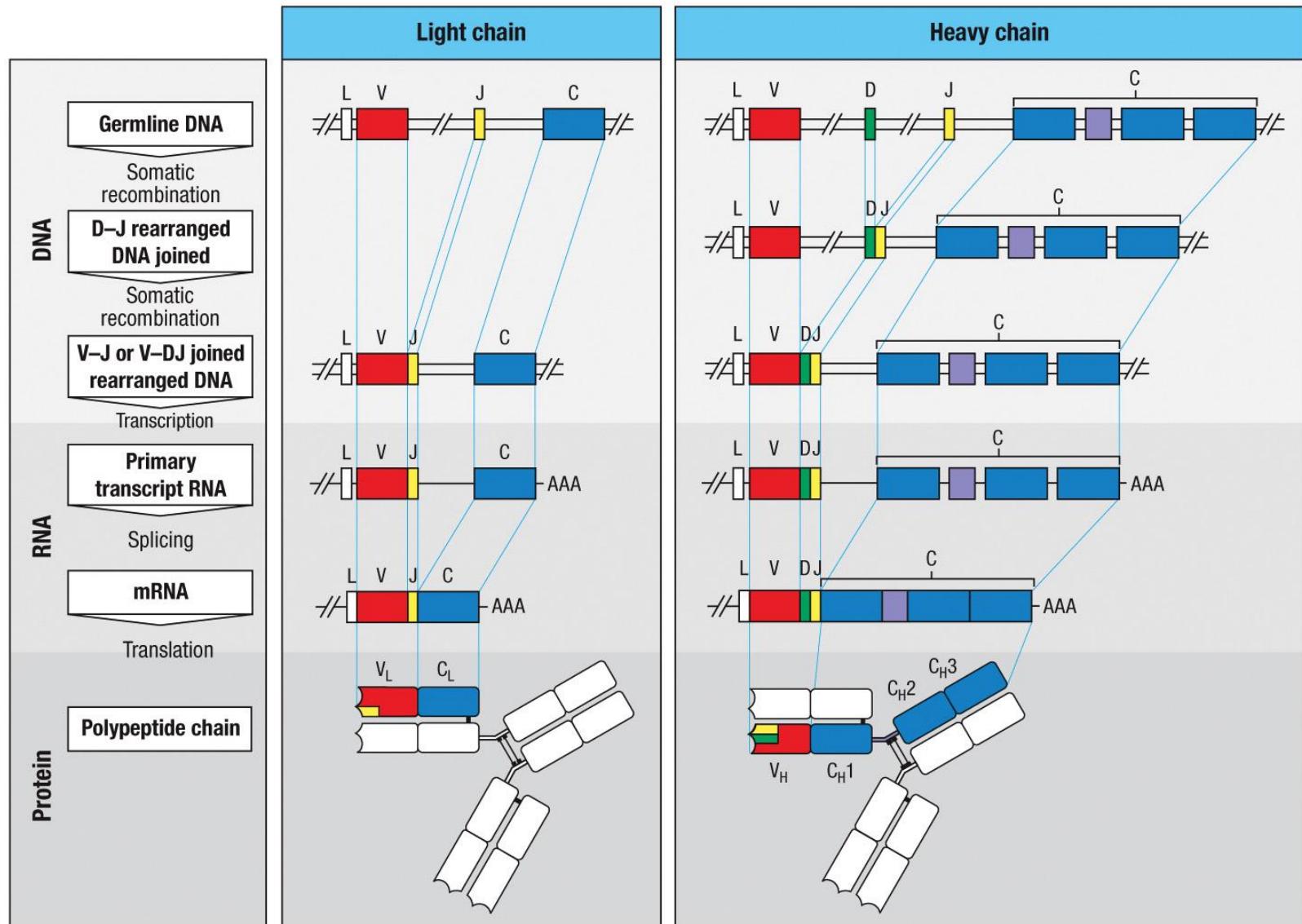


Antibody Structure



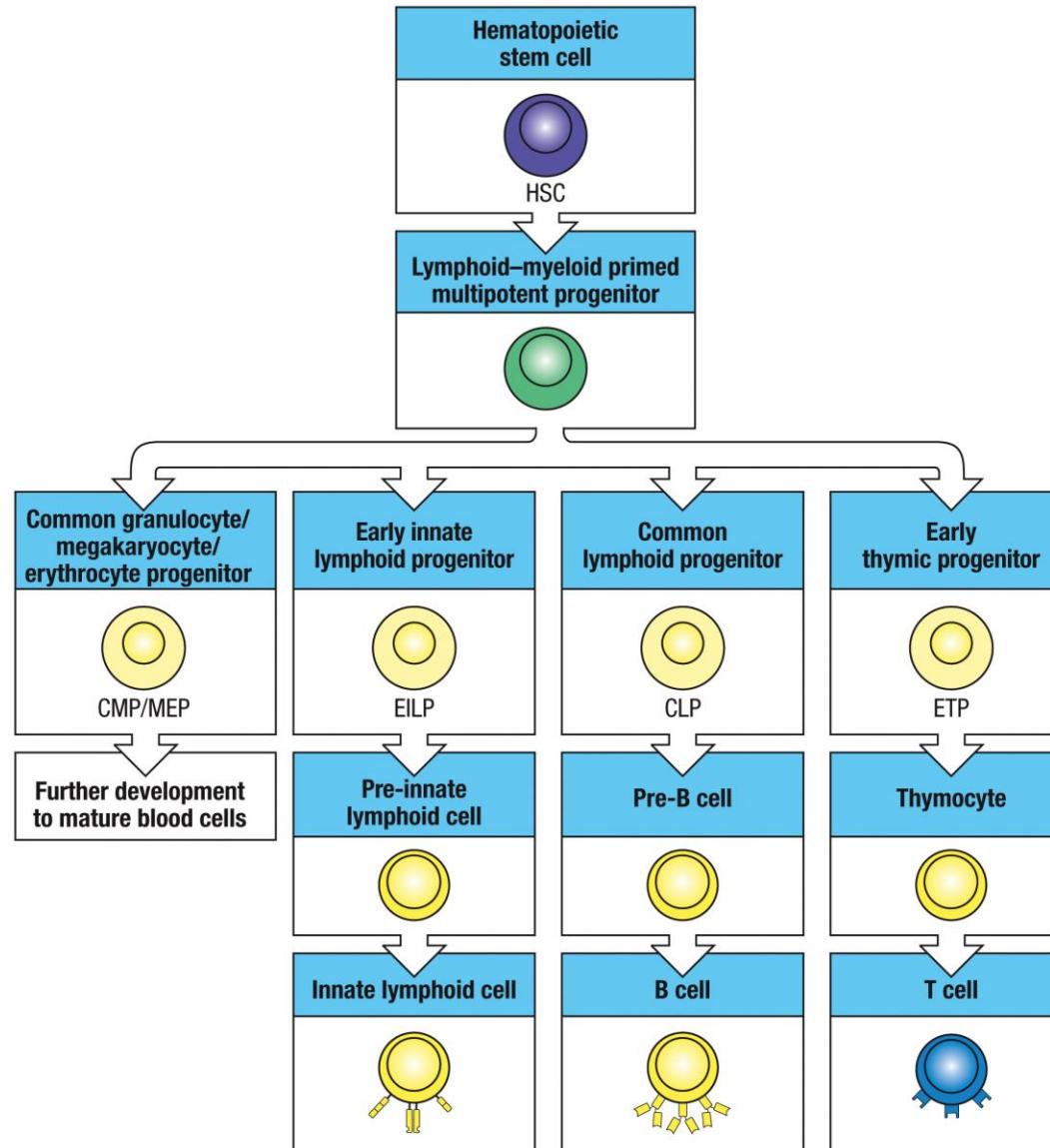
Construction of the Variable Region



Outline

- 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

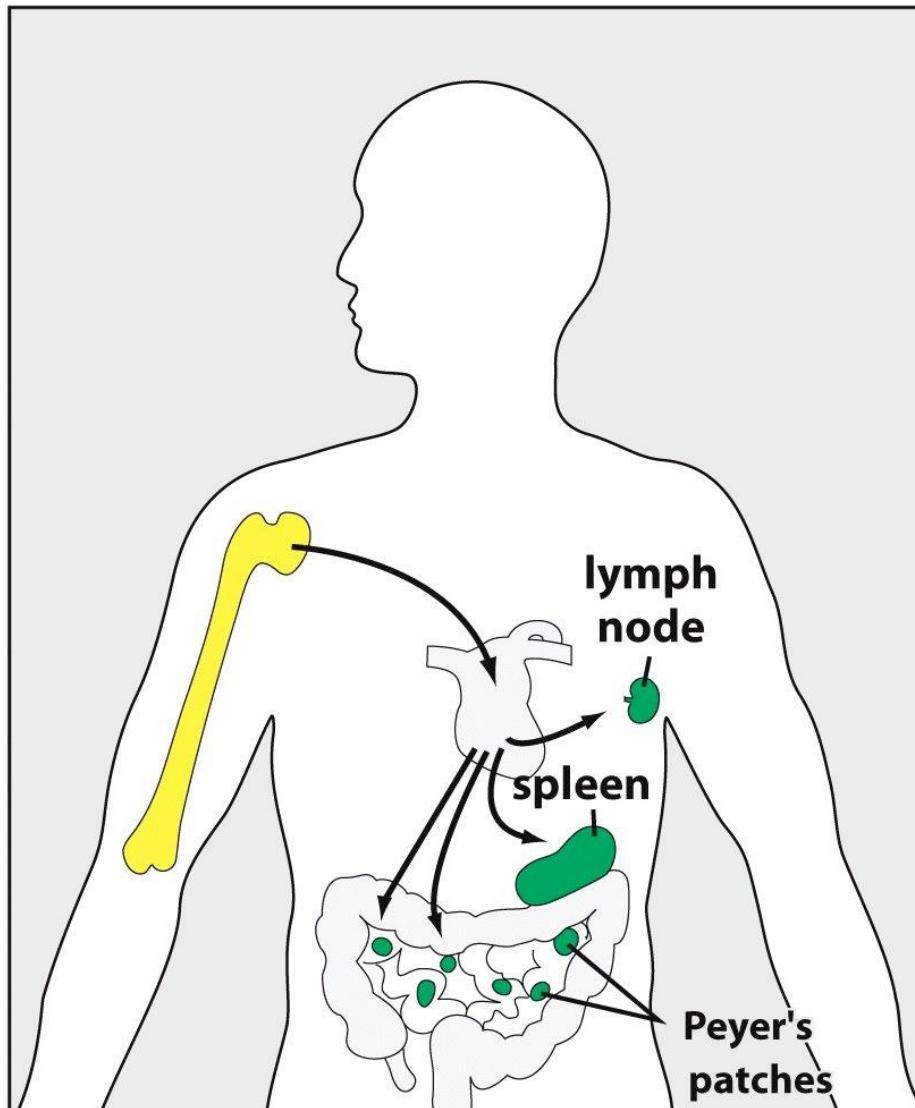


Figure 6.2 The Immune System, 3ed. (© Garland Science 2009)

Phases of B Cell Development

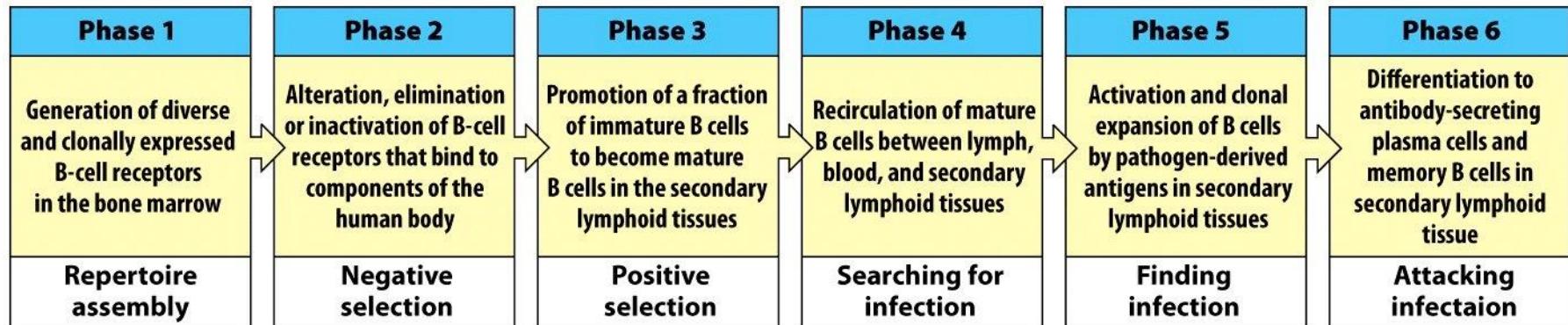
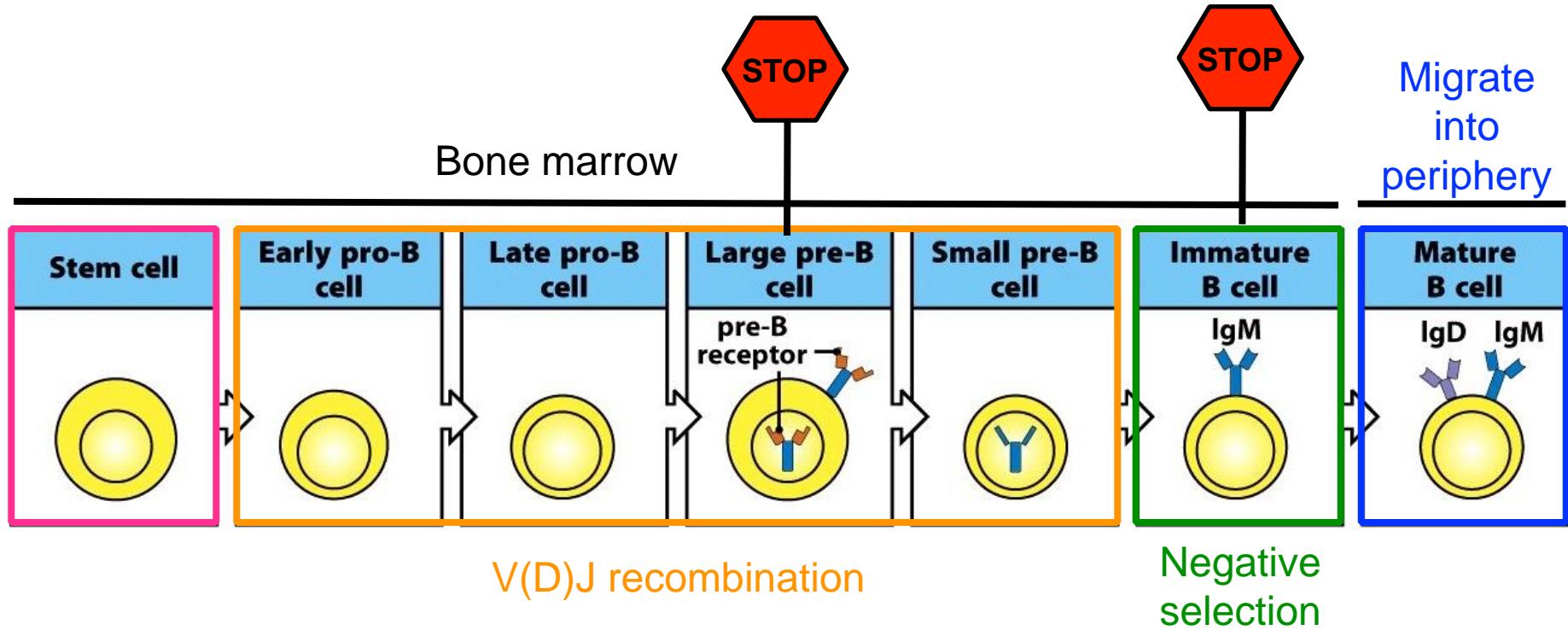


Figure 6.1 The Immune System, 3ed. (© Garland Science 2009)

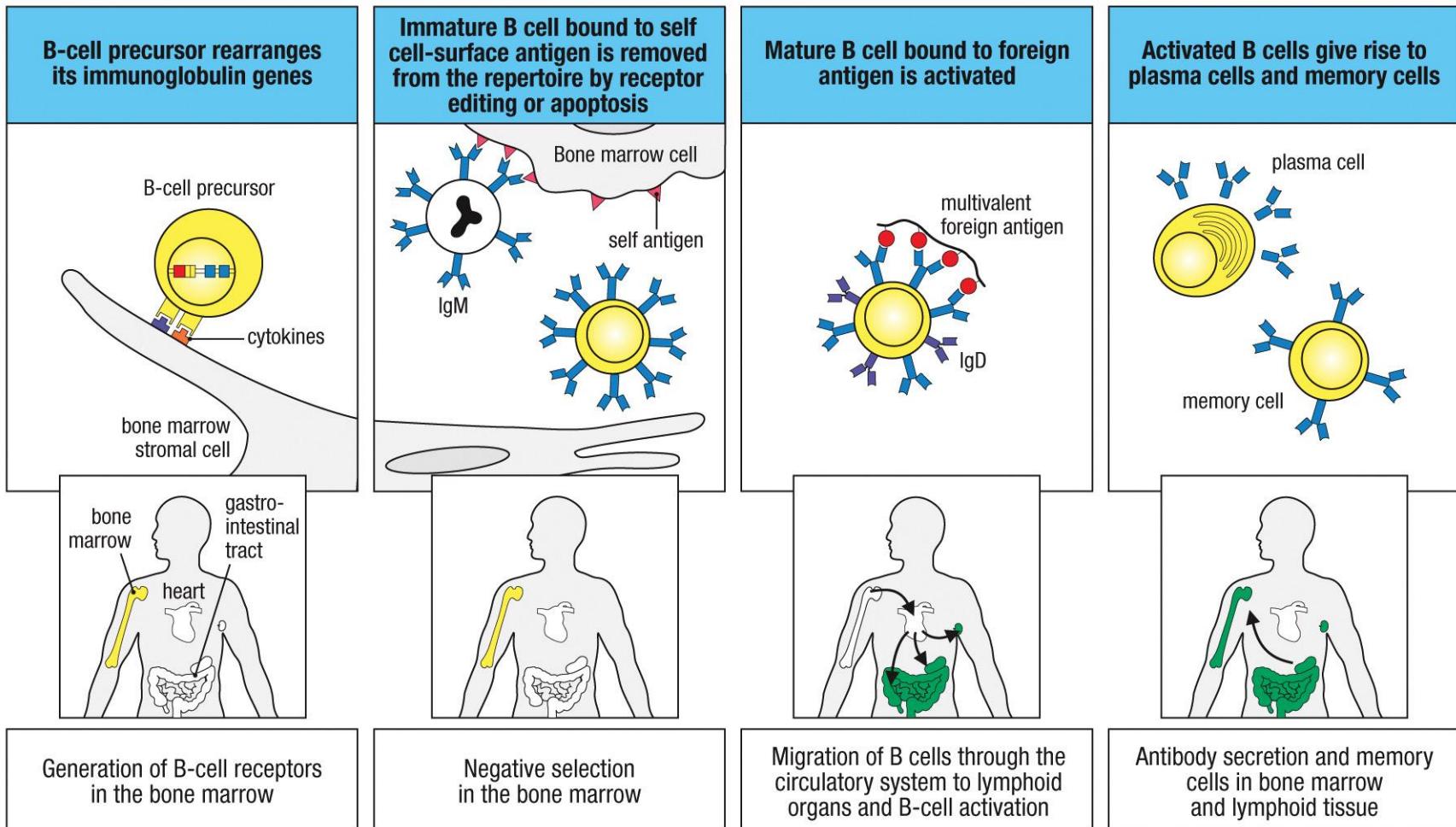
Bone marrow

Periphery (secondary lymphoid tissues)

Stages of B-Cell Development



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



Stages of Lymphocyte Development

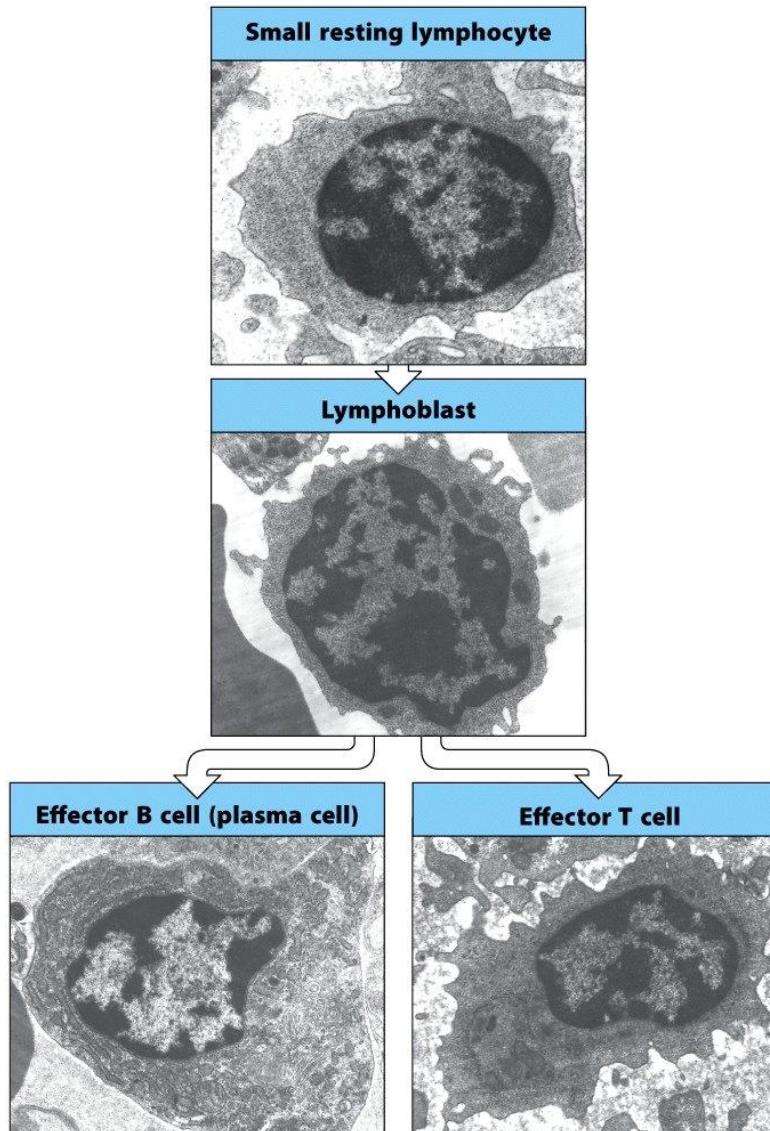
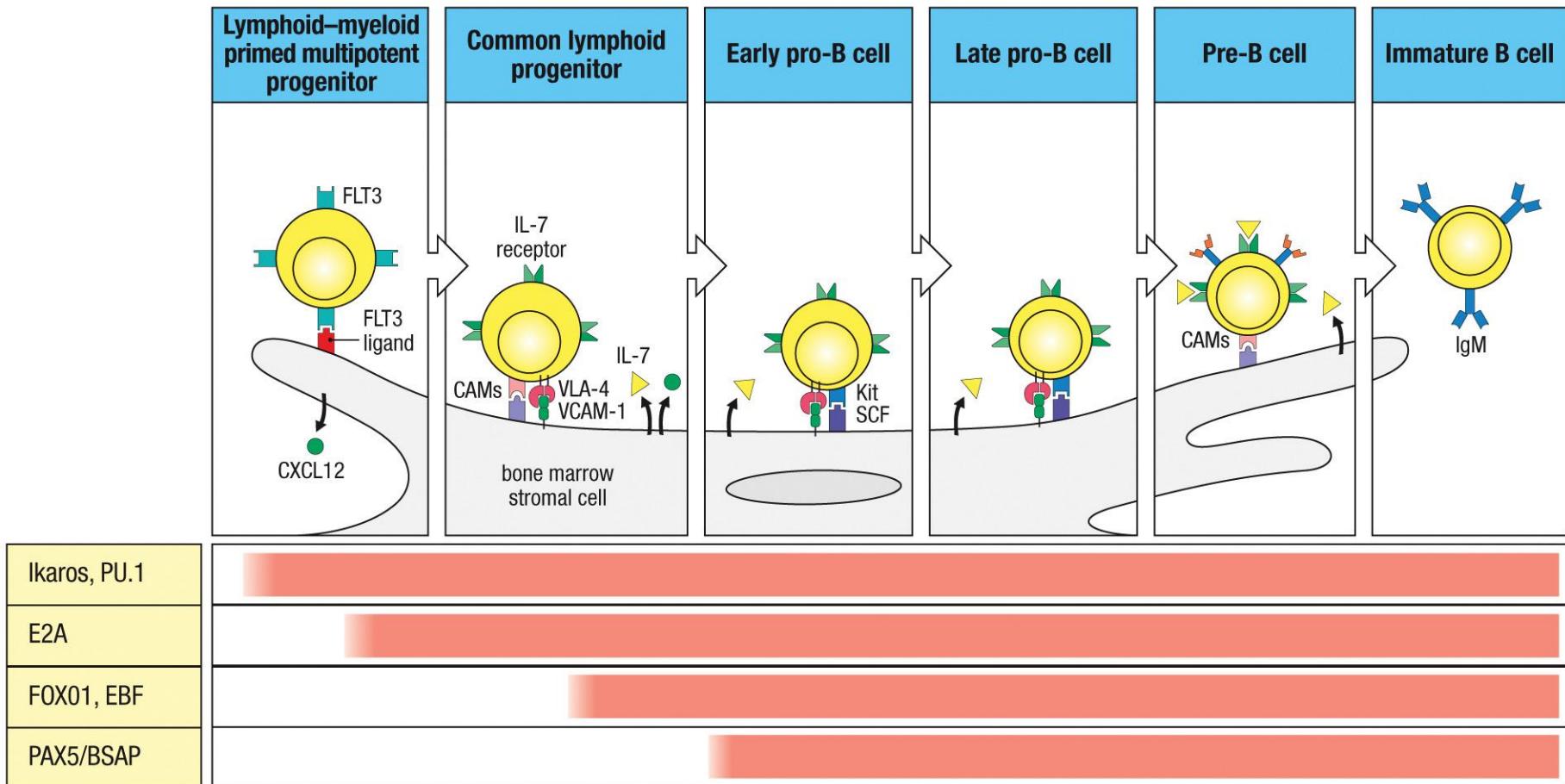
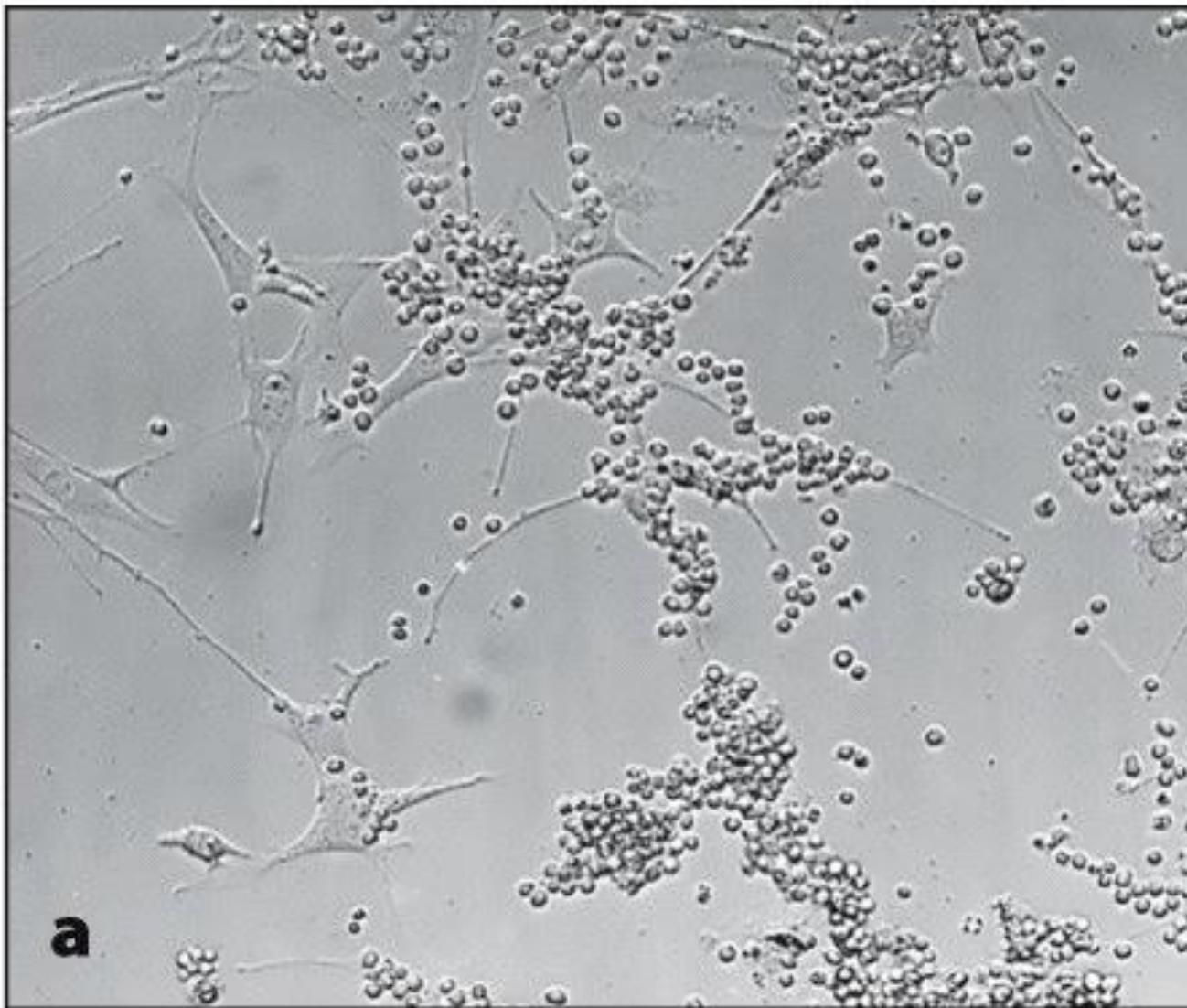


Figure 1-23 Immunobiology, 7ed. (© Garland Science 2008)

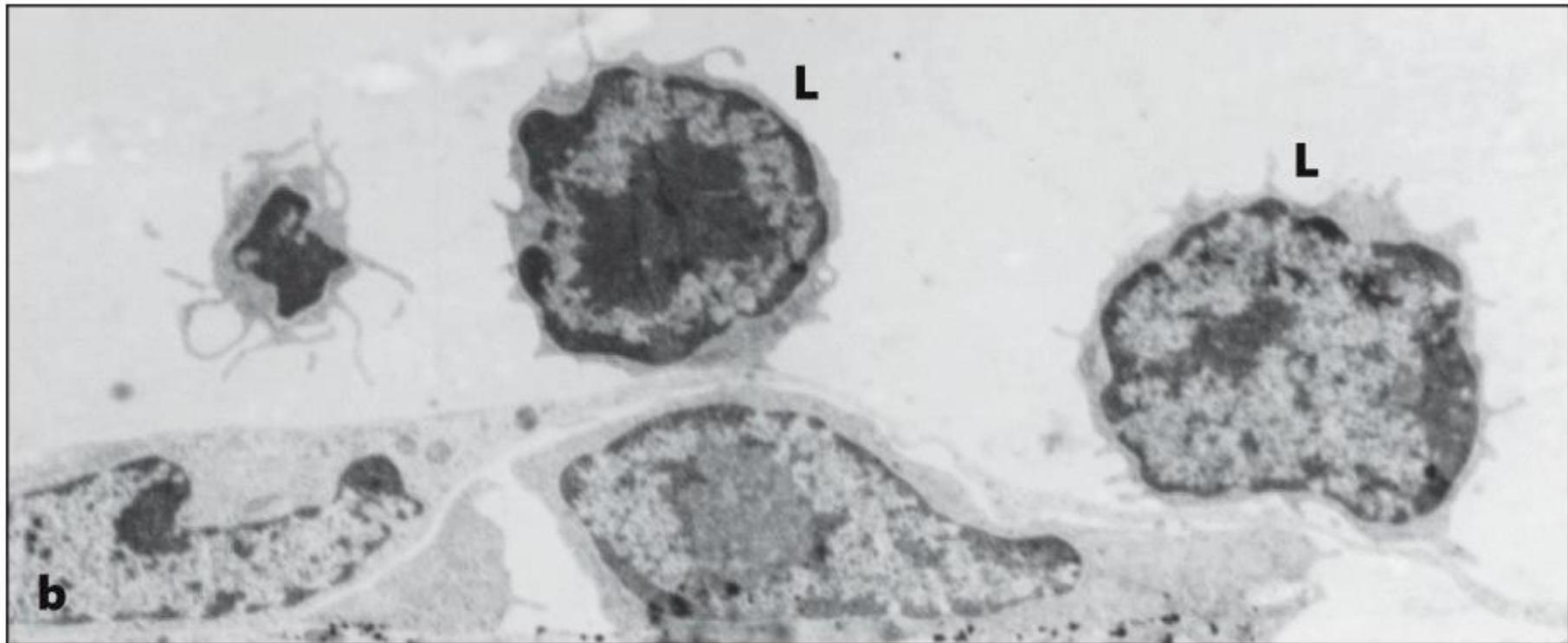
Early Stages of B-Cell Development Are Dependent on Stromal Cells



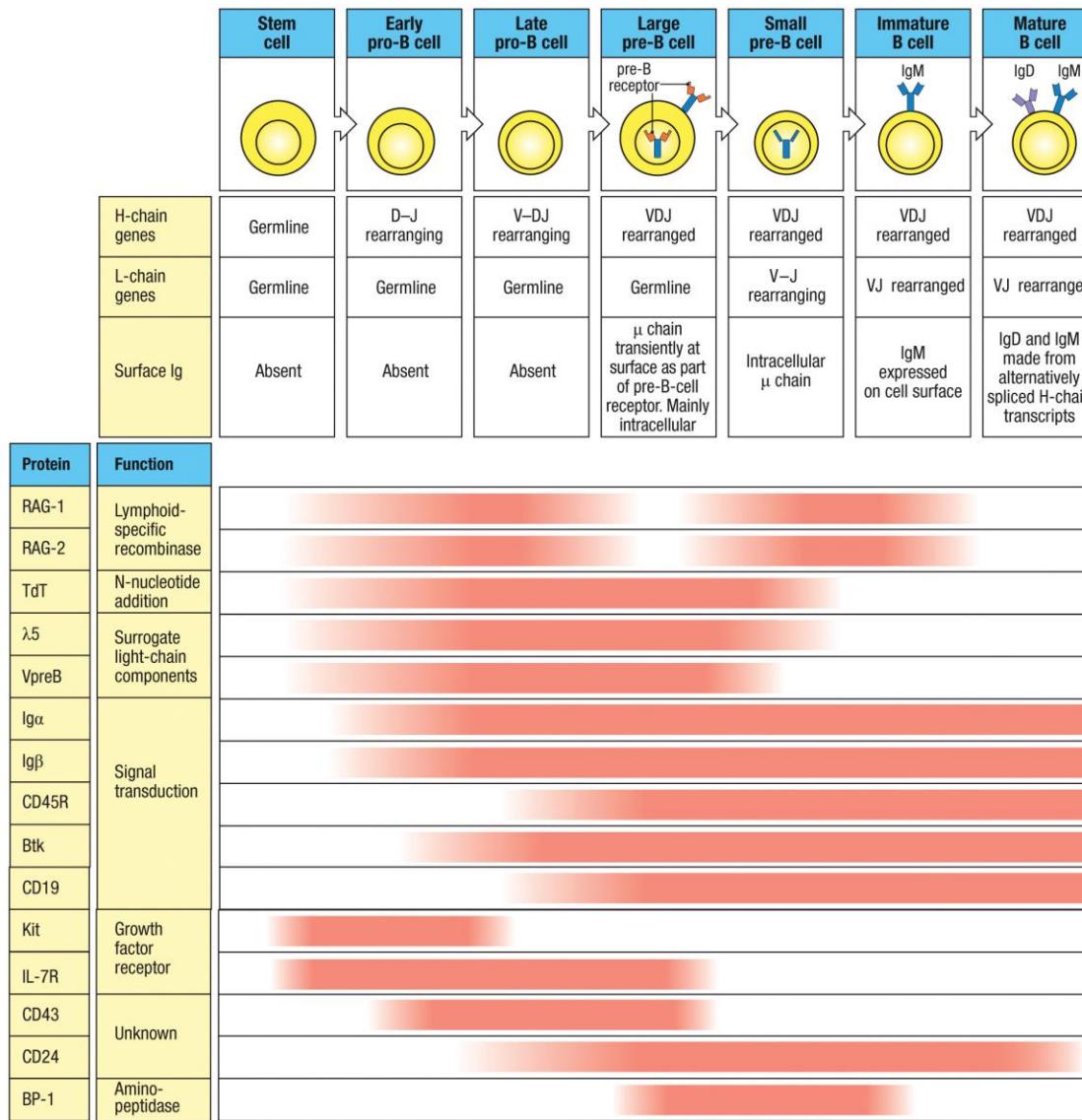
B-Cells Interact With Stromal Cells During Development



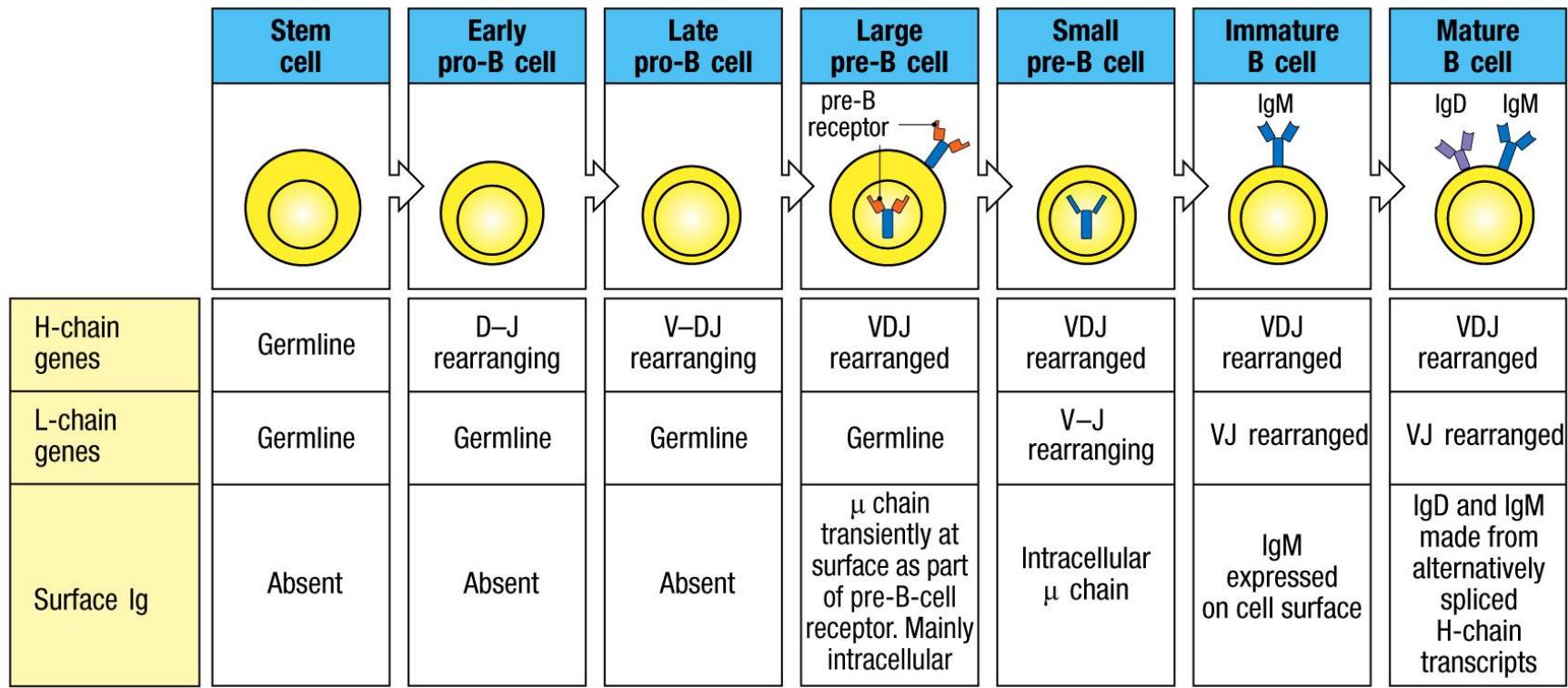
B-Cells Interact With Stromal Cells During Development



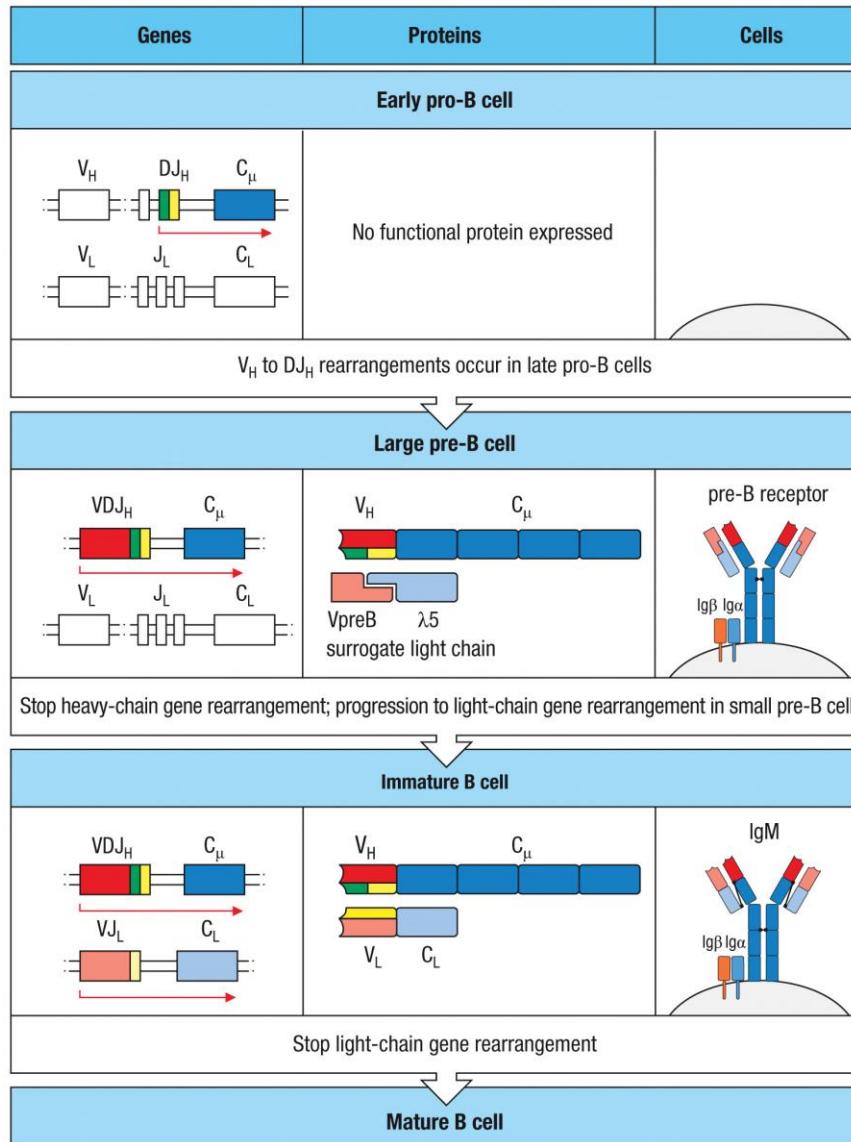
Protein Expression During B-Cell Development



B-Lineage Development



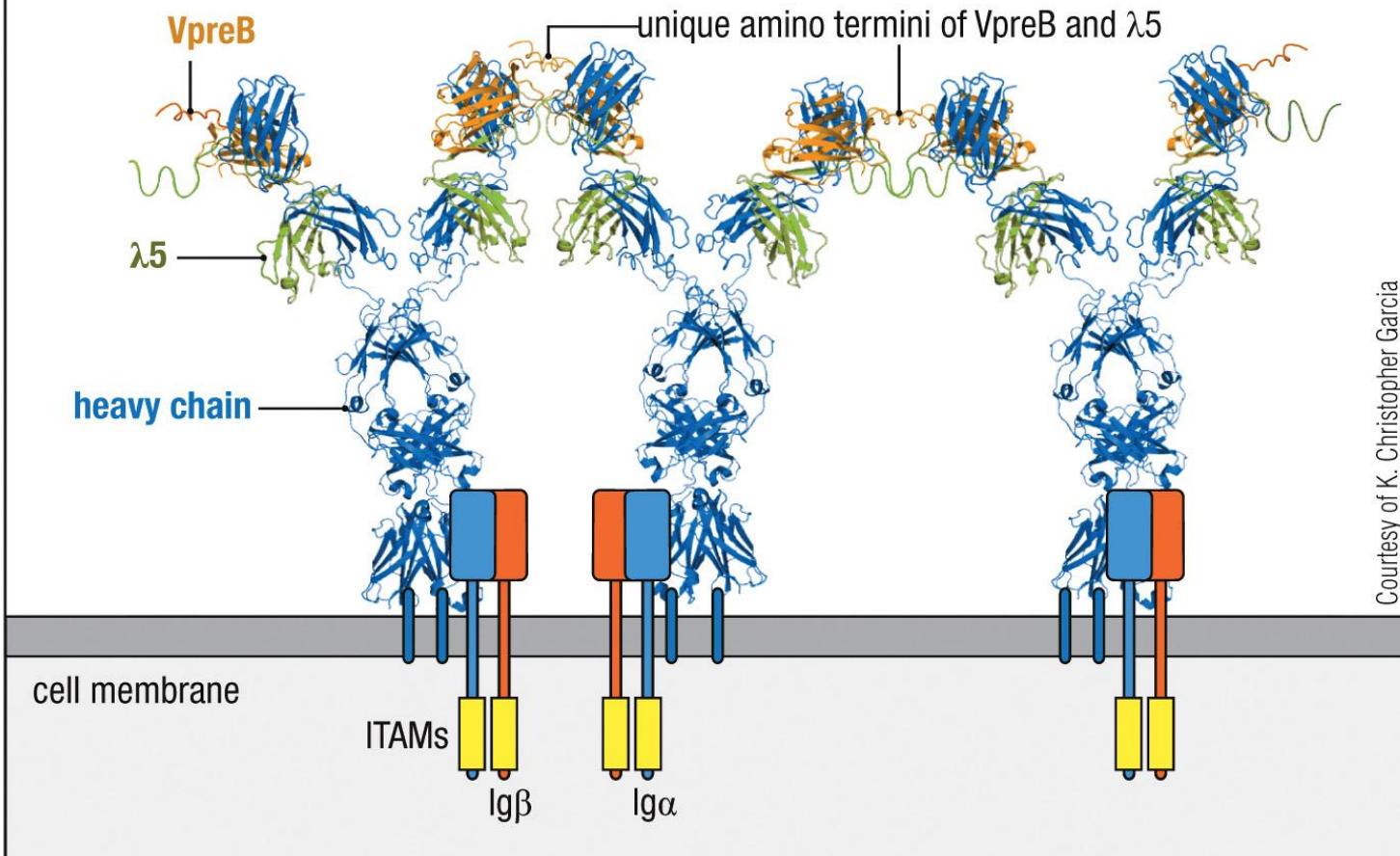
Pre-B-Cell Receptor Assembly



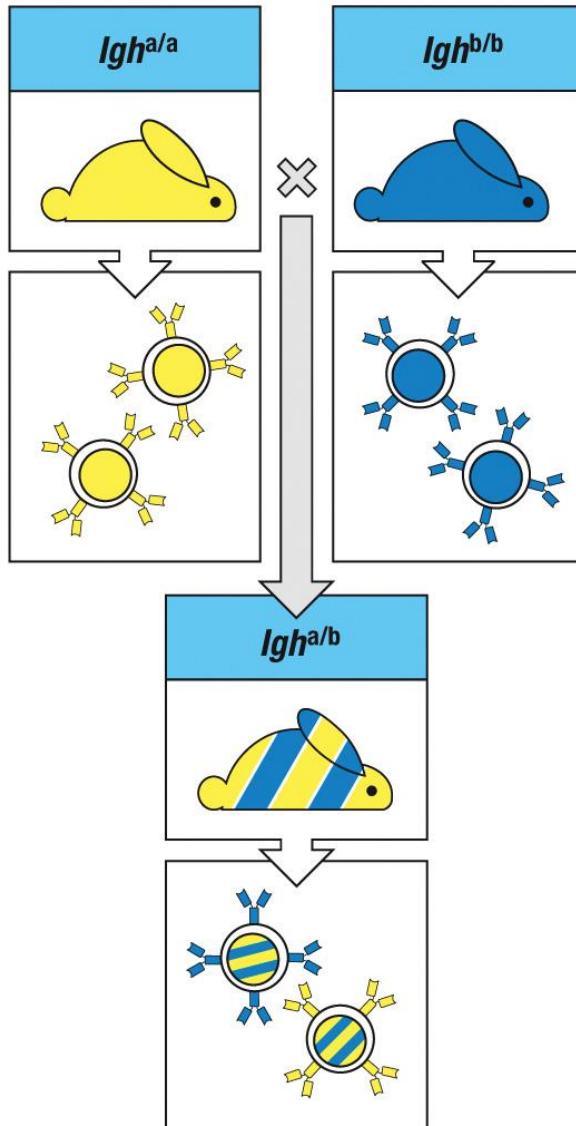
Courtesy of K. Christopher Garcia

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

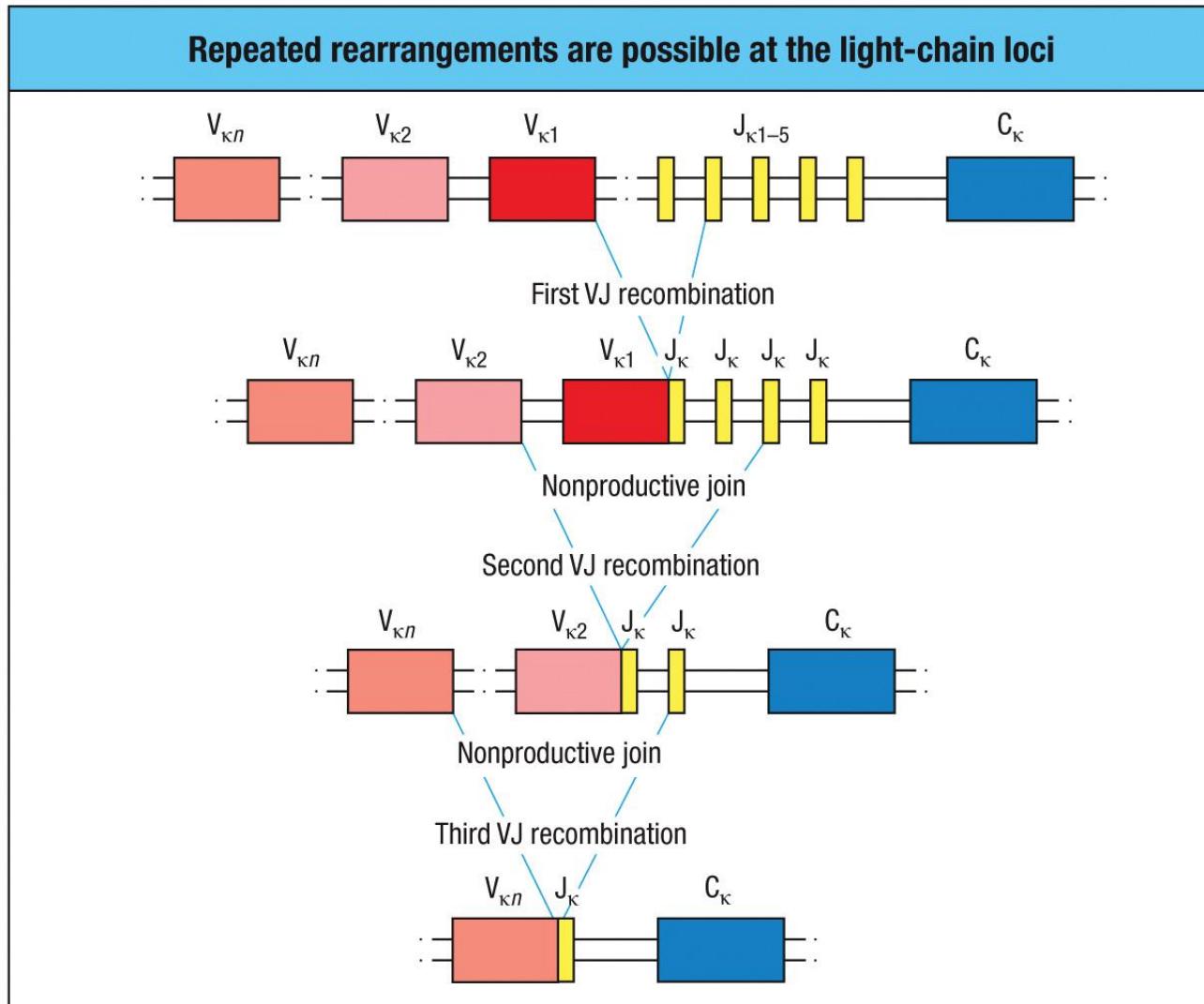


Allelic Exclusion in B-Cells



Generation of Productive V(D)J Rearrangement

Rearrangement of light chain is usually successful



Steps of Immunoglobulin Gene Rearrangement

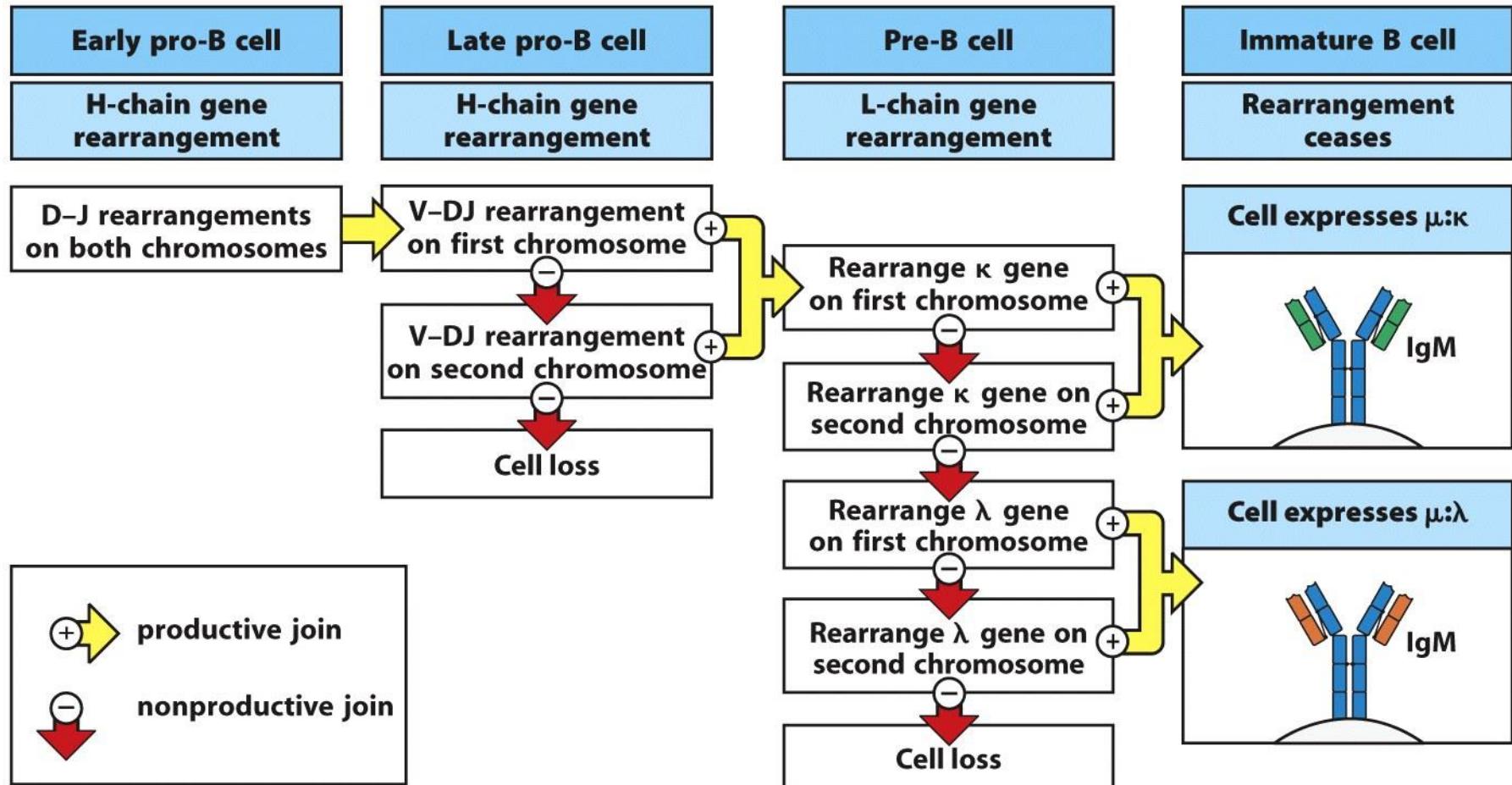


Figure 8.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

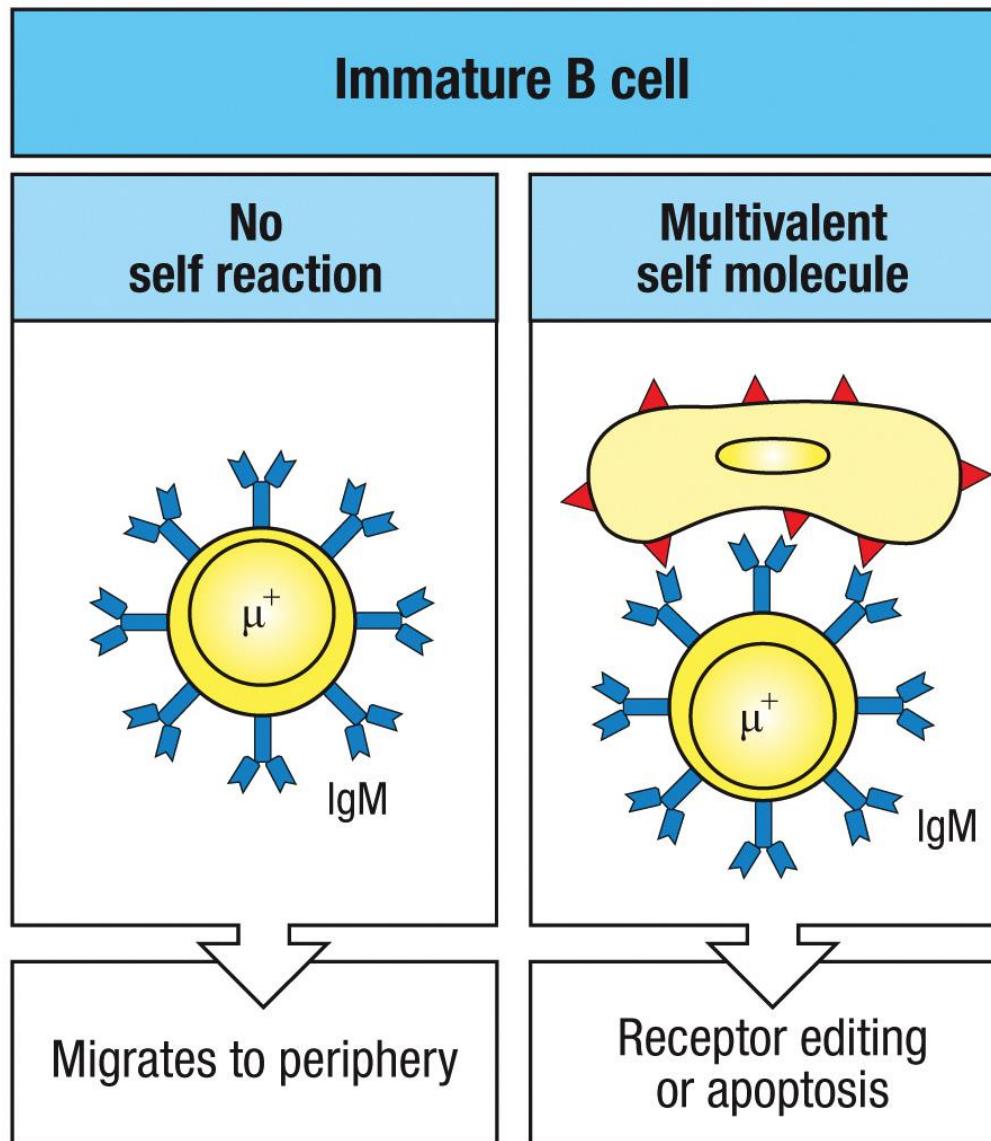
Question

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

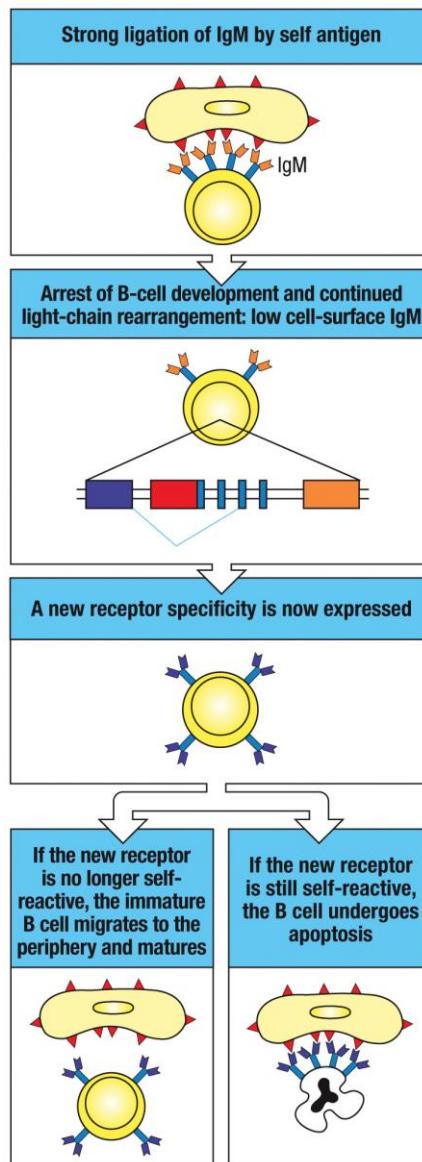
Outline

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

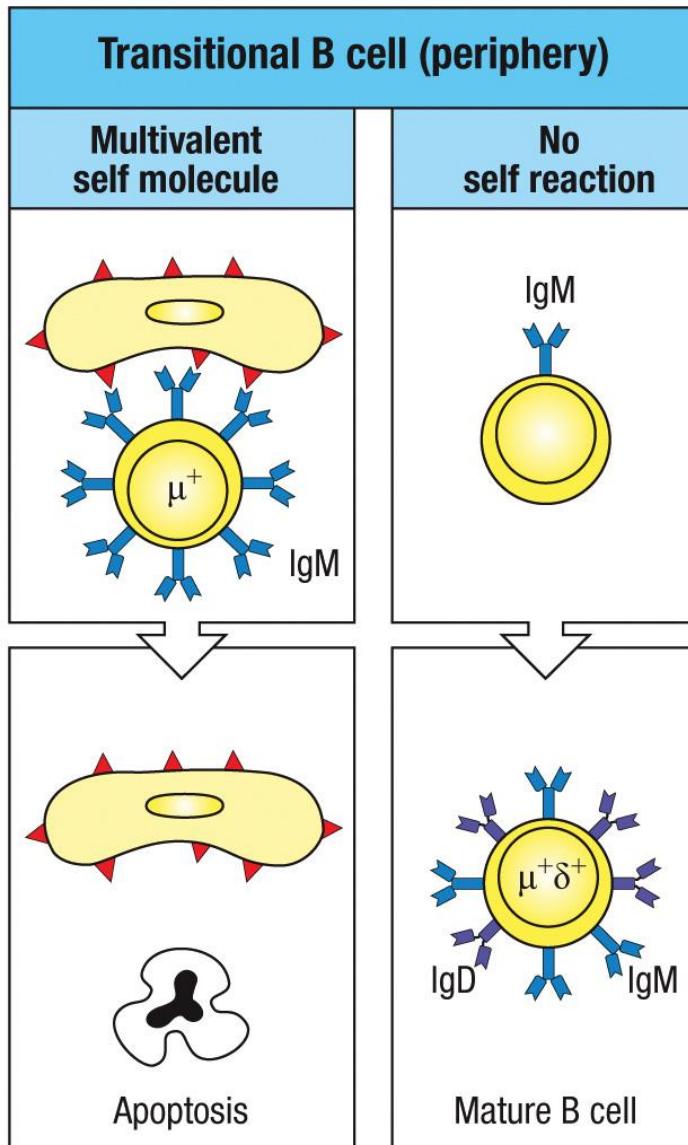
Self-Reacting B-Cells Are Deleted During Development



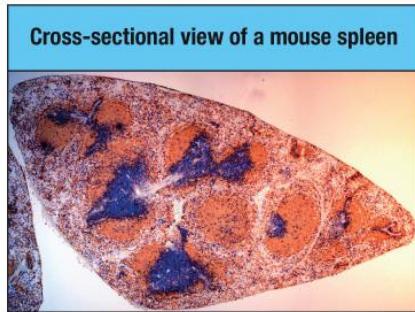
Receptor Editing Can Rescue Self-Reacting B-Cells



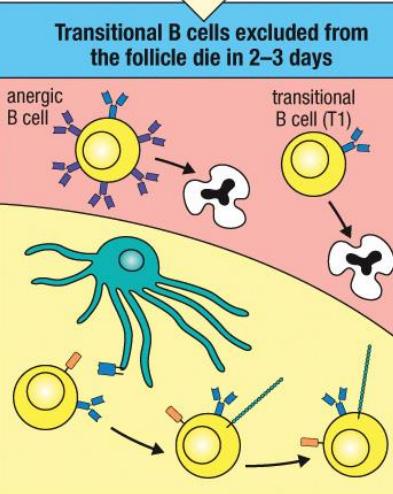
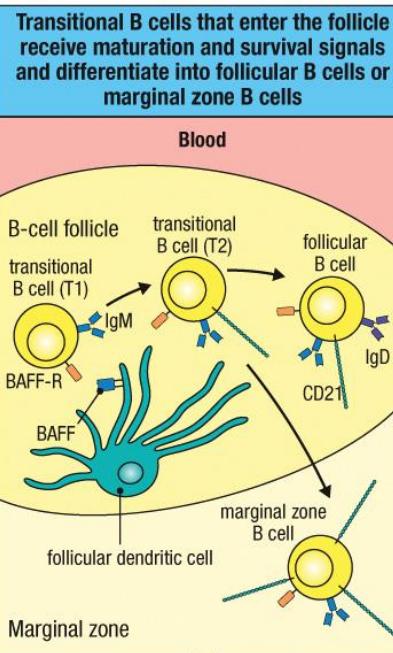
Transitional B cells



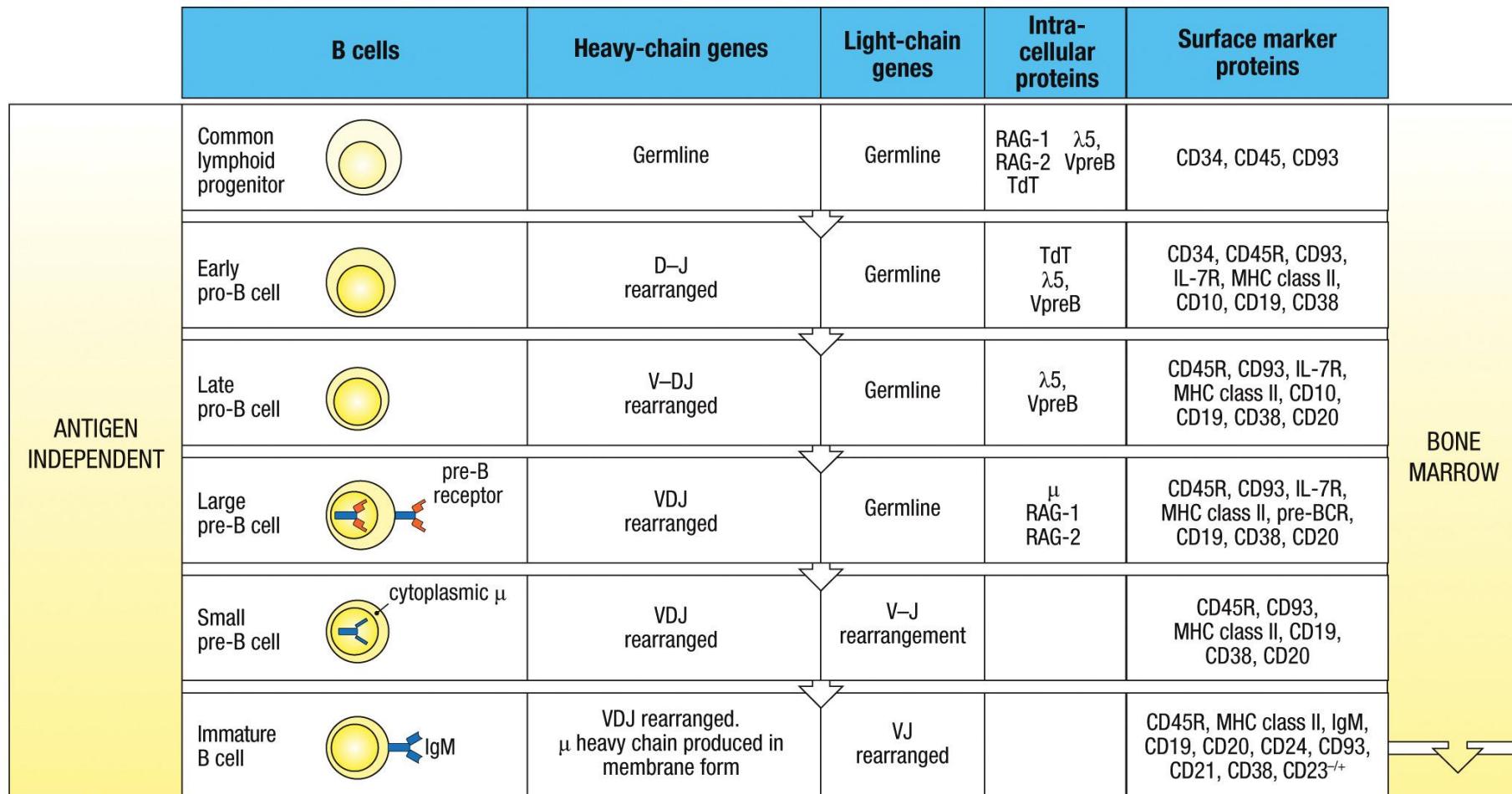
Transitional B cells complete their maturation in B-cell follicles in the spleen



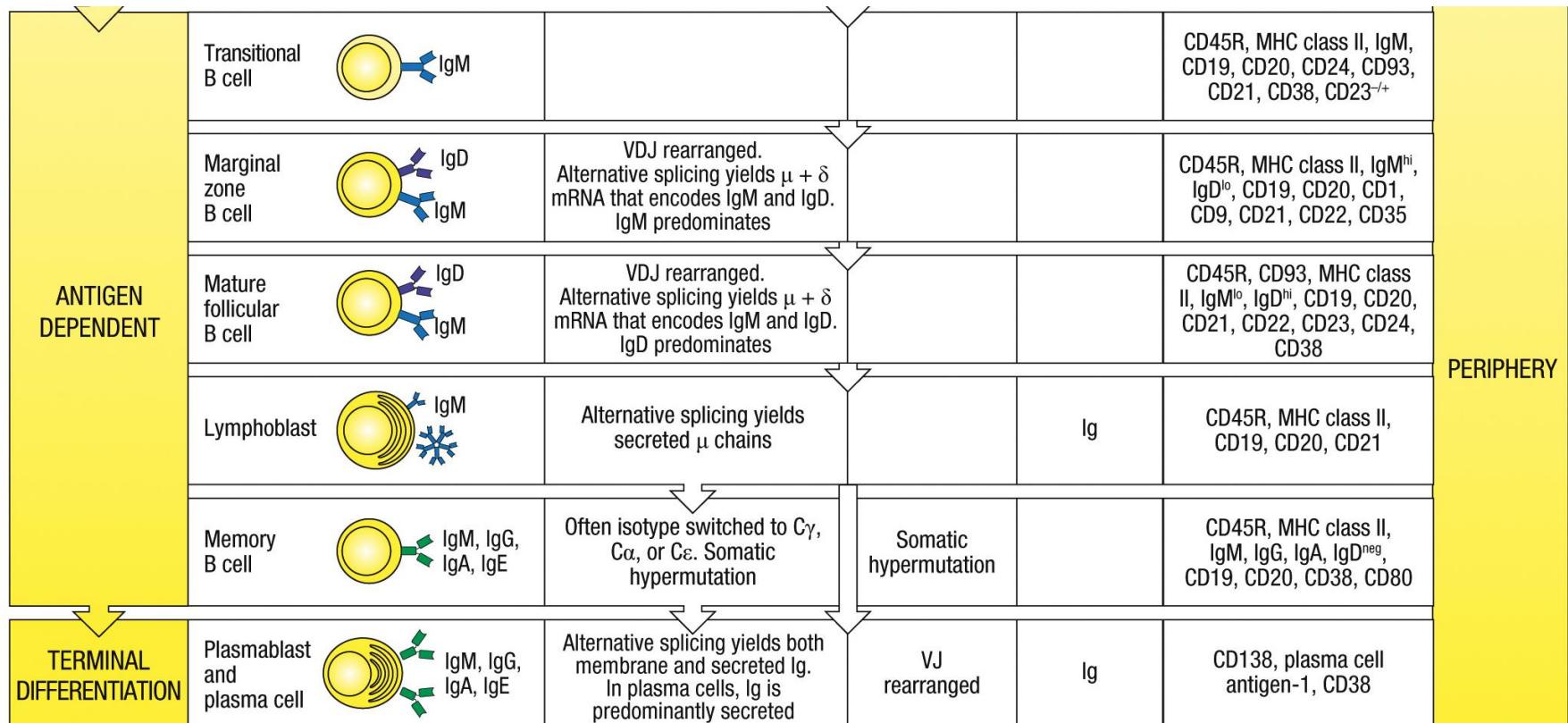
Micrograph courtesy of Xiaoming Wang and Jason Cyster. Howard Hughes Medical Institute and Department of Microbiology and Immunology, UCSF



B-Cell Development



B-Cell Development



B-Cell Population Dynamics

B cells are produced throughout the life time.

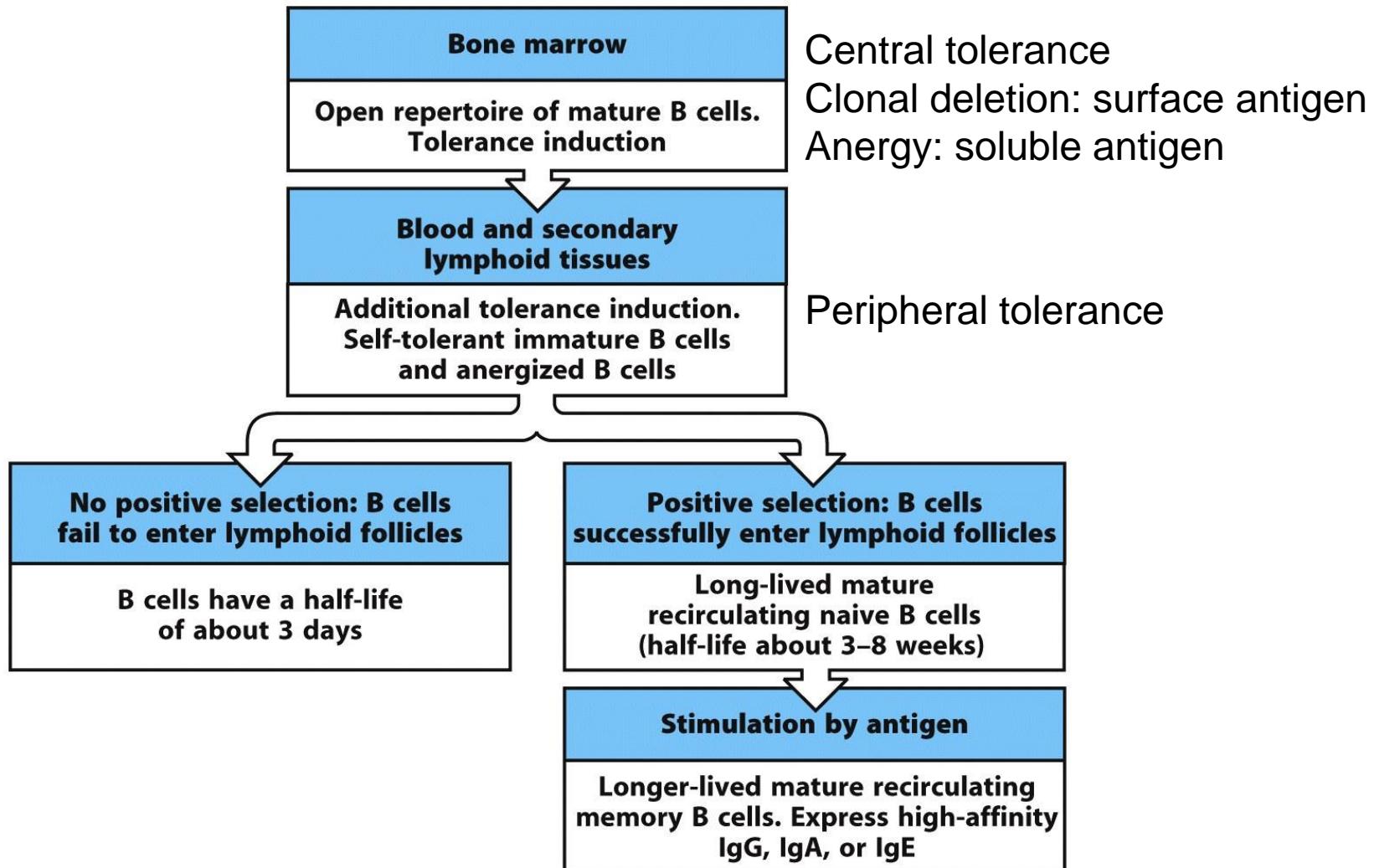


Figure 8.39 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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	?

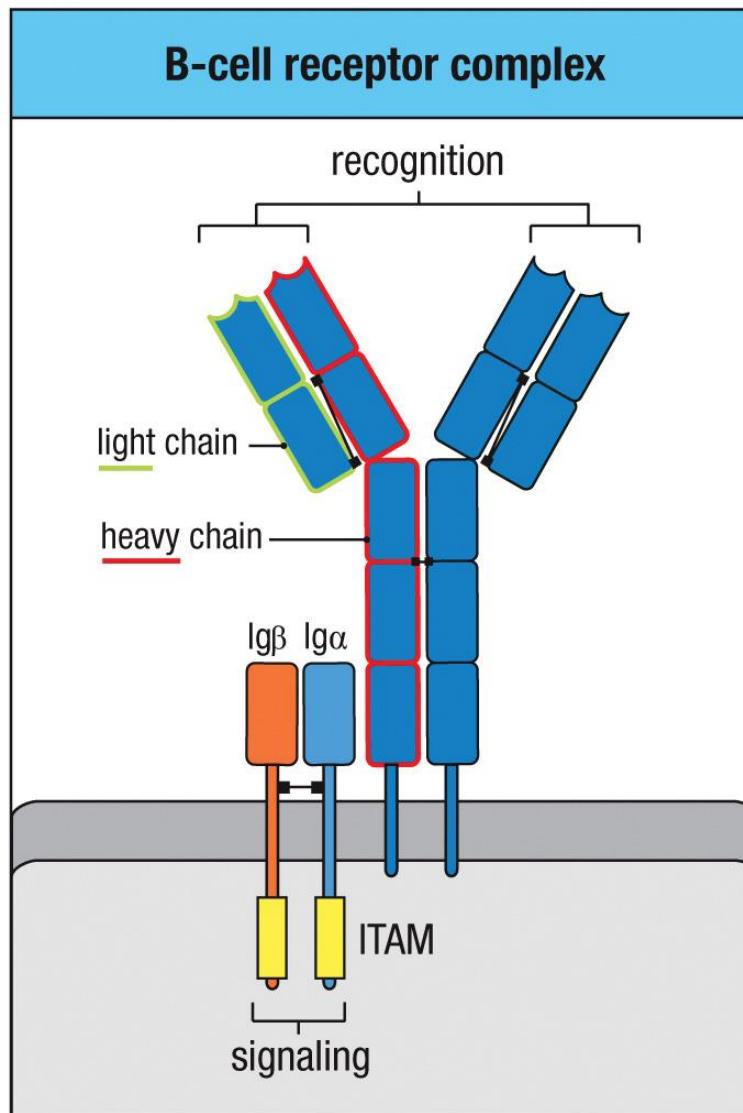
Question

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

Outline

- 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

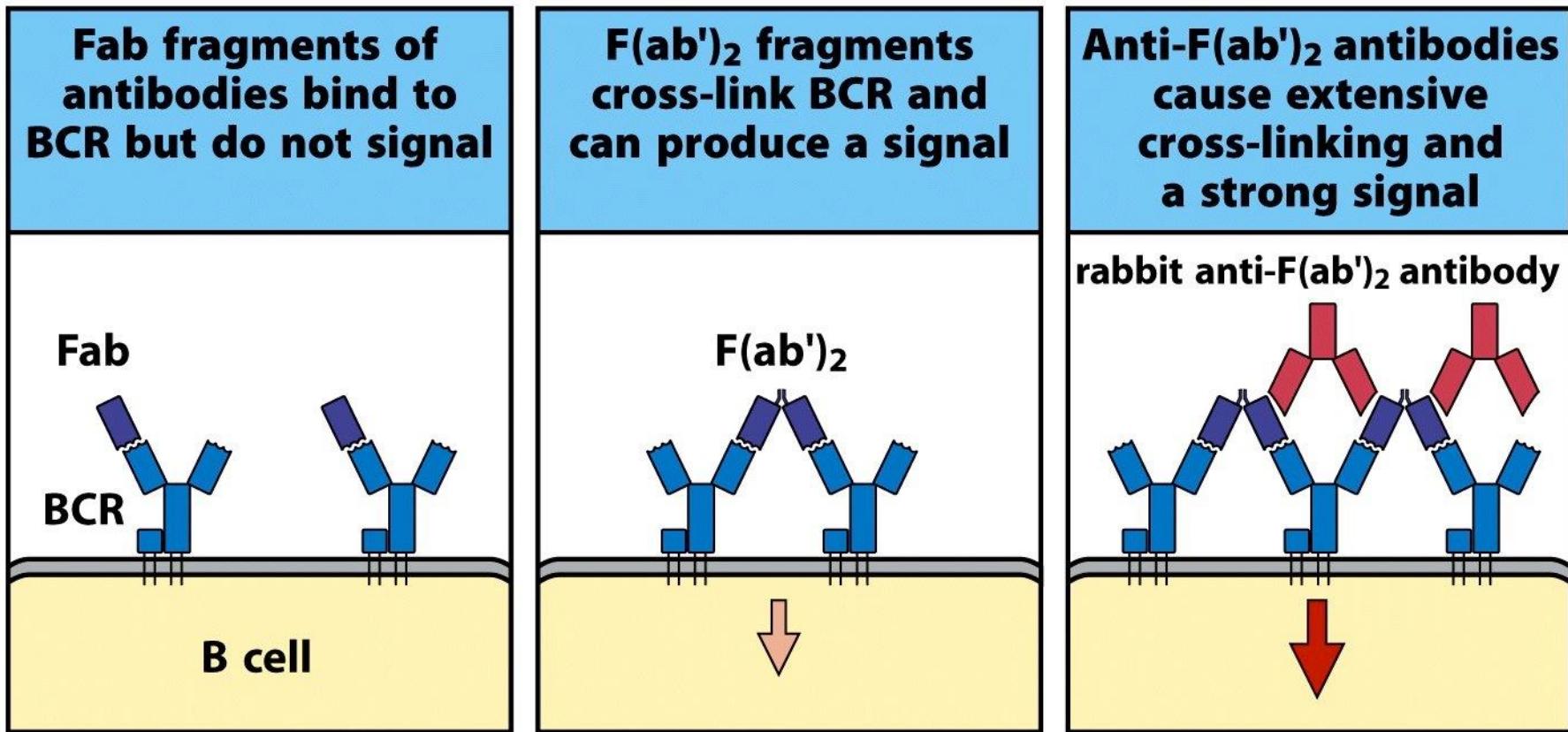
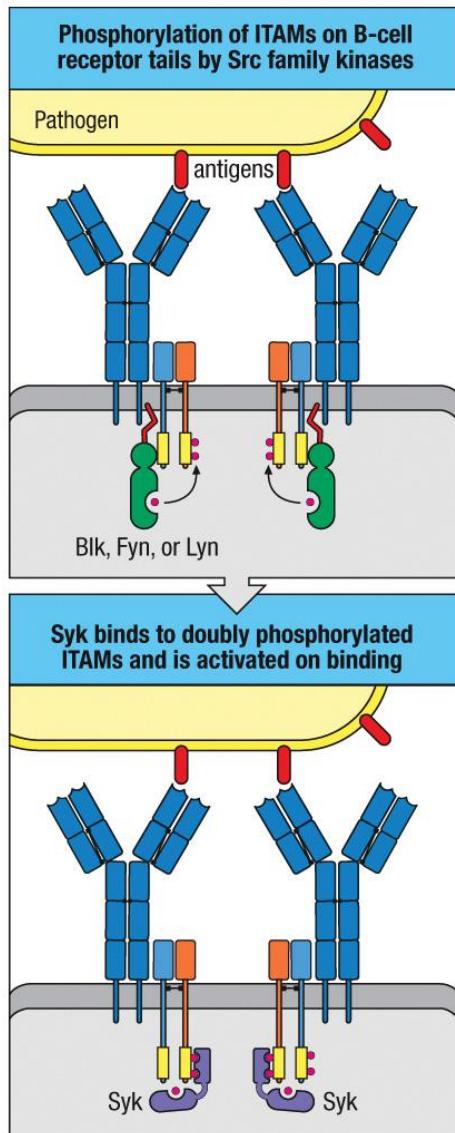
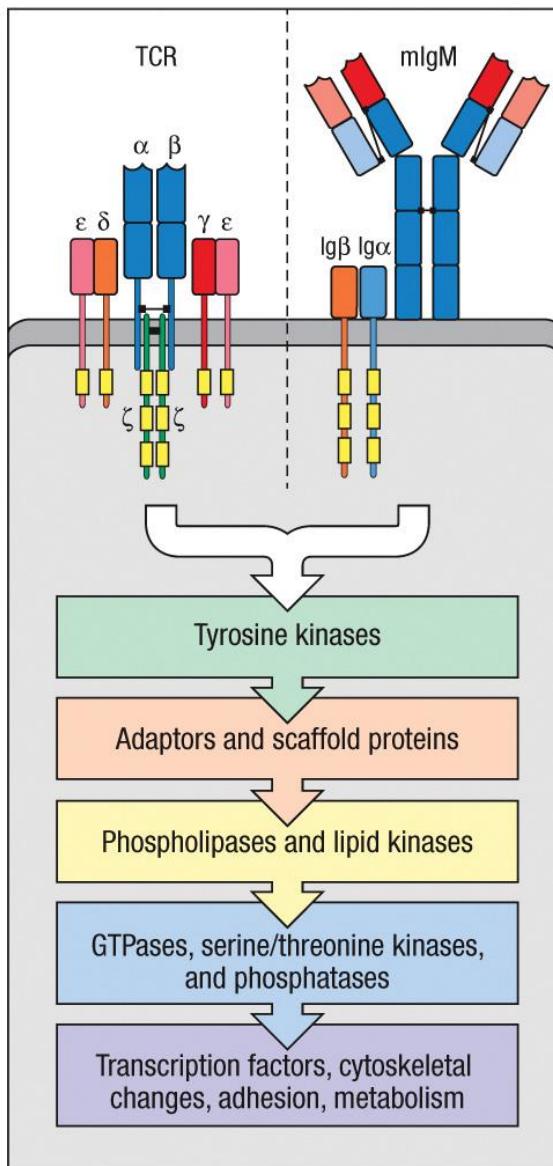


Figure 6-11 Immunobiology, 7ed. (© Garland Science 2008)

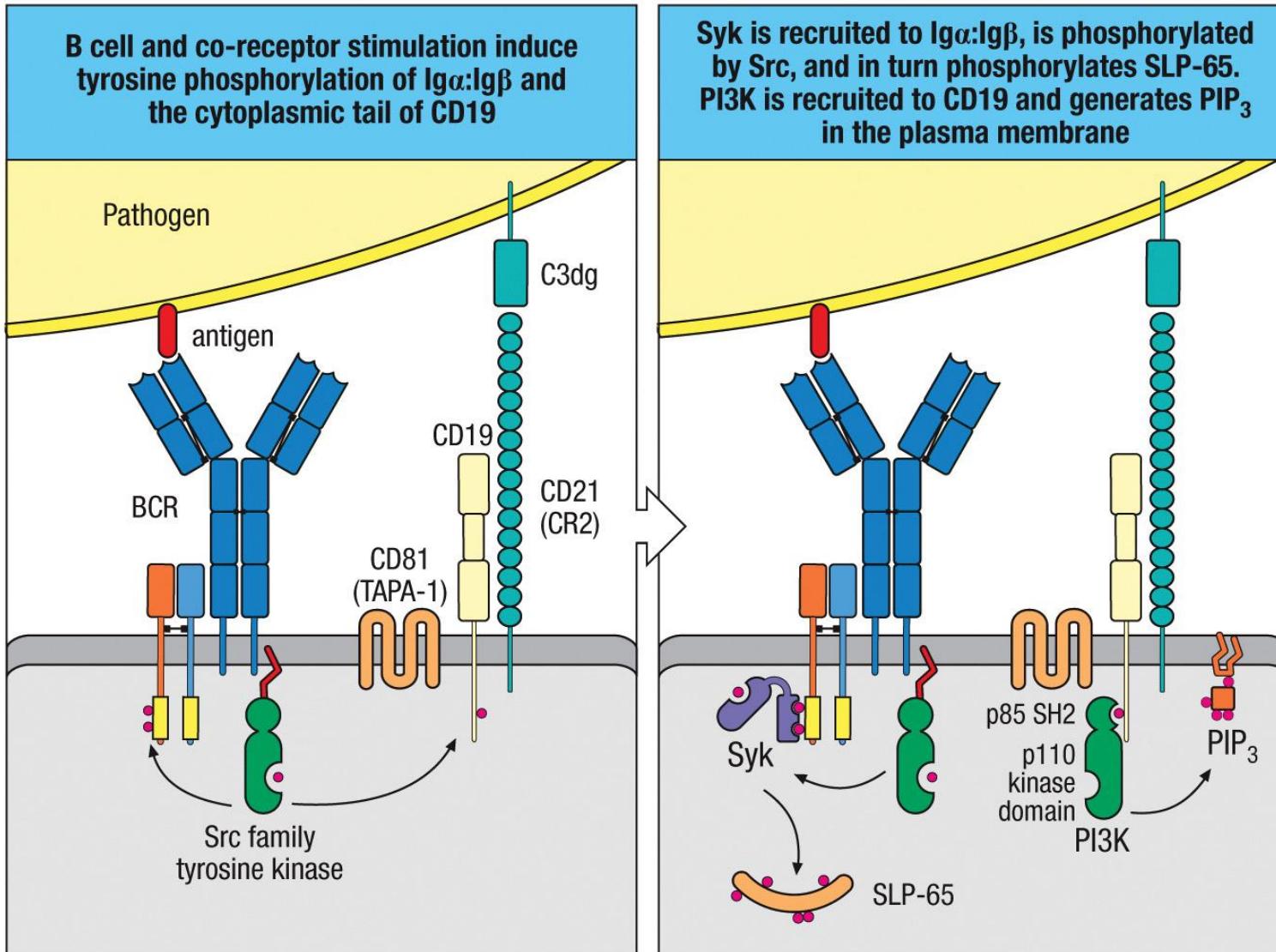
Signaling Through BCR



Signaling Through BCR



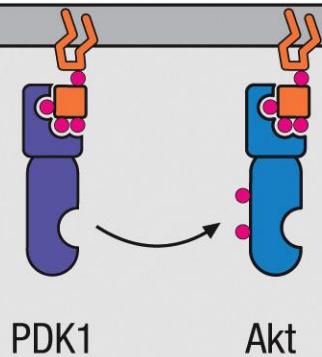
B Cell Co-receptor Signaling



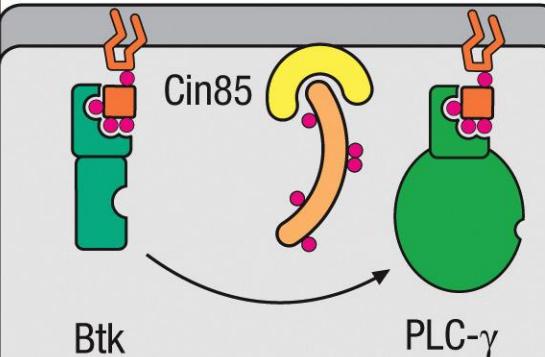
B Cell Co-receptor Signaling

PIP₃-dependent events

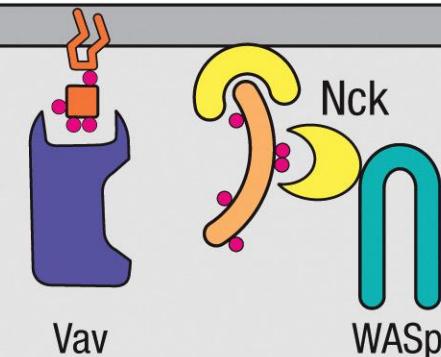
PIP₃ recruits PDK1 and Akt, leading to Akt activation



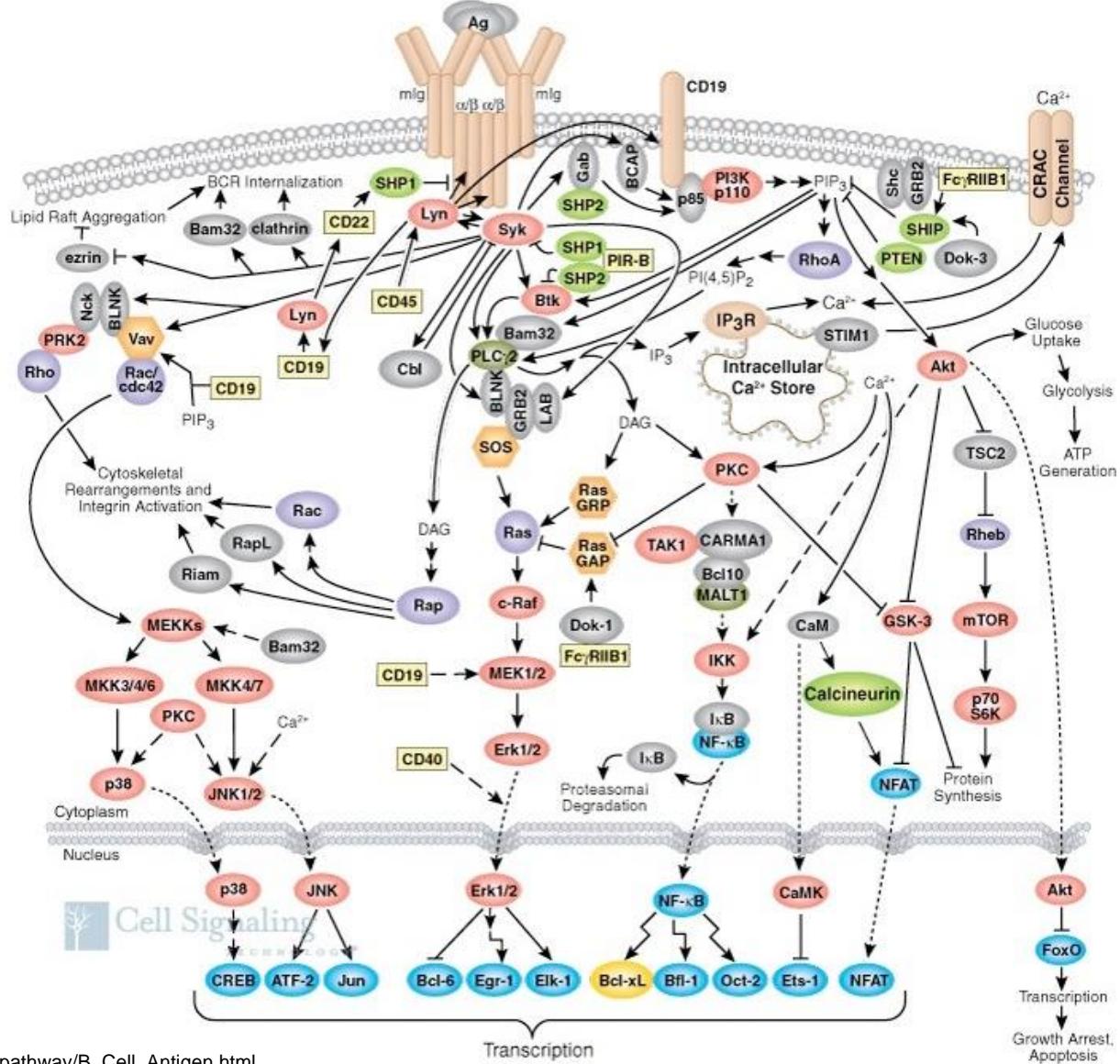
Btk phosphorylates and activates PLC- γ



Vav activates WASp, leading to actin polymerization



Signaling Through BCR



Question

- How is the BCR activated?

Outline

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

Case Study: X-linked Agammaglobulinemia

- 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

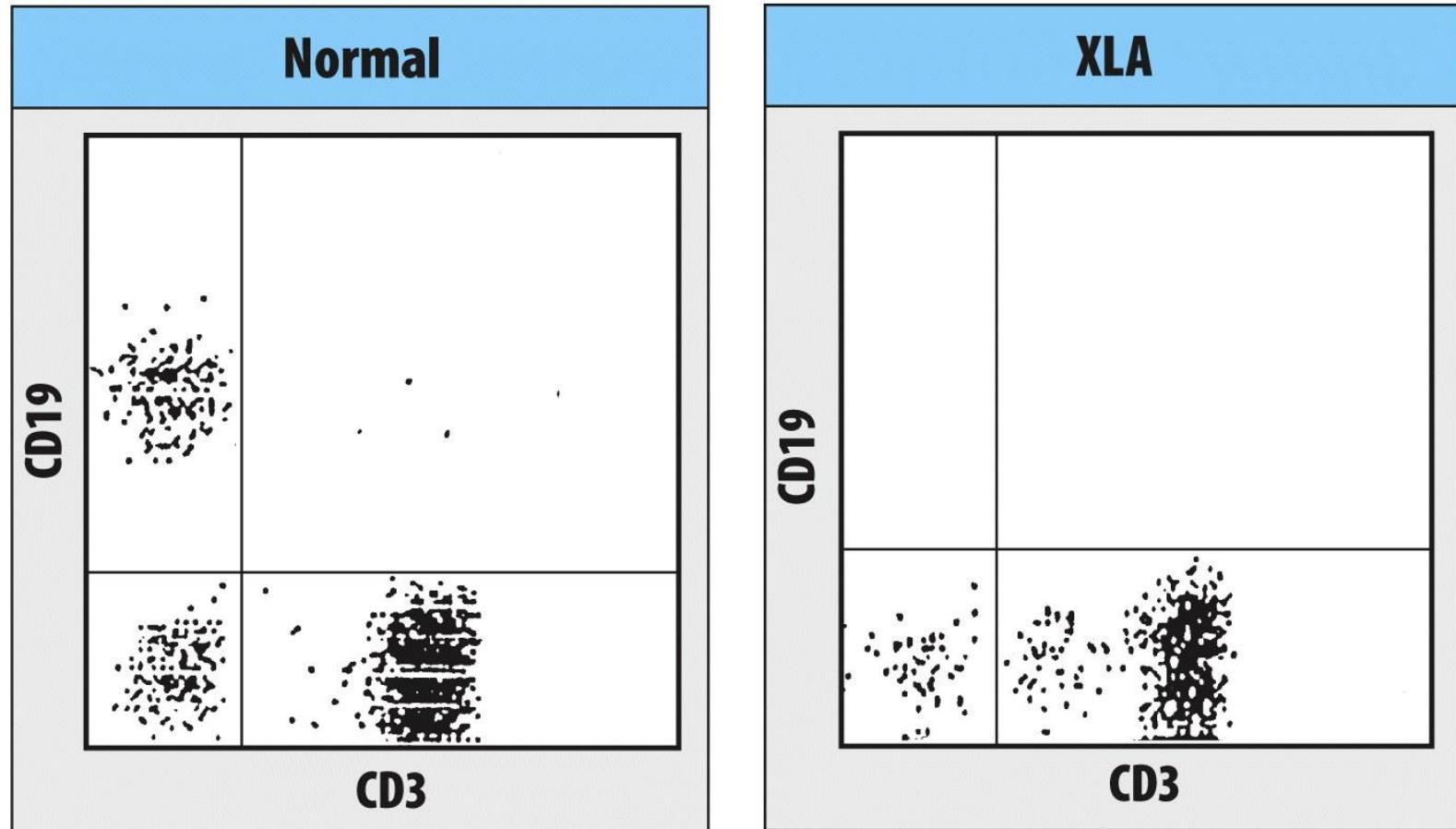


Figure 1.4 Case Studies in Immunology, 6ed. (© Garland Science 2012)

X-linked Recessive Disease

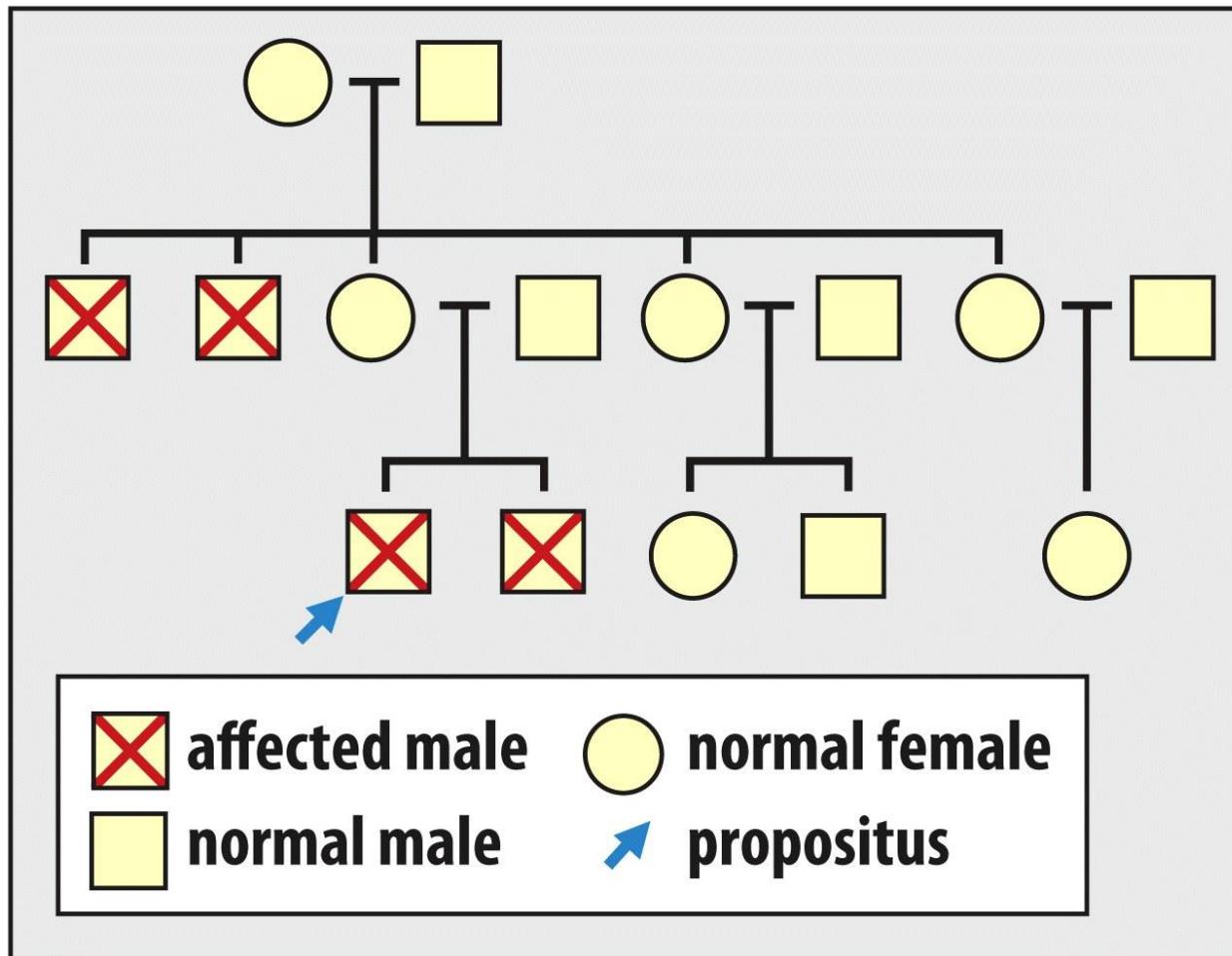
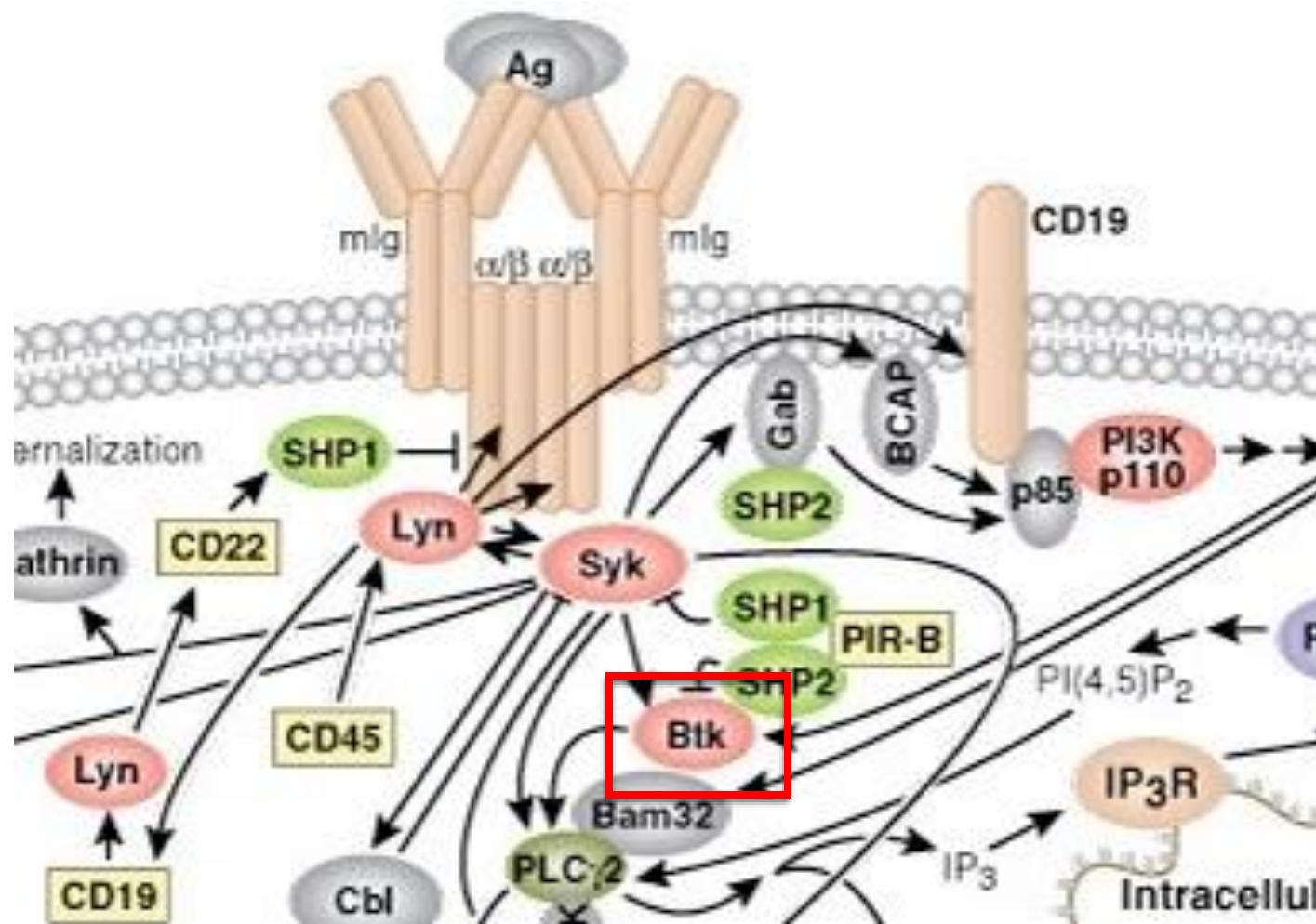


Figure 1.5 Case Studies in Immunology, 6ed. (© Garland Science 2012)

Defect in Btk



What's Wrong with the Patient?

Absent of B cells and antibodies
Susceptible to extracellular bacteria

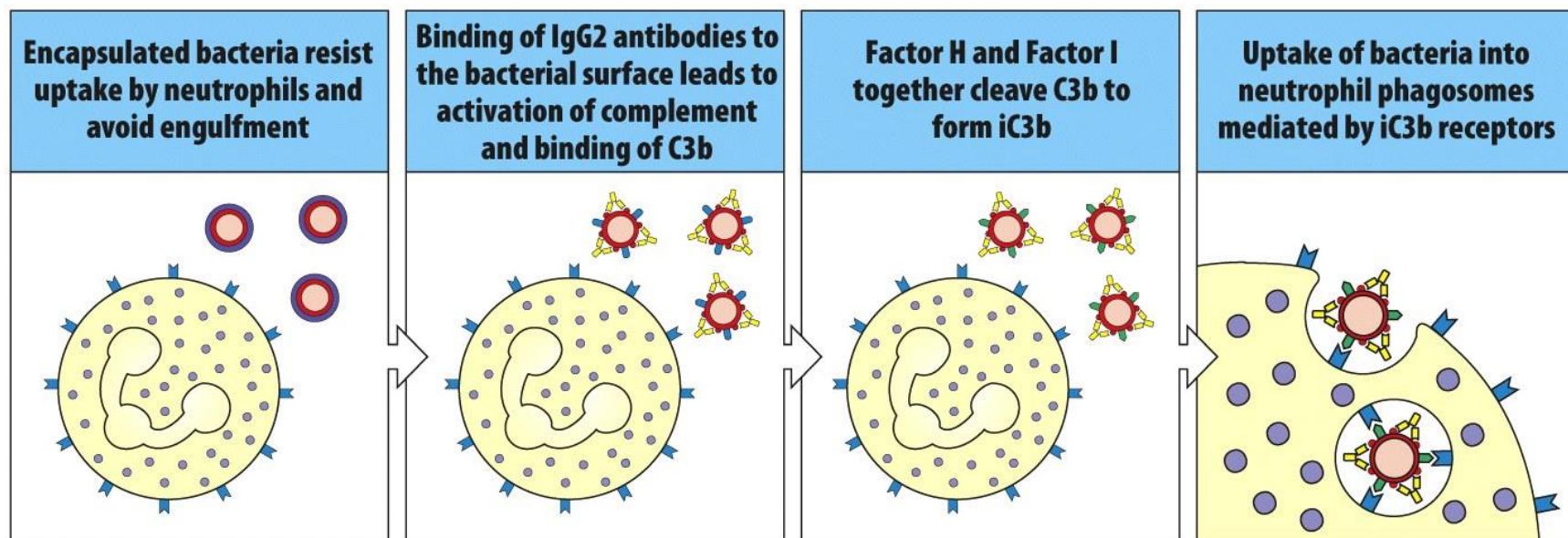


Figure 1.6 Case Studies in Immunology, 6ed. (© Garland Science 2012)