Antibody

An antibody is a proteinaceous substance belonging to the immunoglobulin family. It specifically binds to the antigen. The resulting bond has the character of non-covalent interactions. During a specific humoral-type immune response, these substances are formed by B-lymphocytes and **plasma cells**, which arise from B-lymphocytes as part of terminal differentiation. Immunoglobulins are found in vertebrates in *blood serum*, **body fluids** and also on the **surface of B-lymphocytes**. Antibodies have short half-lives - from 2 to 23 days. They play a crucial role in the body's defense.

Function

Antibodies are used to defend against:

- **extracellular** bacteria,
- **intracellular** bacteria (to a much lesser extent),
- **parasites**,
- **toxins** - by neutralizing the toxin, preventing the adhesion of the microorganism.

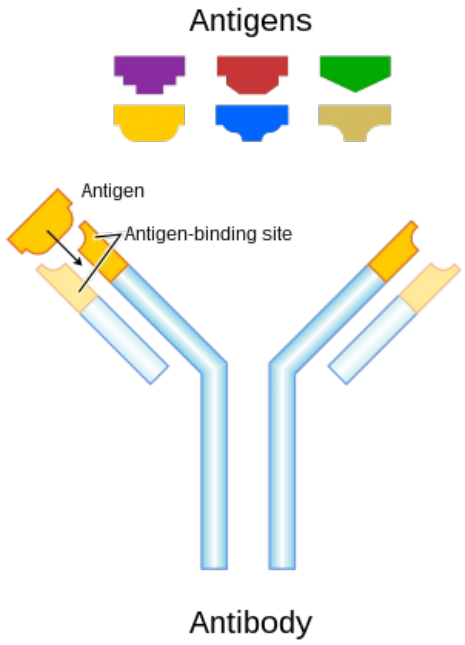
They activate some components of the immune system:

- **activate cytotoxic reactions** - by activating the complement cascade or NK-cells,
- **initiation of an inflammatory response** - degranulation of mast cells or basophils,
- **opsonization** - facilitating phagocytosis.

In vitro, antibodies for antigen-binding specificity are used to detect various molecules (immunochemistry, immunohistochemistry, ELISA, etc.).

Structure

Each antibody is composed of **two** identical **heavy** chains (designated H as *heavy*) and **two** identical **light** chains (L according to *light*). Light and heavy chains differ in the **number of amino acids** and **molecular weight**. The chains are linked together by **covalent disulfide bridges**. The whole macromolecule has the shape of the letter **ypsilon** with swinging arms. We always find one disulfide between the light and heavy chains; there is usually a different number between the two heavy chains - depending on the class and subclass of the antibody. Immunoglobulin chains can be divided into several according to certain similarities in the structure of **homologous domains**.



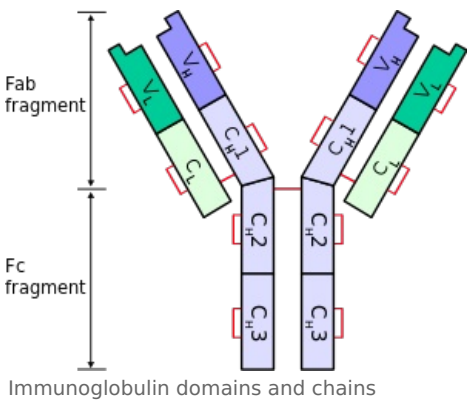
Immunoglobulin structure

Light chains

They consist of a **variable** and a **constant domain** - these are called $\mathbf{V_L}$ and $\mathbf{C_L}$. They occur in two types: **κ** and **λ**. These show some differences in the constant range. In one immunoglobulin molecule, **both** chains are always of the **same type**. In humans, the type κ is more common.

Heavy chains

They always have **one variable domain** and **three (IgA, IgD, IgG)** or **four (IgE, IgM) constants**. Similar to light chains, $\mathbf{V_H}$ and $\mathbf{C_H1\text{-}4}$ are referred to herein. For the division of antibodies into classes (*IgA, IgD, IgE, IgG, IgM),* the type of **heavy** chain that is present in the molecules is authoritative. There are **five** of these species - they are usually denoted by Greek letters (**α, δ, ε, γ, μ**). They differ in both **composition** and **size**. **The constant region**, formed by constant domains (**Fc fragment**) in the predominant heavy chains is **identical** in all antibodies of the same class. **The variable region** varies according to the B-cell clone by which it is produced. The sugar components of the molecule bind to the heavy chain.



Immunoglobulin domains and chains

Binding place

The light and heavy chain variable domains form a **binding site**. In fact, both chains do not occupy the conformation shown in the figure but are twisted into compact globules, so-called **immunoglobulin domains**. The cause of this internal rotation is *disulfide bridges*. Opposing domains always have a homologous amino acid sequence.

Hinge area

Immunoglobulin molecules can be cleaved by the plant enzyme papain. This takes place on a heavy chain in the so-called **hinge area**. The antibody can be divided into three parts:

- two parts containing both branched arms (ie the whole light and part of the heavy chain), the so-called **Fab-fragment**,
- the second part contains the remaining parts of both heavy chains, connected by disulfide bridges, the so-called **Fc-fragment**.

Antigens can bind to Fab fragments, and Fc fragments bind to **receptors on the surface of leukocytes**. Similarly, antibodies are cleaved by **pepsin**, but then one Fc fragment and one *bivalent* Fab fragment are formed.

Features

Hypervariable sections

The antigen specifically binds to the **variable regions of the heavy and light chains**. These allow immediate contact. These are actually cleats of the chains at their **N-termini**. They are the cause of **spatial complementarity**, reminiscent of the specific bond between the enzyme and the substrate.

Number of binding sites

Varies by immunoglobulin class:

- IgG has two (*bivalent*),
- secretory IgA four,
- IgM is theoretically ten, but the practical binding is only about half.

The antigen-antibody complex is not bound covalently, but only by **non-chemical interactions**. The formation does not correspond to stoichiometric conditions. If a **precipitate** is formed, its maximum amount corresponds to the equivalence zone - however, if there is an excess of any of the components, the amount of precipitate already decreases, because the **optimal spatial network** is not arranged (see figure). However, in some other types of interactions, immunocomplexes may be soluble.

Antigen-antibody complex size

It is very different. Some are so **large** that we can observe them with an electron microscope. **Small complexes** have a short half-life, do not bind complement and are not pathogenic. **Medium-sized complexes** are deposited in tissues and can thus be a characteristic feature of various diseases.

Antigen-antibody interactions

It can also cause:

- **clustering**,
- **lysis**,
- **immobilization of cells** (red blood cells),
- **complement fixation.**

In some cases, binding of the appropriate immunoglobulin may partially or even completely **neutralize the bacterial toxin**.

Antibody production and their other functions

The human body is capable of producing more than a **million** different antibodies. This huge diversity is not only caused by genes (there are only hundreds of them) - but each *L-chain* is the product of at least *three* separate genes, the *H-chain of four*.

Antibodies are active in several ways in defending the body. **Immunoglobulins** bound to surface antigens, e.g. in a microorganism, attract the **initial fragments** of the complement cascade (**C1**) and thus activate it in a **classical way**. This causes the **death of the bacterium** by two mechanisms:

1. **opsonization** - binding of antibody and certain components of complement - indicates the microorganism and attracts it for phagocytes,
2. **complement system** - creates a complex that forms **pores in the cytoplasmic membrane** and thus causes leakage of microbial organelles.

Immunoglobulins also form one of the components of lymphocyte receptors, **BCR** and **TCR**:

BCR

It is composed of its own **surface immunoglobulin**, with Ig heavy chains (most commonly **IgM** or **IgD**) crossing the membrane and **associated signalling molecules** - they also cross the membrane, these are referred to as **Igα** and **Igβ**. They are associated with *Janus-type cytoplasmic* **tyrosine kinases** (**JAK**). The binding of the antigen

to at least **two** BCR molecules brings the associated proteins closer together, activates the tyrosine kinases and **triggers the signalling cascade**.

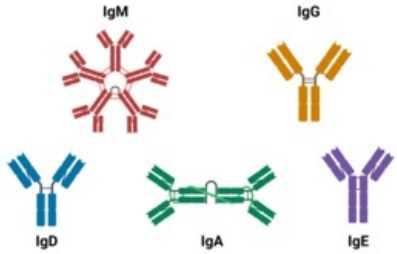
TCR complex

Composed of an immunoglobulin-like **antigen-recognizing module** - it is composed of transmembrane **α** and **β** or **γ** and **δ chains** and associated with the **CD3 complex of associated proteins**. **T-lymphocytes** with α-β type TCR receptors can only recognize antigen when bound to the surface of antigen-presenting cells, in complex with **MHC II proteins**.

Classes

According to the construction of the constant part of the heavy chain, we divide antibodies into **classes**. There is a significant difference between individual Ig classes in the representation of carbohydrates:

- in **IgG** - 2-3%,
- in **IgA** - 5-8%,
- in **IgM** - 12%,
- in **IgD** - 9-14%,
- in **IgE** - 12%.



Forms of immunoglobulins

IgG

IgG is the most important **class of antibodies**. It makes up ¾ all antibodies in the serum, its concentration is **10 g/l**. It creates 4 subclasses (IgG1-4), which differ from each other in their opsonization properties, binding to complement and the time for which they are active. It is also the only class of antibodies capable of crossing the placenta. Therefore, newborns have the same values as adults. The lowest level in a healthy individual is **between the 3rd and 6th months** of postnatal life (transient hypogammaglobulinemia). This leads to the susceptibility of newborns to infectious diseases.

Building

The IgG molecule is composed of two light and two heavy chains. Light chains consist of 1 variable and 1 constant immunoglobulin domain. Heavy chains are composed of 1 variable and 3 constant domains. IgG antibodies occur in monomeric form.

Importance

- **opsonization** - FcR receptors for IgG Fc fragments occur on neutrophils and macrophages,
- **complement activation in a classical way** - after IgG binding to antigen,
- **secondary immune response** - repeated encounter with antigen,
- **neutralization of toxins** - after IgG binding, the toxin is blocked and neutralized by the formation of an immunocomplex.

IgA

IgA antibodies are also called mucosal antibodies. This is because B-lymphocytes are produced , which occur in the mucous membranes. Their serum concentration is **1.5 g/l**, but overall they are the most abundant antibodies in the body. Their half-life is about 1 week.[1]

Structure

IgA antibodies are structurally similar to IgG. Their molecule consists of 2 light and 2 heavy chains. Light chains consist of 1 variable and 1 constant immunoglobulin domain. The heavy chain consists of 1 variable and 3 constant domains. Unlike IgG, they can occur as monomers , more often as **J-chain-linked** dimers. The dimeric form of IgA occurs in serum, when IgA is secreted to the mucosal surface, it is still associated with the so-called *secretory component*. It is a protein attached to a normal IgA dimer and protects the antibody against cleaving enzymes.[1]

Function

- **blockade of adhesion molecules** - they react with bacterial adhesion molecules,
- **opsonization** - binds to specific Fc-α-receptors of phagocytes.

IgA does not have the ability to activate complement.[1]

IgM

IgM antibodies make up 10% of all **antibodies** in the serum, with a concentration of **1-1.5 g/l**. IgM monomer is an integral part of the B-cell membrane (BCR). IgM has a short half-life, unlike IgG, they remain in plasma only shortly after the antigen is eliminated.

Structure

The whole IgM antibodies form a pentamer, the individual subunits are connected in a circle by cystine bridges and one J chain. Due to this structure, they do not penetrate into the tissues, they remain in the vascular bed. Theoretically, this arrangement creates 10 antigen-binding sites, in practice five are usable, and the others are spatially blocked. The subunits have a similar structure to IgE antibodies, their heavy chain consists of 1 variable and 4 constant immunoglobulin domains.

Function

- **activates complement** - after the binding of IgM to the antigen, complement binds to the immunocomplex, which is activated in a classical way,
- is the only one that responds to polysaccharide antigens (AB0 system),
- **agglutination** - IgM is able to bind a lot of antigens and therefore easily forms *agglutinate*.

At the onset of a specific immune response, they are generated first, their production does not require isotype switching. If a fetus infection occurs, IgM is present at birth. There is a small amount of secretory IgM production.

IgM **has no** opsonization function.

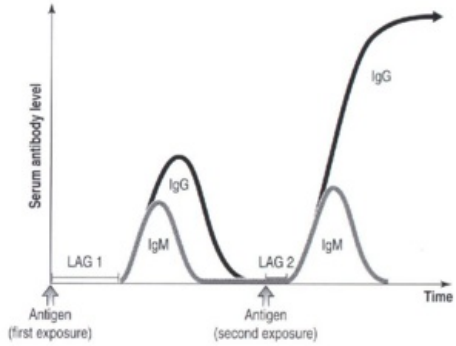
Diagnostic significance

- **for secondary immune responses** - positive IgM for antigen indicates an acute infection

It is especially effective against bacteria and viruses

IgD

Monomeric antibody. It is relatively under-represented in serum. It has a relatively low affinity for antigens. It is found mainly *on the surface of B-lymphocytes*, where it has the function of a **receptor for antigen** - it forms BcR (B-cellular receptor). It induces the **release of histamine** from mast cells and basophilic leukocytes. After binding to the antigen, it also participates in the **development of hay fever** or **allergic asthma**.



Antibody dynamics

IgE

Of all the antibodies, it has the shortest half-life. We find it in an amount even lower than IgD (serum concentration 0.5 g / l) - this also causes its short catabolic half-life. It is **homocytotropic** - it soon binds to other cells of its own body (mast cells, basophils) to FcεRI receptors. In the bound state, it is far more stable than a free one. It releases mediators of inflammation (histamine, serotonin, prostaglandins, leukotrienes).

IgE antibodies are responsible for **early hypersensitivity reactions**. Their increased concentration is common in **allergic** (atopic) **reactions**. They also have a role in antiparasitic defense (stimulates processes of expulsion): mediators, vasodilation, coughing, gutting, increased intestinal peristalsis, diarrhea. They occur especially in the spleen, tonsils, mucous membranes of the lungs and mucous membranes of the gastrointestinal tract.

Links

Realted articles

- Mucosal immune system
- Autoantibodies
- Therapeutic use of immunoglobulins
- IgG
- IgM
- IgA
- IgE and IgD
- Plasma proteins
- Antigen

References

1. HOŘEJŠÍ, Václav and Jiřina BARTŮŇKOVÁ. *Basics of immunology.* 3rd edition. Prague: Triton, 2008. 280 pp. ISBN 80-7254-686-4

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