Lec.8: Immunoglobulins

Functions of Immunoglobulins:

The main categories of antibody action include the following:

- Neutralization, in which neutralizing antibodies block parts of the surface of a bacterial cell or virion to render its attack ineffective
- Agglutination, in which antibodies "glue together" foreign cells into clumps that are attractive targets for phagocytosis
- Precipitation, in which antibodies "glue together" serum-soluble antigens, forcing them to precipitate out of solution in clumps that are attractive targets for phagocytosis
- Opsonization ,refers to the ability of antibodies to promote and/or enhance the engulfment of antigens by phagocytes. In the case of opsonization, binding of pathogen (antigen)-antibody complexes to an Fc receptor on phagocytes will induce internalization of the complex and internal digestion of the pathogen in lysosomes .
- Antibody-dependent cell-mediated cytotoxicity (ADCC) ,antibody-antigen complexes are bound by Fc receptors on NK cells and granulocytes, thus directing the cytotoxicity of these cells toward the antigen targeted by the antibody.
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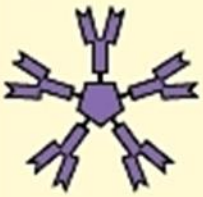
- Complement activation (fixation), in which antibodies that are latched onto a foreign cell encourage complement to attack it with a membrane attack complex, which leads to the following:
  - Lysis of the foreign cell
  - Encouragement of inflammation by chemotactically attracting inflammatory cells

Name	Type	Description
IgA	2	Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogensAlso found in

		saliva, tears, and breast milk.
IgD	1	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens.It has been shown to activate basophils and mast cells to produce antimicrobial factors.
IgE	1	Binds to allergens and triggers histamine release from mast cells and basophils, and is involved in allergy. Also protects against parasitic worms.
IgG	4	In its four forms, provides the majority of antibody-based immunity against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to the fetus.
IgM	1	Expressed on the surface of B cells (monomer) and in a secreted form (pentamer) with very high avidity. Eliminates pathogens in the early stages of B cell-mediated (humoral) immunity before there is sufficient IgG.

Isotype	Structure	Placental transfer	Binds mast cell surfaces	Binds phagocytic cell surfaces	Activates complement	Additional features
IgM		-	-	-	+	First Ab in development and response.
IgD		-	-	-	-	B-cell receptor.
IgG		+	-	+	+	Involved in opsonization and ADCC. Four subclasses; IgG1, IgG2, IgG3, IgG4.
IgE		-	+	-	-	Involved in allergic responses.
IgA		-	-	-	-	Two subclasses; IgA1, IgA2. Also found as dimer (sIgA) in secretions.

Table 43.1 The Five Classes of Immunoglobulins

IgM (pentamer) 	IgMs are the first circulating antibodies to appear in response to an initial exposure to an antigen; their concentration in the blood then declines rapidly. Thus the presence of IgM usually indicates a current infection. IgM consists of five Y-shaped monomers arranged in a pentagonal structure. The numerous antigen-binding sites make it very effective in agglutinating antigens and in reactions involving complement. IgM is too large to cross the placenta and does not confer maternal immunity.
IgG (monomer) 	IgG is the most abundant of the circulating antibodies. It readily crosses the walls of blood vessels and enters tissue fluids. IgG also crosses the placenta and confers passive immunity on the fetus. IgG protects against bacteria, viruses, and toxins in the blood and lymph, and triggers action of the complement system.
IgA (dimer) 	IgA is produced by cells in mucous membranes. The main function of IgA is to prevent the attachment of viruses and bacteria to epithelial surfaces. IgA is also found in many body secretions, such as saliva, perspiration, and tears. Its presence in the first milk produced helps protect the infant from gastrointestinal infections.
IgD (monomer) 	IgD antibodies do not activate the complement system and cannot cross the placenta. They are mostly found on the surfaces of B cells, probably functioning as antigen receptors that help initiate the differentiation of B cells into plasma cells and memory B cells.
IgE (monomer) 	IgE molecules are slightly larger than IgG and represent only a small fraction of the antibodies in the blood. The tails attach to mast cells and basophils and, when triggered by an antigen, cause the cells to release histamine and other chemicals that cause an allergic reaction.

Immunoglobulins variants :

An antigenic determinant is the specific chemical determinant group or molecular configuration against which the immune response is directed. Because they are proteins, immunoglobulins themselves can function as effective antigens when used to immunize mammals of a different species.

When the resulting anti immunoglobulins or antiglobulins are analyzed, three principal categories of antigenic determinants can be recognized—isotype, allotype, and idiotype :

1-Isotype Determinants

Isotypes are antigenic determinants that characterize classes and subclasses of heavy chains and types and subtypes of light chains . Isotypes are the dominant type found on the immunoglobulins of all animals of a species.

Importance

Antibodies to isotypes are used for the quantitation of Ig classes and subclasses in various diseases, in the characterization of B cell leukemia and in the diagnosis of various immunodeficiency diseases.

2-Allotype Determinants

The second principal group of determinants is found on the immunoglobulins of some, but not all, animals of a species. Antibodies to these allotypes (alloantibodies) may be produced by injecting the immunoglobulins of one animal into another member of the same species.

The allotypic determinants are genetically determined variations representing the presence of allelic genes at a single locus within a species. Different members of a species will therefore differ from one another with respect to which particular alleles of a given isotype they received from their parents. The presence of particular allotypes, like isotypes, can be readily detected in those normal sera in which they are present.

Allotypes represent slight differences in the amino acid sequences of heavy or light chains of different individuals. Even a single amino acid difference can give rise to an allotypic determinant, although in many cases there are several amino acid substitutions that have occurred.

In practice however we obtain anti-allotype antisera from women who have had multiple pregnancies or from people who have received blood transfusions or from some patients with rheumatoid arthritis.

In man the allotypic differences are localized to the constant region of the heavy and light chains .

Individual allotypes are found in individual members of a species. All allotypes are not found in all members of the species. The prefix Allo means different in individuals of a species.

Importance:

1. Monitoring bone marrow grafts - Bone marrow grafts that produce a different allotype from the recipient can be used to monitor the graft.
2. Forensic medicine - Km and Gm allotypes are detectable in blood stains and semen and are useful in forensic medicine.
3. Paternity testing - The immunoglobulin allotypes are one of the characteristics used in legal cases involving paternity.

3-Idiotype Determinants

An antigenic specificity (epitope) which distinguishes a particular combination of the antigen recognition site from all others. Thus, a particular monoclonal immunoglobulin (a myeloma protein, for example) will bear an idiotype different from any other. Unlike isotypes or allotypes, particular idiotypes can generally be detected only in sera from myeloma patients. Idiotypes are localized on the Fab fragment of the Ig molecules.

Identical specificity means that all antibodies molecules have the exact same hypervariable regions.

Idiotypes are localized on the Fab fragment of the Ig molecules. Specifically, they are localized at or near the hypervariable regions of the heavy and light chains. In many instances the actual antigenic determinant (i.e. idiotype) may include some of the framework residues near the hypervariable region.

Importance

1. V region marker - Idiotypes are a useful marker for a particular variable region.

2. Regulation of immune responses - there is evidence that immune responses may be regulated by anti-Id antibodies directed against our own Id's.

3. Vaccines - In some cases anti-idiotypic antibodies actually stimulate B cells to make antibody and thus they can be used as a vaccine. This approach is being tried to immunize against highly dangerous pathogens that cannot be safely used as a vaccine.

4. Treatment of B cell tumors - Anti-idiotypic antibodies directed against an idiotype on malignant B cells can be used to kill the cells. Killing occurs because of complement fixation or because toxic molecules are attached to the antibodies.

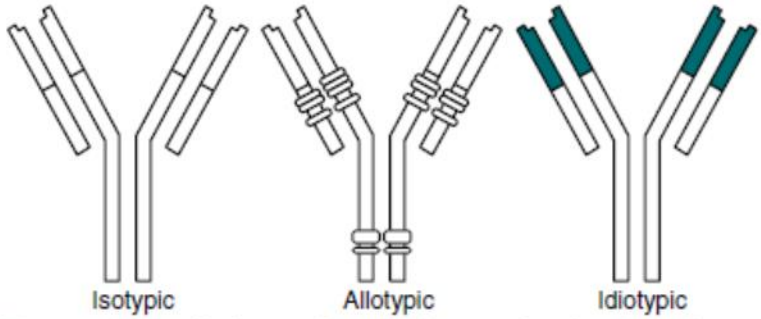


Figure 2-13 Variants of antibodies—antigenic determinants. *(Adapted from Turgeon ML: Fundamentals of immunohematology, ed 2, Baltimore, 1995, Williams & Wilkins.)*

ANTIBODY SYNTHESIS

The production of antibodies (B lymphocytes and plasma cells) directed against the antigen. Production of antibodies is induced when the host's lymphocytes come into contact with a foreign antigenic substance that binds to its receptor. This triggers activation and proliferation, or clonal selection. Clonal expansion of lymphocytes in response to infection is necessary for an effective immune

response. However, it requires 3 to 5 days for a sufficient number of clones to be produced and to differentiate into antibody-producing cells. This allows time for most pathogens to damage host tissues and cells Whether a cell-mediated response or an antibody response takes place depends on how the antigen is presented to the lymphocytes; many immune reactions display both types of responses. The antigenicity of a foreign substance is also related to the route of entry. Intravenous and intraperitoneal routes are stronger stimuli than subcutaneous and intramuscular routes.

Subsequent exposure to the same antigen produces a memory response, or anamnestic response, and reflects the outcome of the initial challenge. In the case of antibody production, the quantity of IgM-IgG varies.

Primary Antibody Response

Although the duration and levels of antibody (titer) depend on the characteristics of the antigen and the individual, an IgM antibody response proceeds in the following four phases after a foreign antigen challenge :

1. Lag phase—no antibody is detectable.

2. Log phase—the antibody titer increases logarithmically.

3. Plateau phase—the antibody titer stabilizes.

4. Decline phase—the antibody is catabolized.

Secondary (Anamnestic) Response

Subsequent exposure to the same antigenic stimulus produces an antibody response that exhibits the same four phases as the primary response . Repeated exposure to an antigen can occur many years after the initial exposure, but clones of memory cells will be stimulated to proliferate, with subsequent production of antibody by the individual.

An anamnestic response differs from a primary response as follows:

1-Type of antibody. IgM-type antibodies are the principal class formed in the primary response. Although some IgM antibody is formed in a secondary response, the IgG class is the predominant type formed.

2- Antibody titer. In a secondary response, antibody levels attain a higher titer. The plateau levels in a secondary response are typically 10-fold or greater than the plateau levels in the primary response.

An example of an anamnestic response can be observed in hemolytic disease, when an Rh-negative mother is pregnant with an Rh-positive baby . During the mother's first exposure, the Rh-positive RBCs of the fetus leak into the maternal circulation and elicit a primary response. Subsequent pregnancies with an Rh-positive fetus will elicit a secondary (anamnestic) response.

Class switching[

Class switching is a biological process occurring after activation of the B cell, which allows the cell to produce different classes of antibody (IgA, IgE, or IgG). The different classes of antibody, and thus effector functions, are defined by the constant (C) regions of the immunoglobulin heavy chain. Initially, naive B cells express only cell-surface IgM and IgD with identical antigen binding regions. Each isotype is adapted for a distinct function; therefore, after activation, an antibody with an IgG, IgA, or IgE effector function might be required to effectively eliminate an antigen. Class switching allows different daughter cells from the same activated B cell to produce antibodies of different isotypes. Only the constant region of the antibody heavy chain changes during class switching; the variable regions, and therefore antigen specificity, remain unchanged. Thus the progeny of a single B cell can produce antibodies, all specific for the same antigen, but with the ability to produce the effector function appropriate for each antigenic challenge. Class switching is triggered by cytokines; the isotype generated depends on which cytokines are present in the B cell environment.

Class switching occurs in the heavy chain gene locus by a mechanism called class switch recombination (CSR). This mechanism relies on conserved nucleotide motifs, called switch (S) regions, found in DNA upstream of each constant region gene (except in the δ-chain). The DNA strand is broken by the activity of a series of enzymes at two selected S-regions. The variable domain exon is rejoined

through a process called non-homologous end joining (NHEJ) to the desired constant region (γ, α or ε). This process results in an immunoglobulin gene that encodes an antibody of a different isotype.