

Physiology of IgA and IgA Deficiency

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Although secretory immunoglobulin A (IgA) is important in mucosal immunity, selective IgA deficiency is the most common primary immunodeficiency of humans. In most cases this defect is not associated with any illness. The reasons for this are unknown, but other immunological compensations might provide sufficient or complete restitution. Alternatively, it is possible that IgA deficiency alone may not predispose to disease, but additional immunological abnormalities might be present in symptomatic individuals. Some IgA-deficient individuals have a reduced antibody response to immunizations (even with normal IgG and IgM levels) and others have deficient responses to bacterial polysaccharides when IgG subclass levels are normal. The physiological role of IgA, the frequency and causes of IgA deficiency, the diseases associated with its absence, and current limited understanding of the pathogenesis of selective IgA deficiency will be reviewed.

KEY WORDS: IgA; IgA transport; mucosal immunity.

BIOLOGICAL FUNCTIONS OF IMMUNOGLOBULIN A

Immunoglobulin A (IgA) was first recognized in serum about 50 years ago as the second-most abundant serum immunoglobulin after IgG. Shortly afterward, IgA in a novel form was found to be the main immunoglobulin in human secretions. While its role in systemic immunity is still not understood, secretory IgA antibodies in secretions can neutralize viruses, bind toxins, agglutinate bacteria, prevent bacteria from binding to mucosal epithelial cells, and bind to various food antigens preventing entry into the general circulation (1–3) (see Table I).

The predominant immunoglobulin that is secreted in mucosal sites is IgA but the pathway that this immunoglobulin takes to find its way into the mucosal secretions is complex. First, IgA must be produced as a dimer by local plasma cells with covalently attached J chain; the

addition of the J chain is essential. Binding of dimeric IgA + J chain complex to the polymeric Ig receptor (pIgR) on the basolateral portion of the epithelial cell stimulates transcytosis of the receptor and attached IgA via clathrin-coated pits through the epithelial cell (4). Cleavage of the receptor at the apical portion of the cell releases dimeric secretory IgA and a portion of the pIgR, the secretory component (SC), and both are discharged into the mucosal lumen. The pIgR transcytoses dimeric or tetrameric IgA equally, although the functional significance of the larger polymers is unclear (5). The attachment of the SC via one disulfide bridge to one alpha chain enhances the resistance of IgA to proteolytic cleavage (6) (see Fig. 1). In addition to the wide range of biological activities found against pathogens in the secretory lumen, polymeric IgA transiting through epithelial cells has functional antibody characteristics and can impede the replication of intracellular viruses (7). IgA also can complex with antigens that have penetrated the lamina propria and transport them across epithelial cells to facilitate antigen exclusion (8).

Although secretory IgA has many known functions, the role of serum IgA is uncertain. Plasma cells producing serum IgA are located predominantly in the bone marrow and to a lesser extent in the spleen (2). Receptors for the Fc portion of IgA are found on monocytes and granulocytes (9, 10). Receptor-bound IgA antibodies activate both granulocytes and monocytes and initiate phagocytosis of bacteria and fungi. These Fc α R may play a role in the catabolism of IgA antibodies and in the clearance of IgA immune complexes from the circulation. Because IgA in the serum does not fix complement by the classical pathway, although it can do so as an aggregate by the alternative pathway (9), it has been suggested that IgA acts as a “discrete housekeeper,” in which foreign antigens are bound by IgA into complexes and removed by the phagocytic system, but with little or no resultant inflammation (11).

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Table I. Specific Secretory IgA Antibody Reactivity Human Colostrum and Milk^a

Bacteria
<i>Escherichia coli</i> O, K antigens, enterotoxin
Salmonella
Shingella
<i>Vibrio cholerae</i>
<i>Bacteroides fragillis</i>
Streptococcus
<i>Bordetella Pertussis</i>
<i>Clostridium diphtheriae</i> , <i>C. tetani</i>
<i>Streptococcus mutans</i>
<i>Neisseria gonorrhoeae</i>
<i>Campylobacter</i>
Viruses
Respiratory syncytial virus
Cytomegalovirus
Influenza A
Arboviruses - Semliki forest
Ross river, Japanese B,
Dengue
HIV
Parainfluenza,
Rotavirus
Echovirus
Coxsackie virus
Rhinovirus
Poliovirus 1, 2, 3
Fungi
<i>Candida albicans</i>
Protozoa
Giardia
Other
Milk proteins
Soy lectin
Wheat gluten, gliadin
Peanut lectin

^aModified from Cunningham-Rundles (25).

SELECTIVE IGA DEFICIENCY IN HEALTHY SUBJECTS

Serum IgA deficiency was first described in children with ataxia-telangiectasia (12), but this deficiency was later identified in other patients and populations of normal subjects. The prevalence of IgA deficiency ranges from 1:223 to 1:1000 in community studies and from 1:400 to 1:3000 in healthy blood donors (13). Because secretory IgA is known to protect mucous surfaces, it is a mystery why most IgA-deficient subjects remain healthy. This lack of disease in IgA deficiency is often attributed to a compensatory increase in secretory IgM (IgM attached to secretory component) (14); the colostrum of IgA-deficient subjects has been shown to contain abundant amounts of IgM (15). The main immunological difference between the IgA-deficient and the normal intestinal tract is the substitution of IgM-secreting plasma cells for IgA-secreting cells (16). This difference is evident in both healthy and ill IgA-deficient subjects. When nodular lymphoid hyperplasia develops, the nodules contain a proliferation of IgM plasma cells.

Although secretory IgM has been shown to be functionally active, it is not clear that it confers the same mucosal protection as secretory IgA. IgA-deficient blood donors harbor poliovirus longer after oral vaccination than do normal subjects (17). Additionally, secretory IgA is subject to rapid degradation in the intestinal lumen (18). Another study of 63 IgA-deficient subjects could not relate salivary IgM levels to health or frequency of illness (19).

In addition to the potential compensation supplied by IgM, Nilssen and co-workers (20) have shown that oral cholera-vaccinated IgA-deficient individuals preferentially activate intestinal IgG-producing cells rather than IgM producing cells. In normal subjects this vaccination produces a predominantly IgA response. Here, IgA deficient subjects with frequent illnesses had a response indistinguishable from healthy subjects, suggesting that there still is much to be learned about the immune compensations that occur in the healthy IgA-deficient subject.

Clinicians usually define selective IgA deficiency as a level of less than 7 mg/dl, since this is the lowest level detectable in many commercial laboratories. However, some individuals diagnosed as deficient actually may produce enough secretory IgA to remain healthy; some IgA-deficient individuals have normal numbers of IgA-bearing plasma cells in the intestine and produce normal levels of secretory IgA (21).

ASSOCIATION OF IGA DEFICIENCY WITH SPECIFIC DISORDERS

Despite the fact that most IgA-deficient subjects are not ill, IgA deficiency has been associated with an astonishing number of specific disorders (12, 21–26). (see Table II).

Sinopulmonary Infections

Recurrent sinopulmonary infections are the most frequent illnesses associated with selective IgA deficiency. Indeed, these infections often represent the reason why quantitative immunoglobulin levels are first obtained and the diagnosis established. The frequency of these infections in IgA-deficient subjects varies considerably. Most infections are caused by minor bacterial pathogens, or, in the absence of exact bacteriological diagnosis, various viral agents. Sinopulmonary infections are more likely to occur in IgA-deficient individuals who have IgG2 subclass deficiency (27, 28), but they also occur in IgA-deficient individuals without a second known defect.

Secretory IgA

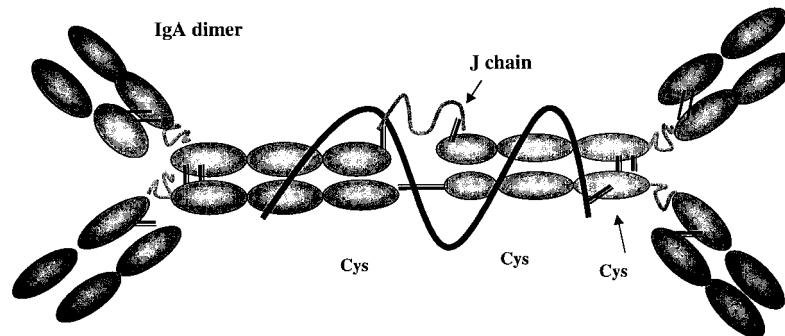


Fig. 1. Dimeric IgA is produced by plasma cells lining the mucosal surfaces. The Fc regions are shown overlapped, with the J chain attached to the CH3 terminal cysteines of one pair of heavy chains; SIgA also includes the secretory component (the secreted portion of polymeric immunoglobulin receptor). The fifth "domain" of the secretory component is shown, with Cys 467 disulfide-linked to the CH2 region of one of the IgA monomers, at Cys 311. Adapted from Fallgreen-Gebauer (6). This couples results from a collaboration of five chromosomes: 1 (SC), 2 (kappa), 4 (J chain), 4 (alpha chain), and 22 (lambda chain.)

Gastrointestinal Diseases

Patients with IgA deficiency have an increased frequency of gastrointestinal diseases, with giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease the most common ailments. In one study, 1 of every 200 patients with celiac disease had IgA deficiency (29). In a recent review, Heneghan *et al* (30) found that of 604 subjects with celiac sprue, 14 had IgA deficiency (2.3%); response to gluten-free diet for these subjects was similar to those without this deficiency. Demonstrating the role of IgA in preventing food antigen from entering the circulation, a common feature of the serum of IgA deficient subjects is the precipitating levels of serum antibodies to cow's milk proteins (31). Up to

50% of IgA-deficient individuals have precipitins to cow's milk (32, 33). In IgA deficiency, the gastrointestinal tract is sufficiently leaky so that in most IgA-deficient individuals, circulating immune complexes develop in their serum 15 to 60 min after drinking a glass of milk (33).

Autoimmunity

A number of autoimmune diseases are associated with selective IgA deficiency and may represent the most common association with IgA deficiency (Table II). In addition to overt autoimmune disease, the sera of IgA-deficient subjects often contain autoantibodies, even in

Table II. Conditions Associated with Selective IgA Deficiency

Condition	Disease
Allergy	Asthma, atopy, eczema
Respiratory tract	Recurrent sinopulmonary infections sarcoidosis, pulmonary hemosiderosis
Autoimmunity	Rheumatoid arthritis ITP, hemolytic anemia, pernicious anemia, systemic lupus erythematosus, Still's disease, transfusion reactions due to anti IgA antibody, dermatomyositis, vitiligo, Sjögren's syndrome, Henoch-Schönlein syndrome primary biliary cirrhosis, autoimmune hepatitis
Gastrointestinal diseases	Giardiasis, Crohn's disease, ulcerative colitis, nodular lymphoid hyperplasia, celiac disease lactose intolerance, malabsorption villous atrophy, achlorhydria, cholelithiasis
Malignancy	Gastric carcinoma and lymphoma
Endocrinopathy	Thyroiditis, Graves disease idiopathic Addison's disease, diabetes mellitus, 21-hydroxylase deficiency
Neurological	Seizures, migraine, sensory neuropathy, myasthenia gravis, cerebral vasculitis
Chromosomal abnormalities	Chromosome 14
Familial history of hypogammaglobulinemia	Common variable immunodeficiency

the absence of disease. Antibodies against thyroglobulin, red blood cells, thyroid microsomal antigens, basement membrane, smooth muscle cells, pancreatic cells, nuclear proteins, cardiolipin, human collagen, and adrenal cells have been identified. A significant proportion of IgA-deficient individuals have serum anti-IgA antibodies that may lead to infusion reactions if traces of IgA are given parenterally (34, 35). However, hospitalized patients, some of whom are certain to be IgA deficient, are not screened for anti-IgA antibodies prior to blood transfusions, since such reactions appear to be quite rare, perhaps on the order of 1.3 per million units of blood or blood products transfused (36). Anti-IgA antibodies are more common in IgA-deficient individuals with undetectable IgA but occasionally may occur when the IgA level is 10 mg/dl or higher. Ferreira (37) and associates found that 39% of their IgA-deficient patients had anti-IgA antibodies; 22% of those in the antibody-positive group had IgA levels between 1.1 and 5 mg/dl and the remaining 78% had IgA levels lower than 1.1 mg/dl.

Allergy

Many reviews suggest that IgA deficiency and allergy are associated (21–26). The most common allergic disorders reported in IgA-deficient individuals are allergic conjunctivitis, rhinitis, urticaria, atopic eczema, food allergy, and bronchial asthma. In one study, reduced IgA response to luminal antigens and a lack of IgM compensation was noted in the mucosa of atopic children (38).

PATTERNS OF INHERITANCE AND GENETICS

In most cases, IgA deficiency appears to be inherited in a sporadic fashion, although familial inheritance in autosomal recessive and autosomal dominant with variable or incomplete expression has been described. Ethnic differences also are known, with higher frequencies in Caucasians and low frequency in the oriental populations studied (39, 40). Oen and colleagues (41) studied relatives of 60 IgA-deficient donors. In 48 families, no additional IgA-deficient members were discovered. In 21 of these families, all first-degree relatives of at least two consecutive generations were studied. For the remaining 12 families, IgA deficiency was found in three generations in one family, in two generations in six families, and in one generation in five families. Thus, among first-degree relatives of affected blood donors, the prevalence of IgA deficiency was 7.5%, a 38-fold increase over that of unrelated donors. A number of older studies noted a higher frequency of mother-to-child inheritance

of IgA deficiency than of father-to-child inheritance (41, 42). More recently, investigating 101 families in which IgA deficiency and common variable immunodeficiency were present in more than one individual, 30 affected children were found to have affected fathers as compared to 118 affected children of normal fathers. In contrast, there were 75 affected children born to affected mothers as compared to 95 affected children born to unaffected mothers (43). One explanation is the potential transplacental passage of anti-IgA antibodies, which could result in IgA deficiency in the infant. Petty and colleagues (44) studied the offspring of IgA-deficient mothers. Of these 27 children, 12 had IgA levels more than 1 standard deviation (SD) below normal and 7 had levels more than 2 SDs below normal. Of the 7 with the lowest IgA levels, 5 had mothers who had anti-IgA antibodies during gestation. Another hypothesis is that the maternal major histocompatibility complex (MHC) tissue type might influence the transmission of IgA deficiency to the offspring (45).

IGA DEFICIENCY AND THE MAJOR HISTOCOMPATIBILITY COMPLEX

An association between IgA deficiency and certain HLA types of the MHC has been noted for some time. Wilton and colleagues (46) studied HLA types in 17 individuals from 13 Australian families with complete or partial IgA deficiency (IgA levels, <30 mg/dl) and found an increased frequency of HLA-A1, HLA-B8, and HLADR3; in addition, of the 29 independent haplotypes observed in the IgA-deficient subjects, 22 included deletions, duplications, or a defective C4 or 21-hydroxylase locus (47). Others have further investigated the connection between the MHC haplotype (HLA-B8, SC01, DR3) and selective IgA deficiency (48). The prevalence of individual immunoglobulin deficiencies in blood donors with this haplotype ranges from 13% to 37%, significantly higher than rates in noncarriers or general controls. There is an increased frequency of IgA and IgG4 deficiency only in homozygotes (13.3% and 30%, respectively) as compared with heterozygotes (1.7% and 3.4%) or noncarriers (1.6% each), suggesting recessive expression (49).

IgA deficiency also has been reported in children with chromosomal abnormalities, particularly those involving chromosome 18. Wilson and associates (50) studied patients with overlapping areas of deletions. The consistently deleted band was 18q21.3, but only two of these patients were IgA deficient. About half of patients with the 18p– syndrome and ring chromosome 18 are IgA-deficient (51). How these abnormalities lead to IgA

deficiency is not understood; no particular area of chromosome 18 is consistently abnormal or deleted. A search for linkage to chromosome 18 in 83 families in whom IgA deficiency and/or common variable immunodeficiency had been identified, using 17 marker loci, did not reveal linkage of the defect to any marker (52).

PATHOGENESIS

A fundamental defect in IgA deficiency is the failure of IgA-bearing B lymphocytes to mature into IgA-secreting plasma cells. It appears to be a defect of stem cells, since IgA deficiency can be transferred by bone marrow engraftment (53). A cardinal feature is that there is a paucity of IgA-bearing gastrointestinal plasma cells (2, 20). There are decreased (but not absent) numbers of IgA-bearing B cells in the peripheral circulation in these patients (54), which bear an immature phenotype; that is, IgA-bearing B cells that also are positive for IgM and IgD (55). The reason that IgA deficient subjects have B cells that fail to switch to the production of IgA is unknown.

T-cell and cytokine defects often have been extensively sought in IgA deficiency, due to the role of T cells and secreted cytokine in B-cell differentiation, but not found. Molecular analyses have demonstrated errors of switch (S) μ to S α rearrangements in peripheral B cells in IgA-deficient subjects. Two types of defects—low expression of both secreted and membrane forms of productive C α mRNA in IgA-switched B cells and impaired IgA switching—were characterized in IgA-deficient subjects homozygous for the central MHC haplotype (HLA-B8, SC01, DR3) (56). In a number of early studies, B cells from IgA deficient subjects were cultured with mitogens to determine their ability to secrete IgA. Pokeweed mitogen (PWM) was reported to cause IgA secretion (57), but subsequent studies using various stimulators found that little if any IgA was actually produced (58). Antigen-stimulated B cells undergo isotype switch and terminal differentiation into IgA-secreting plasma cells under the influence of a number of cytokines; transforming growth factor beta (TGF- β) appears to be a key cytokine in this process, prompting this isotype switch and committing antigen-primed B cells to secrete IgA (59). TGF- β directs switching to IgA by inducing RNA transcripts from unrearranged Ig C α genes before switch recombination in both mouse and human B cells and B cell lines. TGF- β can direct IgA switching in human B cells in the presence of PWM and activated cloned CD4⁺ T cells. Serum levels of TGF- β in IgA-deficient sera were less than that of normals, but the biological meaning of this unclear,

since the levels of mRNA for TGF- β were the same as in normals (60). B cells of IgA-deficient subjects secrete some IgA in culture when activated with *Staphylococcus aureus* and cultured with anti-CD40 and IL-10 (61, 62). To add an additional complication to the issue of pathogenesis, transient or permanent IgA deficiency may develop after therapy with various drugs (13, 23, 24, 26).

ANIMAL MODELS OF IGA DEFICIENCY

In addition to the nude mouse, which is IgA deficient, there are a few other animal models of IgA deficiency. Transgenic IgA $-/-$ knockout mice have been generated by targeting the entire IgA switch region and the 5' half of the constant region (63, 64). A second model emphasizes the role of TGF- β 1 in isotype switch and secretion of IgA, since the TGF- β 1 knockout is partially IgA deficiency (65) and the TGF- β 1R knockout has impaired mucosal IgA responses (66). Similarly, mice with a deletion of IL-5 α -chain (IL-5R α $-/-$) have reduced levels of IgA in mucosal secretions as compared to wild-type mice, but the levels of IgA in serum are not reduced (67). The tumor necrosis factor (TNF) and lymphotoxin α (a double knockout, TNF/LT- α $-/-$) mouse has only low numbers of total IgA-producing cells and no Peyer's patches or mucosal IgA. Selective IgA deficiency also occurs in several strains of inbred dogs but the immune mechanism are unknown. (68).

CONCLUSIONS

There is much to understand about the role of IgA in human immunity. IgA is the most abundant immunoglobulin made and also the most discarded. IgA is the second-most prevalent immunoglobulin in serum, but its role in systemic immunity is unknown. Secretory IgA has a known biological activity against a number of pathogens and can be shown to serve as a barrier preventing the permeation of foreign antigens and pathogens; on the other hand, lack of IgA does not usually result in a perceptible immune defect.

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