

T-B collaboration

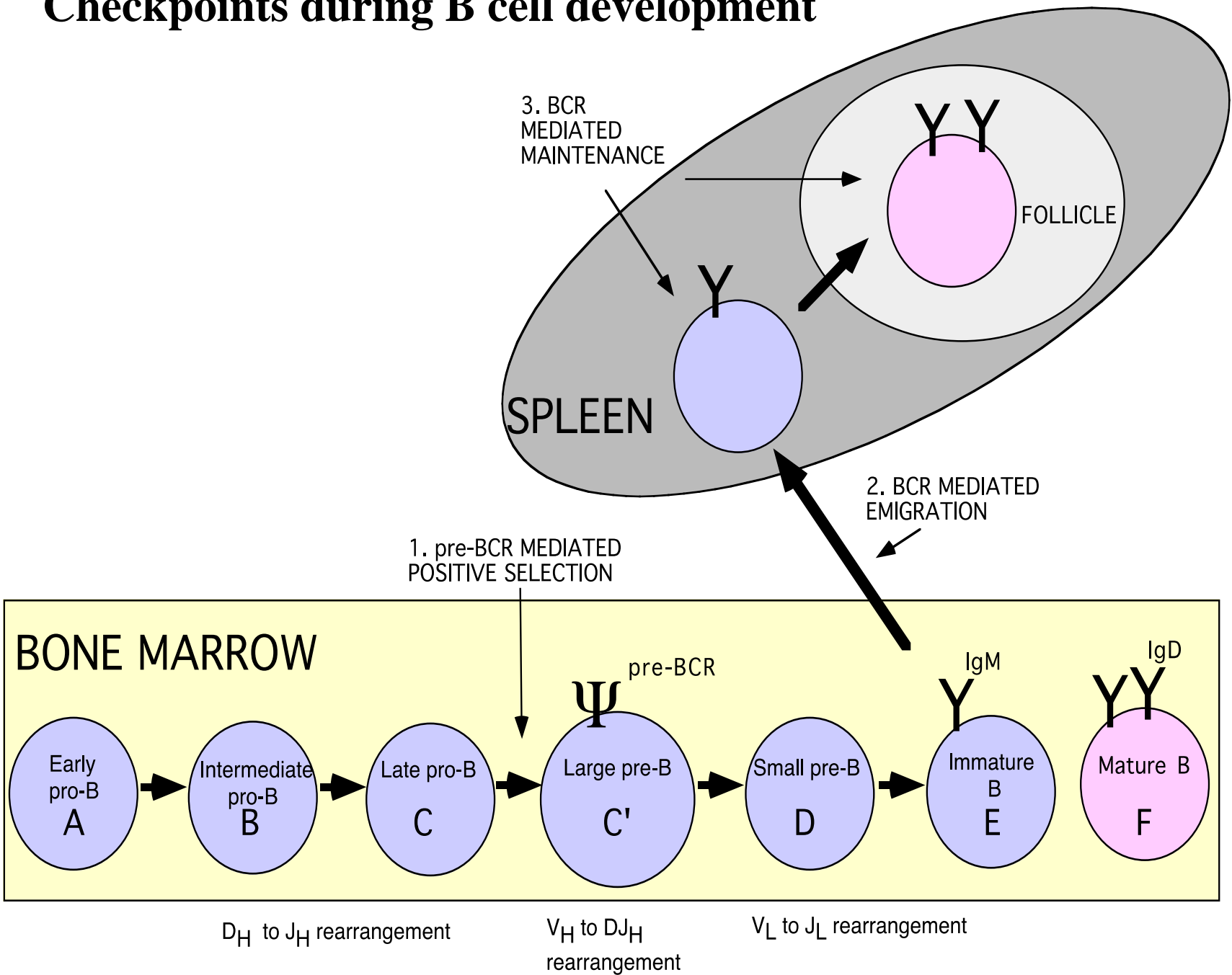
Shiv Pillai MD, PhD
Ragon Institute, Massachusetts General
Hospital
Harvard Medical School



OUTLINE

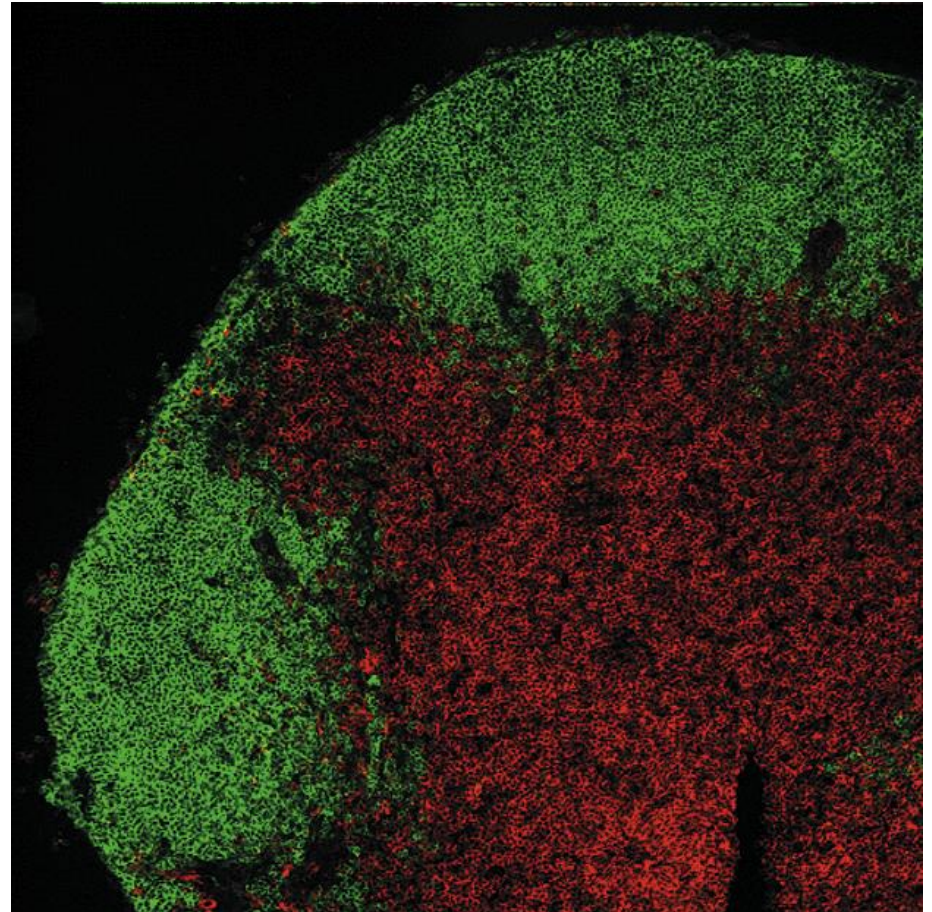
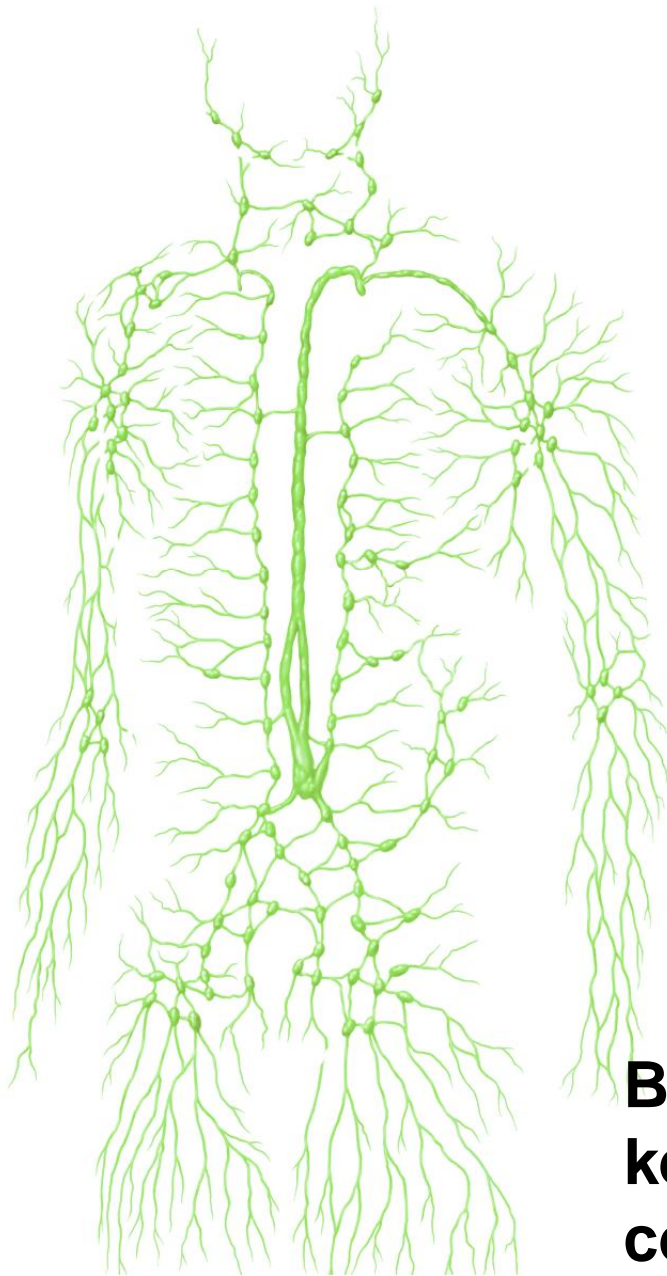
1. T-Dependent Activation
2. The Extrafollicular focus
3. The Germinal Center Response
4. Somatic Hypermutation and Affinity Maturation
5. Isotype switching
6. Plasma cell development
7. Quietly into the Night

Checkpoints during B cell development



SLOs - T and B cell zones

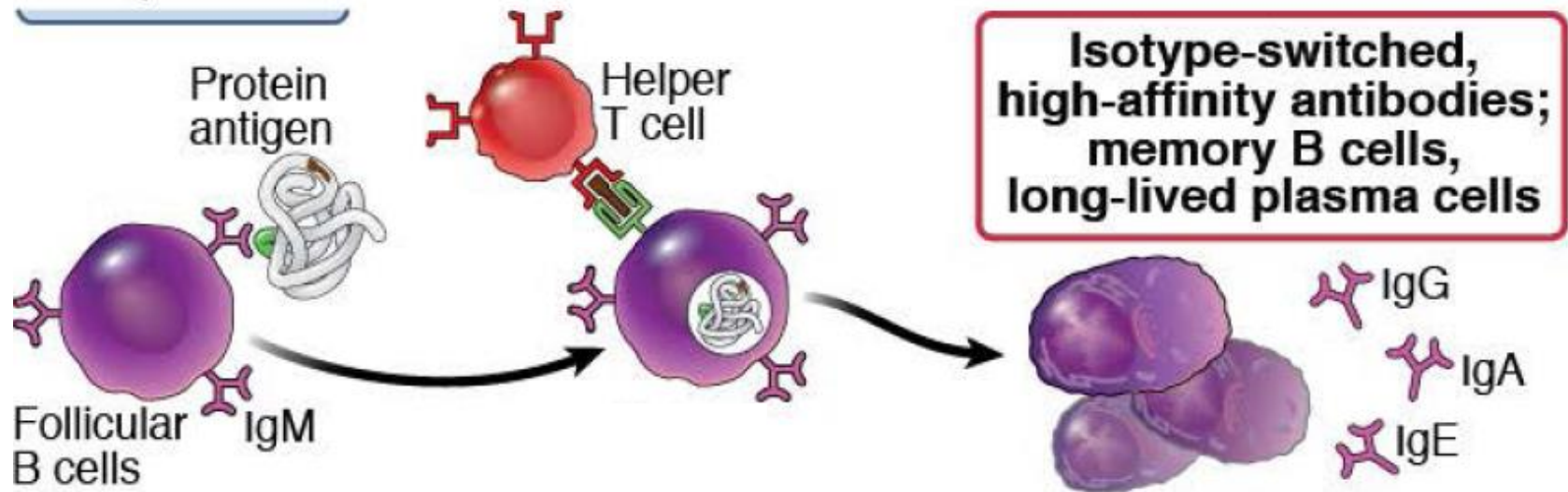
**CXCL 13 brings naive
B cells to follicle**



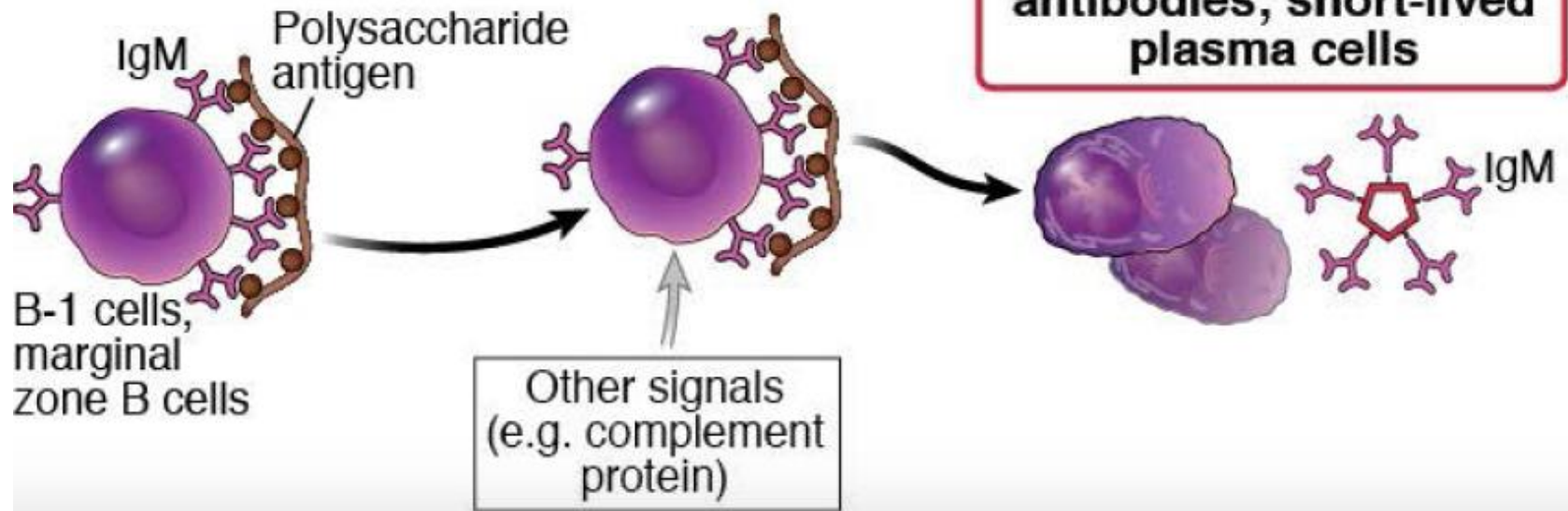
**BAFF
keeps B
cells alive**

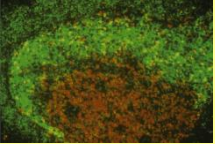
**CCL19 and CCL21
draw naive T cells
to T cell zones**

T-dependent



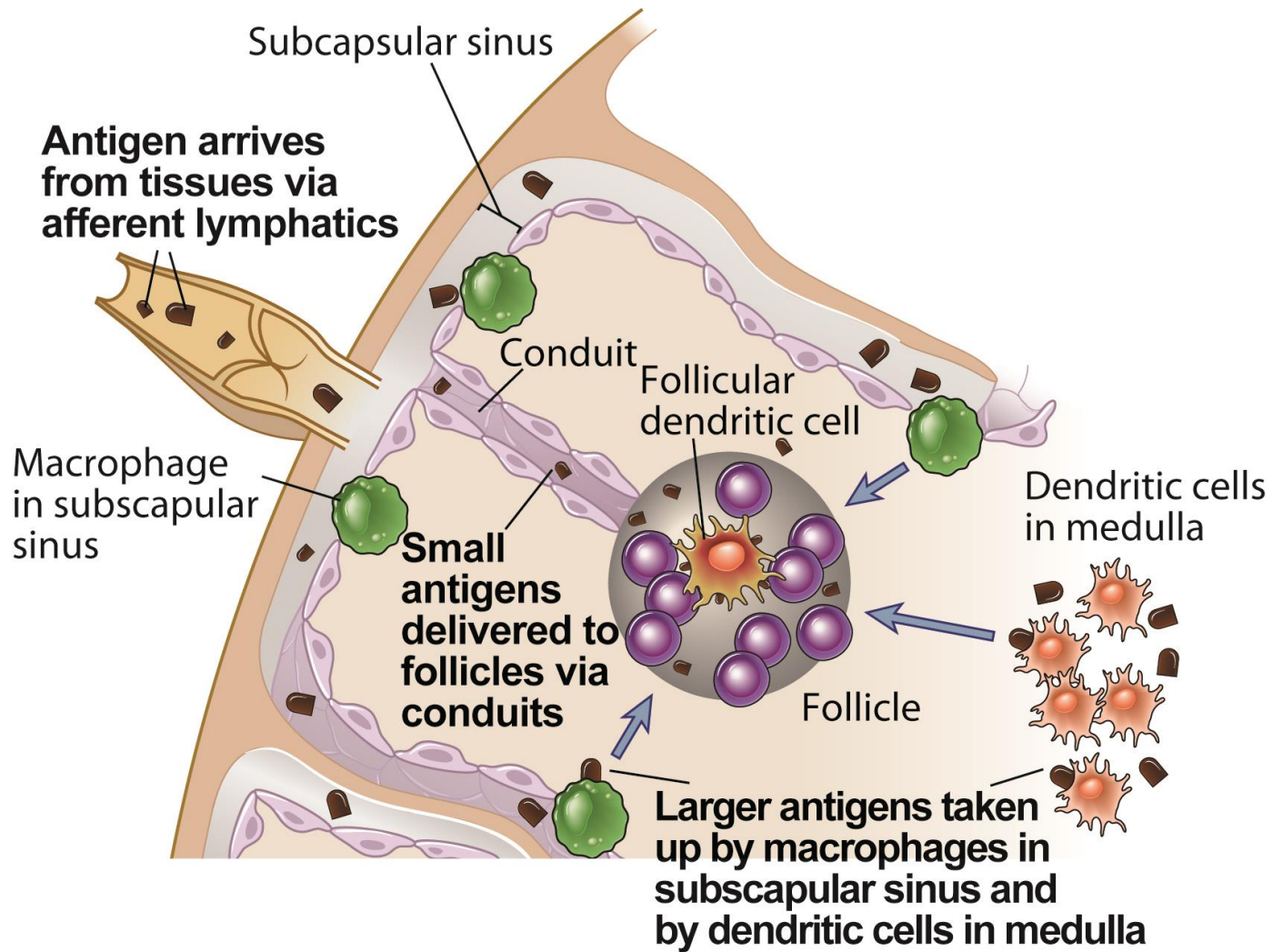
T-independent



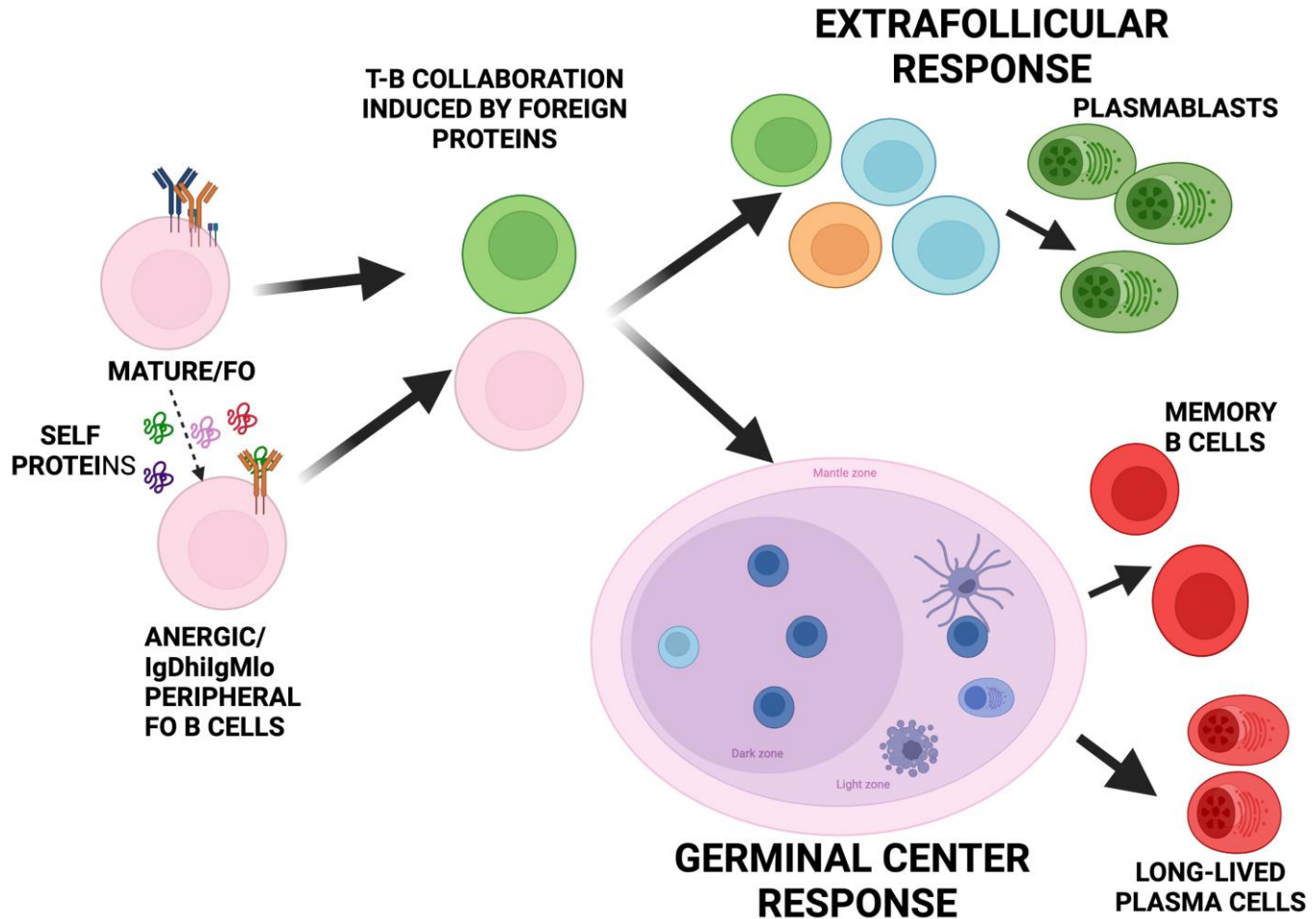


T-DEPENDENT ACTIVATION OF B CELLS

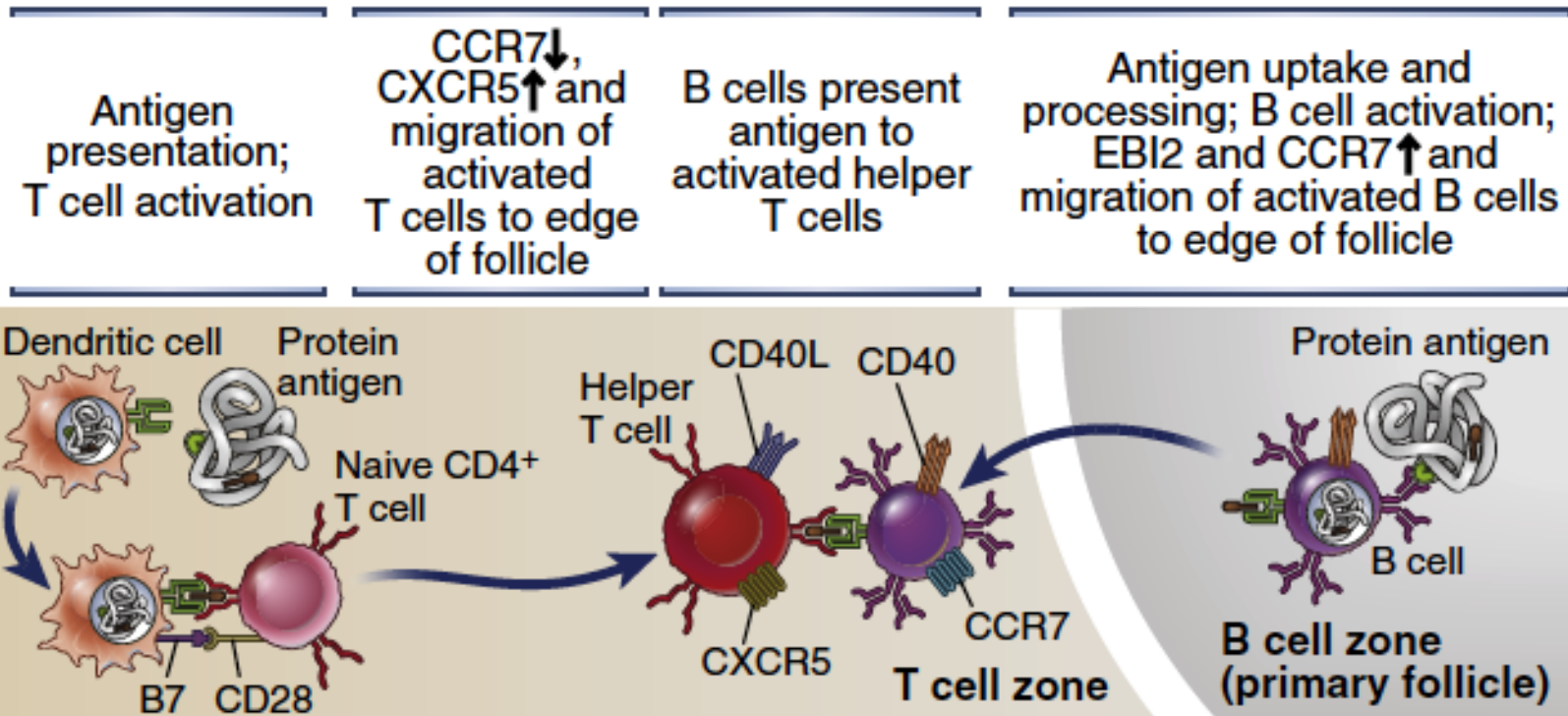
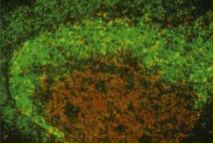
Antigen Delivery to Follicular B cells

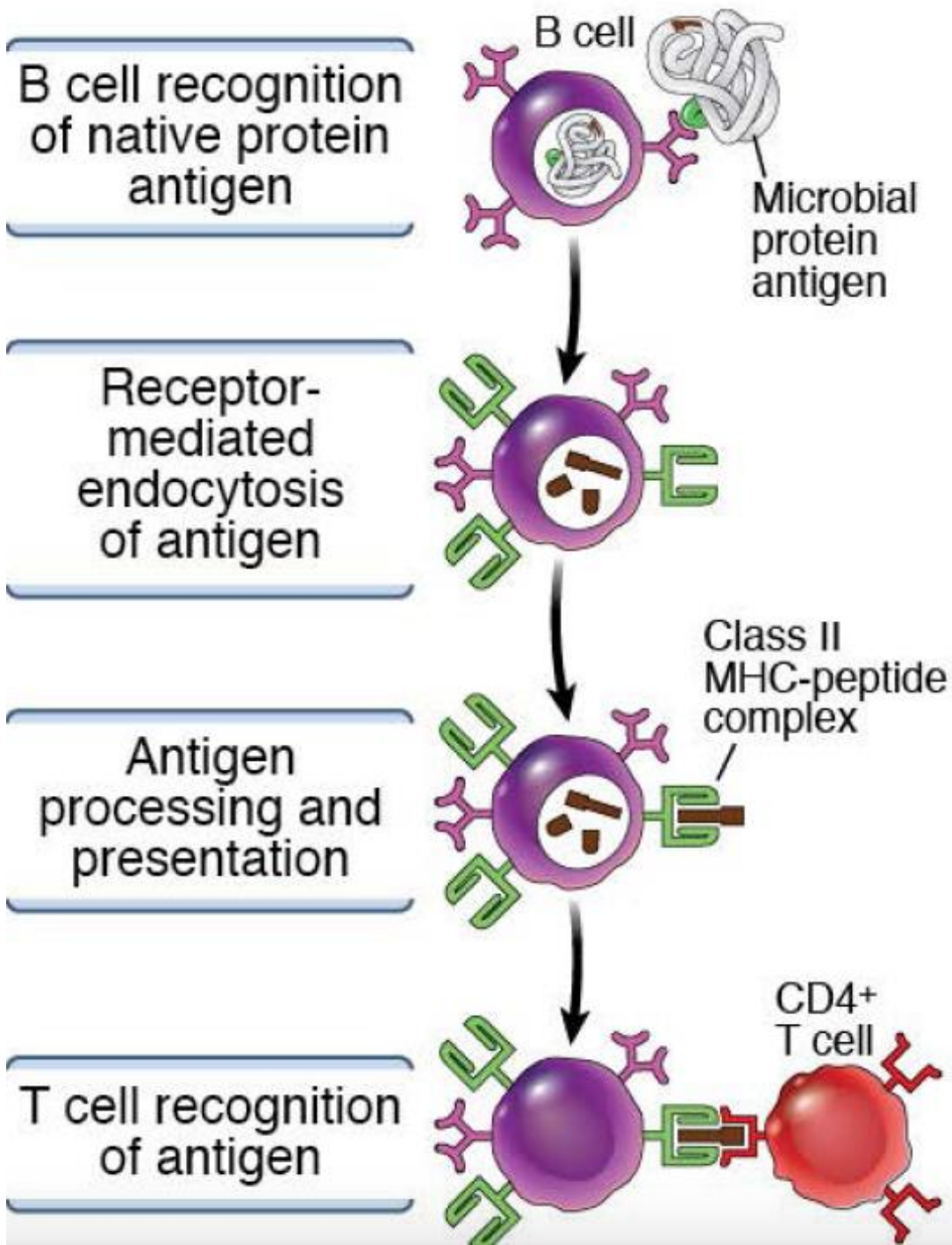


EXTRAFOLLICULAR vs GERMINAL CENTER RESPONSES

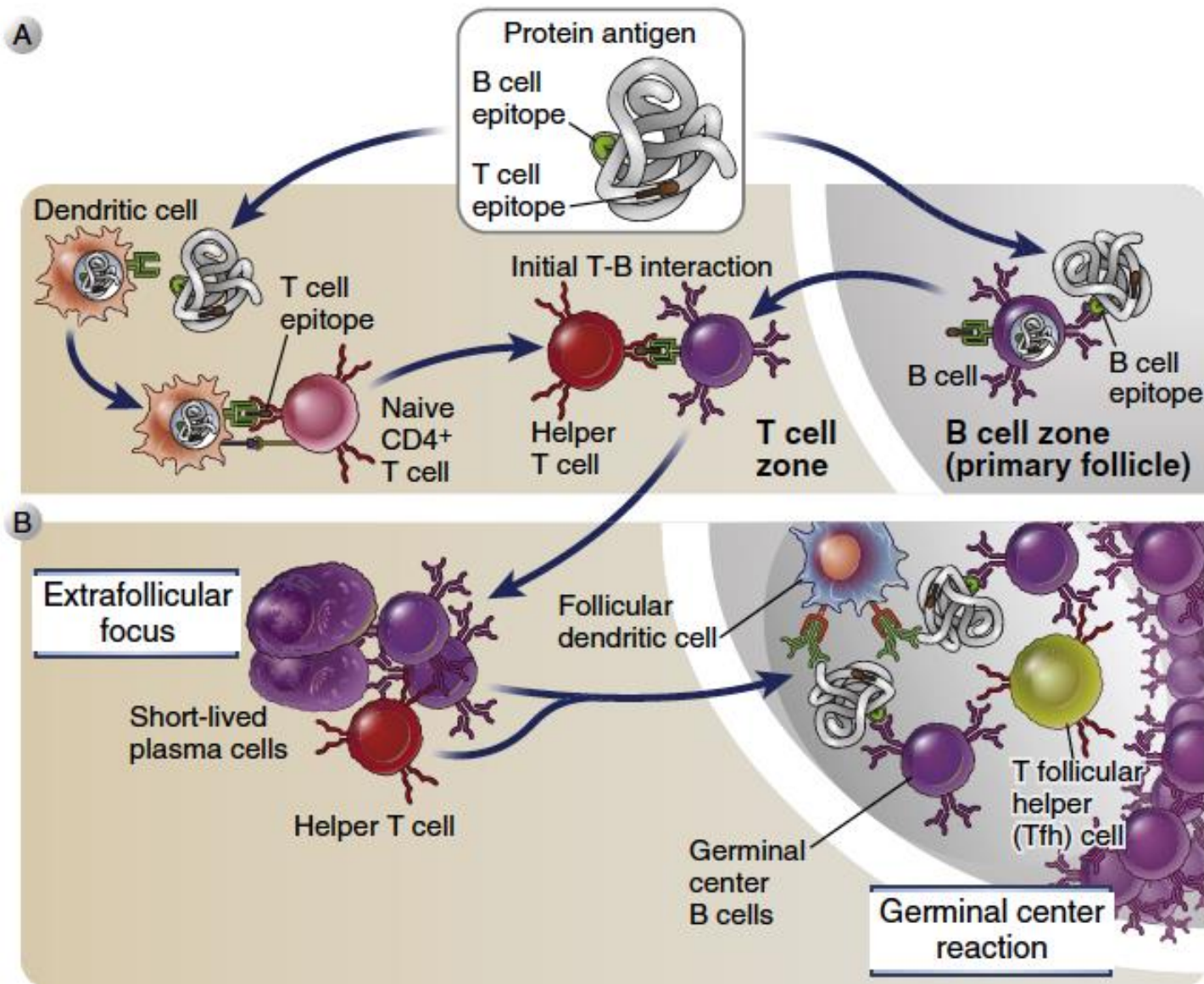


T-B cell Migration and Interactions

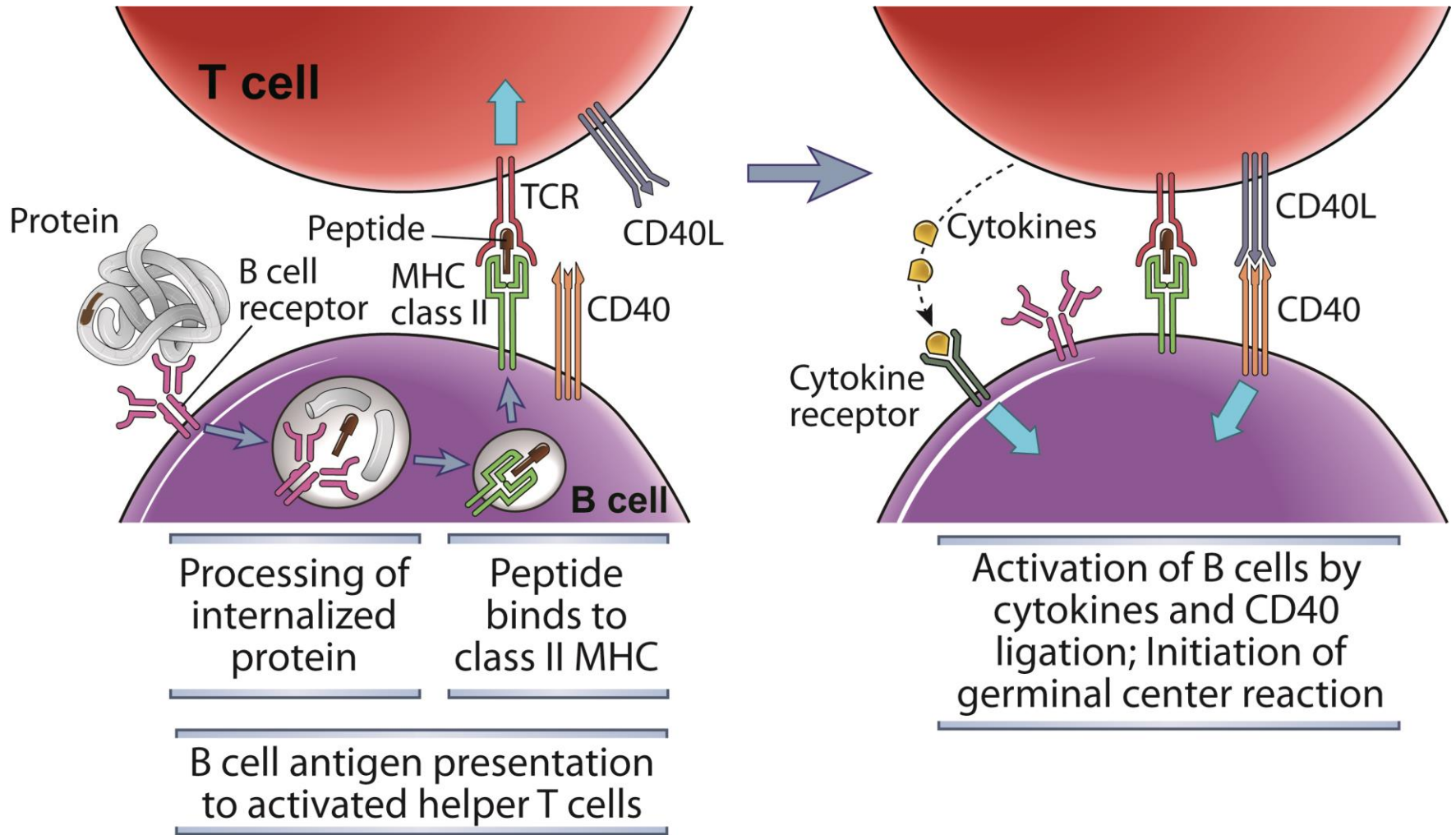




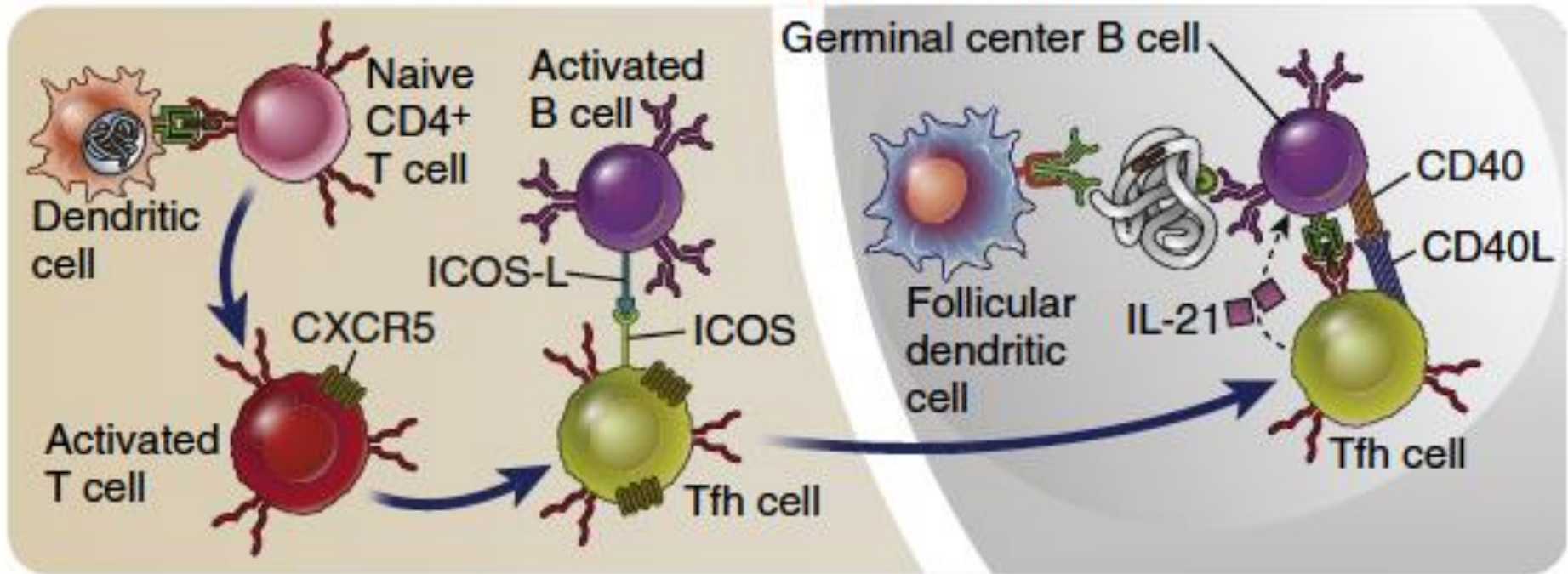
Events in T-Dependent Humoral Responses



Helper T cell Activation of B Cells



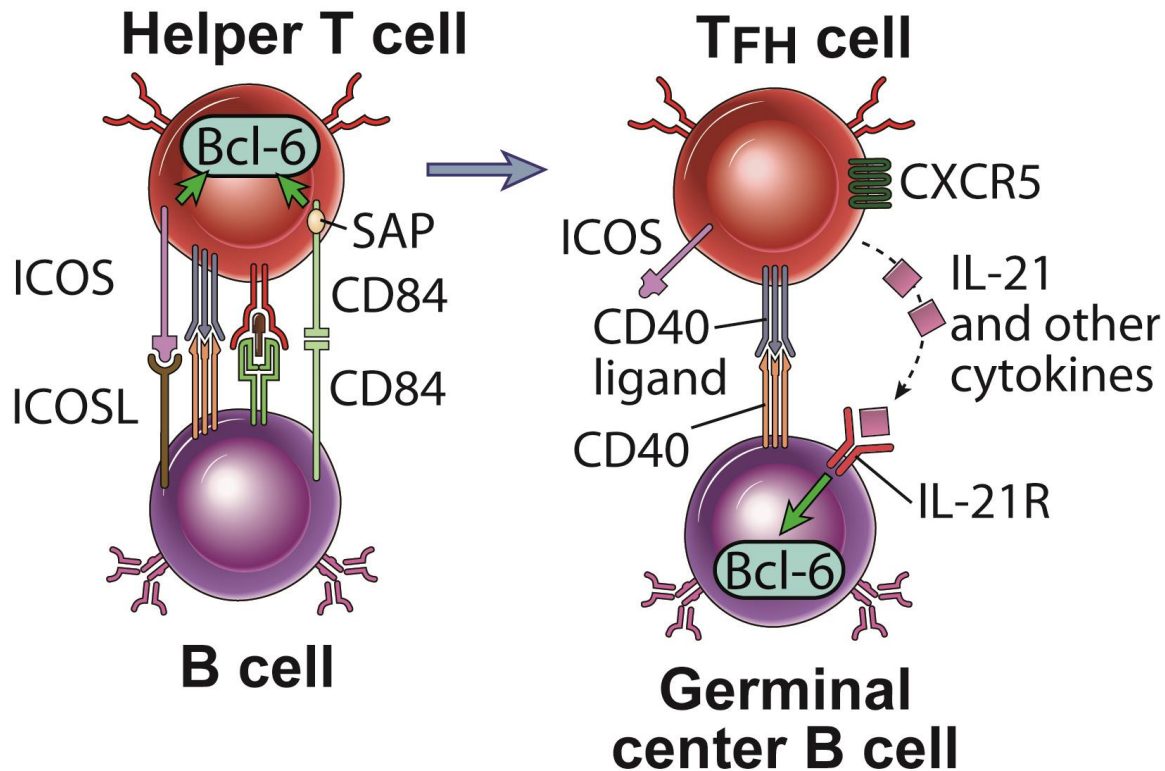
Events in T-Dependent Humoral Responses



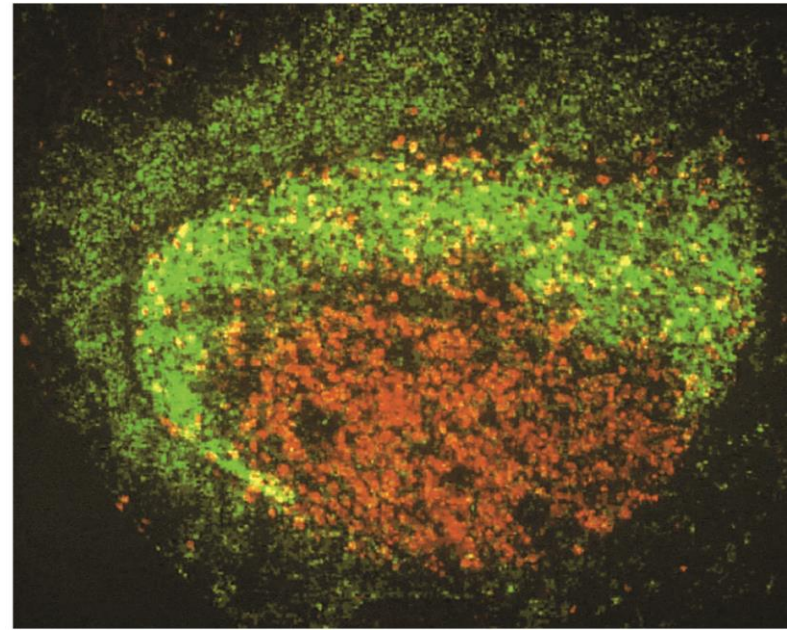
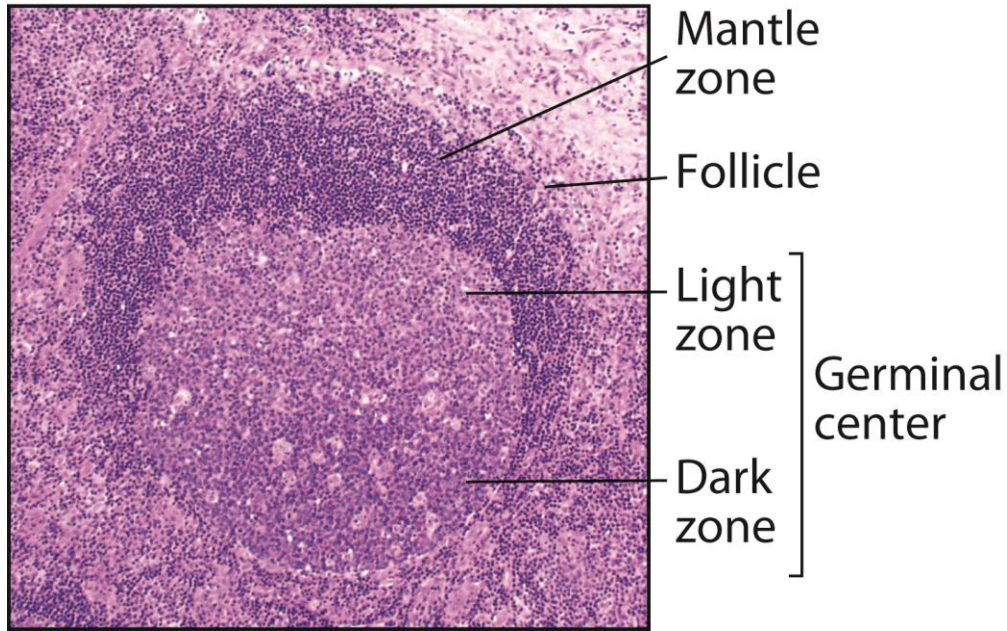
T Follicular Helper Cell Induction and Function

Induction of T_{FH} cells by B cells

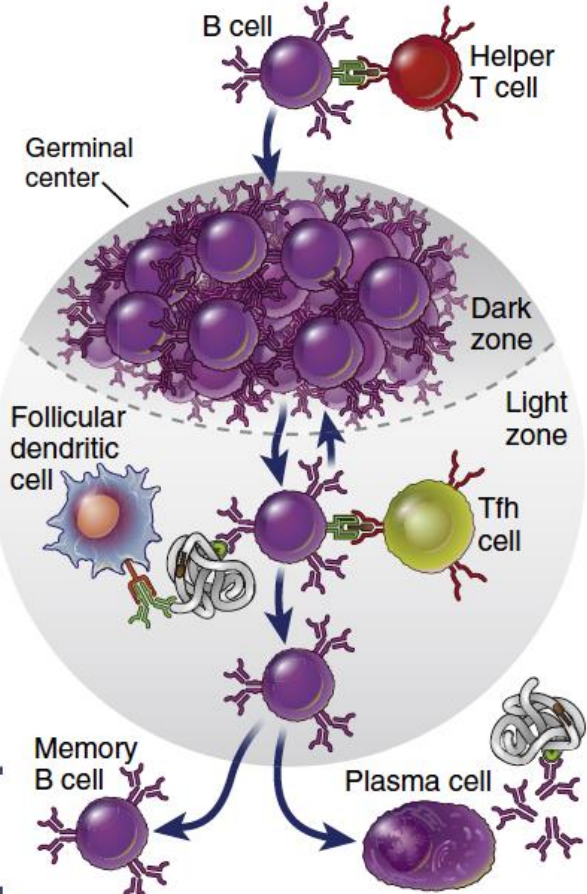
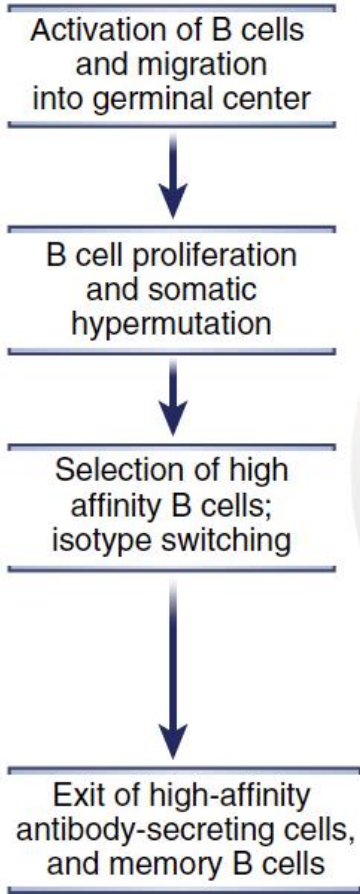
Induction of germinal center B cells by T_{FH} cells



Germinal Centers in Lymphoid Organs



REPEATED CYCLES OF SHM AND SELECTION

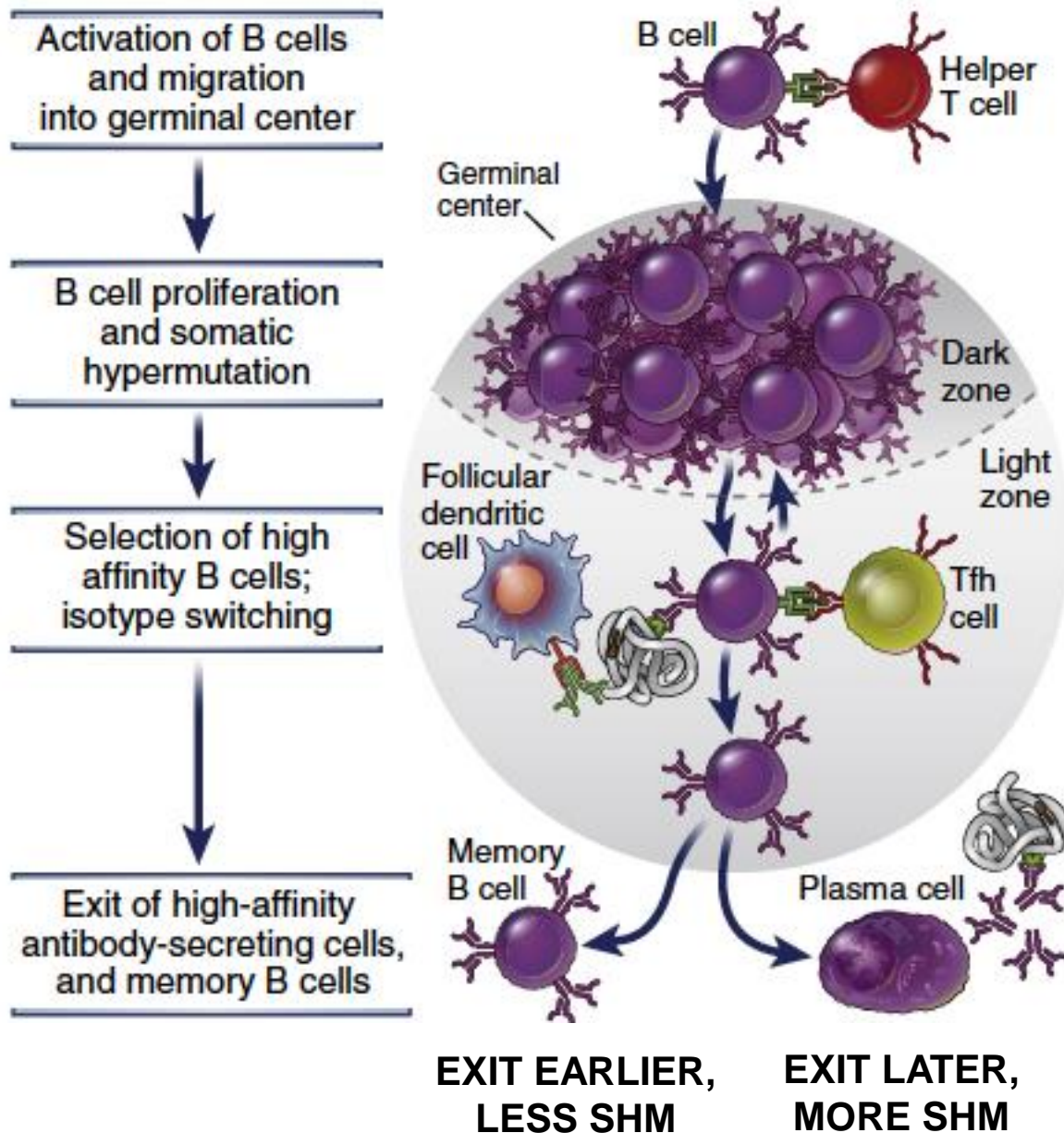


AFTER REPEATED DIVISIONS CELLS LOSE CXCR4 AND MIGRATE TO LIGHT ZONE



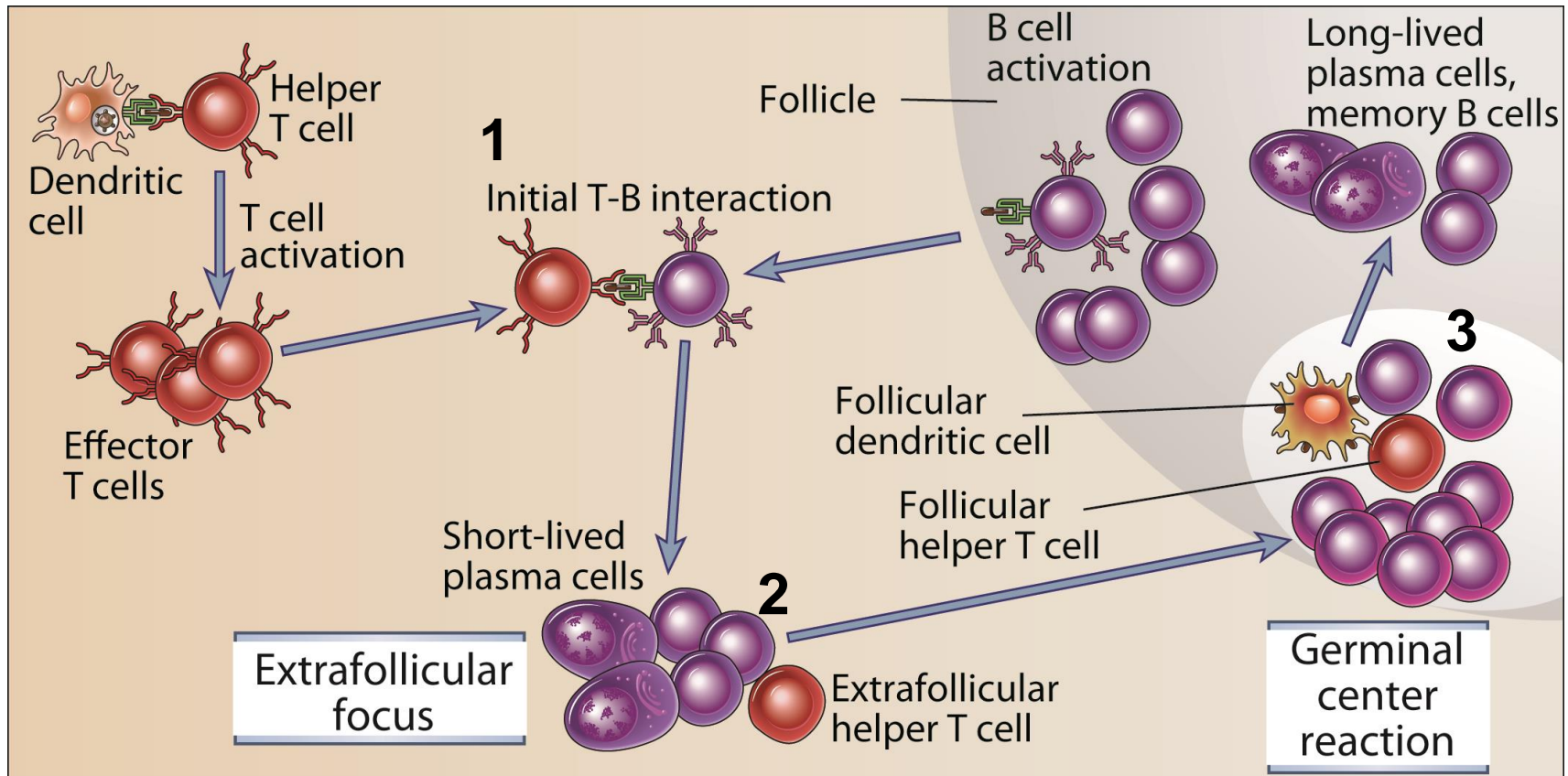
SELECTED CELLS INDUCE CXCR4 AND RETURN TO DARK ZONE

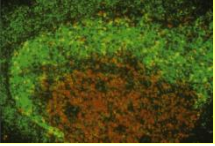
THE GERMINAL CENTER REACTION



T regs outside the follicle as well as TFR cells regulate the number of T follicular helper cells. In their absence there are too many TFH cells, Promiscuous B cell selection and autoimmunity

Events in T-Dependent Humoral Responses



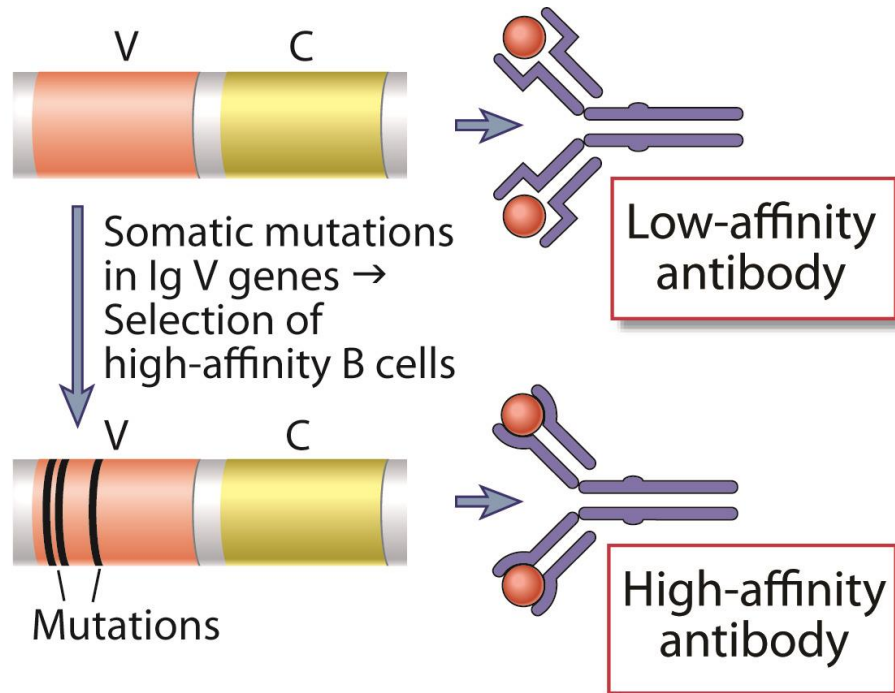


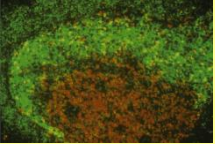
Sequential T-B interactions in immunity

1. **T → B - Forms extrafollicular B cell focus**
2. **B → T - Generates T follicular helper cells**
3. **T → B - Selection of high affinity B cells in light zone by T_{FH} cells**

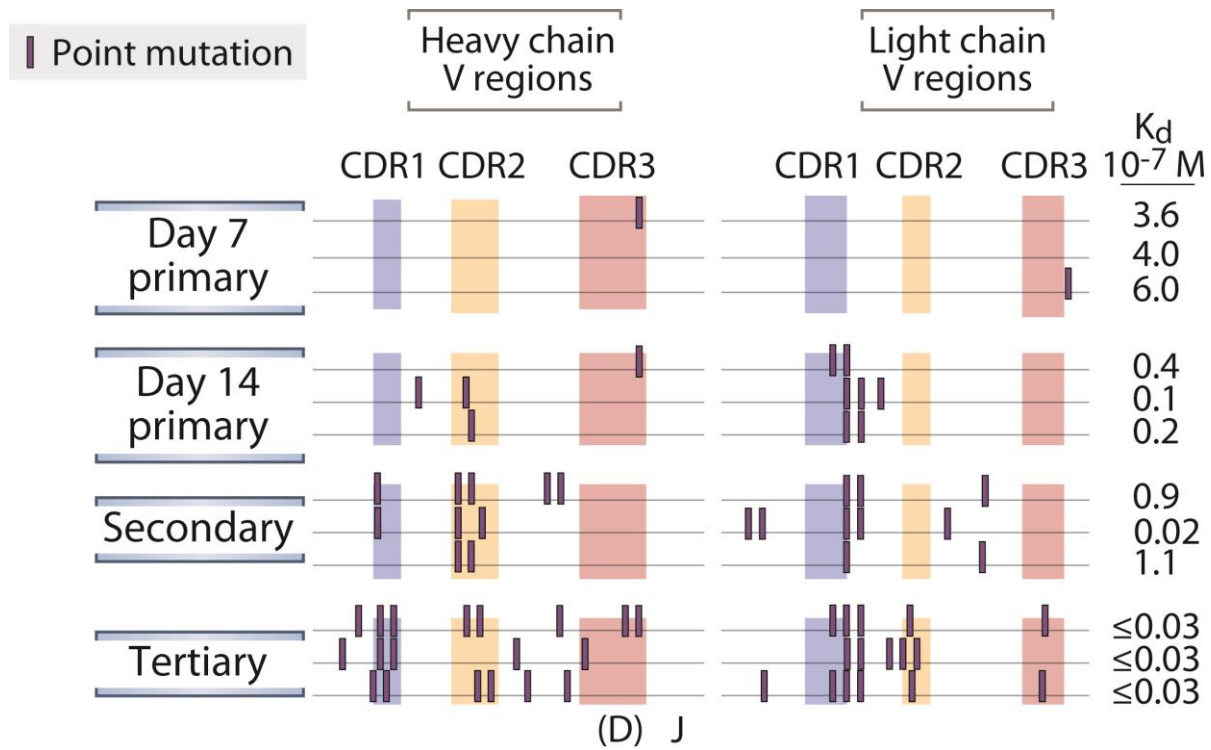
Somatic Hypermutation

An Overview of Affinity Maturation





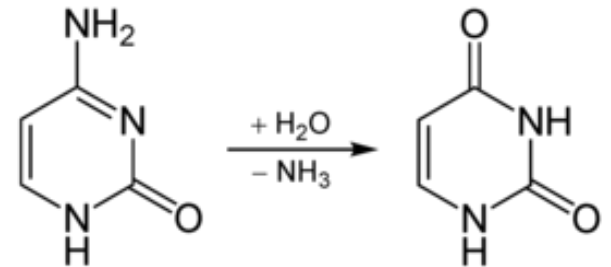
Somatic Mutations in Ig V genes



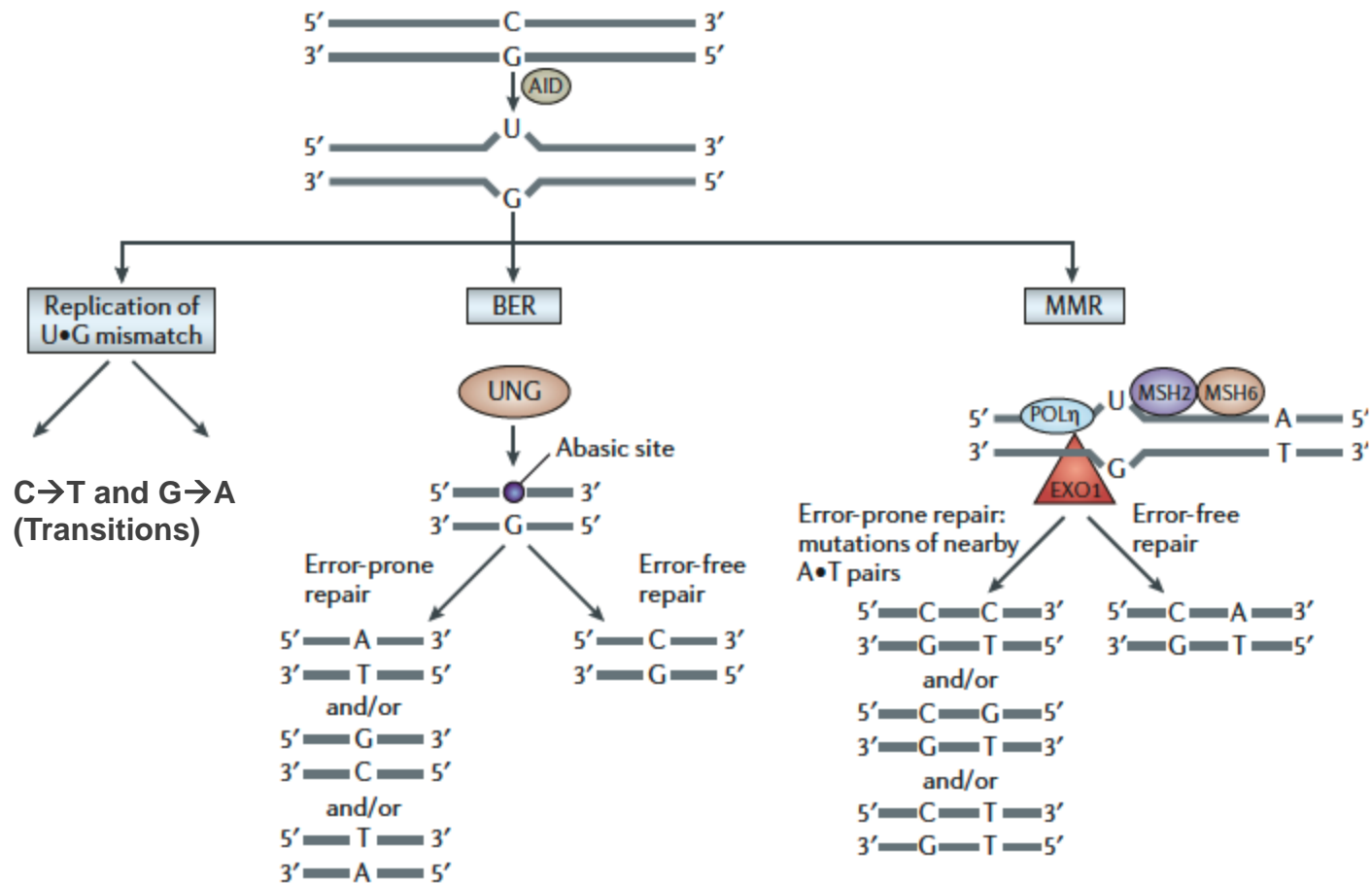
AICD (aka AID)

Activation Induced Cytidine Deaminase

CONVERTS C TO U IN SINGLE
STRANDED DNA



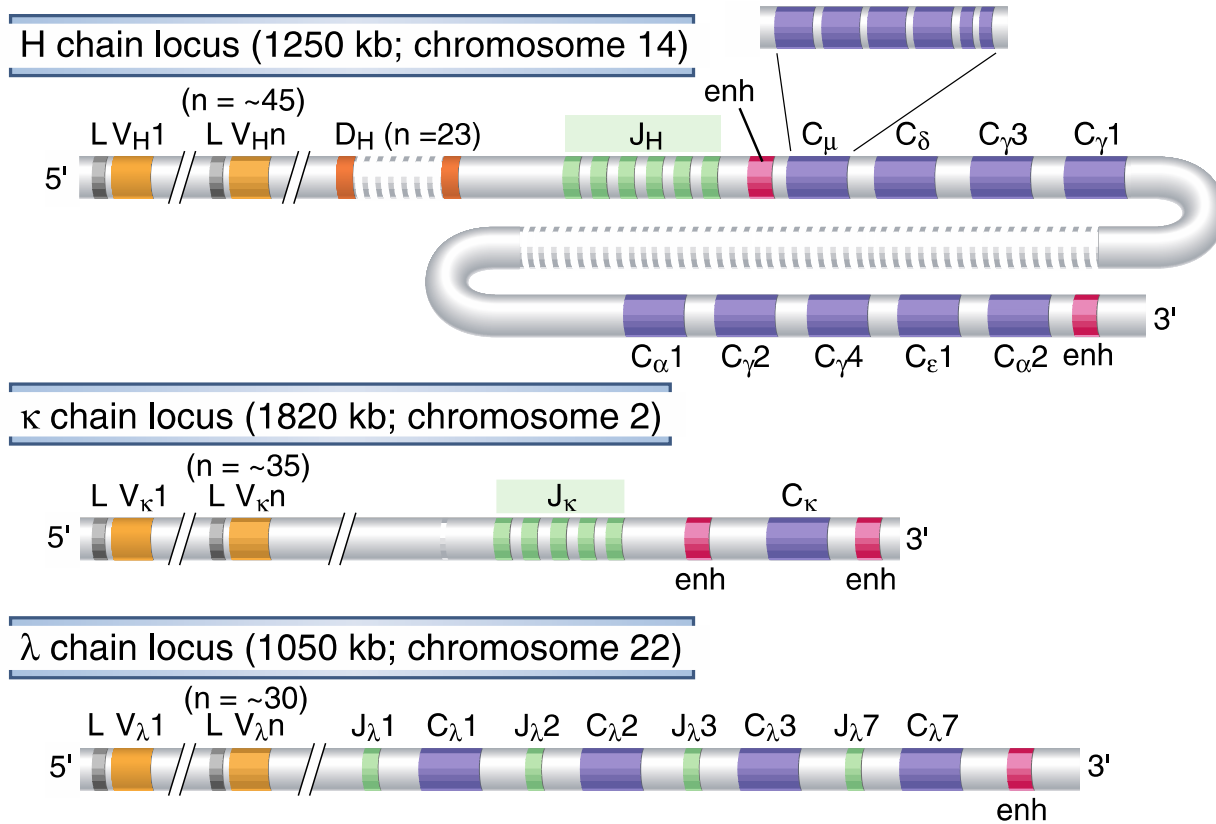
AID C→U MUTATION FOLLOWED BY ERROR-PRONE REPAIR CREATES SOMATIC HYPERMUTATION



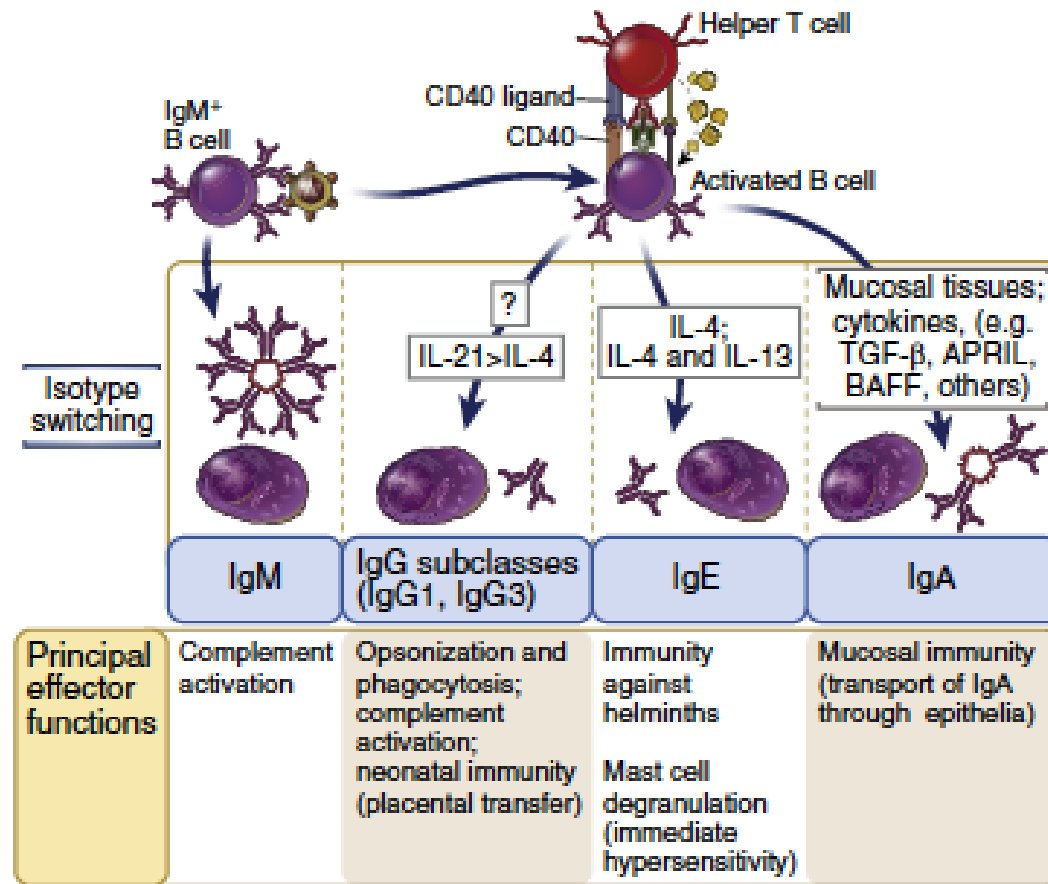
Based on Odegard and Schatz, NRI 2009

Isotype Switching

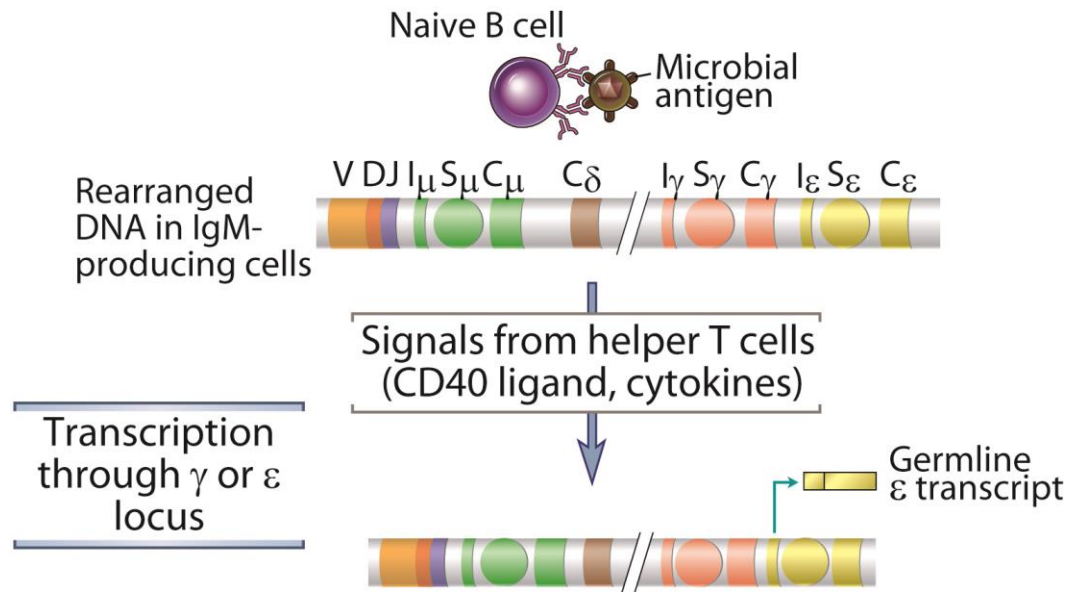
HUMAN IMMUNOGLOBULIN GENES

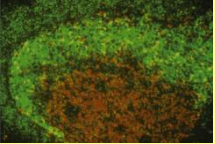


CD40 INDUCES AID AND CYTOKINES MADE MAINLY BY EXTRAFOLLICULAR “PRE - T_{FH}” CELLS OPEN SPECIFIC LOCI

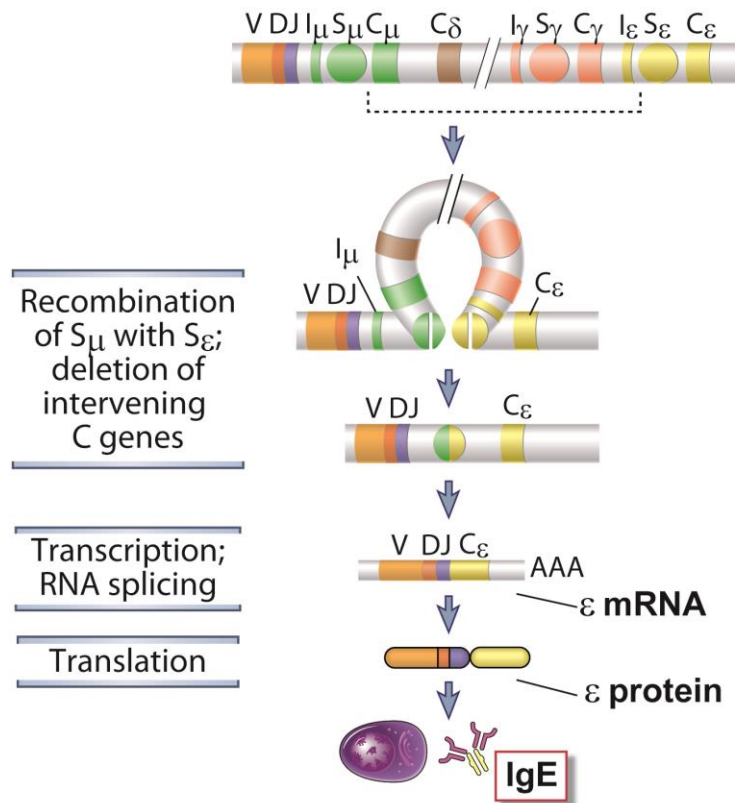


Heavy Chain Isotype Switching





Heavy Chain Isotype Switching



Terminal differentiation into plasma cells

Signals: BCR, CD40, Cytokines such as IL-21 and IL-6

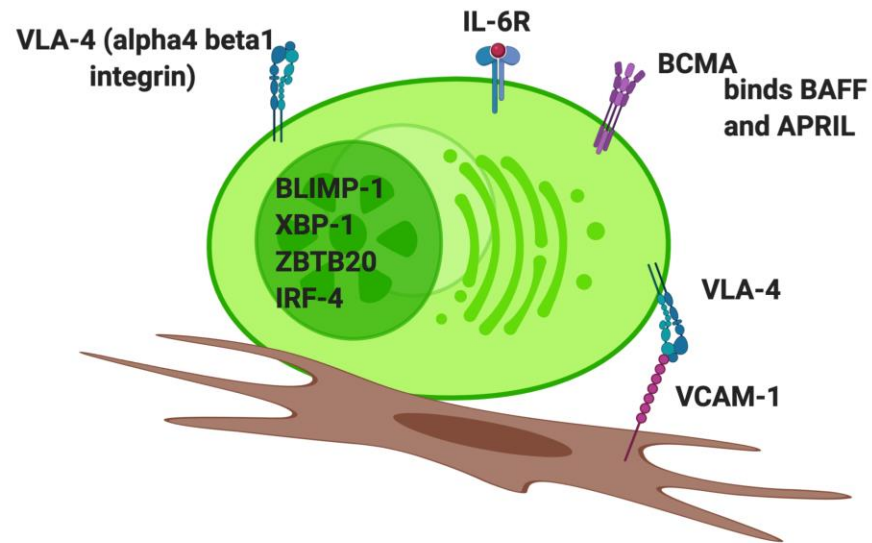
Transcription Factors: IRF4 and BLIMP-1 induce the XBP-1 transcription factor, ER stress signals control splicing of XBP-1

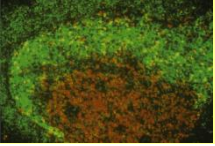
ZBTB20 also induced

Survival: BAFF family receptor BCMA required for survival of long-lived plasma cells in Bone marrow

VLA-4 ($\alpha 4\beta 1$ integrin) also may be required for maintenance in niche and survival)

LONG-LIVED PLASMA CELL MAINTENANCE IN THE BONE MARROW NICHE





Quietly into the night.....