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Immunoglobulin A

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Abstract

Immunoglobulin A (IgA) is an antibody that is located and functions in the mucosal surfaces and in serum of humans. IgA is produced in the largest amounts of any antibody class, probably due to the large surface area it must protect. It has two forms as defined by location and function, serum and secretory. The secretory form has a structure referred to as the secretory piece that allows IgA to maintain its structure even in harsher conditions such as tears, saliva, the GI tract and respiratory system. IgA opsonizes poorly and is also a poor activator of complement. Nevertheless, it is one of the initial antibody classes responsible for immune protection at the mucosal surfaces.

Introduction

Two major forms of IgA (IgA1 and IgA2) have been found in common in humans. IgA1 is slightly longer than IgA2, giving it more "reach" than IgA2, thus able to reach two pathogens with one molecule potentially. IgA makes up about 13% of the total immunoglobulin concentration in serum. The concentration in serum at 2-3 mg/mL where it is second behind IgG as the second most prevalent antibody. It has a half-life of about 25 days. IgA has agglutination capability and if aggregated it has been hypothesized to activate the alternate pathway of complement. Secretory IgA predominates at the mucosal surfaces with estimates that the average human generates about 60 mg of IgA per day per kilogram of body weight. Secretory IgA is without question the first line of antibody defense at the body's external surfaces. Serum IgA is found more internally in blood and blood associated tissues.

Structure

IgA as an immunoglobulin has two identical heavy and two identical light chains [1]. Individual chains resemble IgG in overall appearance. There is a hinge region that separates the chains into two Fab (Fraction antigen binding) regions and an Fc or Fraction crystalized region (as with IgG). The two forms of IgA may be distinguished by the locations in which they predominate. Serum IgA is found more closely associated with lymphoid tissues and is the predominant form of IgA in serum. It is a single monomeric form of the molecule. Secretory IgA is found more predominantly in secretions such as the gastrointestinal track, tears and sweat. Both can be in a membrane bound form. Secretory IgA is also found in saliva, and the colostrum secretions. It is also present in small amounts in the blood. The structure of secretory IgA is comprised of two monomeric IgA molecules, the secretory component and the J chain. The secretory component of IgA protects the molecule from being degraded by proteolytic and other enzymes that may erode other antibody molecules including serum IgA, thus allowing activity in acidic regions of the body. The J chain which occurs in pentameric IgM as well joins the two molecules together at the Fc regions. It is a 15 kDa peptide and is expressed by antibody producing cells. The secretory component (about 80 kDa) which stabilizes the dimeric IgA is formed from binding to the one dimeric IgA bound to the polymeric immunoglobulin receptor at the basolateral side of the epithelium [2]. The receptor is responsible for transport of dimeric IgA into the secretions, namely the polymeric immunoglobulin receptor (pIgR) [3]. This is the secretory component composition that stabilizes the molecule to harsh environmental conditions and environments such as the GI track and tears. This receptor is expressed as an integral membrane protein on the surface of epithelial cells lining mucosal membranes and binds newly synthesized polymeric IgA at the basolateral surface. The receptor–IgA complex is endocytosed and moves across the cell through a series of vesicles to be delivered to the apical surface, where it is active in the environment.

The two forms of IgA are similar in basic structure. Serum IgA will bind to the Fc receptor called CD89, expressed on effector cells to start various inflammatory cascades. When CD89 is ligated, IgA causes degranulation of eosinophils and basophiles, phagocytosis and triggering of the respiratory burst by polymorphonuclear leukocytes leading to the release of TNF, IL-2 and IL-6. Both Secretory and Serum IgA acts as part of the initial inflammatory response and also part of the larger initial immune response to pathogens. This happens by direct interaction with the pathogen which may be bacteria, protozoa or virus. The difference is in the location of action of the different forms of the IgA molecule.

As mentioned, secretory or SIgA predominates in external secretions. The structure of the molecule including the J chain and secretory piece make it possible for the molecule to survive in harsh environments such as those that may occur in tears or in the GI tract [4].

IgA function

As with IgM and IgG, IgA has the ability to neutralize pathogens such as bacteria, virus and protozoans by direct interaction through receptors on the heavy and light chains of the IgA molecule. In its polymeric form it is found most predominantly at or near mucosal surfaces. The monomeric form is considered "minor" in the blood, but

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the major factor in repelling microbial attacks at the skin surface and in the GI track [5].

IgA neutralizes bacteria by direct interaction with fimbriae on the bacteria [5]. This is by the interaction of glycans on the IgA molecule with the sugar dependent regions of the fimbriae. IgA may also directly bind to toxins and neutralize them [6]. Thus, attachment of either toxin or microbe to a mucosal surface is prevented-curtailing infections. In the past it was dogma that IgA does not have the ability to activate the classical complement pathway as the C1q binding site does not exist. However, more recent studies have indicated that IgA may activate the alternate pathway of complement via lectin pathway by binding to mannose binding lectin. This is almost certainly dependent on glycosylation status. The alternate complement activation pathway remains controversial in that the exact triggering mechanism is not understood, but there is appears to be at least a theoretical correlation. Additional research will define this mechanism. Given the redundancy which occurs in animal immunology it is logical to assume that such a pathway exists [7].

The high concentration of IgA in colostrum suggests a passive yet intimate role in immune protection of newborns. Brest feeding has been known for generations to produce "healthier" babies, decreasing morbidity and mortality from gastrointestinal and respiratory track related infections.

This same system plays a role in secretory immunity in general. The levels of complement, and leucocytes counts are low in secretions. So, these immune effector functions that leukocytes and complement mediate normally and are important in protecting internal organs and tissues are less important at the exposed mucosal surfaces.

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