Effector mechanisms of humoral immunity

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Introduction

• Von Behring & kitasato in 1890

...the diphtheria antitoxin serum
Overview

• Targets of humoral immunity:
  ...extracellular microbes and their toxins: -bacteria
  -fungi
  -even viruses?!

• The most effective vaccines are those that stimulate antibody responses

• Can be harmful to tissues in allergy and certain autoimmune diseases
Overview, cont’d

• Antibodies perform their effector functions at sites distant from their production
  ...from lymph nodes, spleen and bone marrow to the blood
  ...across mucosa to lumen
  ...across placenta

• Activation of
  
  Naïve B cells or Memory B cells  →  Short-lived or long-lived antibody-producing plasma cells  →  antibodies

T cells cannot
Overview, cont’d

• Plasma cells derived early or those derived from marginal zone or B1 cells...usually short-lived

• Germinal center-derived class-switched antibody-secreting plasma cells...migrate to bone marrow and produce antibodies for years after the antigen is eliminated ➔ Most of IgG found in serum

...if exposed again, these antibodies in serum are the immediate response, and the memory cell activation will provide a larger burst of antibody production
Overview, cont’d

- **Functions of antibody isotypes in general:**

  - IgG: - opsonization
    - activation of classical complement pathway
    - antibody-dependent cell-mediated cytotoxicity by NK cells
    - Neonatal immunity
    - Feedback inhibition of B cells activation

  - IgM: - activation of classical complement pathway
    - an antigen receptor of naïve B cells (with IgD)

  - IgA: - mucosal immunity (secreted into the lumen)
    - activation of lectin and alternative complement pathway

  - IgE: mast cell degranulation
The major stimuli of isotype switching:
- Cytokines from T cells
- CD40 ligand on activated helper T cells

Due to different microbes:
- Viruses and many bacteria: TH1 response...TH1-dependent IgG isotypes
- Helminths...TH2-dependent IgE antibodies
Functions of antibodies

• Neutralization of microbes and microbial toxins
  ...examples: -influenza uses its envelope hemagglutinin
   -Gram (-) bacteria use pili
   -Tetanus toxin
   -Diphtheria toxin
  ...antibody binding to microbial structures

No function of the Fc part here
Selected examples of vaccine-induced humoral immunity

• Polio vaccine

• Tetanus and diphtheria toxoids (DTP)

• Hepatitis A and B (recombinant viral envelope proteins)

• Pneumococcus and Haemophilus (conjugate vaccine of bacterial capsular polysaccharide and protein)
Functions of antibodies

• Opsonization and phagocytosis
  ...important receptors:
  - Fc gamma receptors...3 types
    * Fc gamma receptor I (CD64) has the highest affinity, and binds IgG1 and 3 ...its expression is induced by IFN-gamma
    * Fc gamma receptor IIB...inhibitory
Functions of antibodies

• Antibody-dependent cell-mediated cytotoxicity (ADCC)
  ...first described in NK cells (when they bind by their Fc receptors to Fc of antibodies coating the target cell)
  Then they secrete IFN-gamma and release their killing molecules
Functions of antibodies

- Antibody-mediated clearance of helminths
  ...IgG or IgA that coat helminths will bind to Fc receptors on eosinophils ➔ degranulation of major basic protein...etc.
  ...IgE receptors that recognized helminths...will induce mast cell degranulation via high-affinity IgE receptor

Chemokines and cytokines from mast cells also attract eosinophils and activate their degranulation

Bronchoconstriction + motility in GI and respiratory tracts ➔ clearance of helminths
How did B cells secrete antibodies that performed the functions that we have discussed???

(B cell activation and antibody production)
B cell activation and antibody production

• In secondary lymphoid organs, antigens are concentrated and displayed to incoming naïve B cells on specialized APCs (follicular dendritic cells (FDCs))

Only found in lymphoid follicles

They do not express MHC II molecules
...instead they retain Ag-Ab complexes on their surface by their Fc receptors or complement receptors
B cell activation and antibody production, cont’d

• Secondary lymphoid organs trap antigens:
  ...spleen ➔ blood-borne antigens
  ...lymph nodes ➔ antigens from afferent lymphatics
  ...mucosa-associated lymphoid tissues (MALT) ➔ antigens from surrounding mucosal epithelia

Examples:
- Peyer’s patches in gut
- tonsils
- (adenoids) in nasopharynx
B cell activation and antibody production, cont’d

• If the B cell does not encounter antigen it will go to the circulation again

• If the B cell encounters antigen, it will bind by BCR and internalize the complex, then the antigen is degraded...in lymph nodes, this occurs in follicles

• In case of protein antigens, the peptides will be carried with MHC II to the surface of B cell

• Now for the B cell to be activated, it needs another signal from an activated T cell (in case of protein antigens)...continue in next slide

...now B cells migrate into a region rich in T cells in secondary lymphoid organ

Paracortex in lymph node and periarteriolar lymphoid sheath in spleen
B cell activation and antibody production, cont’d

...the T cell became active because it recognized the Ag with MHC II on the APC (dendritic cell)

*These protein antigens required B-cell-T-cell collaboration
...and they are called: Thymus-dependent (TD) antigens

= T cell-dependent antigens
B-cell-T-cell collaboration

Activation of T cell; expression of CD40 ligand, cytokine secretion

Activation of B cell by cytokines and CD40 ligation

B cell proliferation and differentiation

Dendritic cell

B7-1 and B7-2 are costimulators on DC

Helper T cell

Cytokines

Cellular and Molecular Immunology, Abbas 6th edition...modified
• Upon B cell activation, some become plasma cells which migrate to bone marrow or intestinal lamina propria (where they secrete the Abs for several weeks)
...others go to the follicle where they proliferate rapidly and form the germinal center...somatic hypermutation occurs here
B cell activation and antibody production, cont’d

• Now the affinity of BCRs is tested by the antigens carried on FDCs

  ...high-affinity binding ➔ positive selection (by survival signals from germinal center FDCs and T cells)

  These also stimulate isotype switching

• The positively-selected B cells will undergo more rounds of proliferation, affinity maturation, and plasma cell or memory cell differentiation
B cell activation and antibody production, cont’d

• A brief discussion about thymus-independent (TI) antigens

This is a type of TI that reacts and cross-links BCRs because it has multiple epitopes with same specificity (polyvalent)

They are generally non-protein molecules, e.g., lipids, polysaccharides, nucleic acids...etc.
TI antigens

Another type of TI (different from that in the previous figure) activates alternative pathway of complement generating C3d which binds antigen and augments B cell activation...through complement receptor

Macrophages in splenic marginal zones are particularly efficient in trapping polysaccharide antigens...activate splenic marginal zone B cells

B-1 B cells also respond readily to TI antigens (mainly in peritoneum & mucosal sites)

Also when they secrete natural antibodies (due to polysaccharides from normal flora)

- low affinity
- antibodies are mainly of IgM type
- limited isotype switching to some IgG subtypes
- no affinity maturation
- most are polyvalent
Thank You