THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
November, 2022; 2(11), 1837-1844

Immunoglobulins: Structure, Types and Applications

Rathod PG[1*], Chauhan JM[2]
[1*]Department of Veterinary Physiology and Biochemistry, College of Veterinary Science and Animal Husbandry, Navsari, Kamdhenu University, Gujarat, India
[2]Department of Veterinary Pathology, College of Veterinary Science and Animal Husbandry, Junagadh, Kamdhenu University, Gujarat, India

Introduction

An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y shaped protein produced mainly by plasma cells that is used by the immune system to neutralize pathogens such as pathogenic bacteria and viruses. The antibody recognizes a unique molecule of the pathogen, called an antigen, via the fragment antigen-binding (Fab) variable region. Each tip of the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for one particular epitope it is place where (similarly, analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can tag a microbe or an infected cell for attack by other parts of the immune system, or can neutralize its target directly (for example, by inhibiting a part of a microbe that is essential for its invasion and survival). Depending on the antigen, the binding may impede the biological process causing the disease or may activate macrophages to destroy the foreign substance. The ability of an antibody to communicate with the other components of the immune system is mediated via its Fc region (located at the base of the "Y"), which contains a conserved glycosylation site involved in these interactions. The production of antibodies is the main function of the humoral immune system.

Antibodies are secreted by B cells of the adaptive immune system, mostly by differentiated B cells called plasma cells. Antibodies can occur in two physical forms, a soluble form that is secreted from the cell to be free in the blood plasma, and a membrane-bound form that is attached to the surface of a B cell and is referred to as the B-cell receptor (BCR). The BCR is found only on the surface of B cells and facilitates the activation of these cells and their subsequent differentiation into either antibody

Popular Article
Published: 20.11.2022

factories called plasma cells or memory B cells that will survive in the body and remember that same antigen so the B cells can respond faster upon future exposure.

In most cases, interaction of the B cell with a T helper cell is necessary to produce full activation of the B cell and, therefore, antibody generation following antigen binding. Soluble antibodies are released into the blood and tissue fluids, as well as many secretions to continue to survey for invading microorganisms. Antibodies are glycoproteins belonging to the immunoglobulin superfamily. They constitute most of the gamma globulin fraction of the blood proteins. They are typically made of basic structural units—each with two large heavy chains and two small light chains.

There are several different types of antibody heavy chains that define the five different types of crystallisable fragments (Fc) that may be attached to the antigen-binding fragments. The five different types of Fc regions allow antibodies to be grouped into five isotypes. Each Fc region of a particular antibody isotype is able to bind to its specific Fc Receptor (except for IgD, which is essentially the BCR), thus allowing the antigen-antibody complex to mediate different roles depending on which FcR it binds. The ability of an antibody to bind to its corresponding FcR is further modulated by the structure of the glycan present at conserved sites within its Fc region. The ability of antibodies to bind to FcRs helps to direct the appropriate immune response for each different type of foreign object they encounter. For example, IgE is responsible for an allergic response consisting of mast cell degranulation and histamine release. IgE's Fab paratope binds to allergic antigen, for example house dust mite particles, while its Fc region binds to Fc receptor ε. The allergen-IgE-FcRε interaction mediates allergic signal transduction to induce conditions such as asthma.

Structure

Antibodies are heavy (~150 kDa) globular plasma proteins. The size of an antibody molecule is about 10 nm.[40] They have sugar chains (glycans) added to conserved amino acid residues.[4][41] In other words, antibodies are glycoproteins.[4] The attached glycans are critically important to the structure and function of the antibody.[4] Among other things the expressed glycans can modulate an antibody's affinity for its corresponding FcR(s). The basic functional unit of each antibody is an immunoglobulin (Ig) monomer (containing only one Ig unit); secreted antibodies can also be dimeric with two Ig units as with IgA, tetrameric with four Ig units like teleost fish IgM, or pentameric with five Ig units, like mammalian IgM. The variable parts of an antibody are its V regions, and the constant part is its C region.

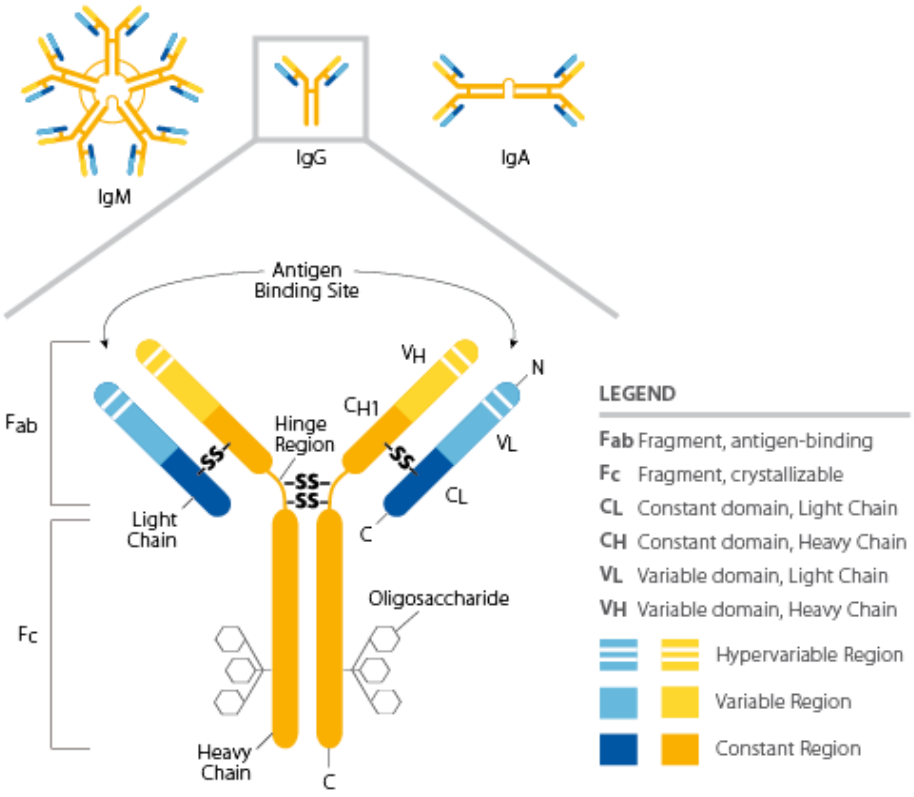
Heavy chain

Popular Article
Published: 20.11.2022

There are five types of mammalian Ig heavy chain denoted by the Greek letters: α, δ, ε, γ, and μ. The type of heavy chain present defines the class of antibody; these chains are found in IgA, IgD, IgE, IgG, and IgM antibodies, respectively.[1] Distinct heavy chains differ in size and composition; α and γ contain approximately 450 amino acids, whereas μ and ε have approximately 550 amino acids. Each heavy chain has two regions, the constant region and the variable region.

Light chain

In mammals there are two types of immunoglobulin light chain, which are called lambda (λ) and kappa (κ). A light chain has two successive domains: one constant domain and one variable domain. The approximate length of a light chain is 211 to 217 amino acids.



Types:

IgG

IgG molecules are created and released by plasma B cells. Each IgG has two antigen binding sites. IgG antibodies are large globular proteins with a molecular weight of about 150 kDa made of four peptide chains. It contains two identical γ (gamma) heavy chains of about 50 kDa and two identical light chains of about 25 kDa, thus a tetrameric quaternary structure. IgG is the most abundant antibody isotype in the blood (plasma) and extracellular fluid, accounting for 70-75% of human immunoglobulins (antibodies), allowing it to control infection of body tissues.

Popular Article
Published: 20.11.2022

Function

IgG detoxifies harmful substances and is important in the recognition of antigen-antibody complexes by leukocytes and macrophages. IgG is transferred to the foetus through the placenta and protects the infant until its own immune system is functional. IgG also plays an important role in antibody-dependent cell-mediated cytotoxicity (ADCC) and intracellular antibody-mediated proteolysis. IgG is also associated with type II and type III hypersensitivity reactions.

IgM

IgM is the largest antibody, and it is the first antibody to appear in the response to initial exposure to an antigen. In the case of humans and other mammals that have been studied, the spleen, where plasmablasts responsible for antibody production reside, is the major site of specific IgM production. IgM usually circulates in the blood, accounting for about 10% of human immunoglobulins. IgM has a pentameric structure in which five basic Y-shaped molecules are linked together. B cells produce IgM first in response to microbial infection/antigen invasion, Although, IgM has a lower affinity for antigens than IgG, it has higher avidity for antigens because of its pentameric/hexameric structure. IgM, by binding to the cell surface receptor, also activates cell signaling pathways.

IgA

Immunoglobulin A (IgA, also referred to as sIgA in its secretory form) is an antibody that plays a crucial role in the immune function of mucous membranes. The amount of IgA produced in association with mucosal membranes is greater than all other types of antibodies combined. In absolute terms, between three and five grams are secreted into the intestinal lumen each day. This represents up to 15% of total immunoglobulins produced throughout the body. IgA is abundant in serum, nasal mucus, saliva, breast milk, and intestinal fluid, accounting for 10-15% of human immunoglobulins. IgA forms dimers (i.e., two IgA monomers joined together). IgA in breast milk protects the gastrointestinal tract of neonates from pathogens.

IgE

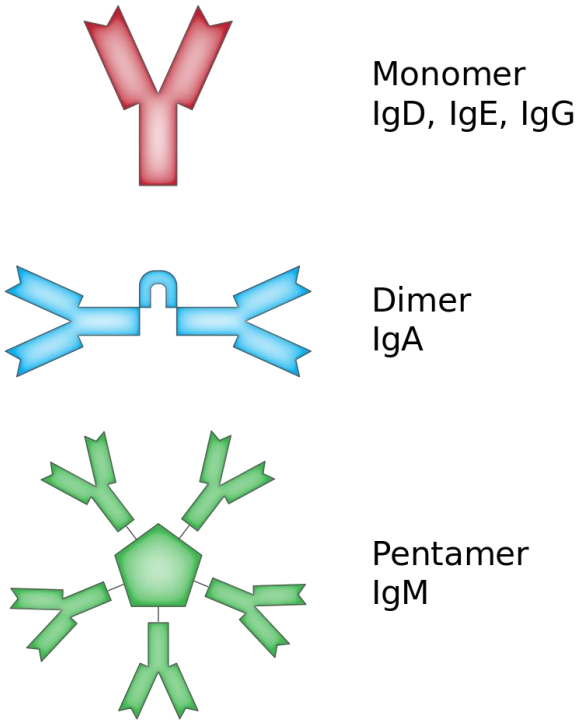
Immunoglobulin E (IgE) is a type of antibody that has only been found in mammals. IgE is synthesised by plasma cells. Monomers of IgE consist of two heavy chains (ε chain) and two light chains, with the ε chain containing 4 Ig-like constant domains. IgE's main function is immunity to parasites such as helminths like Schistosoma, Trichinella spiralis, and Fasciola hepatica. IgE is utilized during immune defense against certain protozoan parasites such as Plasmodium falciparum. IgE also has an essential role in type I hypersensitivity, which manifests in various allergic diseases, such as allergic asthma, most types of sinusitis, allergic rhinitis, food allergies. IgE is present in minute

Popular Article
Published: 20.11.2022

amounts, accounting for no more than 0.001% of human immunoglobulins. Its original role is to protect against parasites. In regions where parasitic infection is rare, IgE is primarily involved in allergy.

IgD

IgD accounts for less than 1% of human immunoglobulins. IgD may be involved in the induction of antibody production in B cells, but its exact function remains unknown.



Applications

Medical applications

Disease diagnosis

Detection of particular antibodies is a very common form of medical diagnostics, and applications such as serology depend on these methods. For example, in biochemical assays for disease diagnosis, a titre of antibodies directed against Epstein-Barr virus or Lyme's disease is estimated from the blood. If those antibodies are not present, either the person is not infected or the infection occurred a very long time ago, and the B cells generating these specific antibodies have naturally decayed.

In clinical immunology, levels of individual classes of immunoglobulins are measured by nephelometry to characterize the antibody profile of patient. Elevations in different classes of immunoglobulins are sometimes useful in determining the cause of liver damage in patients for whom the diagnosis is unclear. For example, elevated IgA indicates alcoholic cirrhosis, elevated IgM

Popular Article
Published: 20.11.2022

indicates viral hepatitis and primary biliary cirrhosis, while IgG is elevated in viral hepatitis, autoimmune hepatitis and cirrhosis.

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 red blood cell surface antigens in immune mediated haemolytic anaemia are 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.

Practically, several immunodiagnostic methods based on detection of complex antigen-antibody are used to diagnose infectious diseases, for example ELISA, immunofluorescence, Western blot, immunodiffusion, immunoelectrophoretic, and magnetic immunoassay. Antibodies raised against human chorionic gonadotropin are used in over-the-counter pregnancy tests. New dioxaborolane chemistry enables radioactive fluoride (^{18}F) labelling of antibodies, which allows for positron emission tomography (PET) imaging of cancer.

Disease therapy

Targeted monoclonal antibody therapy is employed to treat diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, and many forms of cancer including non-Hodgkin's lymphoma, colorectal cancer, head and neck cancer and breast cancer (Vogel *et al.,* 2001). Some immune deficiencies, such as X-linked agammaglobulinemia and hypogammaglobulinemia, result in partial or complete lack of antibodies. These diseases are often treated by inducing a short-term form of immunity called passive immunity. Passive immunity is achieved through the transfer of ready-made antibodies in the form of human or animal serum, pooled immunoglobulin or monoclonal antibodies, into the affected individual (Ghaffer, 2006).

Prenatal therapy

Rh factor, also known as Rh D antigen, is an antigen found on red blood cells; individuals that are Rh-positive (Rh+) have this antigen on their red blood cells and individuals that are Rh-negative (Rh–) do not. During normal childbirth, delivery trauma or complications during pregnancy, blood from a foetus can enter the mother's system. In the case of an Rh-incompatible mother and child, consequential blood mixing may sensitize an Rh- mother to the Rh antigen on the blood cells of the Rh+ child, putting the remainder of the pregnancy, and any subsequent pregnancies, at risk for haemolytic disease of the new-born. (Urbaniak and Greiss, 2000)

Popular Article
Published: 20.11.2022

Rho(D) immune globulin antibodies are specific for human RhD antigen. Anti-RhD antibodies are administered as part of a prenatal treatment regimen to prevent sensitization that may occur when a Rh-negative mother has a Rh-positive fetus. Treatment of a mother with Anti-RhD antibodies prior to and immediately after trauma and delivery destroys Rh antigen in the mother's system from the fetus. It is important to note that this occurs before the antigen can stimulate maternal B cells to "remember" Rh antigen by generating memory B cells. Therefore, her humoral immune system will not make anti-Rh antibodies, and will not attack the Rh antigens of the current or subsequent babies. Rho(D) Immune Globulin treatment prevents sensitization that can lead to Rh disease, but does not prevent or treat the underlying disease itself.

Research Applications

Specific antibodies are produced by injecting an antigen into a mammal, such as a mouse, rat, rabbit, goat, sheep, or horse for large quantities of antibody. Blood isolated from these animals contains *polyclonal antibodies*— multiple antibodies that bind to the same antigen— in the serum, which can now be called antiserum. Antigens are also injected into chickens for generation of polyclonal antibodies in egg yolk. To obtain antibody that is specific for a single epitope of an antigen, antibody-secreting lymphocytes are isolated from the animal and immortalized by fusing them with a cancer cell line. The fused cells are called hybridomas, and will continually grow and secrete antibody in culture. Single hybridoma cells are isolated by dilution cloning to generate cell clones that all produce the same antibody; these antibodies are called *monoclonal antibodies*. Polyclonal and monoclonal antibodies are often purified using Protein A/G or antigen-affinity chromatography (Kabir *et al.*, 2002). In research, purified antibodies are used in many applications. Antibodies for research applications can be found directly from antibody suppliers, or through use of a specialist search engine. Research antibodies are most commonly used to identify and locate intracellular and extracellular proteins. Antibodies are used in flow cytometry to differentiate cell types by the proteins they express; different types of cells express different combinations of cluster of differentiation molecules on their surface, and produce different intracellular and secretable proteins. They are also used in immunoprecipitation to separate proteins and anything bound to them (co-immunoprecipitation) from other molecules in a cell lysate, in Western blot analyses to identify proteins separated by electrophoresis, and in immunohistochemistry or immunofluorescence to examine protein expression in tissue sections or to locate proteins within cells with the assistance of a microscope. Proteins can also be detected and quantified with antibodies, using ELISA and ELISpot techniques. Antibodies used in research are some of the most powerful, yet most problematic reagents with a tremendous number of factors that must be controlled in any

Popular Article
Published: 20.11.2022

experiment including cross reactivity, or the antibody recognizing multiple epitopes and affinity, which can vary widely depending on experimental conditions such as pH, solvent, state of tissue etc. Multiple attempts have been made to improve both the way that researchers validate antibodies and ways in which they report on antibodies. Researchers using antibodies in their work need to record them correctly in order to allow their research to be reproducible (and therefore tested, and qualified by other researchers). Less than half of research antibodies referenced in academic papers can be easily identified. Antibody regions can be used to further biomedical research by acting as a guide for drugs to reach their target. Several application involve using bacterial plasmids to tag plasmids with the Fc region of the antibody such as pFUSE-Fc plasmid.

References

Borghesi, L., & Milcarek, C. (2006). From B cell to plasma cell. *Immunologic research*, *36*(1), 27-32.

Ghaffer A. (2006). "Immunization". *Immunology — Chapter 14*. University of South Carolina School of Medicine. Archived from the original on 18 October 2010. Retrieved 6 June 2007.
https://en.wikipedia.org/wiki/Antibody

Kabir, S. (2002). Immunoglobulin purification by affinity chromatography using protein A mimetic ligands prepared by combinatorial chemical synthesis. *Immunological investigations*, *31*(3-4), 263-278.

Mian, I. S., Bradwell, A. R., & Olson, A. J. (1991). Structure, function and properties of antibody binding sites. *Journal of molecular biology*, *217*(1), 133-151.

Urbaniak, S. J., & Greiss, M. A. (2000). RhD haemolytic disease of the fetus and the newborn. *Blood reviews*, *14*(1), 44-61.

Vogel, C. L., Cobleigh, M. A., Tripathy, D., Gutheil, J. C., Harris, L. N., Fehrenbacher, L., & Stewart, S. J. (2001). First-line Herceptin® monotherapy in metastatic breast cancer. *Oncology*, *61*(Suppl. 2), 37-42.