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Role of IgD in prevention and treatment of SARS CoV-2 infection "The Unknown Soldier"

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ABSTRACT

COVID-19 presents varied clinical features, ranging from asymptomatic, mild, to acute respiratory distress syndrome (ARDS). People of any age can be infected by the novel coronavirus but some people are at more risk than others of becoming seriously ill with COVID-19. Older people, and people with pre-existing medical conditions (such as asthma, diabetes, and heart disease) appear to be more vulnerable developing severe or even lethal illness. Children can be infected with SARS-CoV-2, and become ill with COVID-19. However, they appear to be less susceptible to infection than adults and their symptoms are generally milder**.** Immunoglobulin D (IgD) has remained an enigmatic antibody class since its discovery more than 50 years ago. The function of secreted IgD has been a longstanding puzzle in immunology**.** In this pandemic, it is the proper time to rediscover its role and find additional therapy to vaccine. In this article I will review IgD discovery, its role in immunity, its concentration in some groups and their susceptibility to infection with COVID 19.

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Introduction

Antibodies or immunoglobulins (Ig) are formed by plasma cells as a humoral immune response to antigens. The first antibodies formed after antigen stimulation are of the IgM class, followed later by IgG and also IgA antibodies. IgD normally occurs in serum in trace amounts. The immunoglobulin G (IgG), is the most abundant antibody isotype in the plasma of the humoral immune response accounts for about 75% of the total Igs of healthy individuals, it detoxifies harmful substances and is important in the recognition of antigen-antibody complexes by leukocytes and macrophages. IgM usually circulates in the blood, accounting for about 10% of human immunoglobulins and it is first produced in response to microbial infection/antigen invasion by B cells. IgA is abundant in nasal mucus, saliva, serum, breast milk, and intestinal fluid, accounting for 10-15% of human immunoglobulins. IgE is present in minute amounts, accounting for no more than 0.001% of human immunoglobulins and its original role is to protect against parasites**.** While IgD accounts for less than 1% of human immunoglobulins and it is may be involved in the induction of antibody production in B cells, but its exact function still unknown (Schroeder and Cavacini, 2010).

Immunoglobulin D (IgD) was discovered in a patient with myeloma more than 50 years ago and remains as the most enigmatic of immunoglobulin classes (Chen and Cerutti 2010). The relative molecular mass and half-life of secreted IgD is 185 kDa and 2.8 days, respectively (Rogentine et al 1966). IgD exists in two forms. On the one hand, IgD is coexpressed with IgM on the surface of mature B cells before antigenic stimulus, as a receptor for

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that antigen (Finkelman et al. 1976; Ruddick and Leslie 1977) and this may explain the success of plasma of recovered patients in some cases of COVID 19 patients. Blood plasma should be collected within 28 days after recovery; therefore, it is suggested to be collected within 3 days after recovery to guarantee the presence of IgD, and on the other, free IgD circulates in the blood where it represents <1% of total immunoglobulin content. Serum IgD can participate in anti-infectious immunity and immune regulation (Vladutiu 2000; Chen and Cerutti 2011; Rigante 2016).

Discovery of IgD

In 1964, physicians David Rowe and John Fahey identified and characterized an unusual myeloma protein in humans while studying multiple myeloma disease with electrophoretic and metabolic properties different from the known Ig classes at that time (Rowe and Fahey 1965 a,b). The myeloma protein displayed no reactivity to the anti-sera against IgM, IgG, or IgA. They suggested that this myeloma protein represented a member of a novel Ig class rather than an abnormal product of the malignant myeloma cells (Rowe and Fahey 1965 a,b). In the late 1970s and early 1980s, IgD was discovered in primates, rodents, and selected species of mammals, including dog, mouse, rat, rabbit, and guinea pig, whereas it was undetectable in other mammals, such as swine, birds, cattle, sheep, and pig (Finkelman et al. 1976; Chen et al. 1982; Preud'homme et al. 2000; Stavnezer et al. 2008). More importantly, IgD and its homologs and orthologs have recently been found in a wide spectrum of species that are evolutionarily much more ancient, such as cartilaginous fishes, bony fishes, amphibians, and reptiles with the exception of birds (Preud'homme et al. 2000; Stenvik et al. 2001). These findings demonstrated that IgD is indeed an ancient because the cartilaginous fishes appeared on earth as many as some 470 million years ago, when jawed vertebrates first evolved and adaptive immune systems first appeared.

IgD is present in plasma and also in human nasal, lacrimal, salivary, mammary, bronchial, pancreatic, and cerebrospinal fluids (Brandtzaeg et al. 1979a; Korsrud and Brandtzaeg 1980) and in the amniotic fluid of pregnant women with concentrations progressively increasing during the first half of pregnancy (Cederqvist et al. 1978) Only trace amounts of IgD are present in intestinal mucosal secretions (Brandtzaeg et al. 1979a; 1979b; Brandtzaeg and Korsrud 1984; Bjerke et al. 1986). The distribution of soluble IgD largely correlates with the distribution of IgD-producing B cells. Intestinal mucosa, liver, peripheral lymph nodes, spleen, and bone marrow contain very few IgD producing B cells, while tonsils, adenoids, salivary, and lachrymal glands, and nasal mucosa harbor abundant IgD-producing B cells (Brandtzaeg et al. 1979a, 1979b; Korsrud and Brandtzaeg 1980; Plebani et al. 1983; Korsrud and Brandtzaeg 1981; Brandtzaeg 1989; Chen et al. 2009). IgD-producing B cells can account for up to 20% of all Ig-secreting cells in human tonsils (Chen et al. 2009; Liu et al.1996; Arpin et al. 1998). The reason why they are rarely found in bone marrow and gut associated-lymphoid tissues (GALTs) in healthy individuals is probably because they are not normally generated there and they express a homing profile not in favor of the intestinal mucosa (Johansen et al. 2005). The numbers of IgD-producing B cells in the upper aerodigestive mucosa are drastically increased in patients with IgA deficiency (Brandtzaeg and Nilssen 1995; Brandtzaeg 1995; Brandtzaeg et al. 2005). However, cell-associated IgD includes transmembrane IgD, intracellular IgD, and secreted IgD bound to various cell types. Crosslinking of IgD receptor on T cells was shown to protect T cells from apoptosis (Tamma and Coico 2003). It has also been shown that this IgD receptor could promote the formation of immune synapse between cognate T cells and naïve B cells that express transmembrane IgD and thereby boost antigen presentation and antibody production (Wu et al. 1999; Tamma et al. 2001). Moreover, IgD can largely increase in B cells, in which IgM function is suppressed, suggesting that IgD is largely able to substitute for IgM functions (Lutz et al. 1998). In addition, previous studies have showed that the association of secretory IgD with basophils and mast cells results in the production of antimicrobial factors and the enhancement of respiratory immune resistance (Chen et al. 2009; Edholm et al. 2010).

Role of IgD as an immunomodulator

The function of secreted IgD has been a longstanding puzzle in immunology. Secreted IgD can bind to many pathogenic microorganisms and their products, many of which are virulence factors used in pathogenesis, such as measles virus, *Haemophilus influenzae* adhesin MID (Hag), *Moraxella catarrhalis*, rubella virus, diphtheria toxin, *Escherichia coli*, streptococci streptolysin O (Heiner and Rose 1970; Luster et al. 1976; Swierczynska et al. 1976; Jefferis and Mathews 1977; Sewell et al. 1978; Salonen et al. 1985; Forsgren et al. 2001; Ronander et al. 2008; Chen et al. 2009). Most of these pathogens infecting same anatomic location where IgD is abundant, i.e. the upper aerodigestive MALTs, strongly supports the concept that IgD has protective functions against these pathogens perhaps by contributing to immune exclusion or neutralization. Also, serum IgD was increased in patients with leprosy (Sirisinha et al. 1972), tuberculosis (Buckley and Trayer 1972; Kikindjanin 1981), salmonellosis, infectious hepatitis (Rostenberg and Penaloza 1978), and malaria (Colwell et al. 1971).

Risk factors for Covid 19 and role of IgD

Adults aged over 70 and those underlying health conditions such as respiratory, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were all associated with an increased risk of death in addition to obesity. However, It was found a linear increase of IgD until the age of 10 (Jankowski 1980), followed by a gradual decrease until the age of 14 (Geny et al. 1974) and then steadily decreased with age in adults which correlates with a gradual decline of immunity in older people (Tietz et al. 1992; Haraldsson et al. 2000; Listi et al. 2006). However, some studies found to be restricted to females (Mosedale et al. 2006). Moreover, Serum IgD concentrations were significantly lower in overweight individuals than in those with normal weight. On the other hand, the concentration of IgD showed considerable biological variation, even in people of the same age, from undetectable to 400 mg/liter (Rowe et al. 1968; Dunnette et al. 1977).

On the other hand, myeloma patients are considered to be safe from COVID-19 as reported by Researchers in the IMF's Asian Myeloma Clinical Trials Network (AMN). AMN sites in Beijing; Shanghai; Korea (with multiple myeloma centers); Singapore; and Japan (through the Japanese Myeloma Society), report zero cases of COVID-19 in myeloma patients and no COVID-19-related deaths. In Korea, there were, for example, 109 overall COVID-19 deaths, but none for myeloma patients. In Singapore, only 2 deaths (in total), and in Japan, a total of 52 in the hard-hit areas of Italy, Spain, and France. However, the numbers are relatively small. In Italy, patients and deaths have been in elderly patients late in the disease. Consideration should be taken if they have subjected to chemotherapy or stem cell transplantation. Allergic diseases, asthma, and COPD are not risk factors for SARS-CoV-2 infection. However, there is many intriguing connections of secreted IgD with myeloid cells. Early studies showed that granulocytes, such as neutrophils and eosinophils, could bind significant levels of IgD under certain pathological conditions, such as skin allergy and inflammation (Hunyadi et al. 1976; Dikeacou et al. 1979), although they bound little IgD under physiological conditions (Lawrence et al. 1975; Berretty and Cormane 1979; Walsh and Kay 1986).

Although the first commercial mAb was an anti-respiratory syncytial virus (RSV) antibody used to fight a pediatric respiratory illness, they were widely utilized for long time in cancer and inflammatory disease (Beck 2010; Reichert 2015; Vacchelli 2013) till recently a flurry of human, or humanized, mAbs against cytomegalovirus (CMV), dengue virus, Ebola virus, H5N1 influenza virus, Hendra virus, hepatitis C virus (HCV), herpes simplex virus (HSV) , human immunodeficiency virus (HIV), Marburg virus, Nipah virus, rabies virus, severe acute, respiratory syndrome (SARS) virus, West Nile virus and yellow fever virus have been described in the past few years (Bossart 2009; Berry and Gaudet 2011; Krawczyk et al. 2013; Dejnirattisai et al. 2015; Flyak et al. 2015; Tan 2015). Some of these mAbs are currently being tested in the clinic and include second-generation mAbs with improved neutralizing activity and/or novel target specificities (Both 2013; Corti and Lanzavecchia 2013; Cohen 2013; Klein 2013; Kwong et al. 2013; Euler and Alter 2014; Huang et al. 2014). Finally, antiviral mAbs have already demonstrated partial efficacy when administered after HIV, HCV, or Ebola virus established infections but the neutralizing mAbs was broadly applied in case of HIV that mAbs represent promising, high-added-value therapeutic agents (Barouch 2013 ; Flego 2013; de Jong 2014 ; Qiu 2014).

Advantages of using Recombinant monoclonal antibodies (rAbs)

The main obstacle of using IgD -its short half-life (2.8 days) can be overcomed by using Recombinant monoclonal antibodies (rAbs). Producing rAbs is cheaper than generating mAbs. Indeed, rAbs required less purified antigen to produce than classical mAbs. Moreover, the production time is shorter (weeks *vs*. months). Mass production of rAbs does not required the use of animals (overcomes ethical concerns). rAbs can be produced in several formats like Fab fragments, single-chain variable region fragments (ScFv), diabodies (Dimeric ScFvs) and in several hosts (from bacteria to human cells). We can switch the antibodies of species (from mouse to human), of classes (from IgG to IgE) and of substypes (from an entire IgG form to ScFv) with no immeasurable effort. rAbs offer the specificity and the reproducibility of mAbs with the advantage of recombinant modifications readily available. Thus, they can be used in all applications where classical mAbs are used. rAbs are constructed *in vitro*, outside the constraints of the immune system, using recombinant DNA technologies. The antibody genes are isolated and then incorporated into plasmid DNA vectors, and the resulting plasmids are transformed or transfected into expression hosts such as bacteria, yeast, or mammalian cell lines (similar process to classical recombinant protein production). However, Motavizumab has a serum half-life of approximately 24 days in children. Study of a humanized monoclonal antibody engineered to have increased binding affinity to FcRn to extend the serum half-life in humans. In healthy adult subjects, inclusion of the YTE mutation in the Fc domain of motavizumab (mota-YTE) decreased clearance by 71% to 86% and increased serum half-life 2- to 4-fold (up to 100 days) compared with the parent antibody, motavizumab (Robbie et al. 2013).

Conclusion

Further studies are needed to prove the results and statistics of the previous studies and also elongation the t1/2 of IgD.

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