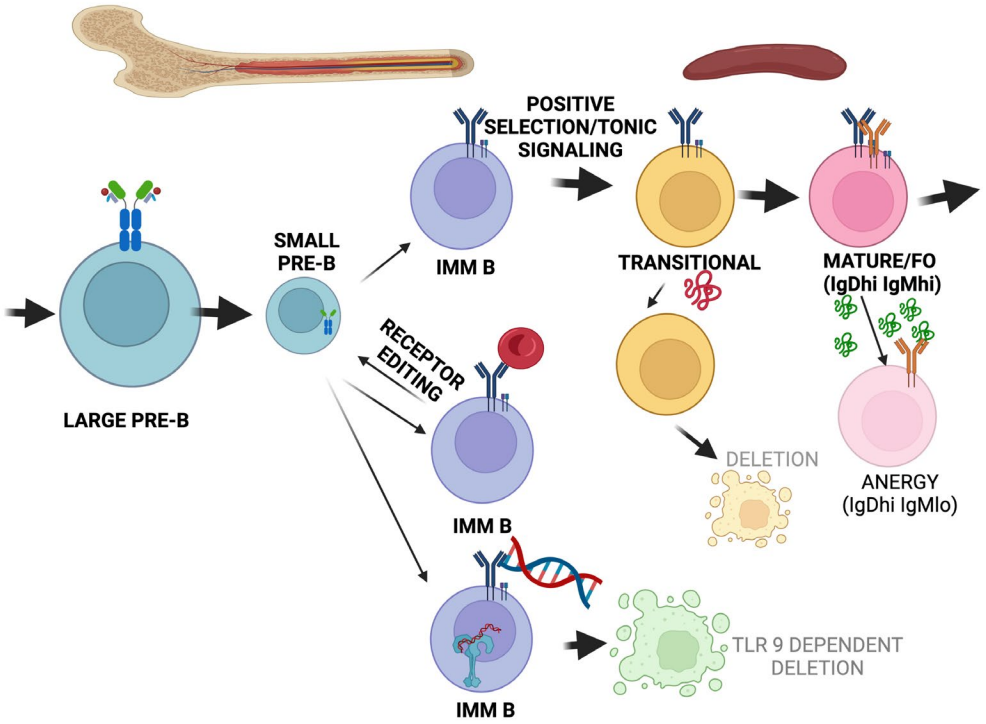
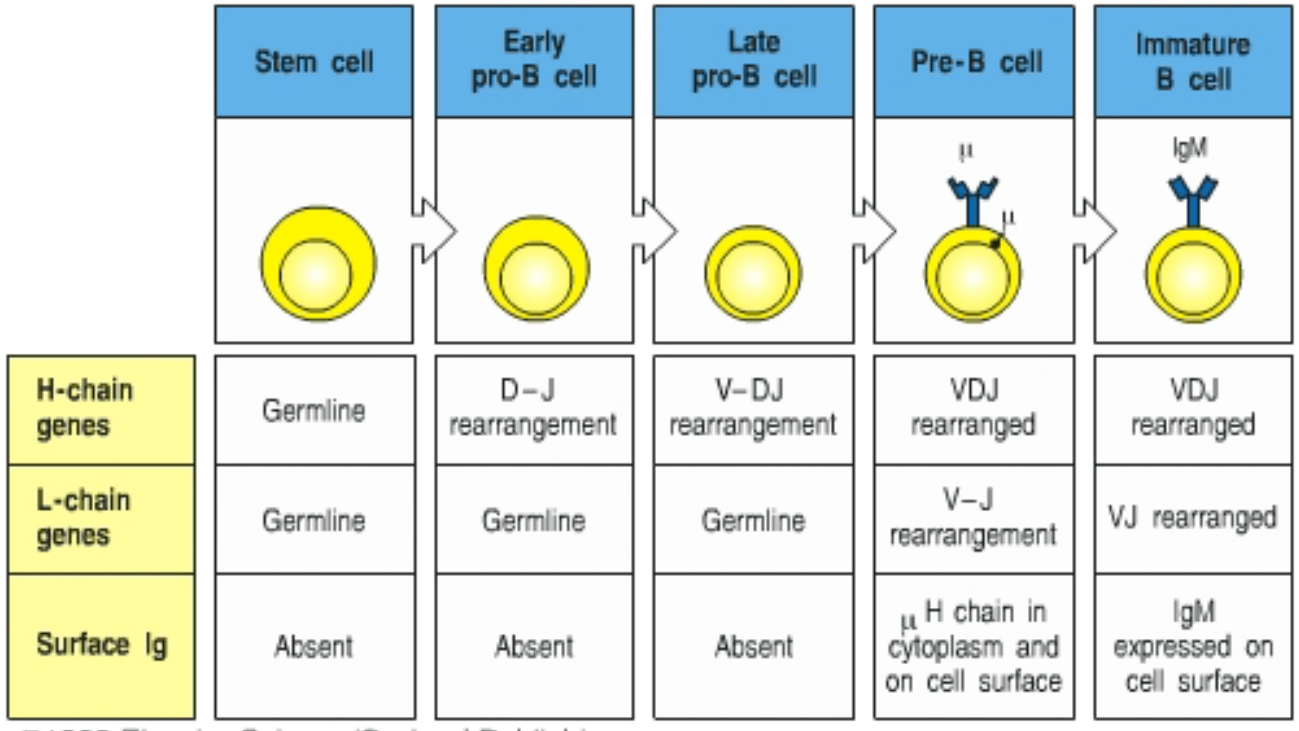
T-B cell collaboration

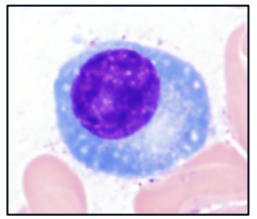
Stephanie Eisenbarth, MD, PhD
Northwestern University
FOCIS Basic Immunology Course
6/17/24

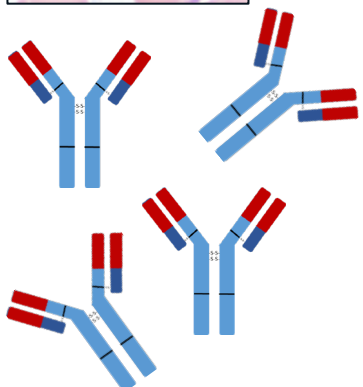
B cell development



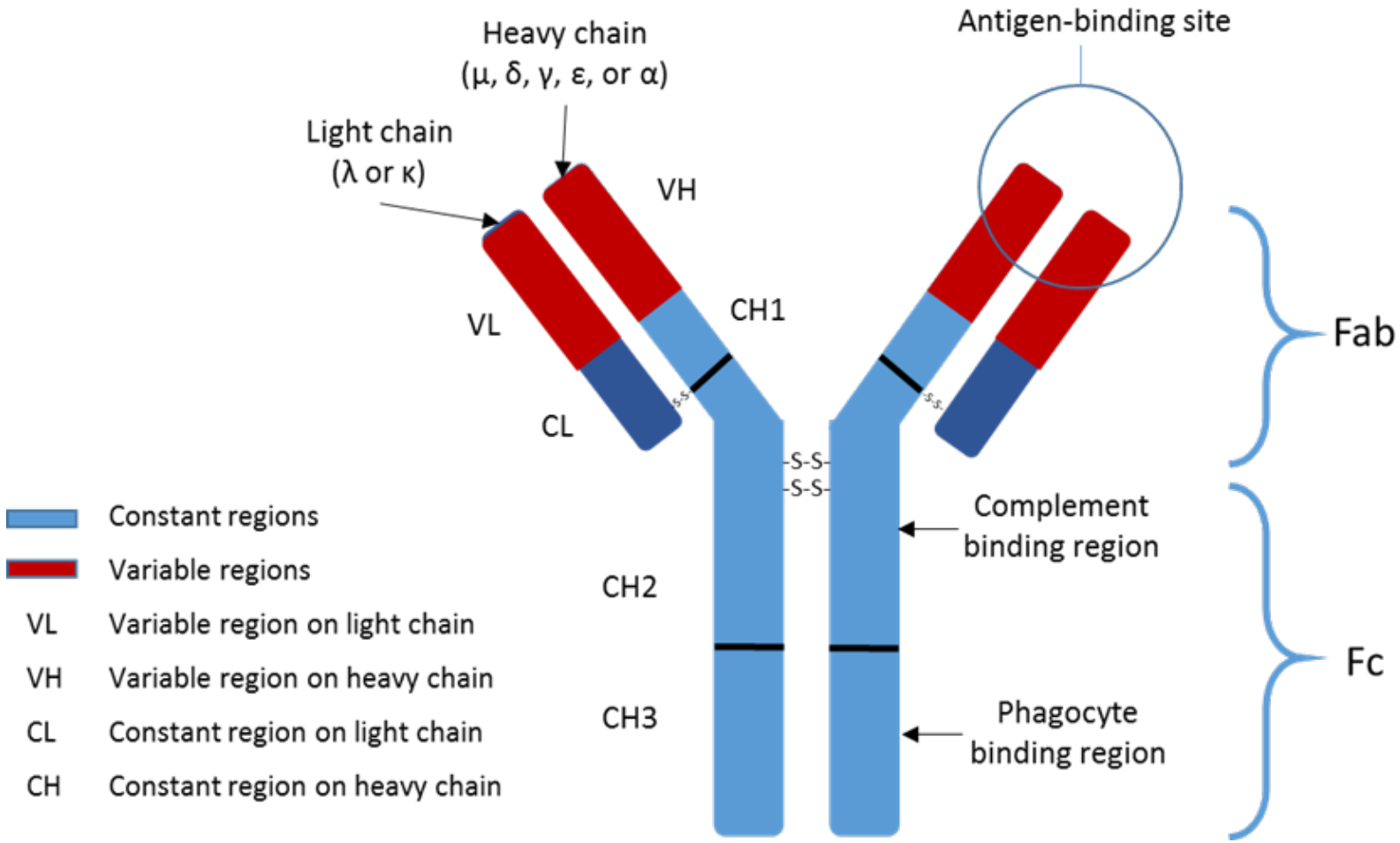


Plasmablast
Plasma Cell





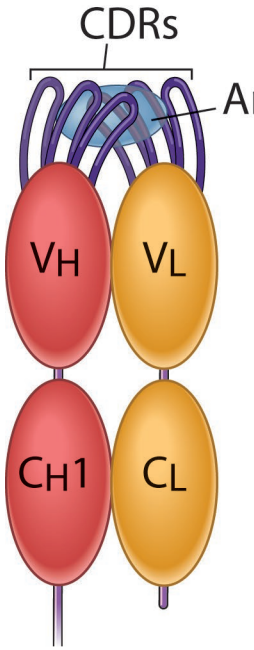
Humoral Immunity = Antibodies

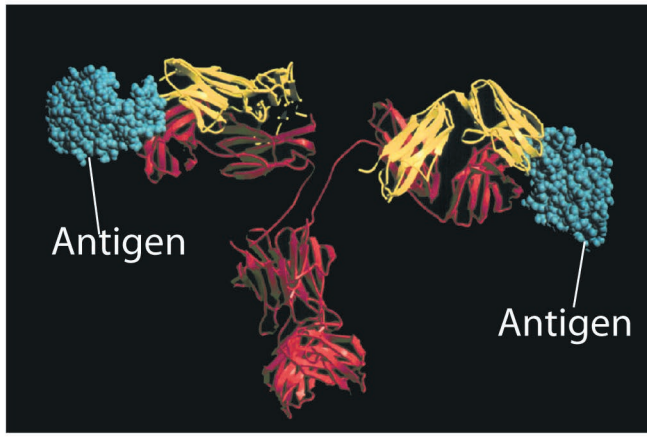


1 site/B cell (antibody) = clonal

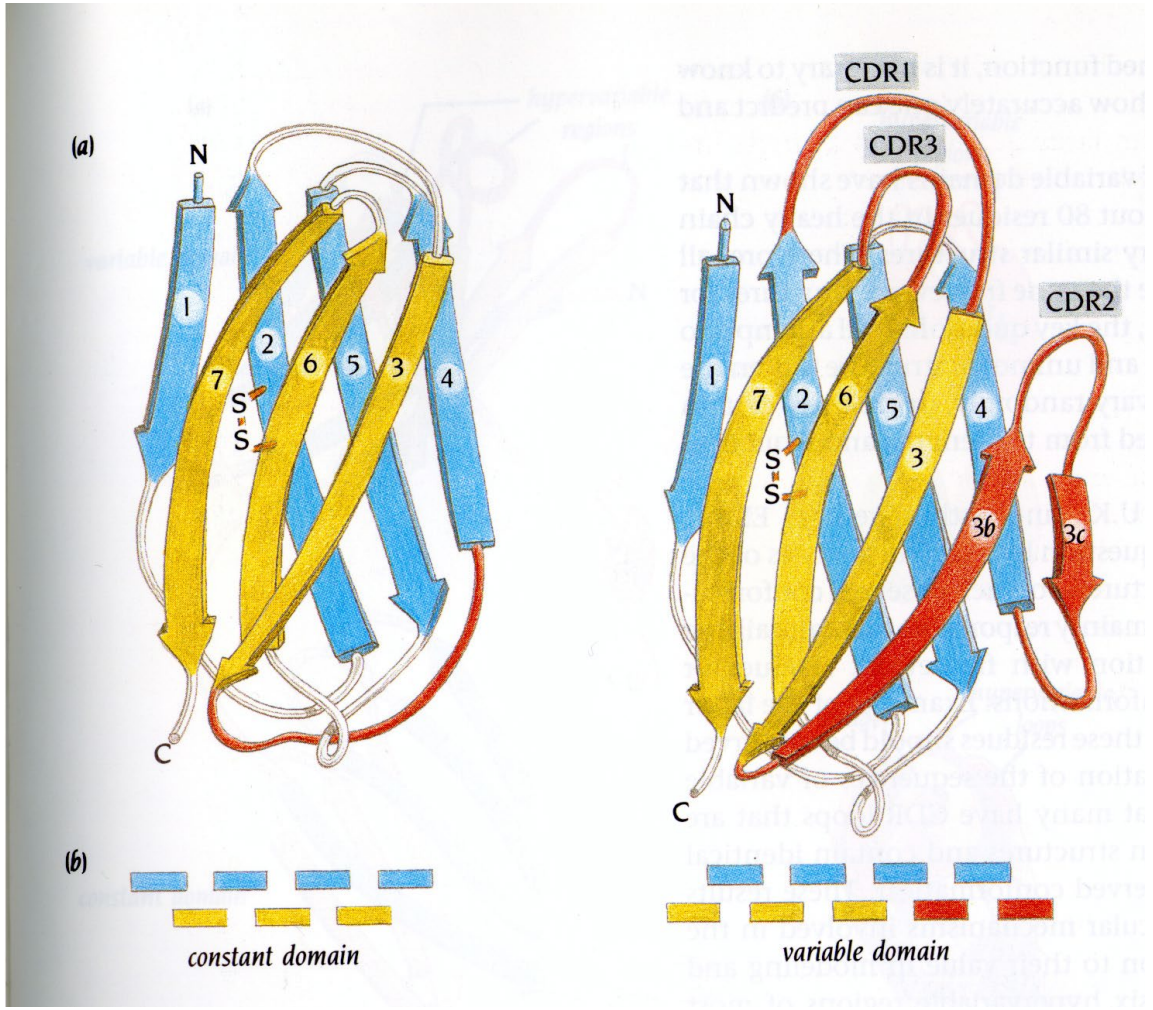
- Heavy chain
  - Mu (IgM), delta (IgD), gamma (IgG), alpha (IgA), or epsilon (IgE) constant region that determines the isotype
  - Isotype subsets
    - IgG1, IgG2, IgG3, IgG4
    - IgA1, IgA2
- Light chain
  - Either a kappa or lambda constant region

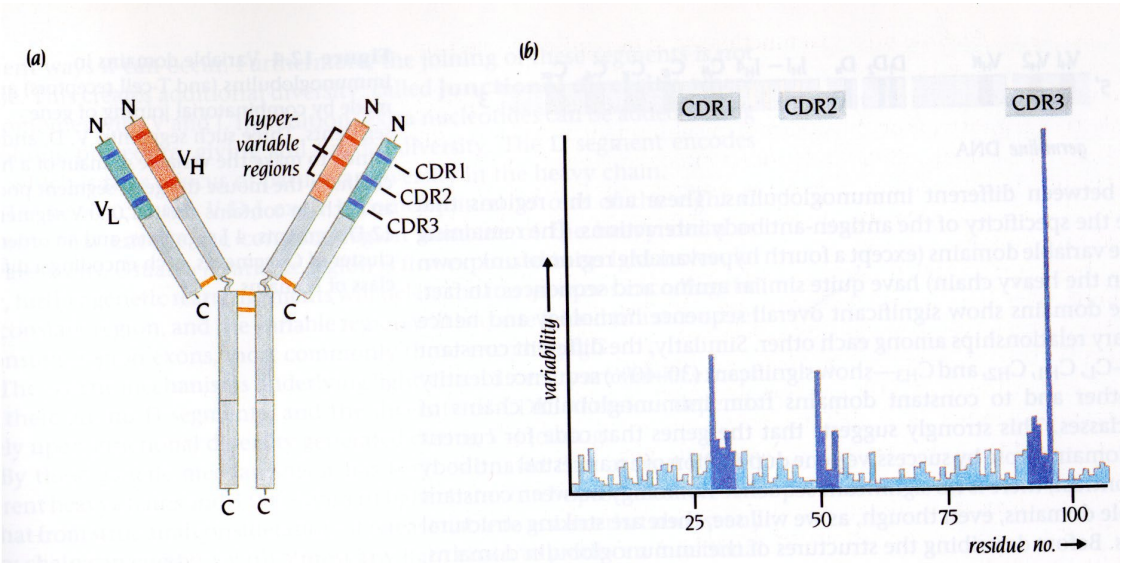
Complementarity determining regions (CDRs) = HyperVariable Regions (HVRs)





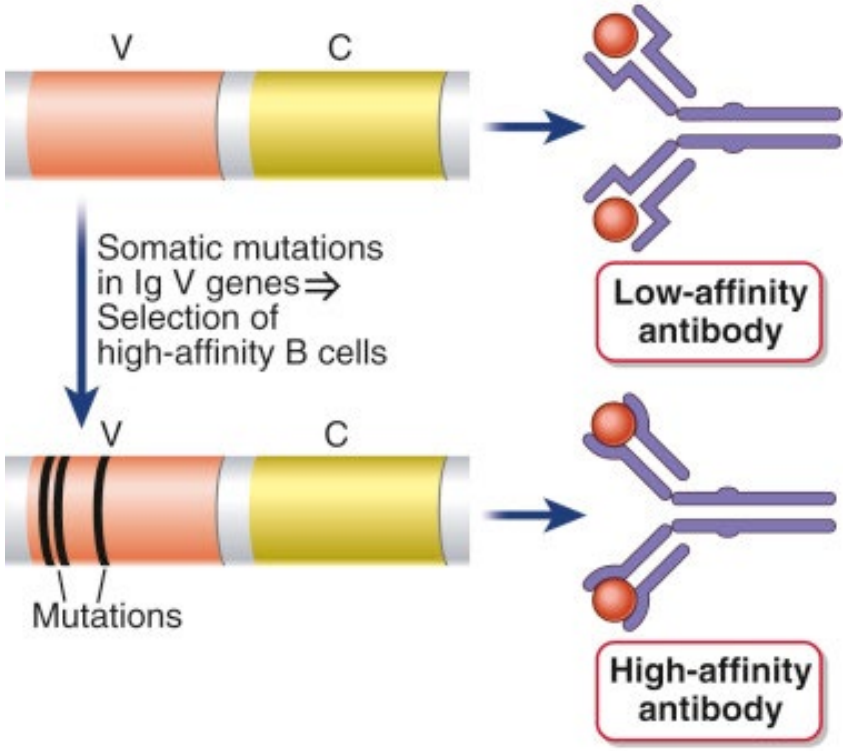
Sites that determine antigen binding



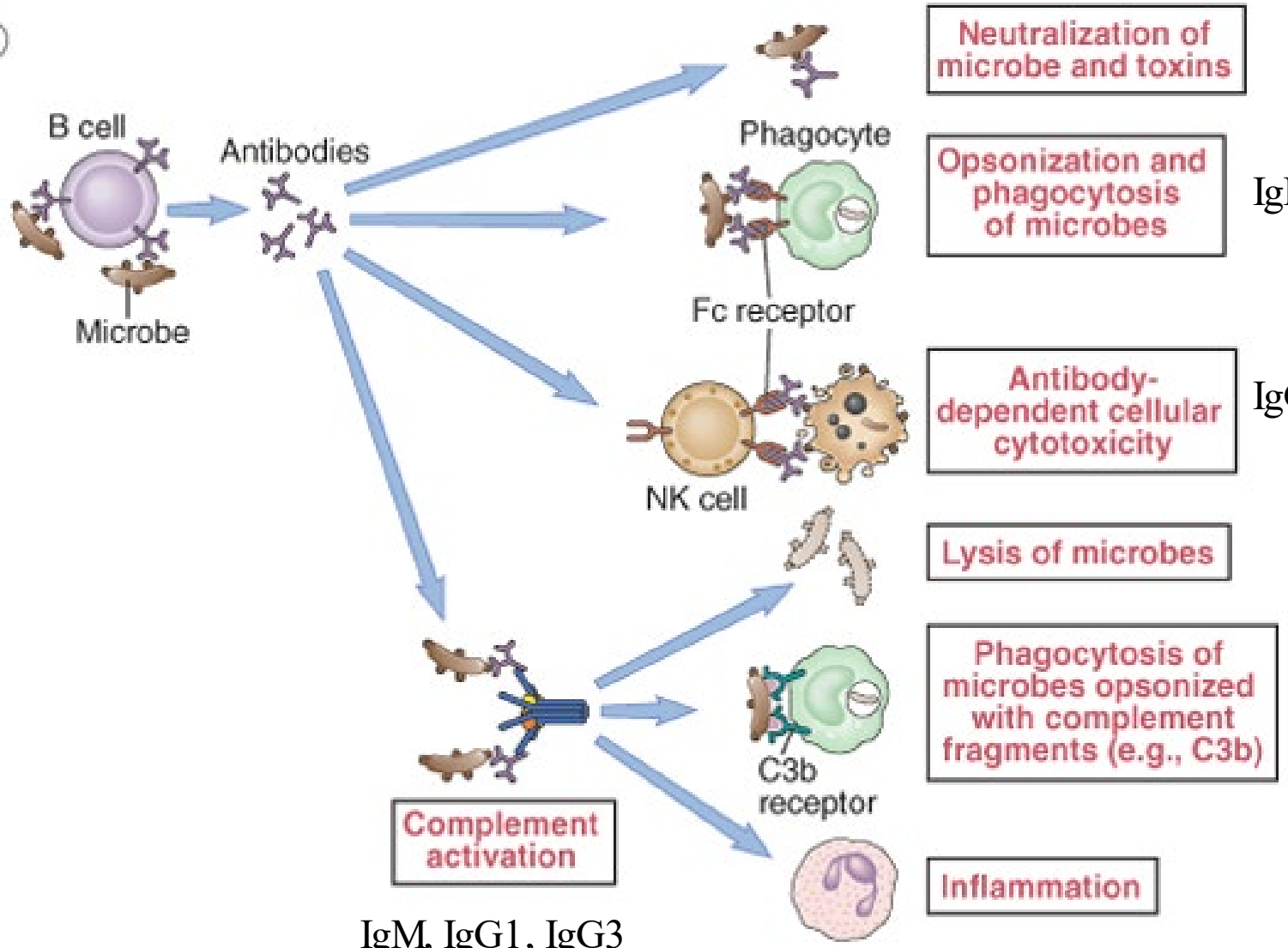


Affinity and avidity

- Affinity refers to the strength of an individual antibody binding to antigen
- If the antibodies are multivalent (i.e. the pentameric form of IgM) then the overall strength of the multiple antibodies binding to multiple antigenic sites is the avidity of the interaction
- Multimeric forms of antibodies serve to increase the avidity of the antibody-antigen interaction

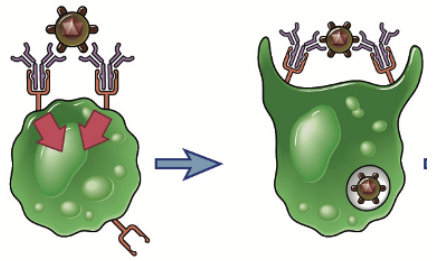


The effector functions of antibodies



IgM, IgG1, IgG3

IgA and IgM (mucosa) - PIGR
IgGs

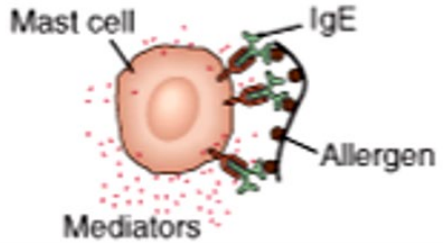


IgM, IgG1, IgG3

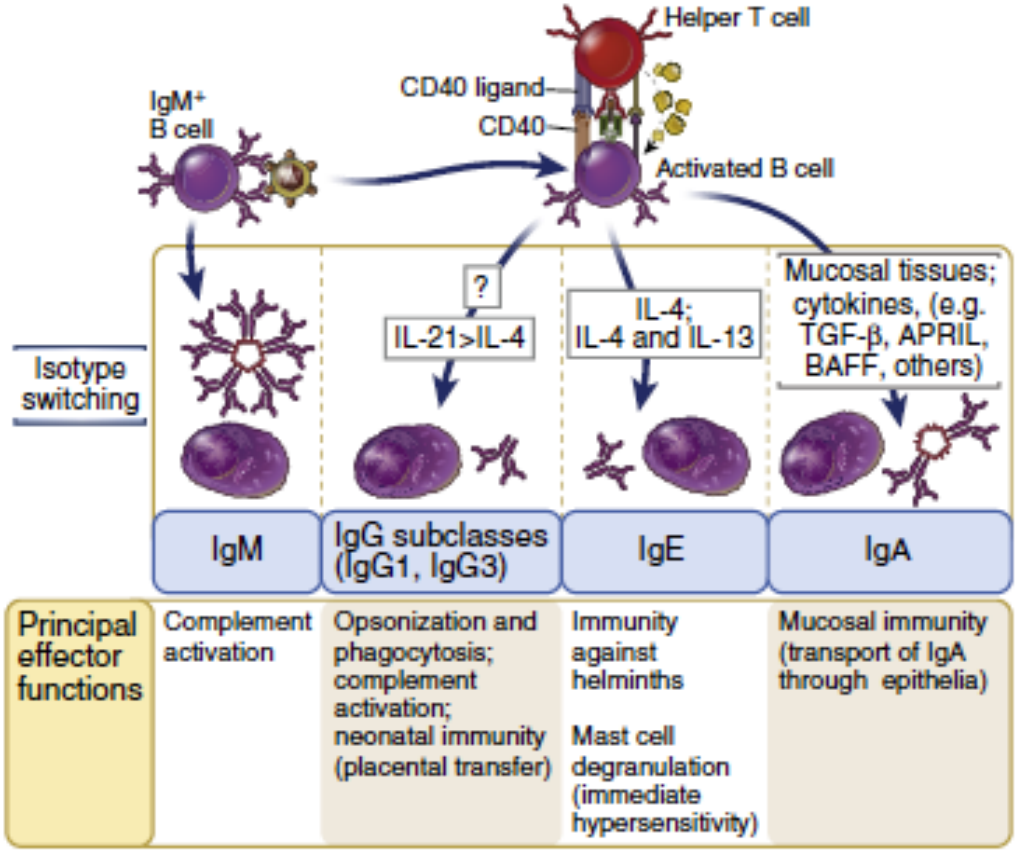
IgG1, IgG3

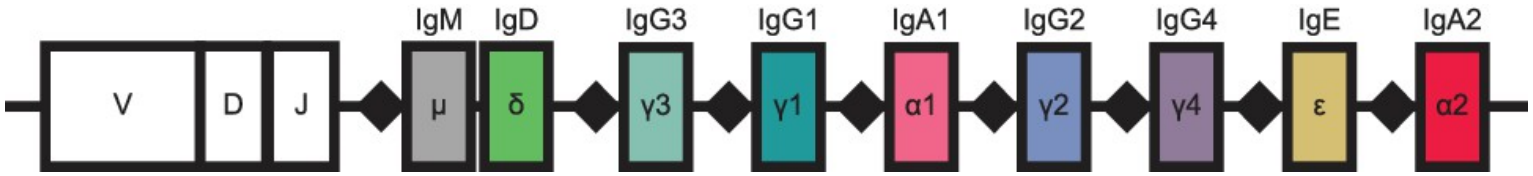
IgE

Sensitization of mast cells → immediate type hypersensitivity

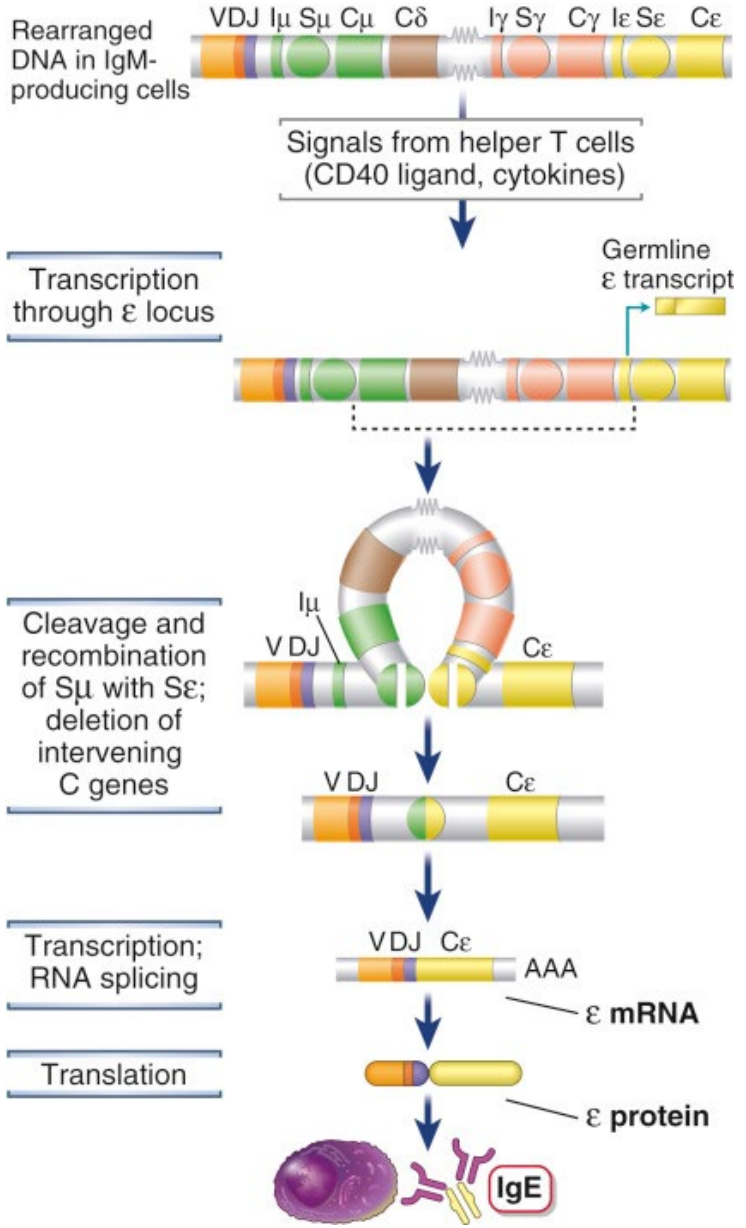


Cytokines direct class switching



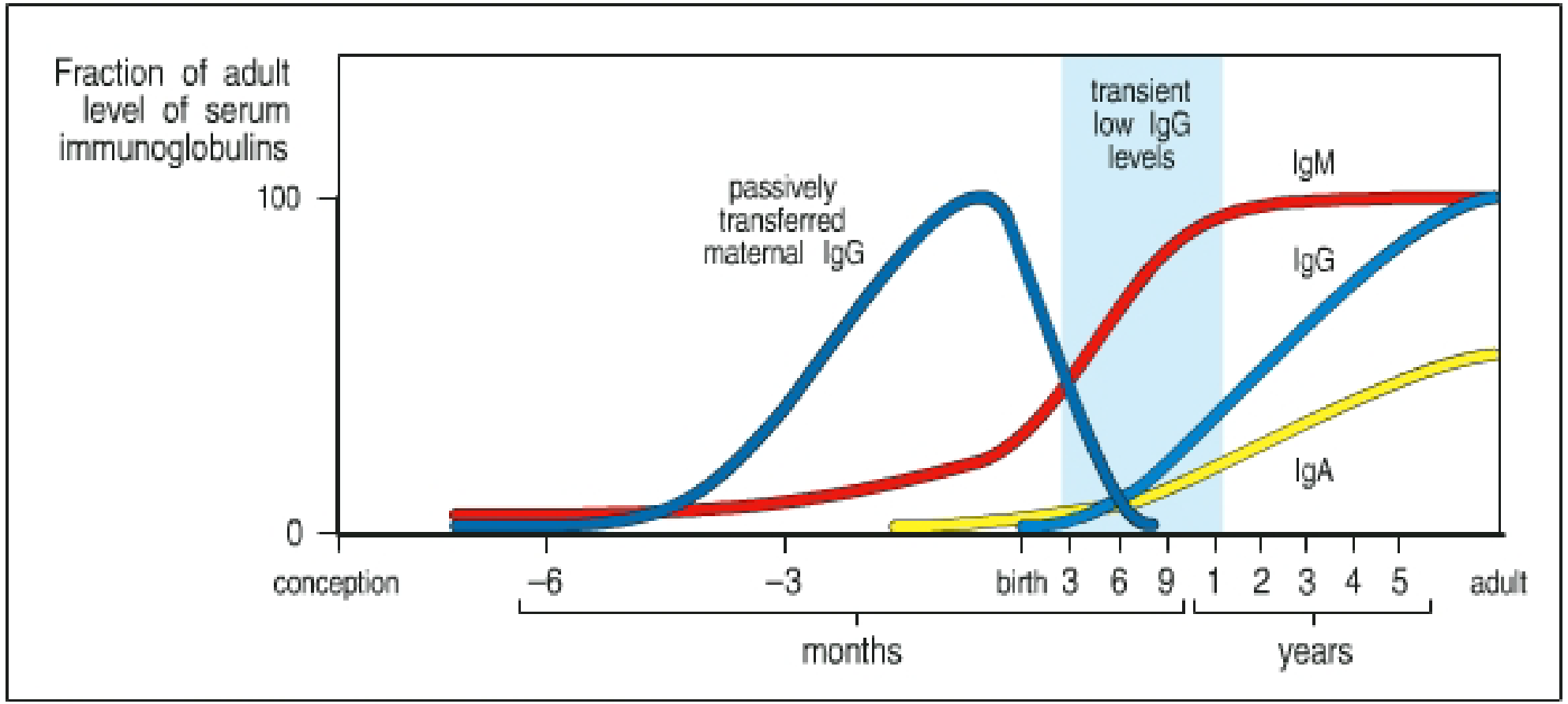


Horns et al eLife 2016



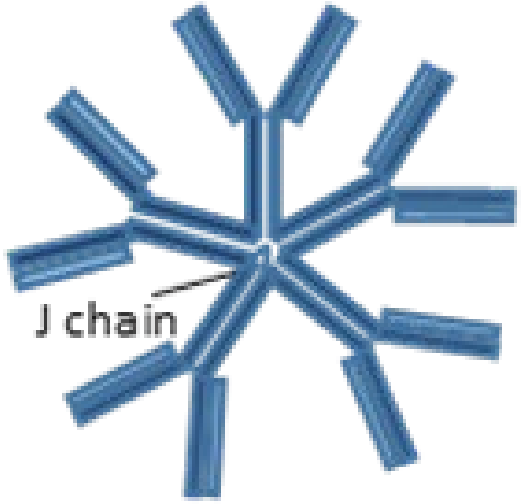
Cellular and Molecular Immunology, Abbas et al.

Immunoglobulin levels during infancy &childhood



Janeway Textbook

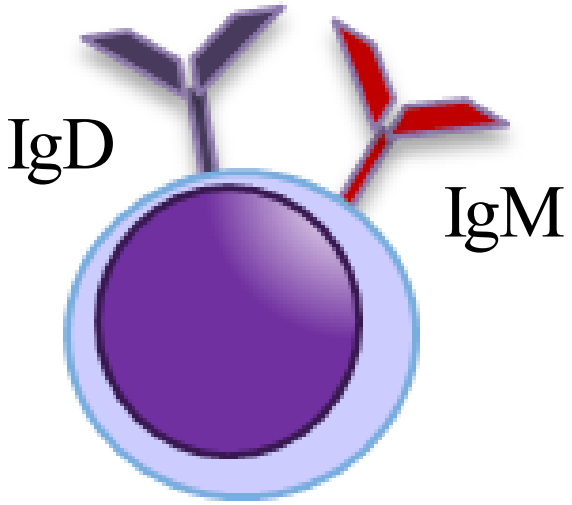
IgM



- Mu heavy chain
- Effectively fixes complement
- Expressed on the surface as the B cell receptor
- First antibody produces in an antibody response (primary response)
- Found as a pentamer to increase avidity (connected by J chains)
- Does NOT cross the placenta

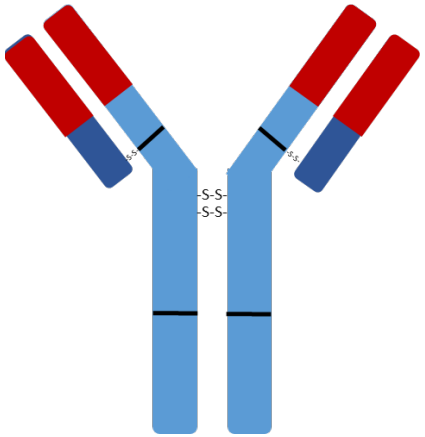
IgD

- Delta heavy chain
- Expressed on naïve B cell surface
  - There is only trace amounts of IgD in the serum
- Function is not well understood



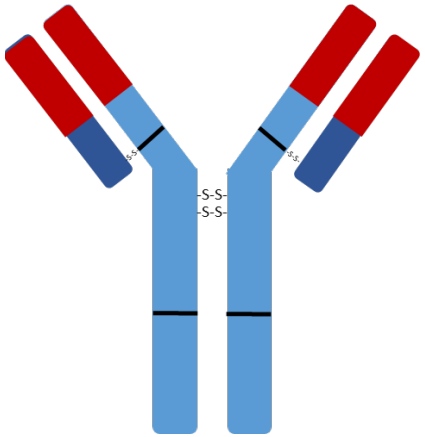
Naïve B cell

IgG



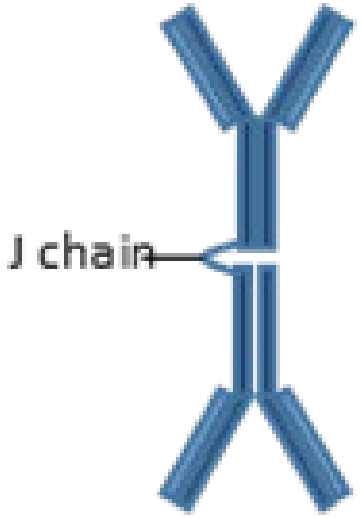
- Gamma heavy chain (1, 2, 3, 4)
- Most effective antibody class in many infections
  - Opsonizes bacteria
    - Many phagocytes express Fc receptors for IgG
  - Fixes complement
  - Neutralizes bacterial toxins and viruses
  - Most abundant in secondary response
- Crosses the placenta

IgE



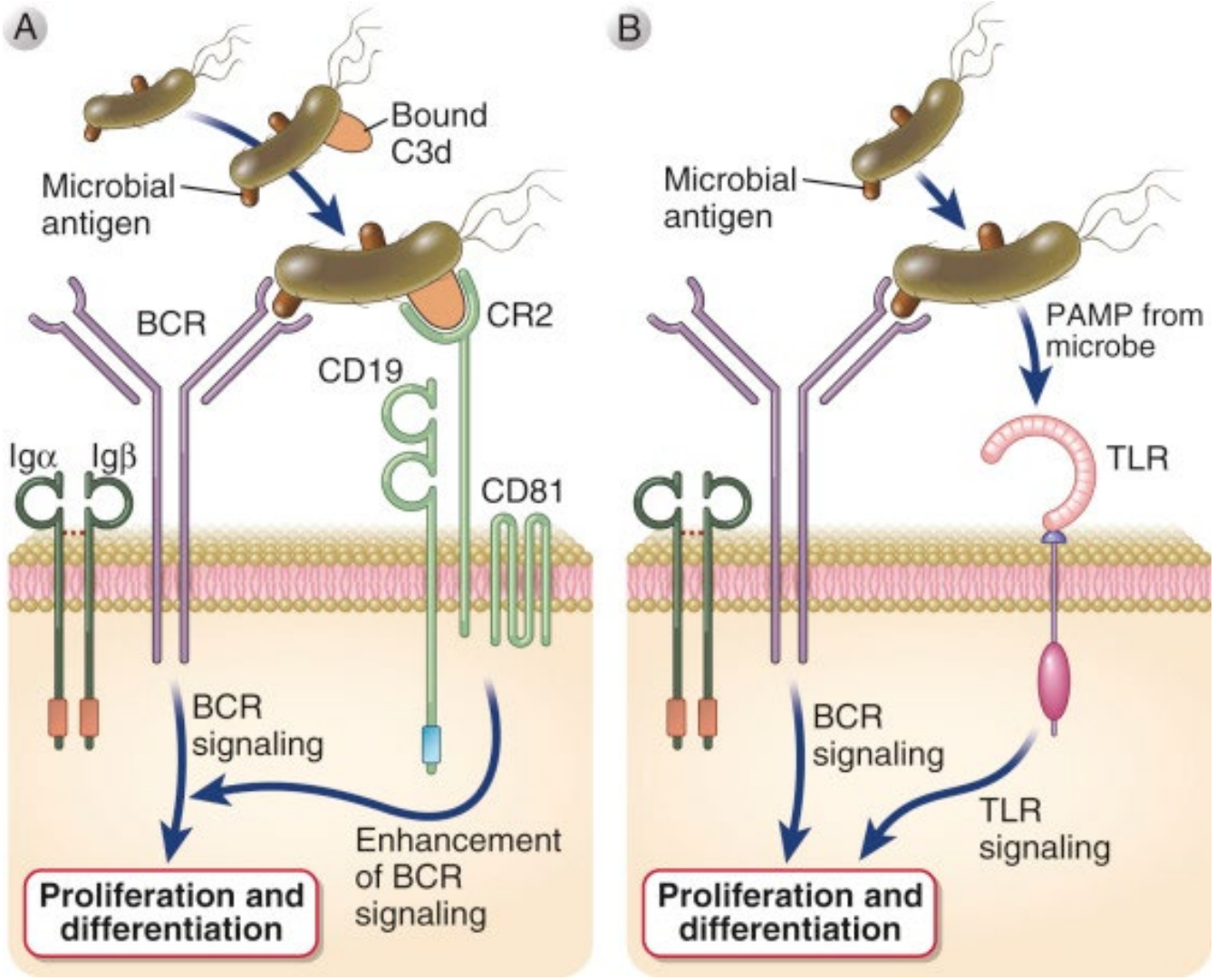
- Epsilon heavy chain
- Antibody dependent cellular cytotoxicity (ADCC)
  - Binds to extracellular parasites
  - May play a role in killing by eosinophils (which have low affinity receptors for the IgE Fc)
- Crosslinks high affinity IgE Fc receptors on mast cells and basophils
  - Release of histamine (allergy and anaphylaxis)

IgA

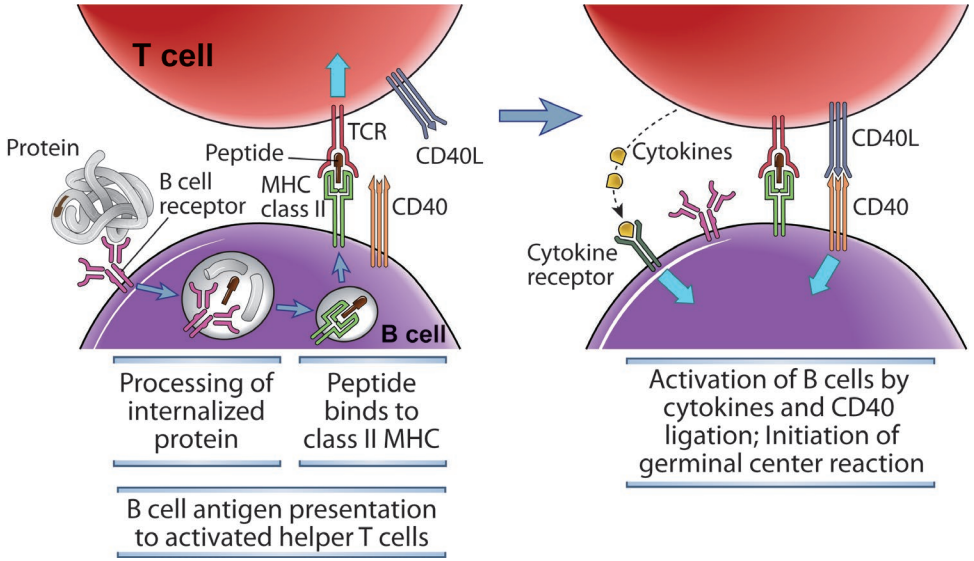


- Alpha heavy chain (IgA1 & IgA2)
- Mucosal immunity
  - Prevents attachment of bacteria and virus to mucosal membranes
- Does NOT fix complement
- Passively transferred in breast milk to infants
- Monomeric in serum or dimeric at mucosa (connected/stabilized by J chains)

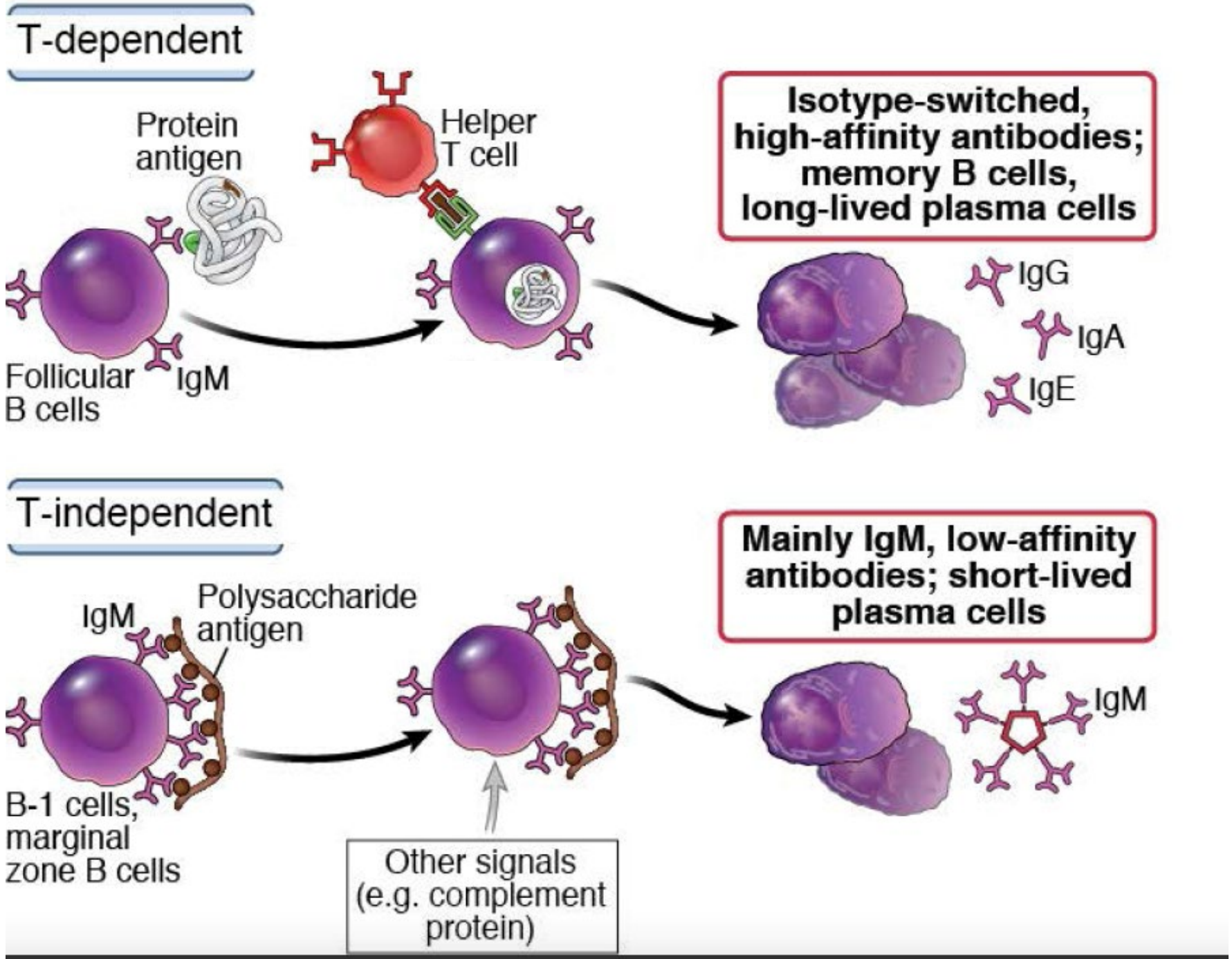
Early B cell activation (TI or TD antigen)



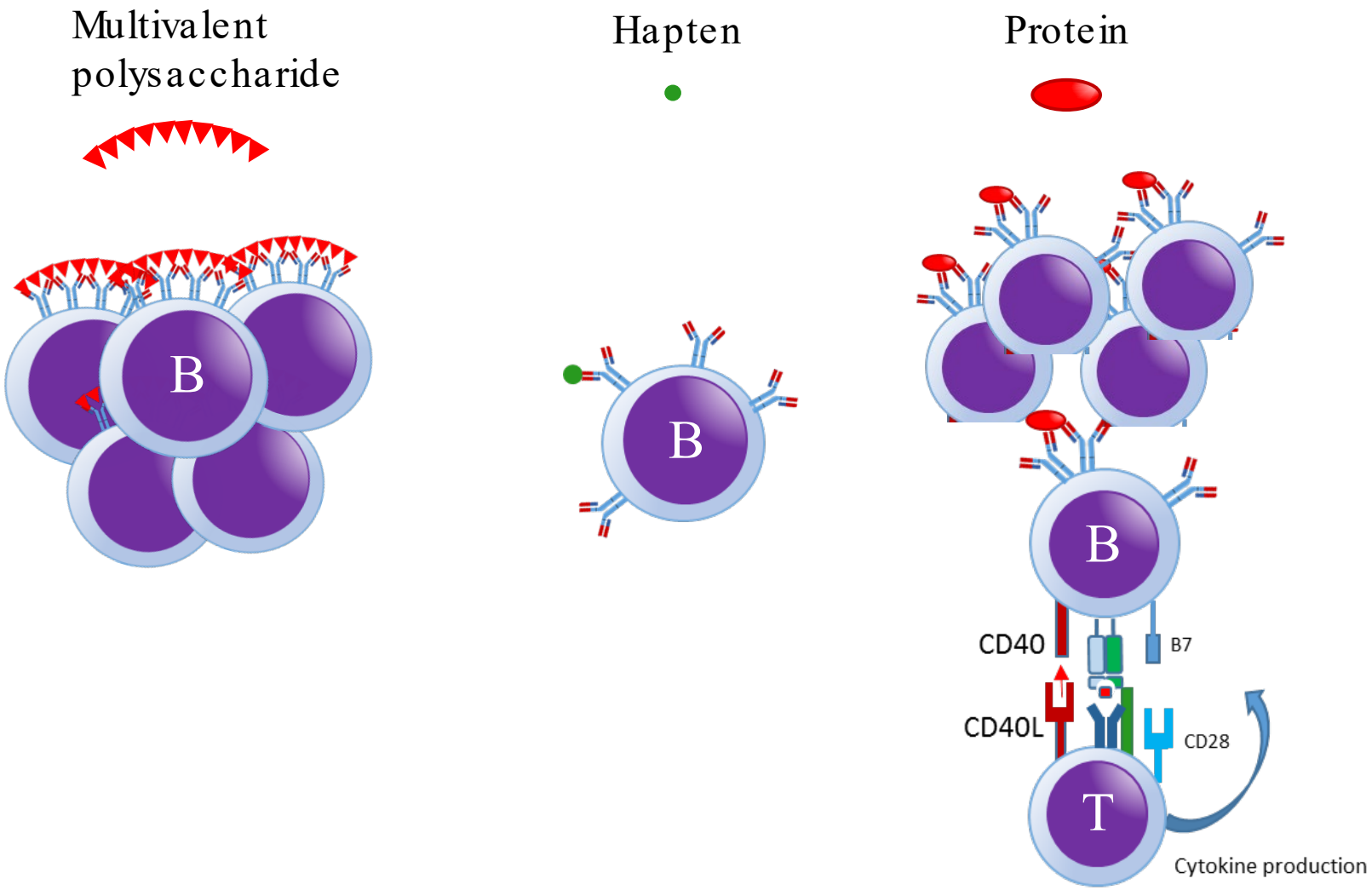
- Recognize antigen through the IgM B cell receptor (BCR) = Antibody clone of B cell
- Receives second signals from complement, TLR, CD4+ T cells, and/or cytokines



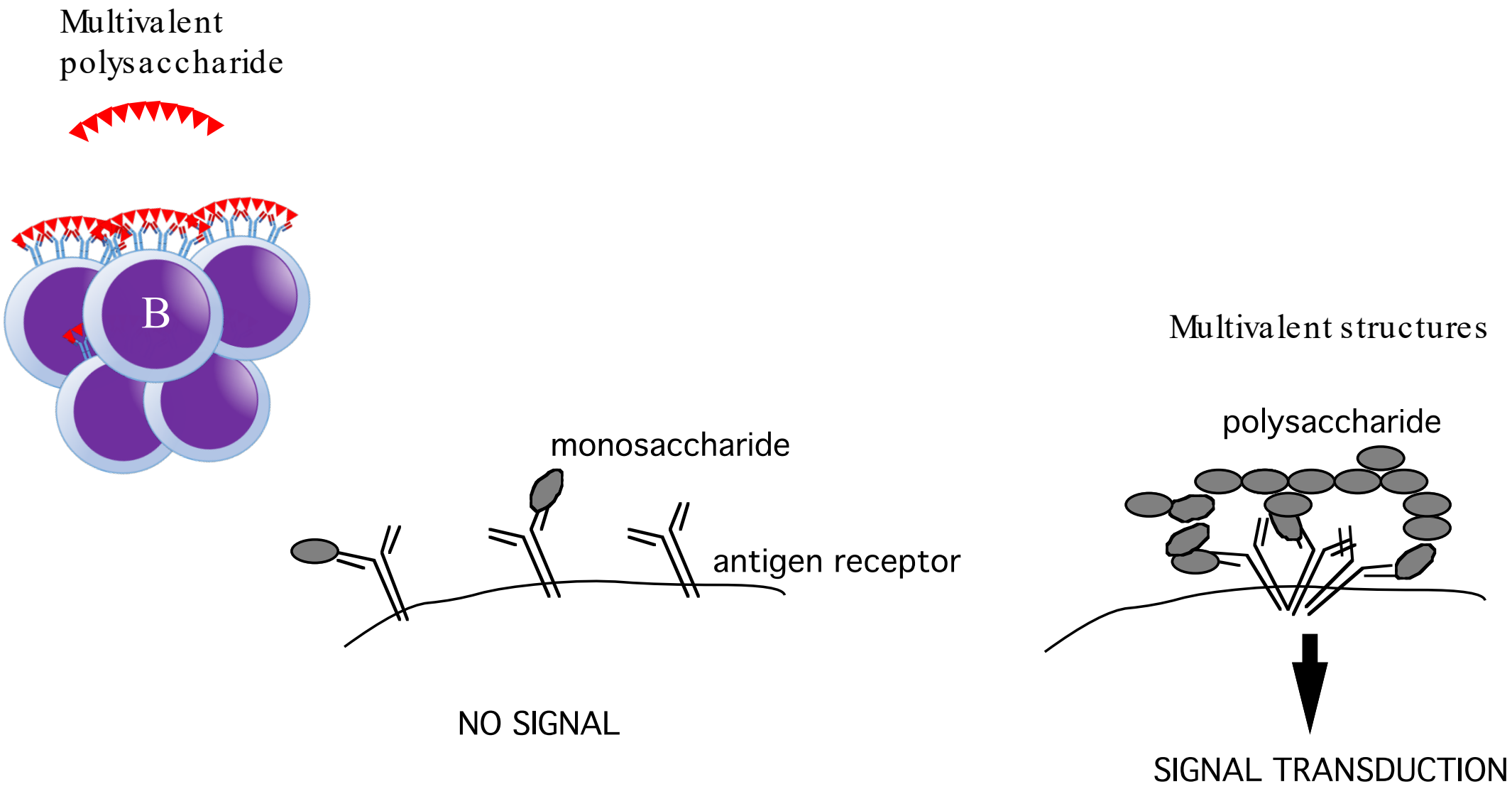
Cellular and Molecular Immunology, Abbas et al.


T-dependent
Protein antigen
Helper T cell
Follicular B cells
IgM
Isotype-switched, high-affinity antibodies; memory B cells, long-lived plasma cells
IgG
IgA
IgE
T-independent
IgM
Polysaccharide antigen
B-1 cells, marginal zone B cells
Other signals (e.g. complement protein)
Mainly IgM, low-affinity antibodies; short-lived plasma cells
IgM

Types of antibody responses

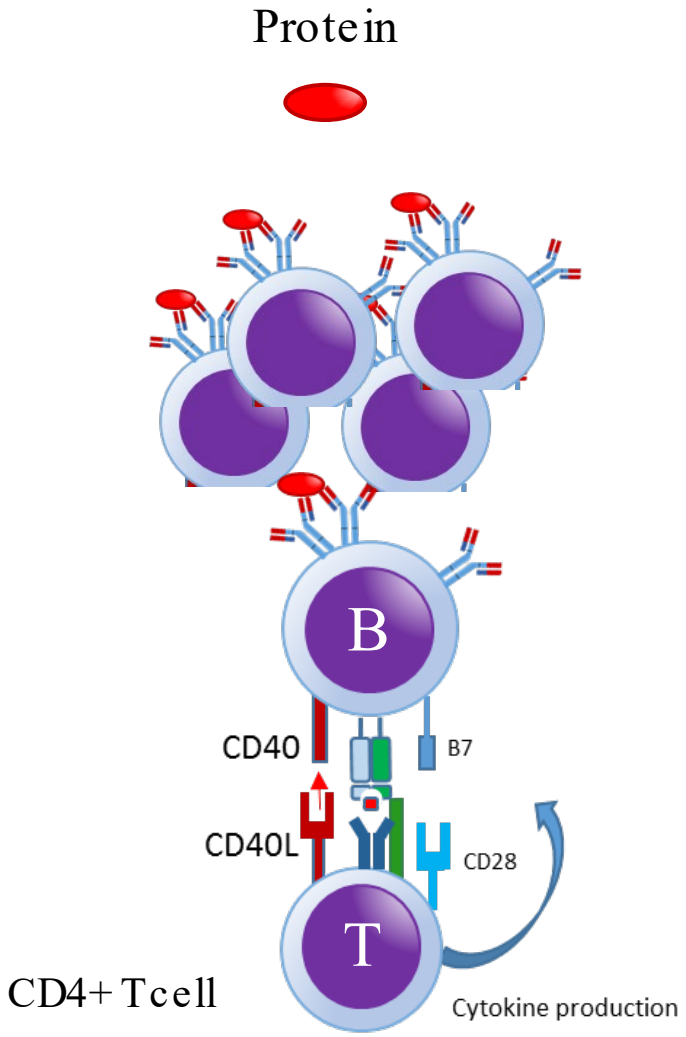


Types of antibody responses: T-independent (TI)

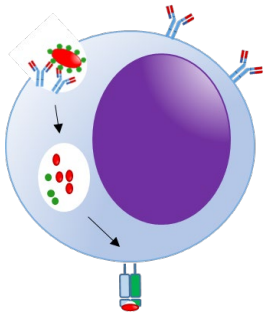


Types of antibody responses: T-dependent (TD)

- Surface IgM BCR recognizes a protein antigen
- B cells express peptides on MHC class II
- The T cell-B cell interaction of CD40/CD40L leads to germinal center formation, class switching, and somatic hypermutation
- Antibodies produced are of high affinity

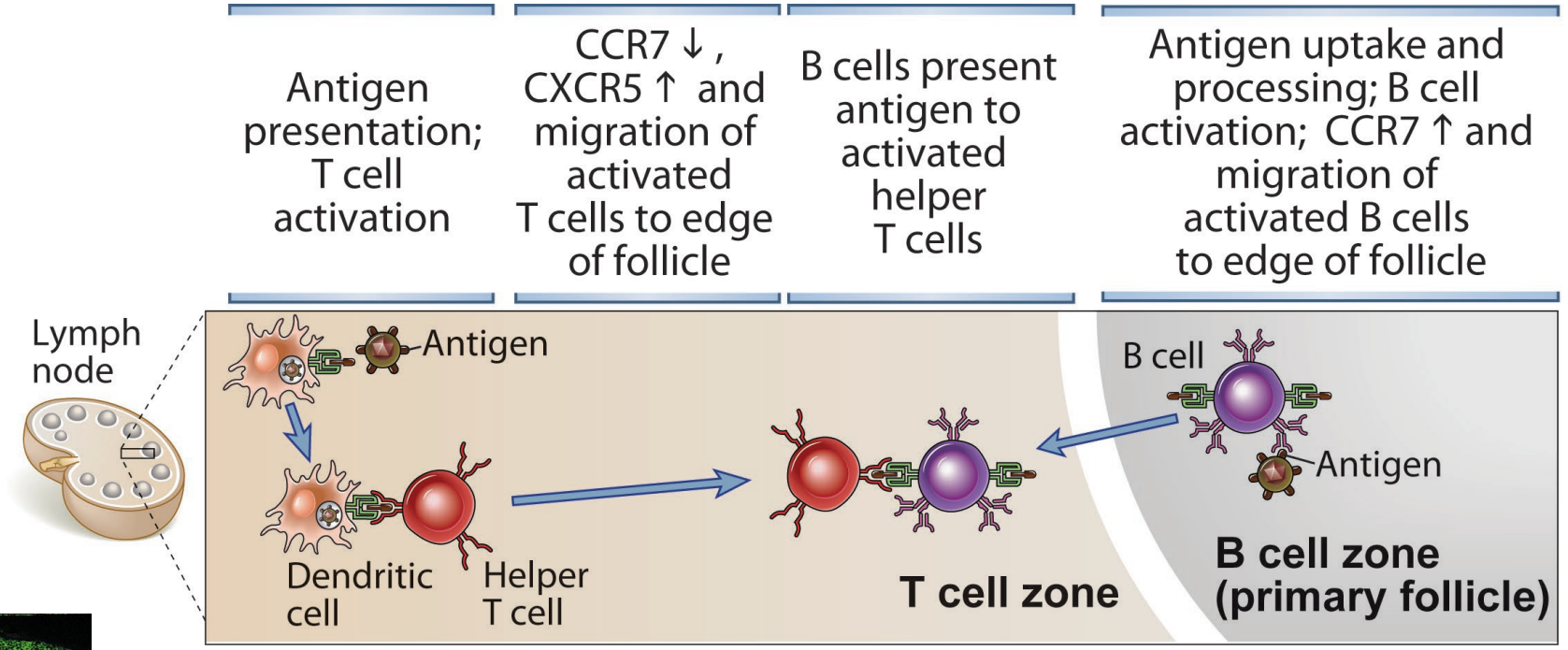


T follicular helper (Tfh) cell
(previously Th2 cells)

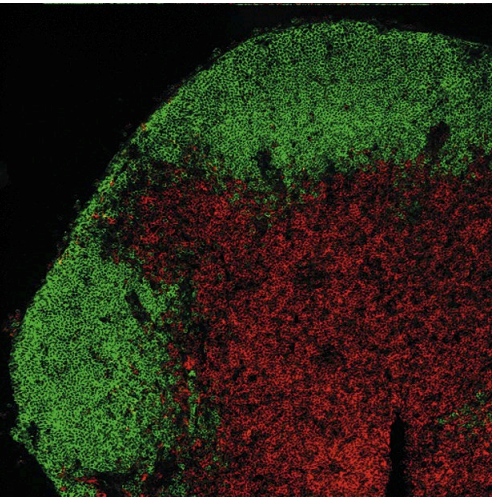


- When the BCR binds antigen, it is internalized into endosomes
- Proteins bound by the BCR are degraded to peptides and expressed on MHC class II.

T&B cell interactions require co-localization in secondary lymphoid organs (SLOs)

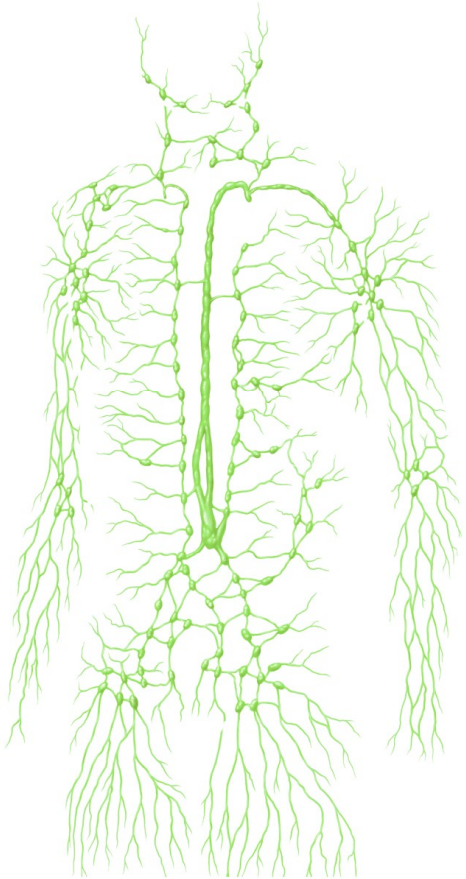


CXCL13 brings naive B cells to follicle

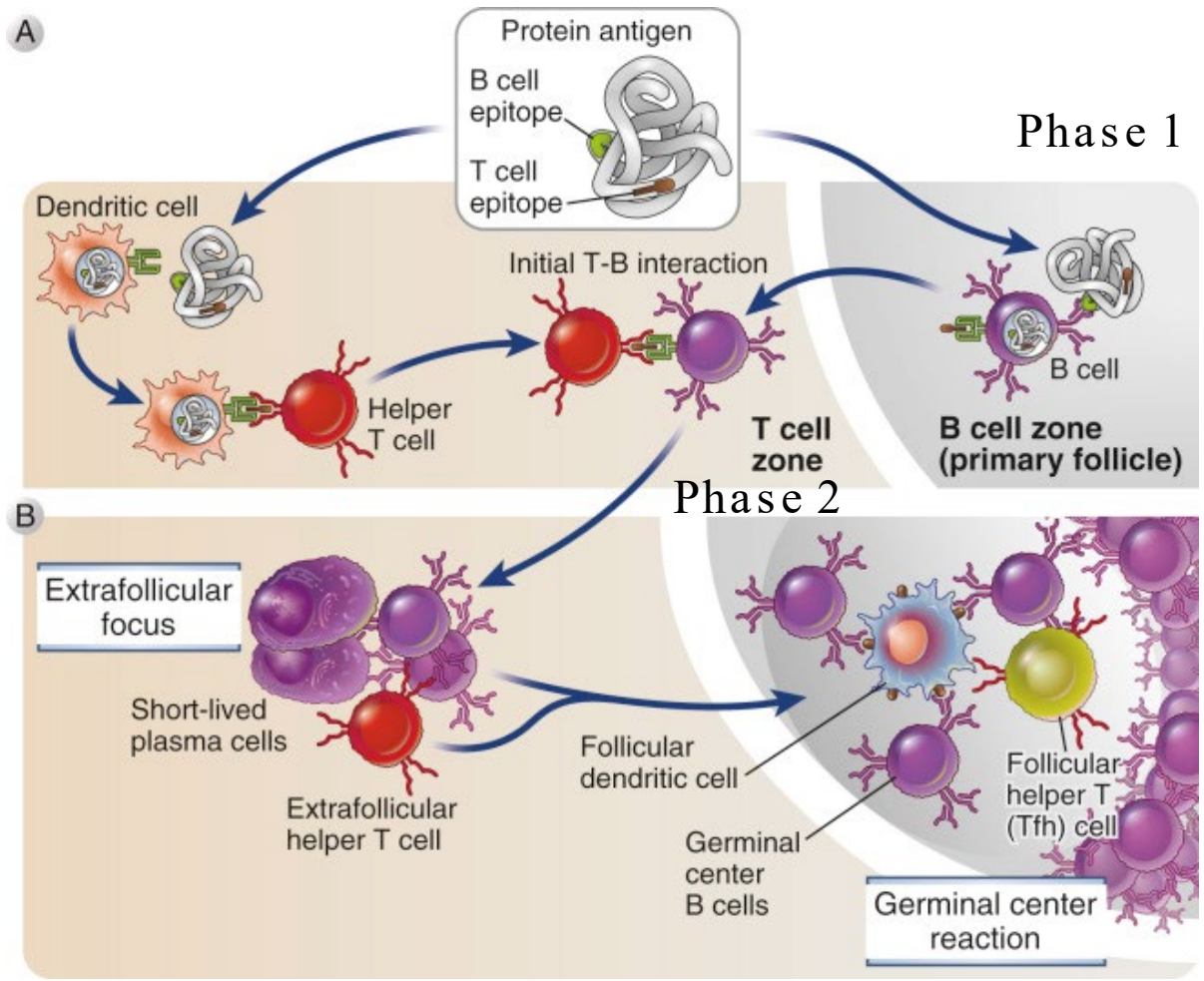


CCL19 and CCL21 draw naïve T cells to T cell zones

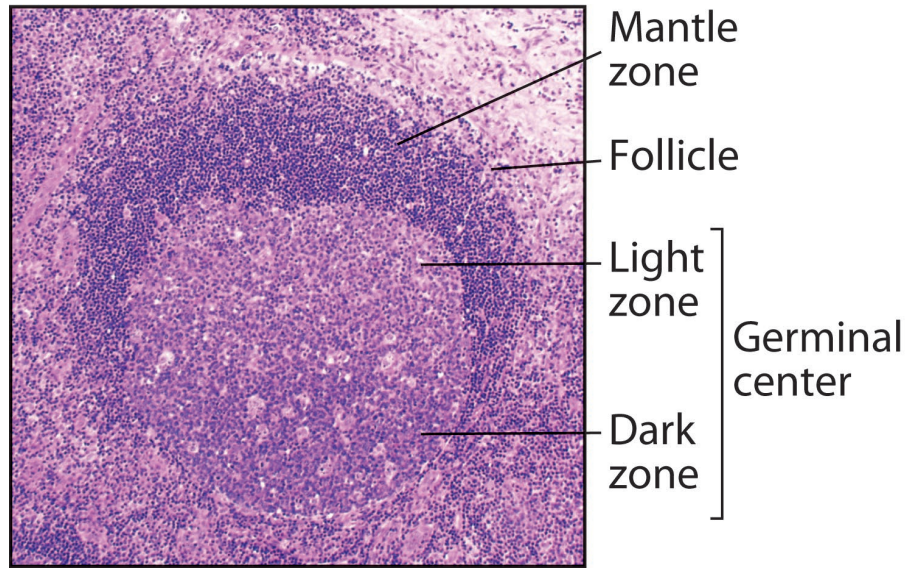
MOST ISOTYPE SWITCHING HAPPENS HERE

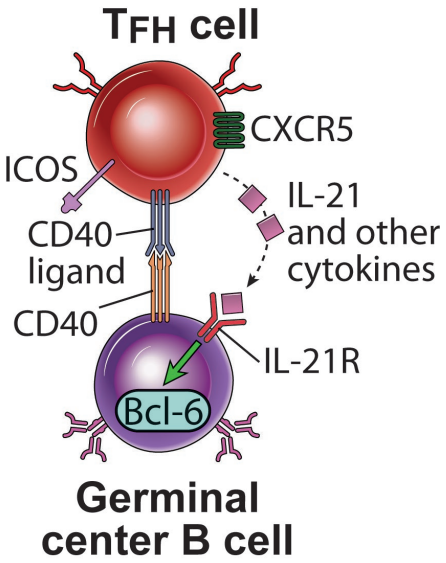


Phases of B cell activation



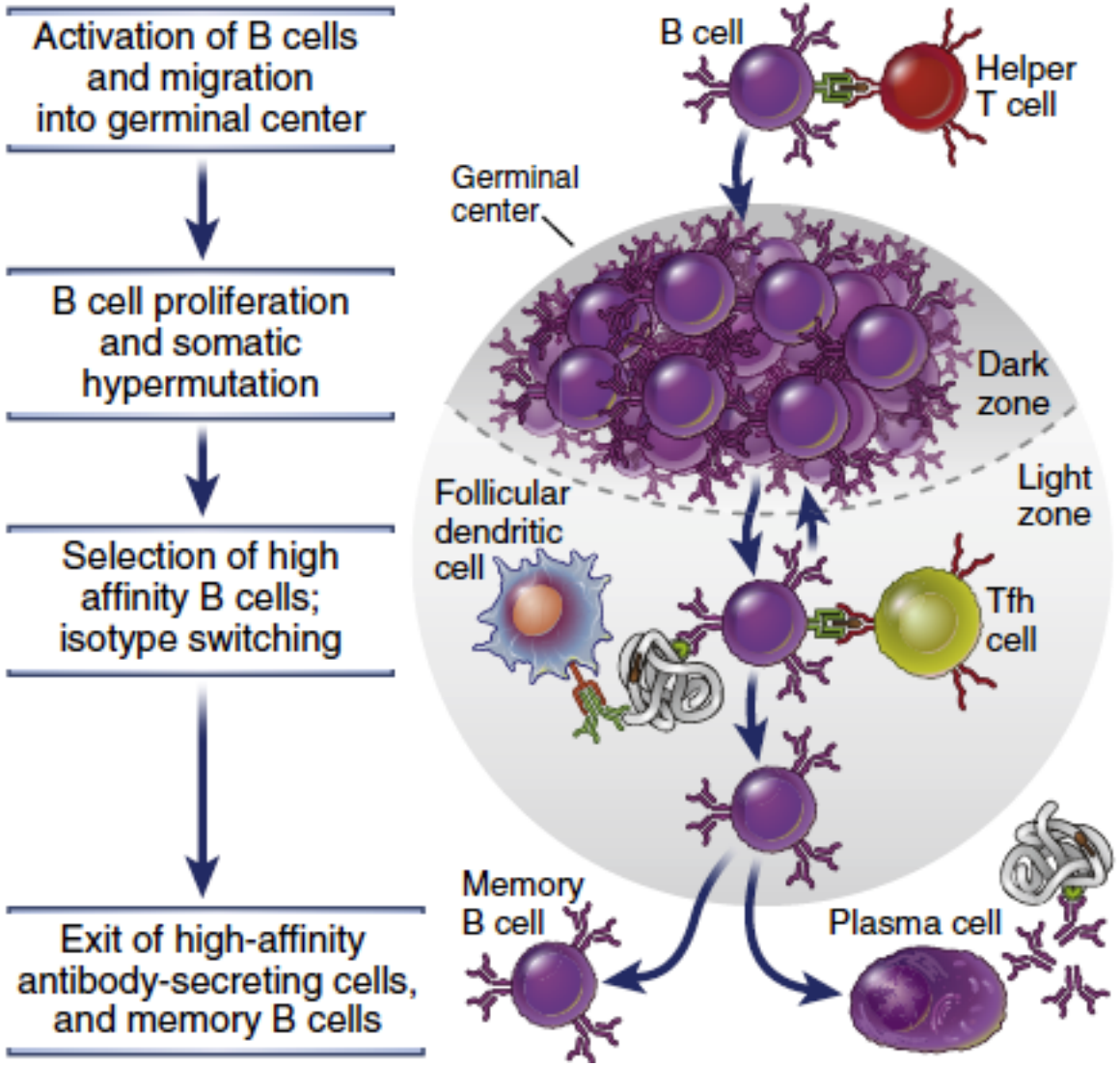
”secondary follicle”

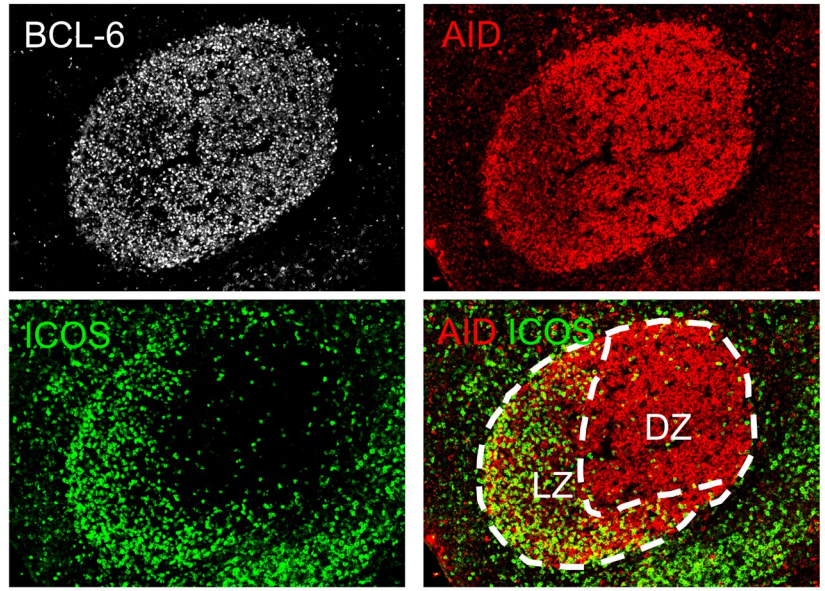




THE GERMINAL CENTER REACTION

Interact with follicular dendritic cells (not DC!) to get antigen if higher affinity antibody





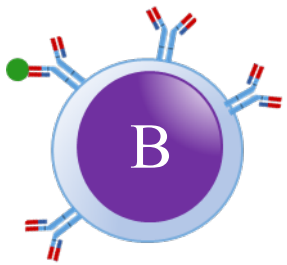
EXIT EARLIER, LESS SHM

EXIT LATER, MORE SHM

Types of antibody responses: haptens

Hapten

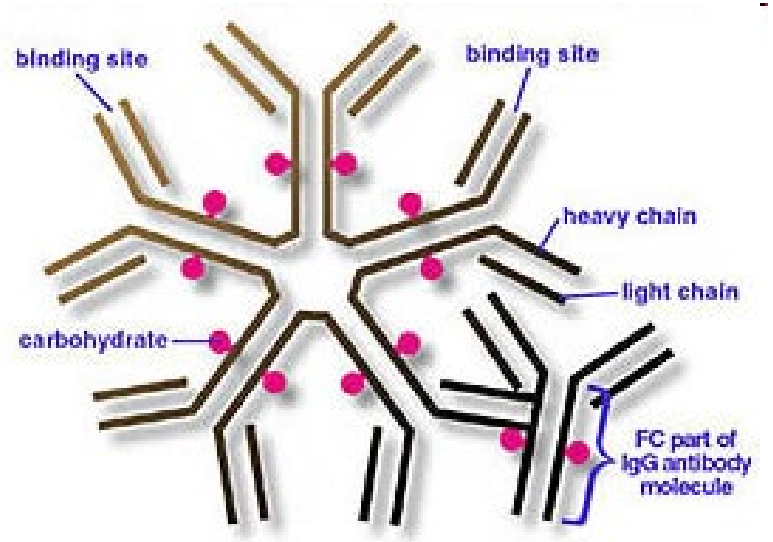
Haptens are small molecules or moieties. They can be recognized by B cells but not T cells

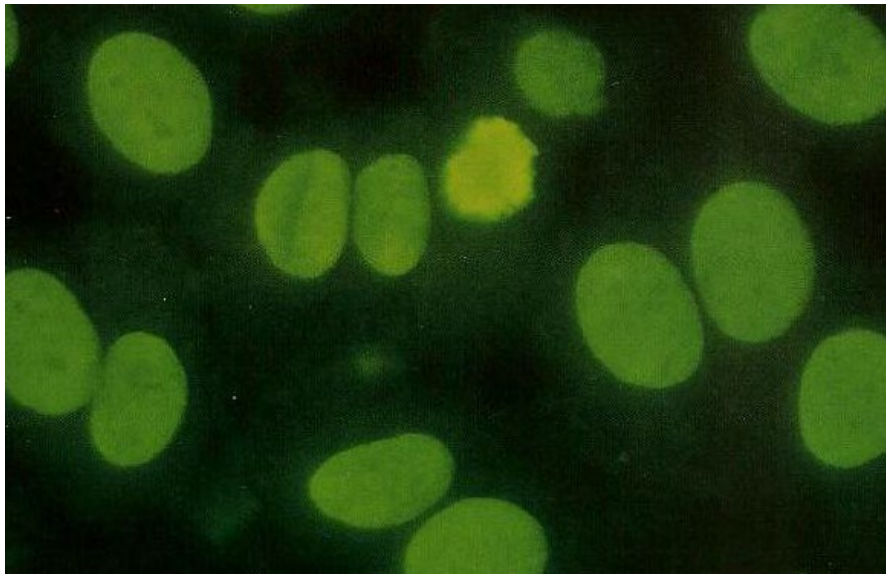


A few clinical correlations

Specific antibodies are used to diagnose disease

- Rheumatoid factor (IgM anti-IgG) and Anti-CCP in Rheumatoid Arthritis
- Anti-nuclear antibodies in Lupus (IgG)
- Anti-tissue transglutaminase in Celiac disease (IgA)
- Anti-pathogen antibodies (e.g. SARSCoV2, EBV, HBV, etc.) (IgM and IgG)
- Anti-allergen antibodies are used to diagnose allergy (IgE)



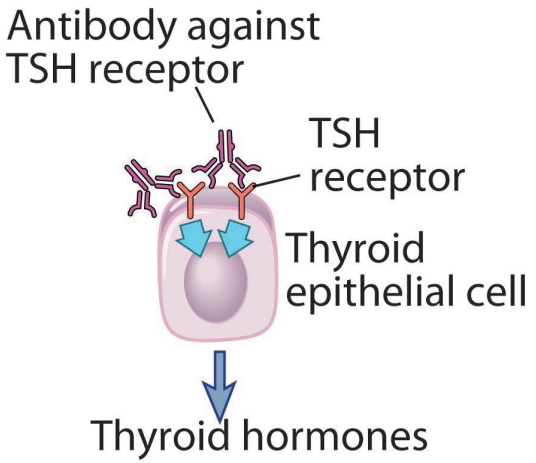


Autoantibodies can cause autoimmune disease

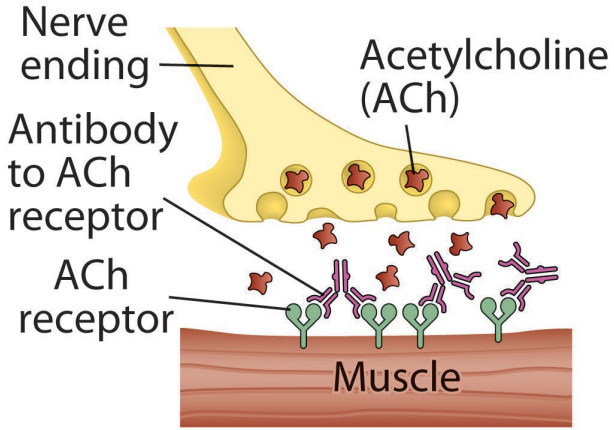
Grave's Disease

Myasthenia Gravis

Abnormal physiologic responses without cell/tissue injury



Antibody stimulates receptor without ligand



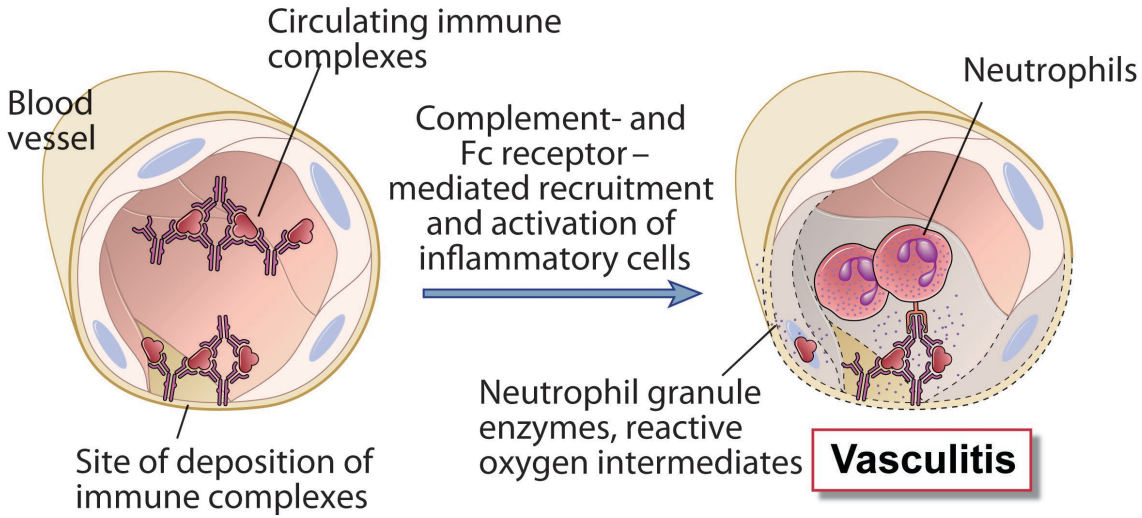
Antibody inhibits binding of ligand to receptor

ANCA (IgG anti-neutrophil cytoplasmic antibodies) in vasculitis

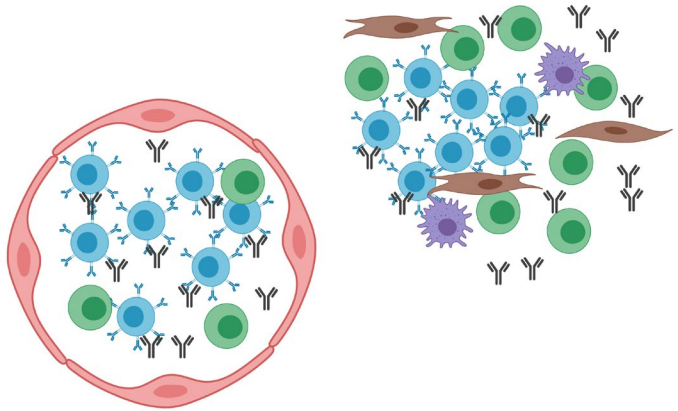
Immune complex–mediated tissue injury

Mechanism of antibody deposition

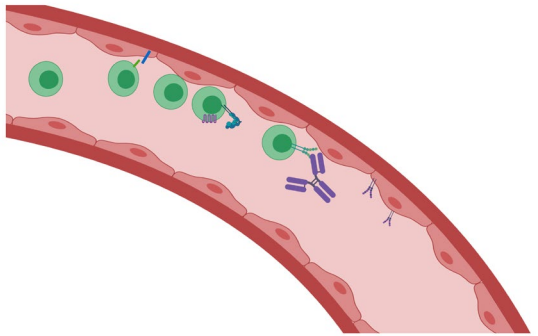
Effector mechanisms of tissue injury



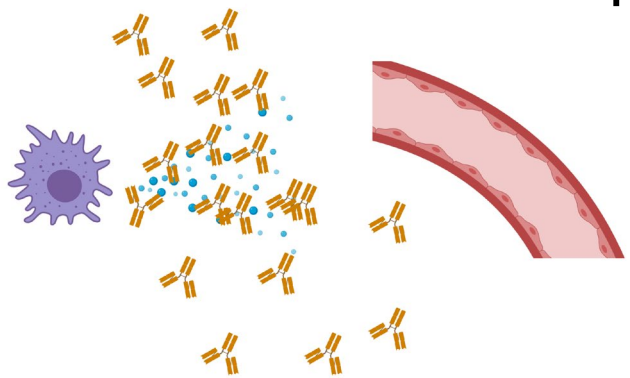
Monoclonal antibodies are used as therapeutics



DEPLETE
CELLS

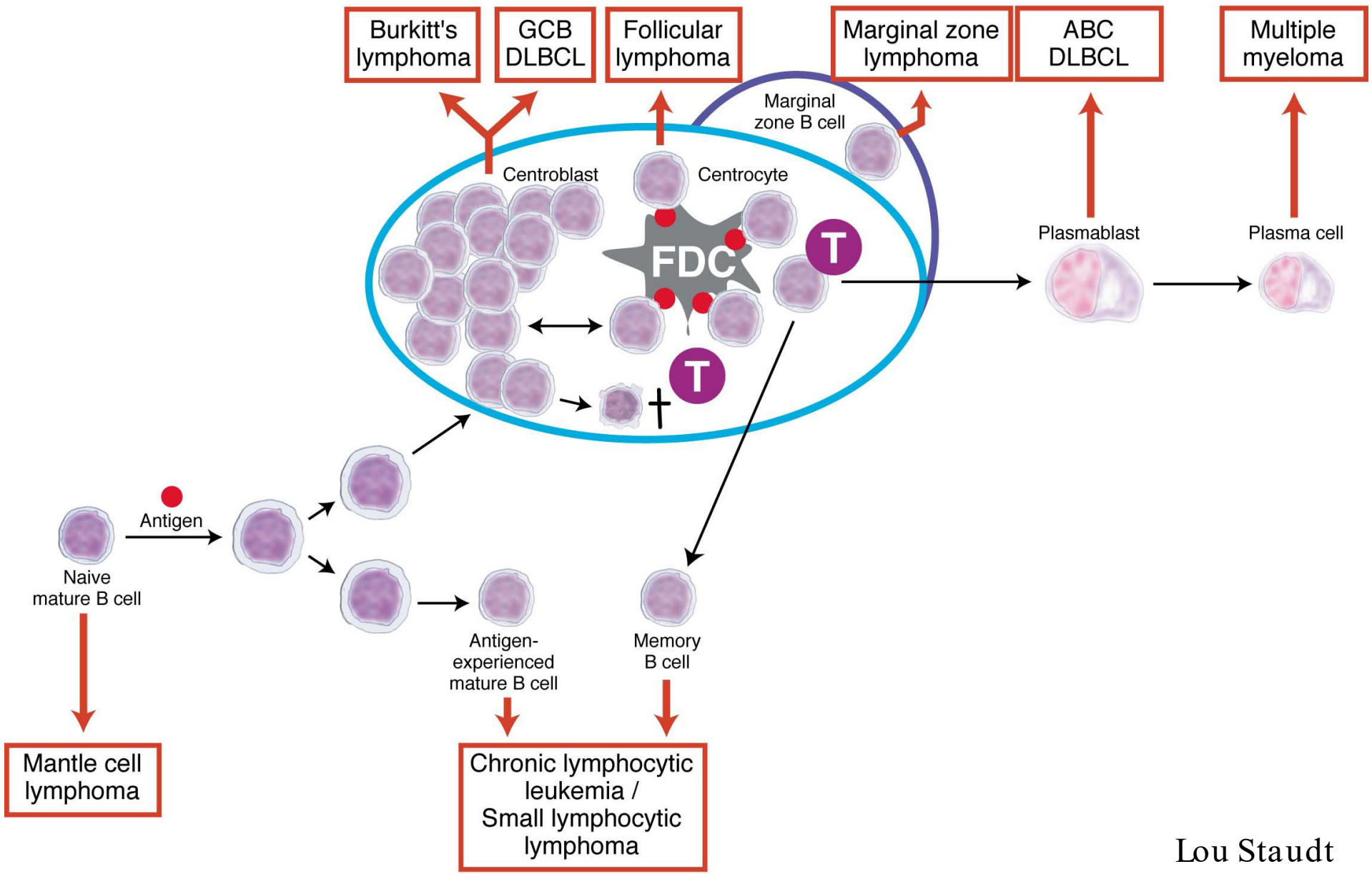


BLOCK
MIGRATION



BLOCK CYTOKINES OR RECEPTORS
OR COMPLEMENT

B Cell Development: A Disaster Waiting to Happen



Lou Staudt

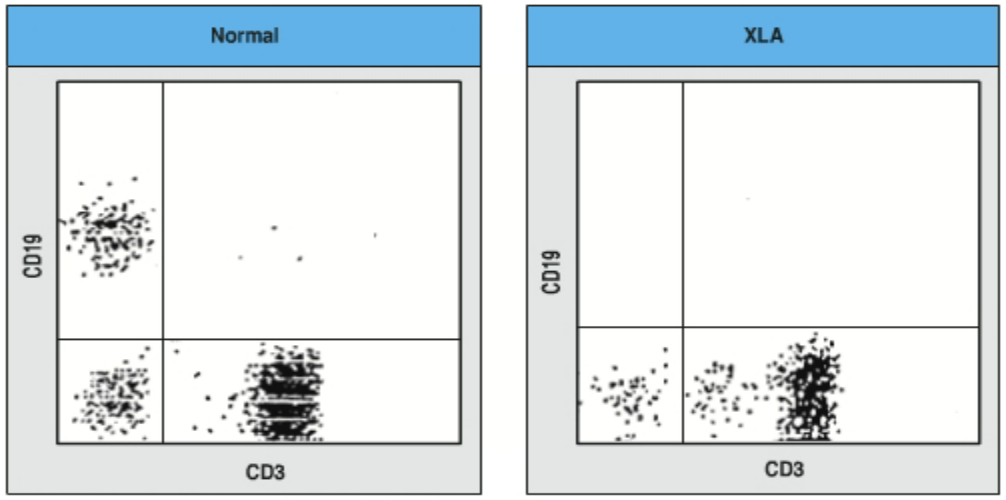
B cell defects cause multiple types of immunodeficiencies

X-linked/Bruton's Aggammaglobulinemia

- Defect in Btk with arrested B cell development

HyperIgM

- Lack of T cell help: X-linked defect in CD40L
- Normal B cell numbers & IgM without other Ig classes
- Increased pyogenic and opportunistic infections



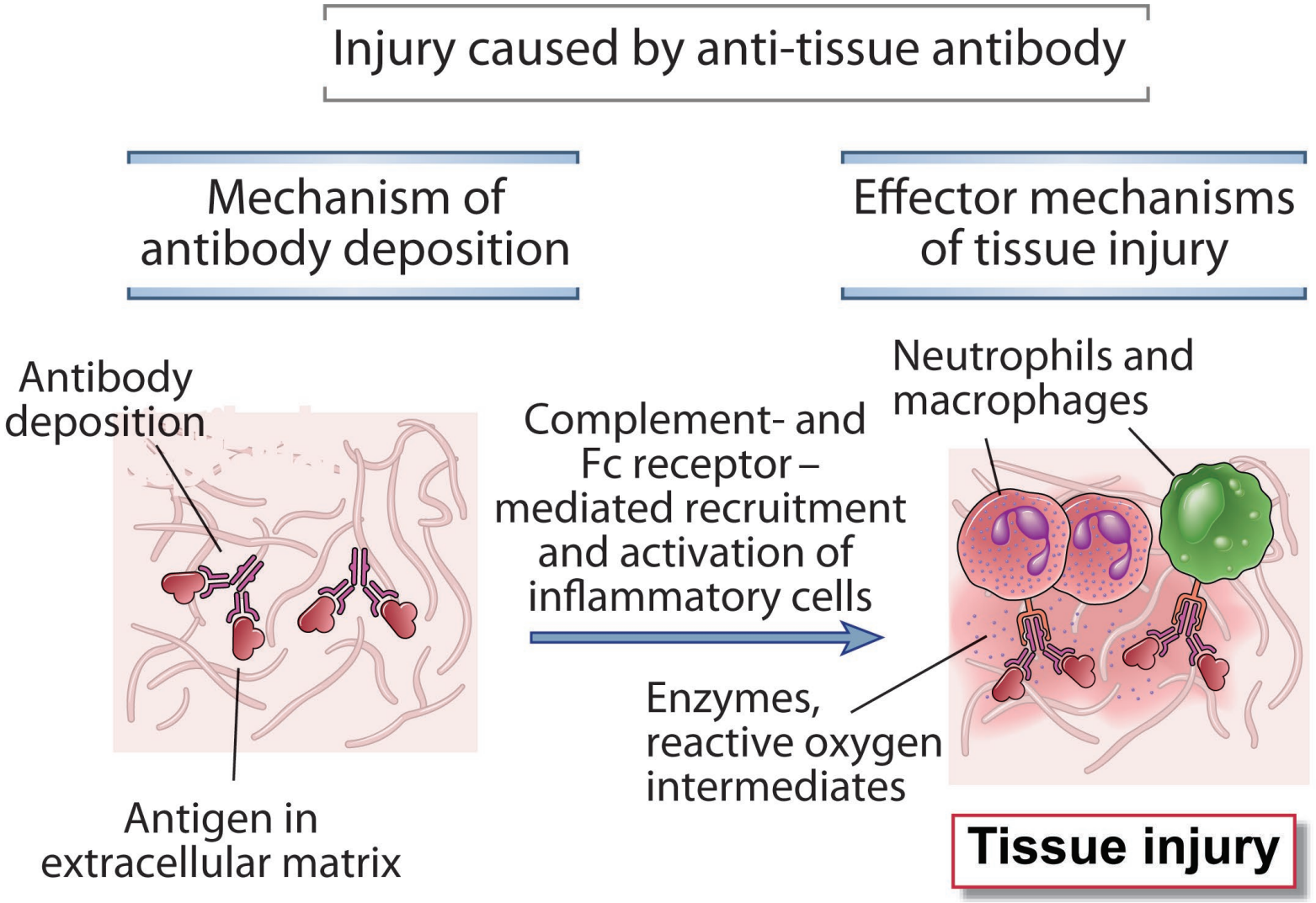
IgA deficiency

- Frequently asymptomatic
- Increased risk for mucosal infections
- Autoimmune association
- Blood transfusion risk (antibodies against IgA)

Common variable immunodeficiency (CVID)

- Multiple etiologies and numerous underlying mutations that effect B cell function & reduced memory B cells
- Overall low immunoglobulins and impaired vaccine responses
  - Low IgG, low IgA, and low or normal IgM
- Increased risk for bacterial, enteroviral and Giardia lamblia infections in late childhood and adulthood
- Autoimmune association and increased risk for lymphoma

Antibodies can cause inflammation and tissue destruction



Thanks to

- Shiv Pillai
- Kristy Wolniak
- Abbas Textbook
- Janeway Textbook

Questions?

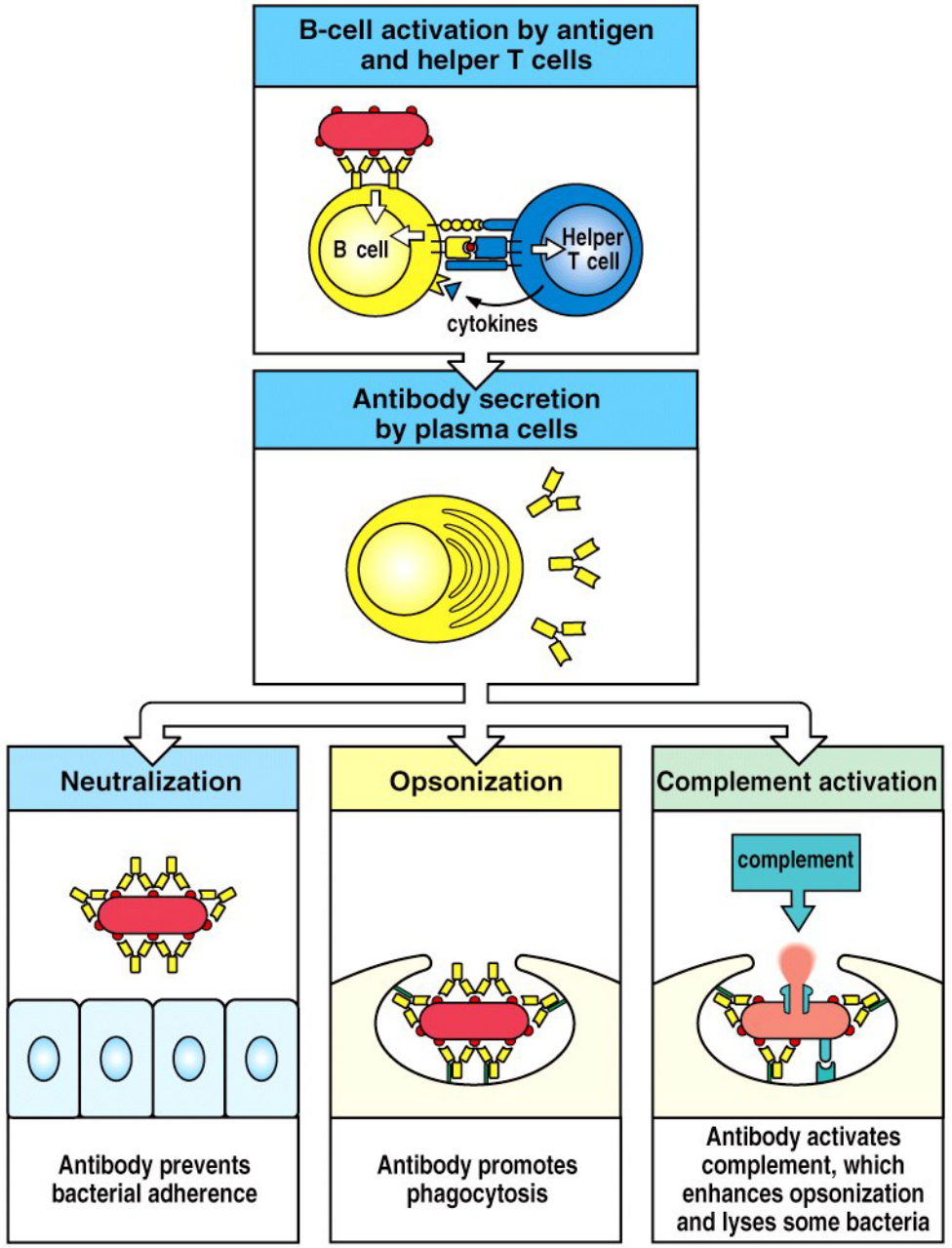
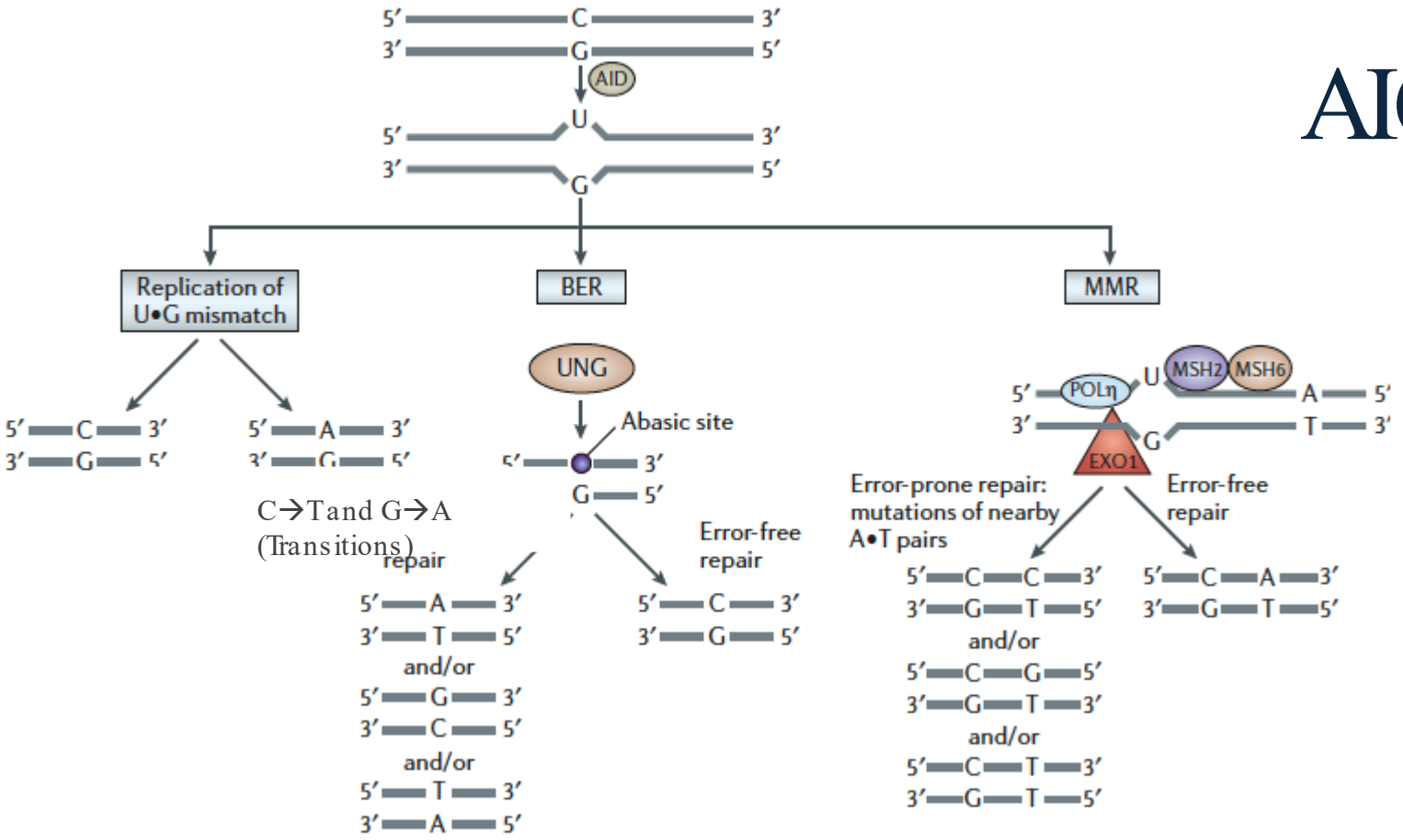


Figure 9-1 Immunobiology, 6/e. (© Garland Science 2005)

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



Based on Odegard and Schatz, NRI 2009

AICD (aka AID)

Activation Induced Cytidine Deaminase

CONVERTS C TO U IN SINGLE STRANDED DNA