B cell activation and antibody production

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FOCiS
Lecture outline

• B cell activation; the role of helper T cells in antibody production

• Therapeutic targeting of B cells
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.
- Activated B cells secrete soluble antibodies of the same specificity as the membrane receptors.
- Antibody responses are specialized and enhanced by signals from helper T cells.
IgG recycling by “neonatal” FcR (FcRn)
B cell activation and antibody production

- Antigen recognition
- Activation of B lymphocytes
- Proliferation
- Differentiation

Effector functions
- Effector cells: antibody secreting plasma cells

- Antibody secretion
- Isotype switching
- Affinity maturation

Naive IgM⁺, IgD⁺ B cell

Activated B cell

Helper T cells, other stimuli

High-affinity IgG-expressing B cell

Memory B cell
**T-independent and T-dependent antibody responses**

**T-independent (TI)**
- clonal expansion; differentiation

**T-cell dependent (TD)**
- 'activation' signal but no clonal expansion
- clonal expansion; differentiation

- **T-independent** antigens are multivalent (e.g. bacterial polysaccharides or repeating determinants on the surface of viruses)
  - responses are fast (within 1-2 days) and predominantly IgM
  - weak in infants and young children

- **T-dependent** antigens must contain a protein component (true of most antigens) so that T cell help can be received
  - responses slower (several days), produce all Ig isotypes (IgM, IgG, IgA, IgE)
  - stronger and can lead to antibody affinity maturation and memory
Steps in T-dependent B cell activation

Initial T-B interaction

Dendritic cell  Antigen

T cell zone

Helper T cell

Initial T-B interaction

B cell zone
(primary follicle)

Antigen

B cell
Steps in T-dependent B cell activation

**Initial T-B interaction**
- Dendritic cell
- Antigen
- Helper T cell
- B cell

**B cell activation**
- Short-lived plasma cells
- Follicular dendritic cell
- Extrafollicular helper T cell
- Follicular helper T (Tfh) cell
- Germinal center B cells
- Long-lived plasma cells
- Extrafollicular focus
- Germinal center reaction
Mechanisms of helper T cell-mediated activation of B lymphocytes

Activated helper T cell expresses CD40L, secretes cytokines

B cells are activated by CD40 engagement, cytokines

B cell proliferation and differentiation
The germinal center reaction

- Some B cells that are activated outside follicles migrate back to form germinal centers, where they undergo isotype switching and affinity maturation, and generate long-lived plasma cells and memory B cells
  - Driven by T cell help (follicular helper T cells)
  - Many of the reactions are dependent on induction of the enzyme AID in B cells
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 IFNγ (or IL-17?)
Immunoglobulin (Ig) heavy chain isotype (class) switching

**Principal effector functions**

<table>
<thead>
<tr>
<th>IgM</th>
<th>IgG subclasses (IgG1, IgG3)</th>
<th>IgE</th>
<th>IgA</th>
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<tbody>
<tr>
<td>Complement activation</td>
<td>Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)</td>
<td>Immunity against helminths</td>
<td>Mucosal immunity (transport of IgA through epithelia)</td>
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</table>

**Helper T cells:** CD40L, cytokines

**Cytokines produced in mucosal tissues, e.g. TGF-β, BAFF, others**

**Various**

IL-4
Ig Heavy chain class (isotype) switching

IgM+ naive B cell

IgG+ memory cell

IgG secreting plasma cell

VDJ  μ  γ  ε  α
55 kb

AID = Activation Induced Deaminase

T cell help (cytokines, CD40L)
Affinity maturation of antibodies

Early antibody response

Response to repeated stimulation with protein antigens

Somatic mutations in Ig V genes ⇒ Selection of high-affinity B cells

Mutations

Low-affinity antibody

High-affinity antibody
“Darwinian” selection of the “fittest” high-affinity B cells in germinal centers

B cell activation by protein antigen and helper T cells

B cells with somatically mutated Ig V genes and IgGs with varying affinities for antigen

B cells with high-affinity membrane Ig bind antigen on follicular dendritic cells (FDCs) and present antigen to helper T cells

B cells that recognize antigen on FDCs or interact with helper T cells are selected to survive; other B cells die
Plasma cells

• Following immunization, serum antibody is detectable for a long time but there are no plasma cells in lymph nodes or spleen
  • Who is making the antibody and where?
Plasma cells

- Following immunization, serum antibody is detectable for a long time but there are no plasma cells in lymph nodes or spleen
  - Who is making the antibody and where?

- Plasma cells generated during GC reaction migrate to bone marrow (and mucosal tissues) and survive for years, producing antibody
  - Much of circulating IgG is produced by long-lived plasma cells, provides initial protection
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?