Review Article

The Possible Role of Immunoglobulin A Monoclonal Antibodies against COVID-19 Infection

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Abstract

The coronavirus adheres to the nasal ciliated epithelium and replicates before transporting it to the nasopharynx. Immunopathogenesis and severity of coronavirus disease 2019 (COVID-19) are influenced by viral and immune system factors. COVID-19 infection is capable of producing an excessive immune reaction in the host that called a cytokine storm. The effect is extensive tissue destruction. Detection and monitoring of the immunopathological changes in patients with COVID-19 may provide potential targets for drug development and discovery, besides it is necessary for clinical management. Immunoglobulin A (IgA) is the most abundant antibody class present at mucosal surfaces, including the upper respiratory tract, providing the first line of defense in mucosal immunity at the primary site of virus infection. Secretory IgA neutralizes the virus without causing inflammation because of its inability to fix and activate the complement cascade. Hence, it is suggested that induction of the mucosal immune response is more desirable to prevent respiratory infection to avoid unregulated inflammatory innate responses and impaired adaptive immune responses that may lead to locally and systemically harmful tissue damage. The advantage of IgA for protecting mucosal surfaces, such as the respiratory tract, relates to the presence of a specialized mechanism for transporting oligomeric IgA across epithelial surfaces.

Keywords: COVID-19, immunoglobulin A, monoclonal antibody

Immunoglobulin a Definition

Immunoglobulin A (IgA) is a glycoprotein made up of heavy (H) and light (L) polypeptide chains. IgA is the main immunoglobulin (Ig) in secretions such as colostrum, saliva, and tears[1-3] and exists in respiratory, intestinal, and genital tract secretions.[4-6] It prevents attachment of microorganisms such as viruses and bacteria to mucous membranes.[7]

IgA 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 more than all other types of antibody combined;[8] IgA, as the main class of antibody present in the mucosal secretions of most mammals, represents the first line of defense against invasion by inhaled and ingested pathogens at the vulnerable mucosal surfaces. Up to 15% of the total immunoglobulins A is produced throughout the body.[9]

IgA is locating at significant concentrations in the serum of many species. where it functions as a second line of defence mediating elimination of pathogens that have breached the mucosal surface, IgA interacts with an Fc receptor called FcαRI (or CD89), which is expressed on immune effector cells, to initiate inflammatory reactions. Ligation of FcαRI by IgA containing immune complexes causes antibody-dependent cell-mediated cytotoxicity (ADCC), degranulation of eosinophils and basophils, phagocytosis by monocytes, macrophages, and neutrophils, and triggering of respiratory burst activity by polymorphonuclear leukocytes.[10]

In humans, following antigen presentation to T helper cells, and differentiation of Th to Th2, the cytokines IL-10, IL-4

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Access this article online

Quick Response Code:

Website: www.matrixscimed.org

DOI: 10.4103/MTSM.MTSM_27_20

How to cite this article: Hameed RM, Mirdan Al-Ibraheemi MK, Obayes Al-Khikani FH, Hasan NF, Salman Almosawey HA, Al-Asadi AA. The possible role of immunoglobulin A monoclonal antibodies against COVID-19 infection. Matrix Sci Med 2020;4:96-102.

Received: 16-07-2020, **Revised:** 21-07-2020, **Accepted:** 04-08-2020, **Published:** 09-10-2020

and transforming growth factor-beta (TGF)–b are involved in causing the preferential maturation of B cells (B-cell Ab class-switching and differentiation) into B cells that are committed to producing IgA. In humans, there are two types of IgA, predominantly IgA1, found in serum and derived in bone marrow, and IgA2, a secretory form of Ig.[11]

Normal Value of Immunoglobulin A

Reference ranges of IgA may vary based on sex and factors such as alcohol use, chronic conditions, and smoking status.[12] IgA deficiency occurs in 1 in 700 people and may not be associated with the disease. However, selective IgA deficiency widespread in primary immunodeficiency, which often presents an asymptomatic phenotype or mild consequences.[13] The secretion and composition of IgA saliva depend on the activity of the sympathetic and parasympathetic nervous systems. Physical activity, stimulating the autonomous nervous system, may reduce the amount of saliva and/or inhibit its secretion.[14]

The use of monoclonal and polyclonal antibodies against the IgA subtype IgA1 makes it possible to estimate the level of IgA1 and IgA2. The highest concentrations of Igs IgA1 was found in the nasal mucosa, where it represents 95%, and the highest concentration of IgA2 was observed in the colon (62%), compared to the total number of both subtypes of IgA.[15,16]

The decreased level of the salivary IgA is associated with an increased incidence of upper respiratory tract illness.[17] Thus, it may be a useful biological marker of clinical predisposition to diseases of the upper respiratory tract.[18]

Mechanism of Action of Secretory Immunoglobulin A Antibodies

The mucosal system is the first line of immune defense, while the secretory IgA (sIgA) is the first line of mucosal immunity. The mucosal system can maintain the balance in the mucosal immunity by defenses against the pathogens and preserve the commensal microorganisms on the mucosal surface.[19] SIgA has an important role in mediating the adaptive humoral immune defense at mucosal surfaces (respiratory, gastrointestinal, and urogenital tracts).[11]

IgA is predominantly present in mucosal tissues, including the upper respiratory tract,[20] providing the first line of defense in mucosal immunity at the primary site of virus infection. There are three defense functions of IgA includes immune exclusion, intracellular neutralization, and virus excretion.[19] IgA is thought to be able to interact with intracellular pathogens such as viruses, blocking replication, assembly, and/or budding.[21] Besides the function of immune exclusion, a nonspecific immune role, it also played an important role in the specific immunity, and immune regulation sIgA has a critical role in homeostasis between commensal microorganisms and pathogens.[18]

After secretion, IgA can bind to microbes and prevent them from attaching to or penetrating the epithelial lining. IgA in the lamina propria beneath mucosal epithelium may form a complex with antigens and transport them, via the polymeric Ig receptor (pIgR), across the epithelial cells, and into the secretions.[22,23] The antibodies blocked their apical to basal surface transcytosis and transported the viral particles to the apical supernatant.[24] Besides, the advanced glycosylated IgA heavy chain and SC serve as competitive inhibitors of the pathogen adhesion process.[28] Its general mechanism is the immune exclusion of antigens such as prevention of the penetration of the Ag into the organism by confining them to external secretions followed by elimination.

In vitro evidence points to the ability of pIgA undergoing pIgR-mediated transport to prevent virally induced pathology in the upper respiratory and neutralize intracellular viruses such as influenza, Sendai, measles, and human immunodeficiency viruses within epithelial cells.[21,29] sIgA neutralizes pathogens and toxins without causing inflammation because of its inability to fix and activate the complement cascade. In the nose, there may be two lines of defense against influenza viral infection.[30] In the nose, there may be two lines of defense against influenza viral infection. If influenza virus-specific SIgA is present, initial viral infection of the mucosal epithelial cells is prevented, and plasma Ab serves as backup protection. In addition, p-IgA does not induce an inflammatory reaction in the mucosa.[1,31] Therefore, it is suggested that the induction of the mucosal immune response is more desirable to prevent respiratory infection by influenza A viruses.[32] It is reported that the intranasal immunization induces a more efficient cross-protective immune response against the influenza virus than systemic immunization. IgA antibodies are suggested to play a major role in antibody-mediated heterosubtypic immunity.[33,34]

The coronavirus adheres to the nasal ciliated epithelium and replicates before transporting it to nasopharynx via mucociliary action.[35] Increased cholinergic secretion leads to increased release of Igs, then entrapment of viruses in the mucous and periodically the mucous blanket removed. Studies suggest that secretory IgA reduces the coronavirus titer significantly in cell lines.[36]

Role of Immunoglobulin A in Viral Infections

Respiratory tract infections

The upper airways and lungs are mucosal surfaces that are common sites for infection with a variety of inhaled pathogens as viruses and bacteria.[37] Each breath carries in the inhaled air thousands of microparticles and microorganisms into the respiratory tract. Therefore, the induction of immune responses in the respiratory tract is crucial for protection against respiratory diseases without generating inflammatory or immune response.[38] The defense of the respiratory tract against pathogens relies on two distinct mechanisms, located in the airways and the alveolar space, respectively. In the

airways (upper and lower), the mechanical defense appears to predominate include the deposition on the nasal and oropharyngeal surfaces and elimination through sneezing, cough, and mucociliary clearance. The alveolar epithelium lacks mucociliary properties and thus relies mostly on the alveolar macrophages to remove micro-organisms and particles reaching the alveolar space.[39] Besides, the respiratory mucosa is protected primarily by a secretory immune system.[40]

Gastrointestinal infections

Gastrointestinal viral infections are divided into two broad categories based on whether the infection is entero-pathogenic or non-entero-pathogenic. Classical enteropathogenic viruses infect cells that comprise the gastrointestinal system result in gastrointestinal disease symptoms such as diarrhea, malabsorption, vomiting, and pain. The generality of viral gastrointestinal infections is caused by adenovirus, norovirus, rotavirus, and astrovirus. Although nonenteropathogenic viruses enter the body via the gastrointestinal tract, they cause no gastrointestinal to mild disease because they are distributed systemically and cause disease in other organ systems. Examples of important human nonenteropathogenic viruses include coxsackievirus, poliovirus, hepatitis A virus, and echovirus. On the opposite side, HIV can enter through the lower gastrointestinal tract and can be associated with mild gastrointestinal disease. HIV infects cells of the immune system both in systemically and the gastrointestinal tract. Therefore, its most severe effects are on the immune system. Both nonenteropathogenic and enteropathogenic gastrointestinal viruses induce IgA that functions in protective immunity.[41]

Mechanisms of immunoglobulin A induction

IgA responses to gastrointestinal viruses are comprising of high-affinity antibodies that recognize the viruses and neutralize them. High-affinity IgA producing cells is arisen from the actions of helper T cells, within the context of the germinal center environment in the gastrointestinal inductive sites, isolated lymphoid follicles, mesenteric lymph nodes, and Peyer's patches.[42] These helper T cells signal B cells using molecules such as CD40 and TGF-β to induce somatic hypermutation and class switch recombination resulting in the production of high-affinity IgA,[43] thought to function to neutralize the virus in intestinal. Once signaled to become a high-affinity IgA and B cell, the cell leaves the inductive site germinal center and circulates back to the intestinal lamina propria based on such cell surface expression of markers as α4 β7.[42,44-46] This process takes at least seven to ten days following the initial infection of the virus in the gastrointestinal tract.

On the other hand, unmutated low-affinity IgA can be synthesized very rapidly in the gastrointestinal tract in a T cell-independent fashion.[47,48] The primary functions of low-affinity antibody that limit penetration of commensal microbes through epithelial cells[49] but it does not play an important role in limiting pathogens, including gastrointestinal viruses. However, virus-specific intestinal IgA (which is a presumably high affinity) develops rapidly and many acute viral infections are resolved prior to the time required for the generation of germinal centre high-affinity IgA antibody. Mice that have defects in germinal centre formation can develop specific intestinal IgA responses to viruses[50-52], providing other evidence that germinal centre reaction might not be necessary for the production of virus-specific antibody and clearance of infection. Therefore, another possibility is that IgA generated through T cell-independent pathways develop sufficient affinity to limit replication of the virus. Rapid T cell-independent virus-specific IgA antibody responses are generated during many acute virus infections, including VSV, polio, and influenza.[53-61] Virus-specific IgA mediate virus clearance and dissemination prior to the generation of T cell-dependent IgA and limit viral replication.[62] These antibodies can be induced in the absence of CD4+ T cells.[55,63,64] Mice lacking expression of MHC II [65], CD40[66], or CD40L[67] can exhibit IgA antibody class-switching and it is thought that such molecules as APRIL and BAFF produced by epithelial and dendritic cells drive class switch recombination and somatic hypermutation in B cells independently of germinal centres.[68-72] Evidence implicates a greater role for T cell-independent nongerminal center generated virus-specific IgA responses in the intestine.

The factors that effect on immunoglobulin A levels

Concentrations of Ig are affected by demographic factors, metabolic abnormalities in adults, and habits (alcohol and smoking). Besides, serum levels of IL-6 (an inflammation marker) have been determined.[73]

Since confounders were modified, male sex positively correlated with rates of IgA.[73] Heavy drinking positively associated with levels of IgA. Metabolic disorders (obesity and metabolic syndrome) directly linked to rates of IgA. Abdominal obesity and hypertriglyceridemia are the most closely associated components of metabolic syndrome with serum IgA.[74] The IL-jb6 plasma rates were strongly associated with the concentrations of IgA.[75,76]

Exercise provides the human body with numerous stressors that contribute to immunological and physiological improvements. There is a hormonal influence, where intensive exercise contributes to decreased immune function, while mild exercise tends to boost certain areas of immunity. Moderate intensity exercises at a wide range of ambient temperatures do not increase the susceptibility to upper respiratory infection by decreasing s-IgA.[77]

Data demonstrate for the first time that a congested winter fixture schedule induces detectable perturbations to mucosal immunity in professional soccer players. The stress of intense exercise typically stimulates a transient fall in SIgA levels that tend to return toward baseline levels within hours to days, providing there is sufficient recovery, and no infection is present.[78]

Exposure to changes in the atmosphere is often physiologically exhausting, which can impair immunity. Higher SIgA concentrations are observed during winter and the prevalence

of SIgA deficiency and subnormal SIgA levels are lower in the cold season.[79]

A weak negative correlation is observed between the level of sIgA and the stress rating (r =-0.25) only at the final exam.[80]

Immunopathogenesis of COVID-19 infections

The immunopathogenic mechanisms of coronavirus disease 2019 (COVID-19), which cause pneumonia, tend to be, especially, complex. Mutation rates of RNA viruses such as COVID-19 are higher than the DNA viruses, indicating a more effective survival and pathogenesis adaptation.[81]

Immunopathogenesis and severity of COVID-19 are influenced by viral and immune system factors; viral factors include virus type, viral titer, viral load, mutation, and *in vitro* viability of the virus. The individual's immune system factors include physical status, age, nutritional status, gender, neuroendocrine-immune regulation, and genetics (such as HLA genes), these factors determined a person is infected with the virus, the re-infection, and the duration and severity of the disease.[82]

Many COVID-19 patients have mild-to-moderate symptoms, but about 15% progress to extreme pneumonia and about 5% ultimately undergo acute respiratory distress syndrome, septic shock, and/or multiple organ failure.[83,84]

SARS-CoV-2 infection is capable of activation innate and adaptive immune responses. However, unregulated inflammatory innate responses and impaired adaptive immune responses may lead to locally and systemically harmful tissue damage.[85]

Some of the severe COVID-19 infections cases admitted to the intensive care unit revealed high levels of pro-inflammatory cytokines such as IL2, IL10, IL7, granulocyte colony- stimulating factor, IP10, monocyte chemotactic protein 1, macrophage inflammatory protein 1 α, and tumor necrosis factor alpha that are reasoned to begin disease severity.[83]

In patients with severe cases, but not a mild disease, lymphopenia is a common feature, with drastically reduced numbers of $CD4^+$ T cells, $CD8^+$ T cells, B cells, and natural killer cells[83,86] besides a reduced percentage of monocytes, basophils, and eosinophils.[86]

Pneumonia, lymphopenia, depleted lymphocytes, and a cytokine outbreak characterize extreme COVID-19. Major antibody development against COVID-19 is observed; however, it remains to be determined if it is defensive or pathogenic.[85]

COVID-19 infection is capable of producing an excessive immune reaction in the host that called a cytokine storm; the effect is extensive tissue destruction. The protagonist of this storm is IL-6. It is produced by activated leukocytes and acts on a wide number of cells besides tissues. It is capable of promoting the differentiation of B lymphocytes, promoting the growth of some immune cells, and inhibition of the growth of others. It plays an important role in thermoregulation and also stimulates the production of acute-phase proteins. While IL 6's key function is pro-inflammatory, it can have anti-inflammatory effects, too, throughout infectious conditions, allergies, autoimmune disorders, respiratory problems, and certain forms of cancer, IL 6 in effect rises. While IL 6's key function is pro inflammatory, it can have anti inflammatory effects, too, throughout infectious conditions, allergies, autoimmune disorders, respiratory problems, and certain forms of cancer, IL 6 in effect rises.[87]

Cytokines released in the sense of innate immune responses to viral infections are well known to cause the neuroendocrine system to release glucocorticoids and other peptides, which may inhibit immune responses. Viral particles of infectious SARS-CoV-2 were isolated from the gastrointestinal, fecal, and urine samples.[85]

The extent of infection with SARS-CoV-2 is intermediate between that of SARS-CoV and MERS-CoV.[88] Among structural protein roles, the envelope plays a key role in the pathogenicity of viruses, as it facilitates viral assembly and release.[87]

Furthermore, C-reactive protein and D-dimer found to be abnormally high. The high levels of pro-inflammatory cytokines lead to shock and tissue damage in the different organs such as the heart, liver, and kidney, as well as respiratory failure or multiple organ failure.

They also mediate extensive pulmonary pathology, leading to massive infiltration of neutrophils and macrophages, diffuse alveolar damage with the formation of hyaline membranes, and diffuse thickening of the alveolar wall. Spleen atrophy and lymph node necrosis are also observed, indicative of immune-mediated damage in deceased patients.[85]

Monoclonal immunoglobulin A antibody

Monoclonal antibodies are identical Igs, generated from a single B-cell clone. These antibodies recognize binding sites, or unique epitopes, on a single antigen. Derivation of a single epitope and subsequent targeting from a single B-cell clone is what differentiates monoclonal antibodies from polyclonal antibodies.[89] Monoclonal antibody therapies have the potential to offer safety and better specificity than alternative treatments for several complex diseases, such as autoimmune disorders and cancers, also they already have established regulatory precedence and are relatively cost-efficient of produce. Thus, many biopharmaceutical companies are currently building their clinical pipelines around monoclonal antibody platforms.[90]

There are two potential advantages of using the IgA antibody as therapeutic: First, it is useful if the site of virus action is mucosal rather than in the blood since the action of IgA in mucus. Second, the ability of IgA to bind FcaRI found on cytotoxic immune cells and neutrophils, increase the neutrophil and monocyte-dependent phagocytosis.[89] The use of active mucosal immunization protocols designed to generate an IgA response supported by the data indicates that the IgA antibody is efficacious in protecting the airways from viral infection. The

experiments suggest that the advantage of IgA for protecting mucosal surfaces, such as the respiratory tract, relates to the presence of a specialized mechanism for transporting oligomeric IgA across epithelial surfaces.[91] Further, the IgA prevent virally induced pathology in the upper respiratory tract.[31] Thus, IgA antibodies by themselves can protect against respiratory virus infection.[92]

Previous studies reported the properties of a monoclonal IgA, which is protective in passive immunotherapy of tuberculous infection using experimental mouse models.[93] Monoclonal IgA antibody can protect against RSV replication in the lungs if given immediately before the challenge. The topical application of relatively small amounts of monoclonal IgA protects against both upper and lower respiratory tract infections caused by RSV.[94,95] In the H5N1 influenza virus, monoclonal IgA is stable *in vivo* and highly effective against a highly lethal respiratory virus.[96] Anti HA IgA has a greater potential to prevent influenza A virus infection, due to the increase of avidity conferred by its multivalency. This advantage may be particularly important for heterosubtypic immunity.[20] IgA contributes to protection against H1N1 influenza and should target in vaccines, as a result of the effect of nasal IgA in reducing the length of time infectious virus.[97] IgA anti-Sendai virus HN protein monoclonal antibodies were shown to neutralize virus in vitro and in vivo when passively administered to the mouse respiratory tract.[87]

Conclusions

The Coronavirus adheres to the nasal ciliated epithelium and replicates before transporting it to the nasopharynx. Increased cholinergic secretion leads to increased entrapment of viruses in the mucous and release of immunoglobulins. Detection and monitoring the immunopathological changes in patients with COVID-19 may provide potential targets for drug development and discovery besides it is important for clinical management.

IgA is the most abundant antibody class present at mucosal surfaces, including the upper respiratory tract, providing the first line of defense in mucosal immunity at the primary site of virus infection. Since the decreased level of the salivary IgA is associated with an increased incidence of upper respiratory tract illness, it may be a useful biological marker of clinical predisposition to diseases of the upper respiratory tract. IgA is thought to be able to interact with intracellular pathogens such as viruses, blocking replication, assembly, and/or budding. Besides, the advanced glycosylated IgA heavy chain and SC serve as competitive inhibitors of the pathogen adhesion process.

sIgA neutralizes pathogens and toxins without causing inflammation because of its inability to fix and activate the complement cascade. Therefore, it has been suggested that induction of the mucosal immune response is more desirable to prevent respiratory infection to avoid unregulated inflammatory innate responses and impaired adaptive immune responses that may lead to locally and systemically harmful tissue damage.

There are two potential advantages of using the IgA antibody as therapeutic: first, If the site of virus action is mucosal rather than in the blood. second, the ability of IgA to bind FcaRI found on cytotoxic immune cells and neutrophils allows neutrophil and monocyte-dependent phagocytosis.

Monoclonal antibody therapies have the potential to offer safety and better specificity than alternative treatments. The use of active mucosal immunization protocols designed to generate an IgA response supported by the data indicates that the IgA antibody is efficacious in protecting the airways from viral infection. The previous experimental studies suggest that the advantage of IgA for protecting mucosal surfaces, such as the respiratory tract, relates to the presence of a specialized mechanism for transporting oligomeric IgA across epithelial surfaces.

Future experimental studies are certainly needed to detect the functional significance of mucosal and systemic IgA in COVID-19 and the effect of monoclonal IgA antibody to treat the coronavirus patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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