

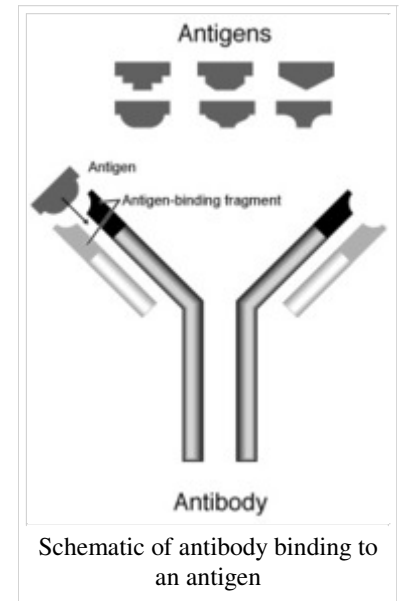
# Antibody

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An **antibody** is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. The production of antibodies is called the humoral immune system.

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## Definition

Immunoglobulins are glycoproteins in the immunoglobulin superfamily that function as antibodies. The terms *antibody* and *immunoglobulin* are often used interchangeably. They are found in the blood and tissue fluids, as well as many secretions. In structure, they are globulins (in the  $\gamma$ -region of protein electrophoresis). They are synthesized and secreted by plasma cells that are derived from the B cells of the immune system. B cells are activated upon binding to their specific antigen and differentiate into plasma cells. In some cases, the interaction of the B cell with a T helper cell is also necessary.

## Structure of the antibody

Immunoglobulins are heavy plasma proteins, often with added sugar chains (see glycosylation) on N-terminal (all antibodies) and occasionally O-terminal (IgA1 and IgD) amino acid residues.

The basic unit of each antibody is a monomer. An antibody can be monomeric, dimeric, trimeric, tetrameric, pentameric, etc. The monomer is a "Y"-shape molecule that consists of two identical heavy chains and two identical light chains connected by disulfide bonds.

There are five types of heavy chain:  $\gamma$ ,  $\delta$ ,  $\alpha$ ,  $\mu$  and  $\epsilon$ . They define classes of immunoglobulins. Heavy chains  $\alpha$  and  $\gamma$  have approximately 450 amino acids, while  $\mu$  and  $\epsilon$  have approximately 550 amino acids. Each heavy chain has a

constant region, which is the same by all immunoglobulins of the same class, and a variable region, which differs between immunoglobulins of different B cells, but is the same for all immunoglobulins produced by the same B cell. Heavy chains  $\gamma$ ,  $\alpha$  and  $\delta$  have the constant region composed of three domains but have a hinge region; the constant region of heavy chains  $\mu$  and  $\epsilon$  is composed of four domains. The variable domain of any heavy chain is composed of one domain. These domains are about 110 amino acids long. There are also some amino acids between constant domains.

There are only two types of light chain:  $\lambda$  and  $\kappa$ . In humans, they are similar, but only one type is present in each antibody. Each light chain has two successive domains: one constant and one variable domain. The approximate length of a light chain is from 211 to 217 amino acids.

The "Y"-shaped monomer has two heavy and two light chains. Together this gives six to eight constant domains and four variable domains. Each half of the forked end of the "Y" is called an Fab fragment. It is composed of one constant and one variable domain of each the heavy and the light chain, which together shape the antigen binding site at the amino terminal end of the monomer. The two variable domains bind their specific antigens.

The enzyme papain cleaves a monomer into two *Fab* (*fragment antigen binding*) fragments and an *Fc* (*fragment crystallizable*) fragment. The enzyme pepsin cleaves below hinge region, so a f(ab)<sub>2</sub> fragment and a fc fragment is formed.

Together, the antibodies in an organism can bind a wide variety of foreign antigens. Somatic recombination events generate this diversity. This is when genes are selected (variable (V), diversity (D) and joining (J) for heavy chains, and only V and J for light chains) to form countless combinations. The main reason that the human immune system is capable of binding so many antigens is the variable region of the heavy chain. To be specific, it is the area where these V, D and J genes are found - otherwise known as the complementarity determining region 3 (CDR3).

The Fc fragment, the stem of the "Y," is composed of two heavy chains that each contribute two to three constant domains (depending on the class of the antibody). Fc binds to various cell receptors and complement proteins. In this way, it mediates different physiological effects of antibodies (opsonization, cell lysis, mast cell, basophil and eosinophil degranulation and other processes).

The variable regions of the heavy and light chains can be fused together to form a single chain variable fragment (scFv), which retains the original specificity of the parent immunoglobulin.

A crude estimation of immunoglobulin levels can be made by protein electrophoresis. Here the plasma proteins are separated into albumin, alpha-globulins (1 and 2), beta-globulins (1 and 2) and gamma-globulins according to weight. Immunoglobulins are all in the gamma region. In myeloma and some other disease states, a very high concentration of one particular immunoglobulin will show up as a *monoclonal* band.

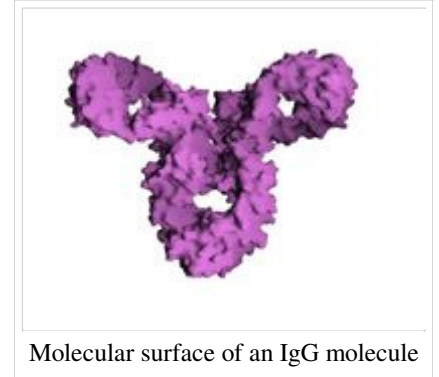
## Isotypes

According to differences in their heavy chain constant domains, immunoglobulins are grouped into five classes, or isotypes: *IgG*, *IgA*, *IgM*, *IgD*, and *IgE*. (The isotypes are also defined with light chains, but they do not define classes, so they are often neglected.) Other immune cells partner with antibodies to eliminate pathogens depending on which *IgG*, *IgA*, *IgM*, *IgD*, and *IgE* constant binding domain receptors it can express on its surface.

The antibodies that a single B lymphocyte produces can differ in their heavy chain, and the B cell often expresses different classes of antibodies at the same time. However, they are identical in their specificity for antigen, conferred by their variable region. To achieve the large number of specificities the body needs to protect itself against many different foreign antigens, it must produce millions of B lymphocytes. It is important to note that, in order to produce such a diversity of antigen binding sites with a separate gene for each possible antigen, the immune system would require many more genes than exist in the genome. Instead, as Susumu Tonegawa showed in 1976, portions of the genome in B lymphocytes can recombine to form all the variation seen in the antibodies and more. Tonegawa won the Nobel Prize in Physiology or Medicine in 1987 for his discovery.

## IgG

IgG is a monomeric immunoglobulin, built of two heavy chains  $\gamma$  and two light chains. Each molecule has two antigen binding sites. This is the most abundant immunoglobulin and is approximately equally distributed in blood and in tissue liquids. This is the only isotype that can pass through the placenta, thereby providing protection to the fetus in its first weeks of life before its own immune system has developed. It can bind to many kinds of pathogens, for example viruses, bacteria, and fungi, and protects the body against them by complement activation (classic pathway), opsonization for phagocytosis and neutralisation of their toxins. There are 4 subclasses: IgG1 (66%), IgG2 (23%), IgG3 (7%) and IgG4 (4%).



- IgG1, IgG3 and IgG4 cross the placenta easily.
- IgG3 is the most effective complement activator, followed by IgG1 and then IgG2. IgG4 does not activate complement.
- IgG1 and IgG3 bind with high affinity to Fc receptors on phagocytic cells. IgG4 has intermediate affinity and IgG2 affinity is extremely low.

## IgA

IgA represents about 15% to 20% of immunoglobulins in the blood, although it is primarily secreted across the mucosal tract into the stomach and intestines. This prevents microbes from binding to epithelial cells in the digestive and respiratory tracts. This immunoglobulin helps to fight against pathogens that contact the body surface, are ingested, or are inhaled. It does not activate complement, and opsonises only weakly. Its heavy chains are of the type  $\alpha$ . It exists in two forms, IgA1 (90%) and IgA2 (10%) that differ in the structure. IgA1 is composed like other proteins, however in IgA2 the heavy and light chains are not linked with disulfide but with noncovalent bonds. IgA1 is found in serum and made by bone marrow B cells, however IgA2 is made by B cells located in the mucosae and has been found to secrete into, colostrum, maternal milk, tears and saliva.

The IgA found in secretions have a special form. They are dimeric molecules, linked by two additional chains. One of these is the J chain (from join), which is a polypeptide of molecular mass 1,5 kD, rich with cysteine and structurally completely different from other immunoglobulin chains. This chain is formed in the antibody-secreting cells. The dimeric form of IgA in the outer secretions also has a polypeptide of the same molecular mass (1,5 kD) called the secretory chain and is produced by epithelial cells. It is also possible to find trimeric and even tetrameric IgA.

Decreased or absent IgA, termed *selective IgA deficiency*, can be a clinically significant immunodeficiency.

## IgM

IgM forms polymers where multiple immunoglobulins are covalently linked together with disulfide bonds, normally as a pentamer or occasionally as a hexamer. It has a large molecular mass of approximately 900 kD (in its pentamer form). The J chain is attached to most pentamers, while hexamers do not possess the J chain due to space constraints in the complex. Because each monomer has two antigen binding sites, an IgM has 10 of them, however it cannot bind 10 antigens at the same time because they hinder each other. Because it is a large molecule, it cannot diffuse well, and is found in the interstitium only in very low quantities. IgM is primarily found in serum; however, because of the J chain, it is also important as a secretory immunoglobulin. Due to its polymeric nature, IgM possesses high avidity, and is particularly effective at complement activation. It is also a so-called "natural antibody": it is found in the serum without any evidence of prior contact with antigen.

In germline cells, the gene segment encoding the  $\mu$  constant region of the heavy chain is positioned first among other constant region gene segments. For this reason, IgM is the first immunoglobulin expressed by mature B cells.

IgM is also by far the physically largest antibody in the circulation. IgM antibodies are mainly responsible for the

clumping (agglutination) of red blood cells if the recipient of a transfusion receives blood that is not compatible with his/her blood type.

## IgD

IgD makes up about 1% of proteins in the plasma membranes of immature B-lymphocytes (coexpressed with IgM) and is also found in serum in very small amounts. It is monomeric and incorporates the  $\delta$  heavy chain in its structure. IgD's function is currently unknown, as mice lacking IgD seem to retain normal immune responses (implying redundancy if not lack of function), and IgD ceases to be expressed in activated B-lymphocytes. It may function as a regulatory antigen receptor.

## IgE

IgE is a monomeric immunoglobulin with the heavy chain  $\epsilon$ . It contains a high proportion of carbohydrates. Its molecular mass is 190 kD. It can be found on the surface of the plasma membrane of basophils and mast cells of connective tissue. IgE may play a large role in defending against parasitic worms. IgE is mainly responsible for allergies, which are hypersensitivities to common substances such as pollen that is generally not harmful. The IgE antibodies are present also in outer excretions. They do not activate complement. Only IgE is heat-labile.

## Function

The antibodies have two primary functions:

- they bind antigens -- see below
- they combine with different immunoglobulin receptors specific for them and exert effector functions. These receptors are isotype-specific, which gives a great flexibility to the immune system, because different situations require only certain immune mechanisms to respond to antigens.

Affinity vs Avidity

- Affinity is the binding strength of the antibody to the antigen.
- Avidity is the number of antigen binding sites.

For example, IgG has higher affinity than IgM, but IgM has higher avidity.

## The humoral immune response

When a macrophage ingests a pathogen, it attaches parts of the pathogen's proteins to a class II MHC protein. This complex is moved to the outside of the cell membrane, where it can be recognized by a T lymphocyte, which compares it to similar structures on the cell membrane of a B lymphocyte. If it finds a matching pair, the T lymphocyte activates the B lymphocyte, which starts producing antibodies. A B lymphocyte can produce antibodies only against the structure it presents on its surface.

Antibodies exist freely in the bloodstream or bound to cell membranes. They are part of the humoral immune system. Antibodies exist in clonal lines that are specific to only one antigen, e.g., a virus hull protein. In binding to such antigens, they can cause agglutination and precipitation of antibody-antigen products primed for phagocytosis by macrophages and other cells, block viral receptors, and stimulate other immune responses, such as the complement pathway.

Antibodies that recognize viruses can block these directly by their sheer size. The virus will be unable to dock to a cell and infect it, hindered by the antibody. They can also agglutinate them so the phagocytes can capture them. Antibodies that recognize bacteria mark them for ingestion by phagocytes, a process called opsonization. Together with the plasma component complement, antibodies can kill bacteria directly. They neutralize toxins by binding with them.

It is important to note that antibodies cannot attack pathogens within cells, and certain viruses "hide" inside cells (as part of the lysogenic cycle) for long periods of time to avoid them. This is the reason for the chronic nature of many minor skin diseases (such as cold sores); any given outbreak is quickly suppressed by the immune system, but the infection is never truly eradicated because some cells retain viruses that will resume the apparent symptoms later.

## Medical applications

Detection of particular antibodies is a very common form of medical diagnostics. Serology depends on these methods. Autoimmune disorders can often be traced to antibodies that bind the body's own epitopes; many can be detected through blood tests. Antibodies directed against RBC surface antigens in immune mediated hemolytic anemia can be detected with the Coombs test. The Coombs test is also used for antibody screening in blood transfusion preparation and also for antibody screening in antenatal women.

"Designed" monoclonal antibody therapy is already being employed in a number of diseases (including rheumatoid arthritis) and in some forms of cancer. Presently, many antibody-related therapies are undergoing extensive clinical trials for use in practice.

## Biochemical applications

In biochemistry, antibodies are used for immunological identification of proteins, using the Western blot method. A similar technique is used in ELISPOT and ELISA assays, in which detection antibodies are used to detect cell secretions such as cytokines or antibodies. Antibodies are also used to separate proteins (and anything bound to them) from the other molecules in a cell lysate.

These purified antibodies are often produced by injecting the antigen into a small mammal, such as a mouse or rabbit. Sometimes, in order to obtain large quantity of antibodies, goats, sheep, or horses are used. Blood isolated from these animals contains *polyclonal antibodies* -- multiple antibodies that stick to the same antigen. The serum (=blood from which blood-clotting proteins and red-blood cells were removed), also known as the antiserum, because it now contains the desired antibodies, is commonly purified with Protein A/G purification or antigen affinity chromatography. If the lymphocytes that produce the antibodies can be isolated and immortalized, then a *monoclonal antibody* can be obtained.

Antibodies are also widely used in immunohistochemical staining.

## See also

- Immunology
- Immunosuppressive drug
- Monoclonal antibody

## References

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- Rhoades RA, Pflanzner RG (2002). *Human Physiology*, 4th ed., Thomson Learning. ISBN 0534421741.
- Janeway CA, Jr. *et al* (2001). *Immunobiology.*, 5th ed., Garland Publishing. (electronic full text via NCBI Bookshelf) (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=imm.TOC&depth=10>) ISBN 0-8153-3642-X.
- Janeway CA, Jr. *et al* (2005). *Immunobiology.*, 6th ed., Garland Science. ISBN 0443073104.

## External links

- How Lymphocytes Produce Antibody (<http://www.cellsalive.com/antibody.htm>)
- Recombination and the Evolution of the Adaptive Immune System (<http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0000016>)

## Antibody databases and protocols

- Antibody Search & Antibody Staining Protocols (<http://www.immunoport.com>)
- Antibody Staining Protocol Database ([http://www.ihcworld.com/antibody\\_staining.htm](http://www.ihcworld.com/antibody_staining.htm))
- Lymphomation: Immunoglobulins (<http://www.lymphomation.org/tests-immunoglobulins.htm>)

### Immune system

Humoral immune system | Cellular immune system | Immunological tolerance | Lymphatic system | White blood cells | **Antibodies** | Antigen (MHC) | Complement system | Inflammation | Clotting factors

### Immune system proteins

MAC complex | Perforin | Antibodies

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Categories: Glycoproteins | Immune system | Immunology

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