


1


B Cells and Antibodies

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2

Lecture outline

- Functions of antibodies
- B cell activation; the role of helper T cells in antibody production
- Therapeutic targeting of B cells

3

The Importance of Antibodies

- Humoral immunity is the defense mechanism against extracellular microbes
 - Most current vaccines work by stimulating effective antibody responses
- Antibodies are mediators of many immune/inflammatory diseases
- Antibodies are used as therapeutic agents

Take home messages

4

Principles of Humoral Immunity

- Antibodies are produced only by B lymphocytes.
- Humoral immune responses are initiated by binding of antigen to membrane bound antibody on B cells.
- Antibody responses are specialized and enhanced by signals from helper T cells.
- Activated B cells secrete soluble antibodies of the same specificity as the membrane receptors.

Take home messages

5

Structure of antibody molecules

The diagram illustrates the structure of an antibody molecule. It consists of two heavy chain domains (VH and CH1) and two light chain domains (VL and CL). The variable regions (VH and VL) contain the Complement-Determining Regions (CDRs), which are responsible for antigen binding. The constant regions (CH1 and CL) determine the antibody's class. A 3D model shows the antibody binding to an antigen.

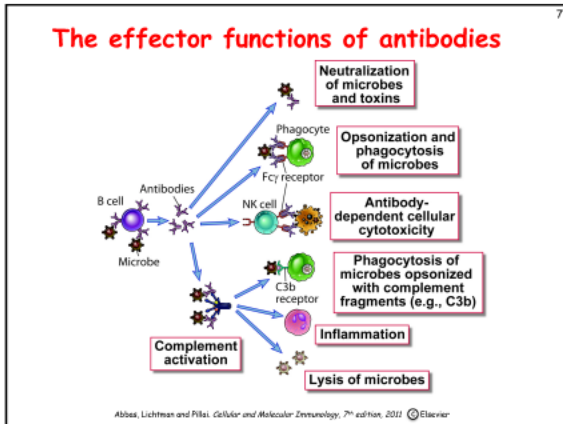
Diverse immunoglobulin (Ig) molecules with different specificities are generated by recombination of gene segments and variations introduced at sites of recombination.

6

B cell activation and antibody production

The flowchart depicts the process of B cell activation and antibody production. It is divided into two main phases: the Recognition phase and the Activation phase. In the Recognition phase, a Resting IgM^{+} , IgD^{+} mature B cell binds to an Antigen. In the Activation phase, the B cell is activated by Helper T cells and other stimuli, leading to Clonal expansion. This results in the formation of Plasma cells (which secrete IgM), IgG-expressing B cells (which undergo Isotype switching to produce IgG), High-affinity Ig-expressing B cells (which undergo Affinity maturation to produce High-affinity IgG), and Memory B cells.

Abbas, Lichtman and Pillai. Cellular and Molecular Immunology, 7th edition, 2011 © Elsevier



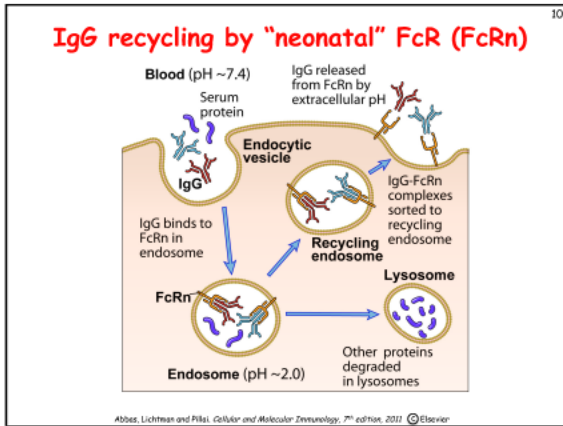
Leukocyte Fc receptors

- Activating Fc receptors on phagocytes (macrophages, neutrophils) ingest opsonized microbes for destruction: FcγRI
- Fc receptor on NK cells binds to opsonized cells and kill the cells (ADCC): FcγRIII
- Fc receptors with other functions: FcγRII, neonatal Fc receptor (FcRn)

Take home messages

Inhibitory Fc receptors

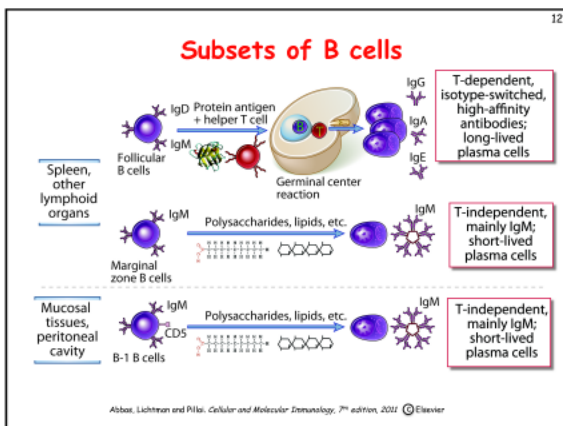
- One class of Fc receptor on B cells (also macrophages and DCs) delivers inhibitory signals: FcγRII
- Function and clinical significance:
 - Terminates B cell responses after antibodies are produced (Ab engages inhibitory FcR): antibody feedback
 - Intravenous IgG (IVIg) is used to treat inflammatory diseases; may work by engaging inhibitory FcR
 - Mutations in *FcγRIIb* gene associated with lupus-like disease in mice; humans? (uncontrolled B cell activation)

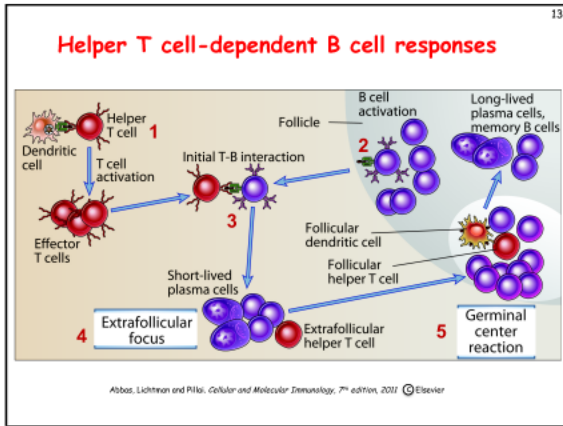


T-independent (TI) and T-dependent (TD) antibody responses

- **TI:** B cells can recognize a wide variety of chemical structures (proteins, polysaccharides, lipids) and make antibodies against these
 - T-independent responses occur in the absence of T cell help (since T cells can recognize only MHC-associated peptides)
 - Relatively simple antibody responses
- **TD:** Helper T cells help B cells and stimulate isotype switching, affinity maturation, and generation of long-lived plasma cells and memory cells
 - T-dependent responses can occur only against proteins (the antigens for T cells)
 - These are the most varied and effective ("sophisticated") antibody responses

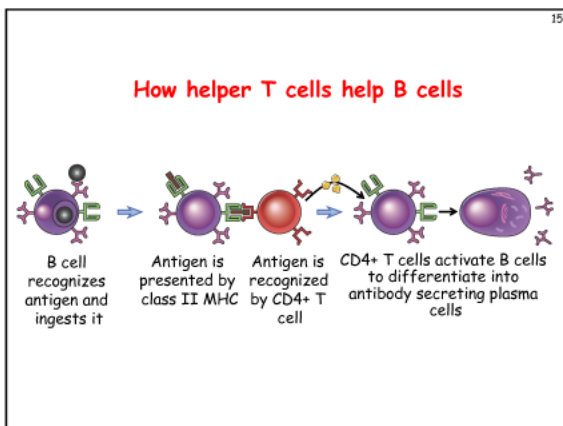
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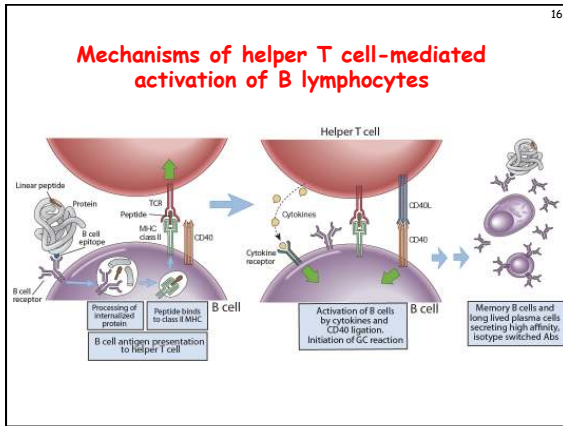




Antibody responses

	<u>Extrafollicular</u>	<u>Follicular</u>
Class switching	Limited	Extensive
Somatic mutation	Low rate	High rate
Antibody affinity	Low	High
Plasma cells	Short-lived (~3 days)	Long-lived (years)





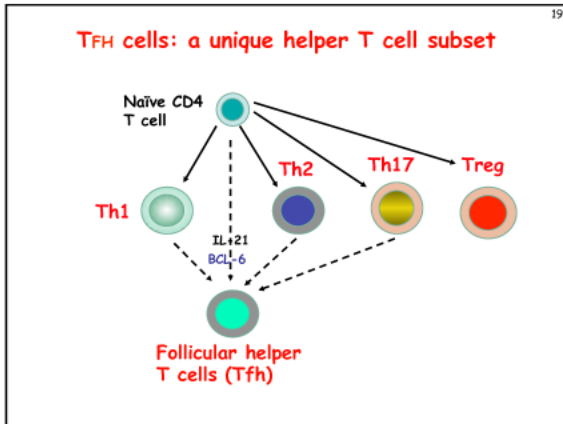
Actions of helper T cells

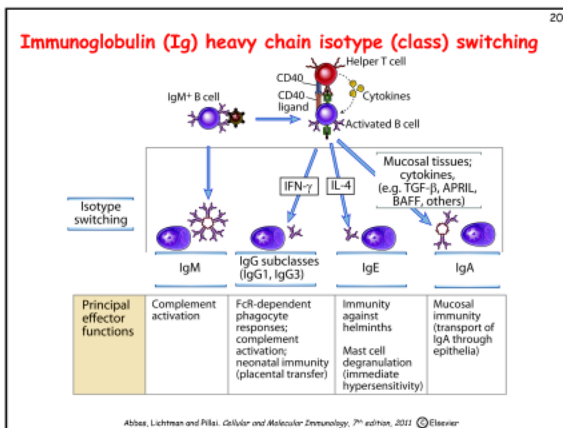
- **Helper T cells stimulate B cells to produce large amounts of antibodies, undergo isotype switching and affinity maturation, and generate long-lived plasma cells and memory B cells**
 - Mostly in germinal centers
 - Role of follicular helper T cells
 - Many of the reactions are dependent on induction of the enzyme AID in B cells

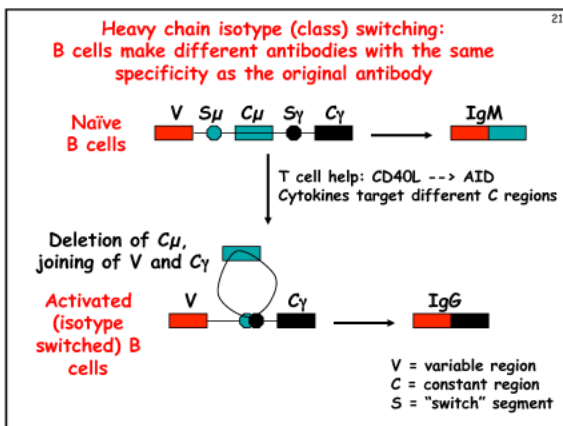
Take home messages

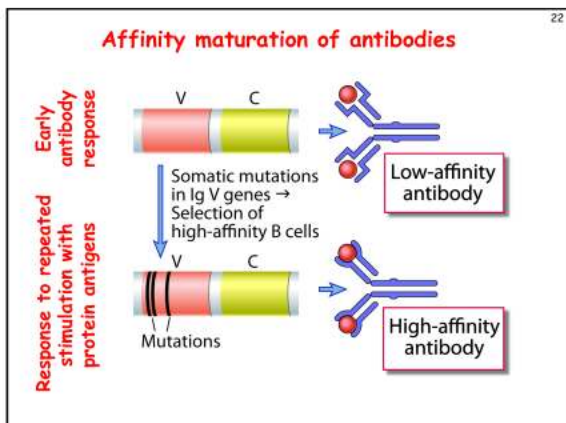
Follicular helper T cells (Tfh)

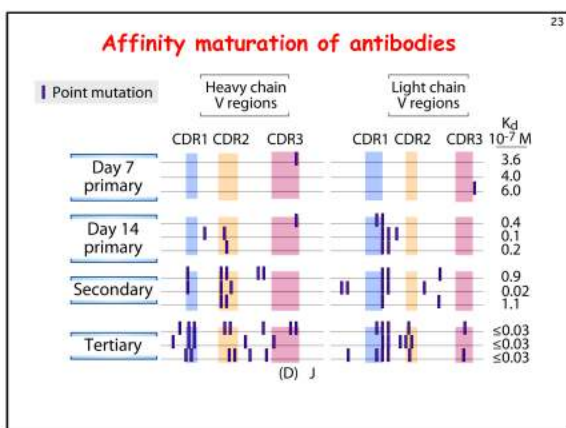
- **Some effector T cells express the chemokine receptor CXCR5, migrate to lymphoid follicles, and help B cells (isotype switching, affinity maturation)**
- **Characteristics of Tfh:**
 - Surface CXCR5, ICOS
 - Transcription factor: **BCL-6**
 - Cytokines secreted: IL-21 + IL-4 or IFN γ (or IL-17?)

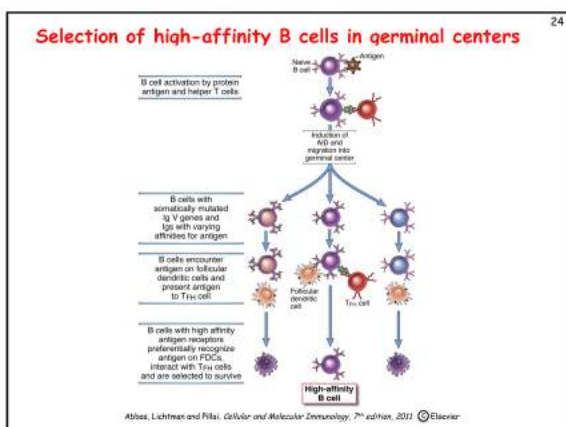












25

Activation-induced deaminase (AID)

- Enzyme induced in B cells by Tfh signals (mainly via CD40); deaminates cytosines to uracils
- Role in isotype switching: DNA breaks created at sites of Us in switch regions; repair leads to recombination of different switch regions
- Role in affinity maturation: Us in V regions are removed, repaired by error-prone repair enzymes → mutations

26

Plasma cells and memory B cells

- Plasma cells generated during GC reaction migrate to bone marrow and survive for years, producing antibody
 - Much of circulating IgG is produced by long-lived plasma cells, provides initial protection
- Some activated B cells develop into memory cells, which recirculate and do not secrete antibody but can be rapidly reactivated to become plasma cells
 - Choice of plasma cells vs memory cells is determined by expression of different transcription factors in the activated B cells

Take home messages

27

The germinal center reaction

- Site of development of sophisticated antibody responses
 - Isotype switching, affinity maturation, long-lived plasma cells, memory B cells
 - Driven by follicular helper T cells (assays for blood Tfh cells in humans?)
- Need to maximize the reaction for development of effective vaccines
- Does dysregulation of the GC reaction contribute to autoimmune diseases?
 - Strong autoantibody responses
 - Generation of self-reactive B cells?
