# Distribution and function of Antibody isotypes (continued)

Antibody production in newborns (Fig. 9.24)

- between 3-12months babies are most susceptible to infection because maternal IgG is lost from the circulation, IgA (milk) from mother is reduced and their adaptive immune system is not yet mature

- IgE: return to this isotype in allergy discussion below

### Effector functions

## Neutralization

Mostly carried out by IgG and IgA, abundant in extracellular spaces and body cavities, respectively.

1. Virus

- Viral infection can be blocked by neutralizing antibodies.

- i.e. influenza and **hemagglutinin** (HA) --binds to certain carbohydrates expressed on epithelial cells of respiratory tract. (Fig. 9.25; recommend reading the figure caption)

2. Bacterial attachment

- Some bacteria need to attach to epithelial cells (i.e. Gonorrhea) or extracellular matrix (e.g. Strep) in order to infect.

- IgA can bind and neutralize attachment. (Fig. 9.26)

3. Toxins

- Many toxins harm by mimicking cellular counterparts

- Many toxins can harm in very small quantities: important for the Ab to diffuse into the tissue fast, bind toxins rapidly and with high affinity.

- Neutralization prevents toxin attachment to host cells (Fig. 9.28)

- Immunization: diphtheria and tetanus toxins are denatured (now called **toxoid**) and given to infants. Toxoids lack toxic activity but retain the antigenic epitopes and therefore induce an immune response to the toxoid and the native toxin.

- **Passive immunization**: when there is no time to induce adaptive immunity (snake venom), neutralizing Ab from another organism is injected (horse).

Complement activation

- Antibodies can activate the complement cascade, which is called the classical pathway (also refers to activation initiated by C-reactive protein, chapter 2).

- IgG (esp. 1 and 3) and IgM are potent complement activators. (Fig. 9.29)

- C1q does not bind to free pentameric IgM or monomeric IgG. Antibody-antigen binding causes changes in Ab conformation (pentameric IgM🡪 **planar** to **staple** form; Fig. 9.30) or Ab clustering (IgG, Fig. 9.34, left), and these can be recognized by C1q.

- the alternative C3 convertase amplifies complement deposition initiated by the classical pathway (Fig. 9.32)

- high affinity IgG can bind to pathogen fragments and activate complement, leading to formation of immune complexes (Fig. 9.34, right)

CR1 is most important for clearing immune complexes from blood

expressed on RBCs

when blood passes through the liver, macrophages strip off the immune complexes from RBC surface (Fig. 9.35)

too much circulating immune complex leads to kidney damage, important in lupus

Opsonization

- **Fc receptors**, which are receptors that bind to the Fc portion of an antibody, are expressed on **effector cells**. These include macrophages, dendritic cells, granulocytes, mast cells. There are many different Fc receptors, each binding to a different isotype.

- Different cell types express different sets of Fc receptors.

- FcR, FcR, and FcR: bind to IgG, IgE and IgA, respectively. (Fig. 9.46)

- Fc receptors belong to the Ig superfamily.

- FcRs are multi-protein complexes (separate Ab binding and signaling components).

- Q: Why don't you get constant activation of effector cells bearing Fc receptors? After all, there are free antibodies circulating in the body at all times.

A: Only when Abs bind to the surface of a pathogen do you get clustering of Ab. This increases avidity of the Fc receptor-Ab interaction. At the same time clustering (and therefore activation) of FcR occurs. Both of these are required for FcR activation.

Types of effector functions initiated by opsonization:

A. Phagocytosis (Fig. 9.41)

- Macrophages, monocytes and neutrophils have **Fc** **receptors** (mainly FcRI) that can bind opsonized pathogens and initiate phagocytosis.

-What if the pathogen is too big for phagocytosis? In such cases (i.e. parasites) effector cells surround the parasite and releases granular contents directly toward the pathogen. The eosinophil is the most common agent of parasitic immune response. (Fig. 9.45)

- IgM doesn't opsonize directly (no Fc receptor for IgM) but leads to complement deposition on pathogen; important for clearance of encapsulated bacteria such as *Strep pneumoniae*

B. **ADCC** (antibody-dependent cell-mediated cytotoxicity)

- NK cells are capable of direct cell lysis.

- They express FcRIII that can recognize opsonized antigens expressed on target cells. Such targets would include virally infected cells that express some viral proteins on cell surface.

- Opsonization of the target triggers lysis of the cell by NK cells through similar mechanisms to that of CTL. (Fig. 9.43)

C. Mast cells and IgE

- IgE: very low levels in blood or extracellular fluid. Mostly bound to mast cell Fc receptors and participates in allergic responses

- Mast cells found in vascularized connective tissues just beneath epithelial layer (including submucosal tissues of gastrointestinal and respiratory tracts). (Fig. 9.23)

- Contains **histamine** and other granule contents that cause **vasodilation** - results in increased blood flow (and therefore migration of effector cells and factors) to the site of immune response.

- FcR has a high affinity for IgE; most IgE in your system is found already bound to FcR on mast cells and basophils.

- Antigen causes crosslinking of FcR and this in turn causes release of granules. (Fig. 9.44)

- mast cell degranulation critical for immunity to parasites in developing world; for example, mast cell activation in gut leads to expulsion of GI contents. In developed countries where parasites are not common, mast cells and IgE are mainly a nuisance 🡪 allergy and asthma

B CELL DEVELOPMENT

Life of a B cell (Fig. 6.1)

B cell precursors rearrange VDJ in the bone marrow.

Immature B cells that are self-reactive are eliminated.

Mature B cells circulate from blood to secondary lymphoid tissues (Fig. 6.2) where they survey for foreign antigens.

Activated B cells give rise to plasma cells and memory B cells.

B cell development occurs in several stages: brief overview (Fig. 6.4)

1) Stem cell (common lymphoid progenitor)

2) **Pro-B** cell stage: two stages - early and late pro-B cell stages. H chain rearrangement

3) **Pre-B** cell stage: two stages - large pre-B cell and small pre-B cell. L chain rearrangement.

4) **Immature B cell**: IgM is expressed on the surface.

Immature B cells (with surface IgM) are subject to selection for self-tolerance; B cells with the IgM that's reactive to self epitopes are eliminated/inactivated during this stage.

5) **Mature B cells**: B cells that have undergone selection now express IgM and IgD on the surface by alternative splicing. They are also called **naive** B cells until they encounter antigens.

Bone marrow provides the environment for B cell maturation. (Fig. 6.5)

- **Bone marrow stromal cells** provide the necessary factors and ligands to B cells for development.

- Stem cells isolated from the bone marrow fail to develop into B cells in vitro unless bone marrow stromal cells are also present.

1) Cell-to-cell contact: Bone marrow stromal cells express adhesion molecules to which B cells bind. **Adhesion molecules** are receptors expressed on the cell surface that allow cell-to-cell adhesion. Many cell types need to be in contact with others in order to survive. Adhesion molecules and their ligands often signal (usually for cell survival), so the B cells may receive signals through adhesion molecules expressed on the stromal cells.

2) Secreted factors: Bone marrow stromal cells also secrete several factors that guide B cells through different stages of development: **SCF** (stem cell factor, recognized by very early B cells), **IL-7** (recognized by late pro-B and pre-B cells), and chemokines (small cytokines involved in migration and activation of immune cells).