ISBN: 978-93-90847-97-6

4. Antibodies

Laksha Gayathri Suresh

Bioengineering Division,
School of Chemical and Biotechnology,
SASTRA Deemed to be University,
Thanjavur, Tamil Nadu, India.

Srichandrasekar Thuthikkadu Indhuprakash,

Diraviyam Thirumalai

Centre for Research in Infectious Diseases (CRID),
Bioengineering, School of Chemical and Biotechnology,
SASTRA Deemed to be University,
Thanjavur, Tamil Nadu, India.

Abstract:

In the battle of fighting against pathogens or antigens, the well-known leading key players that come into picture are the antibodies. Antibodies also called as immunoglobulins shield us by its unique Y-shaped structure serving as a "bullet of the battle". Antibodies which are a part of adaptive immune system hunt down the pathogens when they encounter antigens by neutralizing, capturing and eliminating it from the body. Not only do they attack but they mediate other biological functions as well. These antibodies are well known for its protective effect but sometimes they turn out to be evil by posing deleterious effects on the host tissue itself. Nevertheless, antibodies play the lead role in the cavalry to invade the invaders by activating cascade of events in the pool. Following section will enlighten more about the outlook of antibodies, its role and working.

Keywords: *antibodies, classification, structure.*

4.1 Where Do They Come From?

Well, the journey of production begins from the progenitor lymphoid cell in the bone marrow where it matures to form either progenitor T cell or progenitor B cell. The progenitor T cell migrate to thymus for maturation while the progenitor B cell undergoes somatic recombination to form immature B cell. Each progenitor B cells that give rise to

millions of immature B cell through somatic recombination end up having unique antibodies projecting on their surface. Eventually both the immature B cell and naïve T cell end up in lymph nodes for maturation. Once the antigen presenting cells present the antigen to the naïve T cells in the lymph node, they get so very active that they immediately begin to proliferate and differentiate to form cytotoxic T cells and T helper cells.

With that joy, T helper cells come forward to help its inmate to get activated. Not only that but B cells also get activated on its own by just seeing its antigen. To combat the enemy even more efficiently, they strengthen themselves by expanding its squad and become large in number. And this is called clonal expansion where they differentiate either to memory B cells or antibody secreting plasma cells. And that's how our hero antibody gives its entry in the battle [1].

4.2 But How Do They Look Like?

Antibodies (Ab) aka immunoglobulin (Ig) aka "our heroes" that are released in to the blood stream by plasma cells after the recognition of antigen look alike with almost similar structural components. These antibodies look like Y-shaped arms and it is made of 2 pairs of polypeptide chains. We generally categorize them into heavy and light chains. It is these chains, i.e., 2 identical heavy chains (H) and 2 identical light chains (L) that orient together to form this Y shaped arm. Within these two chains lie two different regions, the variable (V) and constant region (C).

The variable portion in light chain and heavy chain are termed as VL and VH whereas the constant region in light and heavy chain are termed as CL and CH respectively. The main difference between these two regions is that the variable regions with an amino group while the constant region terminate with a carboxy group. The tip portion of the antibody structure to where the antigens generally bind are made of variable regions to enhance specificity against different antigens whereas the remaining portion is made of constant regions.

Now to make the entire structure stable by holding it together, there are di-sulfide bonds that bridge the heavy chains to each other and the heavy chains to light chains. So, in total an antibody has a variable region and a constant region in the light chain.

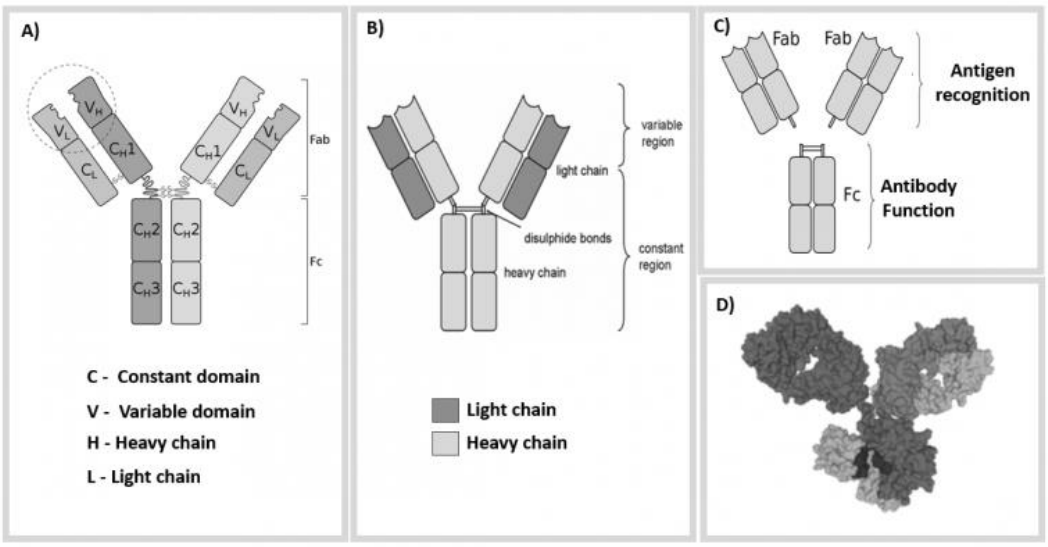


Figure 4.1: (A) constant and variable regions in heavy and light chains (B) light and heavy chains (C) Fab and Fc region (D) 3D structure of antibody (source: https://teachmephysiology.com/immune-system/adaptive-immune-system/antibodies/)

The variable portions of one pair of heavy and light chain, VH and VL come together to form an antigen binding domain (Fab) in the antibody to entrap the antigens. Thus, an antibody has two antigen binding domains. By making differences in the sequence of variable regions, it showcases its unique ability of binding to varied types of antigens.

Wherein the rest of the constant regions in the heavy chain is called the fragment crystallizable region (Fc) [2]. In addition to these, there is something notable in the structure of antibody like the hinge region and the hypervariable region.

The hypervariable regions or the complementarity determining regions (CDRs) are loops that are a part of Fab portion of antibody that are complementary to the sequences found in antigens. To bind to any antigen, an antibody not only requires complementary sequence but also it needs to be flexible so as to enhance its ability to bind to different array of antigens on different surfaces. This flexibility is bestowed by the hinge region, made of amino acids which can be stretched, that is present in the middle portion of heavy chains of IgG and IgA only [3].

There is one other thing called joining (J) chain, a polypeptide protein, part of antibodies dimeric IgA and pentameric IgM, that is released into mucosa and regulates polymeric formation of immunoglobulins [4].

4.3 Do They Work Alone?

Of course not, they do have siblings to get done other works and functions at different sites. They are almost similar in structure except for the constant domain parts and each type of antibody carry out its own notable functions at different locations.

Well, the main five different types of siblings that we come across in our body are immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE), immunoglobulin D (IgD) where IgG, IgE and IgD exist in monomeric state and IgM exist in pentameric state while the IgA in dimer form.

Researchers found that the sequence found in the heavy chain of antibodies fall under five categories and hence given the Greek names like (α) alpha, (μ**)** mu, (*δ*) delta, (γ) gamma and (ε**)** epsilon for the antibodies IgA, IgM, IgD, IgG and IgE respectively.

There are other subclasses for the heavy chains of IgA and IgG [5]. When it comes to the light chain of antibodies, there are again classes like kappa (k) and lambda ***(λ)*** and subclasses like **λ1, λ2, λ3 and λ4. Each class of antibodies can either have kappa or lambda light chains** the basic difference lies in the molecular weight of each antibody.

The largest structure being the pentameric IgM holds the highest molecular weight of about 900,000 Daltons. This is followed by the secretory IgA dimer with about 385,000 Daltons.

The rest of the monomeric antibodies i.e., IgE, IgD and IgG holds the next three consecutive places with about 200, 180 and 150 kilo Daltons respectively.

The difference not only lies in its molecular weight but also in terms of function, the number of antigen binding sites, distribution and even the quantity present in the serum. The following section and the table 4.1 encompass more insights about each type of antibody. Figure 4.2 shows the structure of the five main classes of antibodies

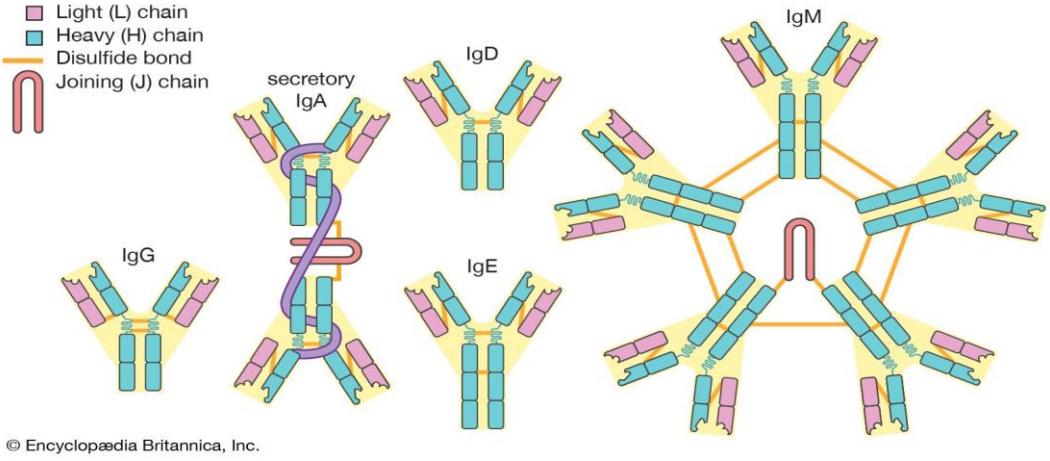


Figure 4.2: (source: https://www.britannica.com/science/immune-system/Classes-of-immunoglobulins)

4.3.1 In More Detail….

A. IgG: The only antibody that is present in ample quantity in the blood serum is this immunoglobulin G. We can also see them on the surface of matured B cells. These constitute about 80% in the serum. These are large globular protein molecules of about 150 KDa and plays a big part in fighting against harmful pathogens and infections.

They have the capacity to bind to pathogens like bacteria, virus, and fungi. IgG is so very important because it provides long term protection against pathogens as they can persist for years after the first exposure. In addition to this, they are also able neutralize the toxins.

The unique function of IgG is that they are the only class of immunoglobulins that have the capacity to pass through placenta to provide humoral immunity to the fetus unlike any other class of molecules because of its low molecular weight [6].

On the other hand, these are associated with type II and type III hypersensitivity reactions.

B. IgA: These are dimeric molecules with a J chain as a secretory molecule of 385 kDa and constitute about 13% in serum. We can find these antibodies specifically in mucous membranes like the respiratory and digestive tracts and also in saliva, breastmilk and tears

to act as first line of defense. Just like IgG, these antibodies also neutralize the bacterial toxins and provides resistance against infections. But these also do the elimination of antigens by using their secretory component around the J chain.

These secretory antibodies provide defensive mechanism against pathogens by enhancing adaptive humoral immunity in the mucosal membranes. So they eliminate the pathogen by this IgA mediated excretory pathway [7].

C. IgM: Five monomeric units attach together to form these largest pentameric IgM antibodies. It's mainly involved in the ABO blood group antigens on the surface of red blood cells.

In addition to this, they are also responsible for mediating phagocytic clearance of pathogens. The very first antibody that forms after exposure to antigens is IgM. Just like IgA, these antibodies also exist in secretory form.

Typically, this antibody displays low binding affinity to antigen but all the 10-arms in the protein come and work together so as to strongly bind to the antigen. Having a molecular weight of 900 kDa, they occupy just 6 % in the serum [2].

D. IgE: This monomeric antibody, IgE, is exclusively seen only in mammals. Only a very minute amount is present in serum of not more than 0.002 %. These are believed to be protective against certain parasites and venoms.

Nevertheless, it's mainly involved in allergic reactions by fighting against allergens and is therefore associated with type I hypersensitivity reactions. They also participate in immune response events by binding to basophils and mast cells [8].

E. IgD: One other monomeric antibody, IgD, constitute only about 1 % in the serum. Though it's in minute amount, antibodies present on the surface of B cells plays its role in induction of production of antibodies.

Just like IgE, they activate basophils and mast cells to mediate the production of anti-microbial factors thereby participating in respiratory human defense [9].

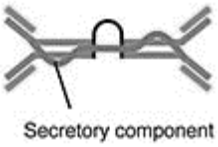
Properties	**IgM**	**IgG**	**IgA**	**IgE**	**IgD**
Number of units	pentamer	monomer	dimer	monomer	monomer
Structure					
Heavy chains	μ	γ	α	ε	δ
Number of Antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000

Table 4.1: Details of five major classes of antibodies

4.4 Do They Take Part only in Antigen-Binding?

Well, one thing that has to be remembered is that antibody not only acts as opsonin and recognizes the pathogen by mediating phagocytosis via their Fc region but they also block different parts of pathogens to prevent its entry and to neutralize them. On the other hand, IgM or IgA antibodies activates the complement system as they bind to different microbial surfaces and mediate the production of anaphylatoxins and other components so as to form membrane attack complex.

So far, the story of antibodies seemed very perfect and incredible by carry out multiple functions by recruiting multiple components to opsonize the pathogens. Most of the time our body keeps on fighting the real foreign bodies or enemies well but sometimes it goes wrong. That is where the entire event of immune response turns out to be a chaotic mess by attacking body's own cells. This problem arises when the antibodies cannot distinguish between one's own self and foreign cells resulting in the attack of host cells that is termed as auto-immune disorder.

4.5 References:

1. "What are antibodies? | Live Science." https://www.livescience.com/antibodies.html (accessed Mar. 28, 2022).
2. "Antibodies - Structure - Classification - Function - TeachMePhysiology." https://teachmephysiology.com/immune-system/adaptive-immune-system/antibodies/ (accessed Mar. 29, 2022).
3. S. Aryal, "Antibody- Introduction, Structure and Classes." https://microbenotes.com/antibody-introduction-structure-and-classes/ (accessed Mar. 29, 2022).
4. J. Mestecky and I. Moro, "Joining (J) Chain," *Encycl. Immunol.*, pp. 1516–1518, 1998, doi: 10.1006/RWEI.1999.0388.
5. R. Küppers, "Overview of the immune system," *Lymphoid Neoplasms 3ed*, pp. 143–155, 2010, doi: 10.1s201/b13424.
6. G. Vidarsson, G. Dekkers, and T. Rispens, "IgG subclasses and allotypes: from structure to effector functions," *Front. Immunol.*, vol. 5, no. OCT, p. 520, 2014, doi: 10.3389/fimmu.2014.00520.
7. R. Curran, "Immunoglobulin A (IgA) | British Society for Immunology." https://www.immunology.org/public-information/bitesized-immunology/receptors-and-molecules/immunoglobulin-iga (accessed Mar. 30, 2022).
8. D. R. Stanworth, "The discovery of IgE," *Allergy*, vol. 48, no. 2, pp. 67–71, 1993, doi: 10.1111/j.1398-9995.1993.tb00687.x.
9. E. S. Edholm, E. Bengten, and M. Wilson, "Insights into the function of IgD," *Dev. Comp. Immunol.*, vol. 35, no. 12, pp. 1309–16, Dec. 2011, doi: 10.1016/j.dci.2011.03.002.