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REVIEW ON IMMUNOGLOBULINS

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ABSTRACT

Immunoglobulins (Igs), as one of the hallmarks of adaptive immunity, first arose approximately 500 million years ago with the emergence of jawed vertebrates. Two events stand out in the evolutionary history of Igs from cartilaginous fish to mammals: (*a*) the diversification of Ig heavy chain (IgH) genes, resulting in Ig isotypes or subclasses associated with novel functions, and (*b*) the diversification of genetic and structural strategies, leading to the creation of the antibody repertoire we know today. This review first gives an overview of the IgH isotypes identified in jawed vertebrates to date and then highlights the implications or applications of five new recent discoveries arising from comparative studies of Igs derived from different vertebrate species. Immunoglobulins are heterodimeric proteins composed of two heavy (H) and two light (L) chains. They can be separated functionally into variable (V) domains that binds antigens and constant (C) domains that specify effector functions such as activation of complement or binding to Fc receptors. The variable domains are created by means of a complex series of gene rearrangement events, and can then be subjected to somatic hypermutation after exposure to antigen to allow affinity maturation. Each V domain can be split into three regions of sequence variability, termed the complementarity determining regions, or CDRs, and four regions of relatively constant sequence termed the framework regions, or FRs. The three CDRs of the H chain are paired with the three CDRs of the L chain to form the antigen binding site, as classically defined. There are five main classes of heavy chain C domains. Each class defines the IgM, IgG, IgA, IgD, and IgE isotypes. IgG can be split into four subclasses, IgG1, IgG2, IgG3, and IgG4, each with its own biologic properties; and IgA can similarly be split into IgA1 and IgA2. The constant domains of the H chain can be switched to allow altered effector function while maintaining antigen specificity.

KEYWORDS: Antibody structure, Antibody function, Immunoglobulin structure, Immunoglobulin function, Immunoglobulin gene rearrangement,

INTRODUCTION

Immunoglobulin's stands for the glycoproteins which are secreted by the plasma cells. Immunoglobulin constitutes of 20% of plasma proteins. Immunogens reacts with the B cells and receptor that are located on B lymphocytes and a signal production takes place which is liable for the activation of transcription factors to stimulate antibodies which are highly specific for antigens which are responsible for B cell stimulation.[1]

1970, Richard Titmus, an English pioneer in the field of social policy, argued in his seminal book "The Gift Relationship" that paying for blood donations would pave the way for the marketing of all tissues and cells Since 1975, the WHA has passed resolutions urging the implementation of a blood supply system founded on voluntary non-remunerated donation and the establishment of not-for-profit blood establishments with the aim of achieving self-sufficiency in blood supply [WHO expert groups have highlighted the urgency of such an approach, but acknowledged in 2013 that legislation was required to achieve this goal In many European countries, VNRD has gained ground in recent years against remunerated, compensated and replacement

donation of labile blood components, such as red blood cells, platelets and freshly frozen plasma Based on clinical evidence, the use of labile components has decreased considerably, particularly for red blood cells, the product driving the collection of whole blood samples. By contrast, since 2004, remunerated donations for commercial plasma derived medicinal products (PDMPs) have increased, with IG as the main driver, hampering efforts to promote VNRD and with a lower level of surveillance to ensure donor safety. Market reports have even predicted a further increase in IG demand over the next five years. These huge differences in collection practices, production and use between cellular blood components and IG have raised concerns about the feasibility of achieving self-sufficiency. We aim here to decipher the causes of the huge increase in IG product use since 2004 and the reasons for the further increase predicted for the near future.

History

The 20th century, the Immunology was come to light as an important scientific study. Novel techniques such as centrifugation, immunoadsorption had been discovered and were using for dissection of the human blood proteins which included antibodies and compliment, at that time it was necessary to name those proteins in constituent manner. Some attempts were followed for designating those terms by Greek words for making a science based nomenclature and for separating it from the normal language, as the similar naming system was already present in physics like alpha and beta. In 1964, the World Health Organization (WHO) coined a proper order for proper naming of each isotype. The original names was given to the proteins by the discovers as IgM, IgG etc.[4-6] the 20th century, the Immunology was come to light as an important scientific study. Novel techniques such as centrifugation, immunoadsorption had been discovered and were using for dissection of the human blood proteins which included antibodies and compliment, at that time it was necessary to name those proteins in constituent manner. Some attempts were followed for designating those terms by Greek words for making a science based nomenclature and for separating it from the normal language, as the similar naming system was already present in physics like alpha and beta. In 1964, the World Health Organization (WHO) coined a proper order for proper naming of each isotype. The original names was given to the proteins by the discovers as IgM, IgG etc.[4-6]

Types of immunoglobulins

The following are five types of immunoglobulins in humans:

1. IgM
2. IgG
3. IgA
4. IgE
5. IgD

IgM

IgM has a molecular weight of 970 Kd and an average serum concentration of 1.5 mg/ml. It is mainly produced in the primary immune response to infectious agents or antigens. It is a pentamer and activates the classical pathway of the complement system. IgM is regarded as a potent agglutinin (e.g., anti-A and anti-B isoagglutinin present in type B and type A blood, respectively), and a monomer of IgM is used as a B cell receptor (BCR).

IgM is a large protein molecule that is responsible for the primary immune response. It is present rapidly upon the body's initial exposure to an antigen, and is effective as a first line of defense for bacterial invasion. IgM is present in the serum as a pentamer, which makes it a large antibody. It is therefore largely confined to the intravascular space. IgM functions through activation of complement and destruction of foreign antigen.

Functions of IgM

IgM antibodies secreted by B cells participate in the neutralization and clearance of pathogens and initiate inflammatory reactions against pathogens through the complement pathway. IgM is the predominant antibody during a primary challenge to an antigen. For some non-peptide antigens, IgM may be the only isotype of antibody secreted on subsequent encounters with the antigen. The primary humoral immune response to a novel pathogen typically requires close to a week before substantial amounts of IgM appear in the blood, and the innate immune response is necessary to fight the infection until the creation of T cells and antibody-secreting plasma cells clonally expanded against the pathogen in sufficient numbers.

IgG

IgG is a monomer with an approximate molecular weight of 146 Kd and a serum concentration of 9.0 mg/mL. IgG is said to be divalent, i.e., it has two identical antigen-binding sites that comprise 2 L chains and 2 H chains joined by disulfide bonds. IgG is synthesized mostly in the secondary immune response to pathogens.

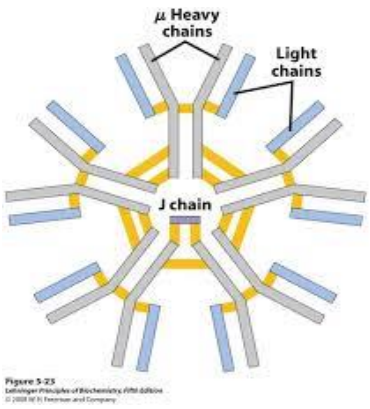

Fig. 1: Structure of immunoglobulinIgG.

IgG can activate the classical pathway of the complement system, and it also is highly protective. The

four subclasses of IgG include IgG1, IgG2, IgG3, and IgG4. IgG1 is around 65% of the total IgG. IgG2 forms an important host defense against bacteria that are encapsulated. IgG is the only immunoglobulin that crosses the placenta as its Fc portion binds to the receptors present on the surface of the placenta, protecting the neonate from infectious diseases. IgG is thus the most abundant antibody present in newborns.

Subclasses of IgG

- There are four IgG subclasses (IgG1, 2, 3, and 4) in humans, named in order of their abundance in serum (IgG1 being the most abundant).
- Subclasses IgG1, IgG2, IgG3, and IgG4 are differentiated on the basis of the size of the hinge region, position of interchain disulfide bonds, and molecular weight. The subclasses also differ in their ability to activate complement.

IgG1

It comprises 60 to 65% of the total main subclass IgG, and predominantly responsible for the thymus-mediated immune response against proteins and polypeptide antigens. It is also involved in opsonization and activation of the complement cascade. A deficiency in IgG1 isotype is typically a sign of a hypogammaglobulinemia.

IgG2

It comprises 20 to 25% of the main subclass and is the prevalent immune response against carbohydrate/polysaccharide antigens. Among all IgG isotype deficiencies, a deficiency in IgG2 is the most common and is associated with recurring airway/respiratory infections in infants.

IgG3

IgG3 comprises around 5 to 10% of total IgG and plays a major role in the immune responses against protein or polypeptide antigens.

IgG4

Comprising usually less than 4% of total IgG, IgG4 does not bind to polysaccharides. Recent studies have shown that elevated serum levels of IgG4 are found in patients suffering from sclerosing pancreatitis, cholangitis and interstitial pneumonia caused by infiltrating IgG4 positive plasma cells. The precise role of IgG4 is still mostly unknown.

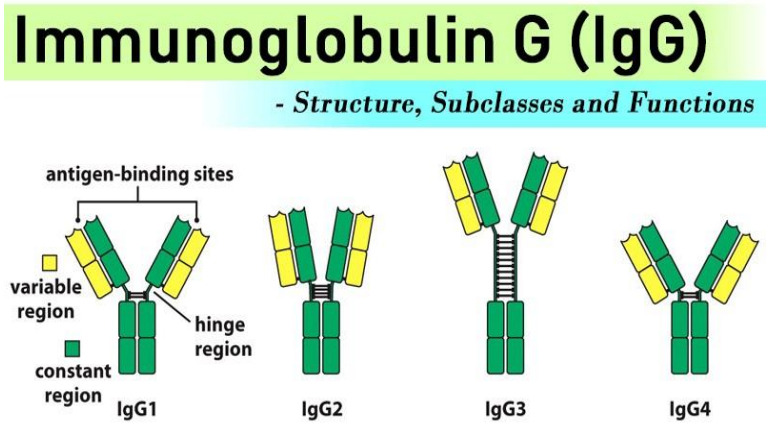

Fig. 2: Types in IgG.

Functions of IgG

IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination; IgG coating of pathogen surfaces (known as opsonization) allows their recognition and ingestion by phagocytic immune cells leading to the elimination of the pathogen itself;

IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination;

IgG also binds and neutralizes toxins;

IgG also plays an important role in antibody-dependent cell-mediated cytotoxicity (ADCC) and intracellular antibody-mediated proteolysis, in which it binds to TRIM21 (the receptor with greatest affinity to IgG in humans) in order to direct marked virions to the proteasome in the cytosol.

IgG is also associated with type II and type III hypersensitivity reactions.

IgA

IgA appears in 2 different molecular structures: monomeric (serum) and dimeric structure (secretory). The serum IgA has a molecular weight of 160 Kd and a serum concentration of 3 mg/mL. Secretory IgA) has a molecular weight of 385 Kd and a mean serum concentration of 0.05 mg/mL. IgA is the major antibody in secretions found in saliva, tears, colostrum, intestinal, genital tract, and respiratory secretions.

It appears in mucosa membranes as a dimer (with a J chain when secreted) and protects the epithelial surfaces

of the digestive, respiratory, and genitourinary systems. IgA possesses a secretory component that prevents its enzymatic digestion. It activates the alternative pathway of activation of the complement system.

Functions of IgA

IgA lacks the site for C1q binding present in IgG and does not bind C1q, and therefore is not expected to activate the classical pathway of complement. Interestingly, a study looking at complement-dependent cytotoxicity of B cells by.

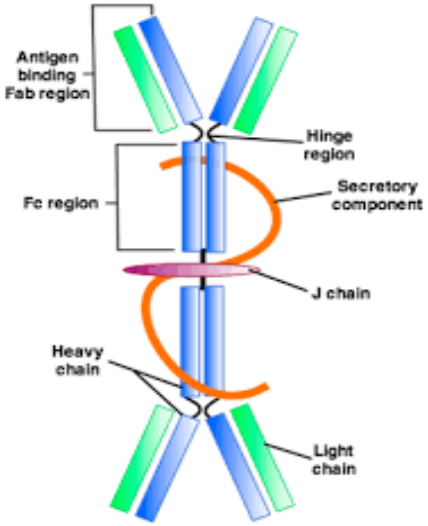

Fig. 3: Structure of IgA.

CD20-specific IgA suggested that complement was activated by IgA. However, in vivo, the activity of the anti-CD20 IgA to deplete B cell targets was not abrogated in C1q- or C3-deficient mice, suggesting that complement activation was not the predominant killing mechanism in action. The ability of IgA to activate the alternative pathway of complement has been somewhat contentious, but the prevailing view is that the reported activation is likely via the lectin pathway as a result of binding to mannose-binding lectin. However, the ability to activate via this route is likely dependent on glycosylation status.

IgE

IgE is a monomer. It has a molecular weight of 188 Kd and a serum concentration of 0.00005 mg/mL. It protects against parasites and binds to high-affinity receptors on mast cells and basophils, causing allergic reactions. IgE is considered the most important host defense against different parasitic infections, including *Strongyloides stercoralis, Trichinella spiralis, Ascaris lumbricoides, and hookworms Necator americanus and Ancylostoma duodenale.*

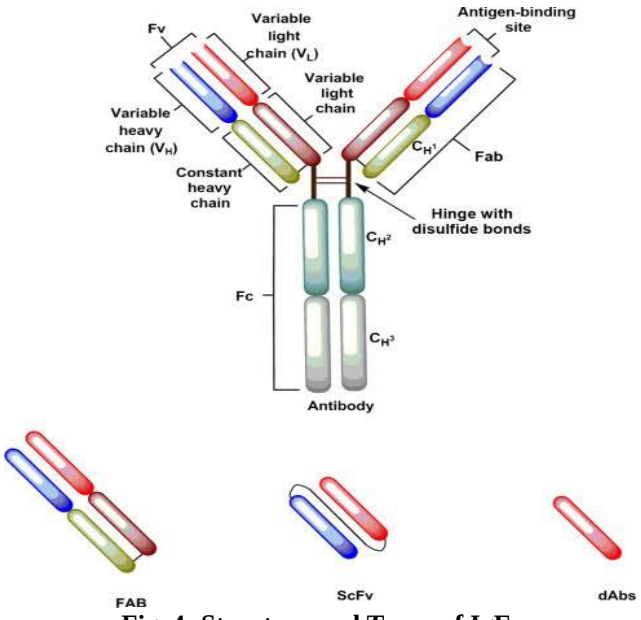

Fig. 4: Structure and Types of IgE.

Functions of IgA

Role of IgE in exerting anti-parasite function: Anti-parasitic IgE and IgE expressed on effector cells such as eosinophils have been shown to confer defense against different parasites (e.g., *Schistosoma* mansoni). Furthermore, IgE engaged with FcεRI or CD23 can improve parasite clearance by human eosinophils, platelets, and macrophages through antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP). Besides, elevated serum titers of parasite antigen-specific IgE have been associated with resistance to parasitic infection.

IgD

IgD is a monomer with a molecular weight of 184 Kd. IgD is present in a meager amount in the serum (0.03 mg/mL) and has an unknown function against pathogens. It is regarded as a BCR. IgD may play an essential role in antigen-triggered lymphocyte differentiation.

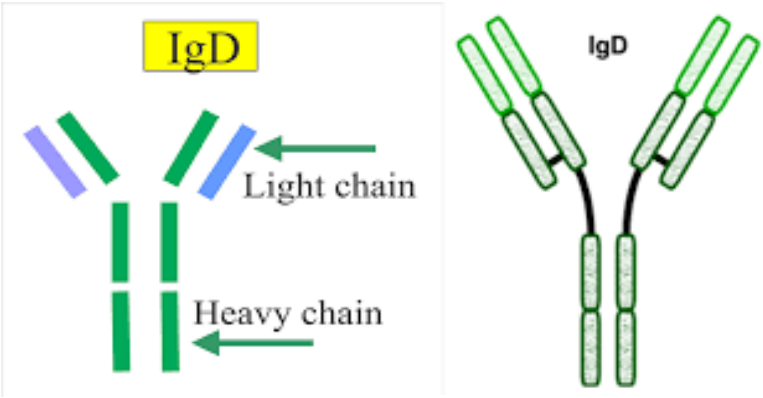

Fig. 5: Structure of Ig D.

Functions of IgD

IgD is found as an antigen receptor on the surface of the majority of human and murine B cells prior to antigenic stimulation and CSR The advantage of having both IgD and IgM with the same antigen specificity on the same cell is still not clear. Initially, it was proposed that the two receptor classes deliver different signals to the B cell). However, contradictory results were obtained. Engagement of IgM on immature B cells *in vivo* and in IgM-transfected cells *in vitro* results in apoptosis, whereas engagement of IgD failed to do so. Reverse results were obtained in another study, which showed that a minimal stimulation with anti-IgD antibodies but not with anti-IgM antibodies induced apoptosis of mature resting B cells.

Clinical significance

Immunoglobulins or antibodies are essential in protecting against bacteria, viruses, and fungi. When there is a deficiency of these glycoproteins, recurrent infectious diseases occur, as seen in the following antibody deficiency disorders

- X-linked agammaglobulinemia
- Transient hypogammaglobulinemia of infancy
- IgA deficiency
- IgG subclass deficiency
- Immunodeficiency with increased IgM
- Common variable immunodeficiency

The most common immunodeficiency is Selective IgA deficiency, characterized by recurrent infections that affect the respiratory, digestive, and genitourinary systems. Recurrent pneumonia, Giardia lamblia infestation, and urinary sepsis are prevalent. The majority of patients can, however, be asymptomatic. They are at higher risk for autoimmune diseases, atopy, and anaphylaxis to IgA-containing products.

CONCLUSION

Immunoglobulins are essential molecules in the immune system, providing protection against pathogens and mediating immune responses. Their diagnostic and therapeutic importance cannot be overstated, as they are integral in managing immunodeficiencies, autoimmune diseases, allergies, and infections. Advances in immunology continue to uncover their potential for targeted therapies and personalized medicine.

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