INSIDER’S GUIDE
SECRETORY IGA

By Ron Grisanti, D.C. & Dicken Weatherby, N.D.
http://www.FunctionalMedicineUniversity.com

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Our First Line of Defense: SIgA

Secretory IgA has been documented to be the predominant immunoglobulin in various external fluids and is produced in the lining of the gut specifically in the **Peyer's patches**. SIgA is also an important part of the defense system found in the saliva, and lives in the mucous membranes of the nose and the lungs.

When a problem is detected, SIgA secretion tends to increase throughout the mucous membranes to bolster our defenses. This line of protection on mucosal surfaces inhibits uptake of antigen and interferes with microorganism adherence to the mucosal epithelium. Cells such as macrophages, neutrophils, hepatocytes and natural killers have surface receptors for IgA.

The SIgA is targeted against anything potentially harmful—bacteria, microscopic parasites, even large food particles that might cause inflammation.

It is important to note that other kinds of antibodies (IgE, IgG, and IgM) specifically **target one** subspecies of invader, such as a particular strain of flu or an allergenic food, but they won't attack any others. This makes SigA quite powerful, in that SigA offers **non-specific immunity**.

In the case of the flu, it is interesting to remember that all other antibodies except IgA will build up and only have a memory for that specific flu bug and ignore all others. But is encouraging to know that the non-specific SigA will attack anything it perceives as a potential threat to the host.

**Clinical Pearl**

In secretions the majority of SigA exists as a dimer linked together by J-chain and protected from a **proteolytic digestion** by **secretory component**.

**IgA- Workhorse of the Gut Immune System**

- The intestinal mucosa has to be able to accurately recognize noxious and/or infectious agents and keep them out.
- The main player in this activity is the immunoglobulin IgA.
- IgA acts against antigens (toxins, pathogenic bacteria, viruses, etc.) to prevent their interaction with the epithelial surface.
- It does this in a way that provides non-inflammatory protection at the mucosal barrier.
• IgA is the only immunoglobulin that does its work without creating a systemic response.

**The Attack of Secretory IgA**

When SigA perceive bacteria, for example, which are typically hundreds of times larger than the antibody, they cover its surface, until it resembles an orange stuck with cloves.

Several hundred SIgA molecules may adhere to the surface of a single invading bacteria. In turn, a rough or uneven surface will be created catch the microbe in the mucous layer that covers the mucosal lining. This mucous acts like a slow conveyor belt, gradually sliding the pathogen, undigested protein antigen through the gut and moving it out of the gut. The bacteria or other antigens are then simply discarded with the spent food in the stool.

If you decrease the body's secretions, you decrease immune defenses.

<table>
<thead>
<tr>
<th>Adherence Factors of SigA</th>
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<tr>
<td>SigA antibodies to microbial surface antigen have been demonstrated to inhibit adherence to pharyngeal, intestinal, and genitourinary tract epithelia, and to tooth surfaces. The hydrophilicity and negative charge of SigA are thought to be important in surrounding a microbe with a hydrophilic shell that repels attachment to the mucosal surface. Agglutination may be an additional mechanism that allows clumped organisms to be swept away in flowing secretions. There is also evidence that human SigA can bind bacteria by means of carbohydrate chains and thereby interfere with their adherence. Inhibition of adherence by SigA antibodies is recognized as a major protective mechanism against pathogens at mucosal surfaces.</td>
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**Functions of sIgA**

• Inhibition of adherence of pathogens
• Mucus trapping
• Viral neutralization
• Neutralization of enzymes and toxins
• Inhibition of antigen penetration into the intestinal lining
• Interaction with antimicrobial factors, such as lactoferrin, peroxidases and lysozymes
• IgA is also involved in oral tolerance, the ability for any particular substance that enters the gut not to stimulate an immune response.

**Roles of SIgA**

• SIgA is skillfully programmed to be tolerant of our friendly flora. Although it will attack anything offensive, it’s somehow able to recognize what belongs there and what doesn’t—no friendly fire.
• SIgA targets only microorganisms that don’t have the right identifier and binds to them—figuratively speaking, only those without the right security ID or badge.
• SIgA has the ability to bind to particles that aren't fully digested or dissolved, typically large food particles, to minimize the wear and tear on the gut and the potential for problems such as leaky gut syndrome.

• Basically SIgA targets both pathogens and food.

• Immunoglobulin A (IgA) in general prevents inflammation. It can reduce the biochemical panic response that can occur when the metabolic alarm system goes off in the body. This warning system includes immune messenger chemicals (the cytokines) that function like sirens sounding the call to respond when a threat is perceived. If the cytokines stimulate too heavy an attack, major inflammation can occur as a protective mechanism. By toning down the metabolic panic and the inflammation that could follow, SIgA maintains the integrity of the lining cells of the gut barrier.

The Missing Link Between GI Dysfunction and Systemic Diseases

Imbalanced secretory IgA (sIgA) levels may provide the link between gut imbalances and systemic illness. Considering SIgA is found throughout the gastrointestinal tract, and in mucus secretions throughout the body and provides a first line of defense against bacteria, food residues, fungi, parasites and viruses it makes sense that low levels can make us more susceptible to infection. In instances where sIgA is low, there is increased risk for adhesion and proliferation of pathogenic organisms, and for associated damage to the intestinal mucosa.

Is it then possible to consider that a fundamental cause of asthma, autoimmune conditions, celiac disease, chronic infections, crohn's disease, candidiasis, food intolerances, allergies, autism and other behavioral problems could be the compromise of this powerful immunoglobulin?

Could very likely be!

On the other hand, levels higher than reference range have been associated with atopic dermatitis, dysbiosis, increased exposure to pathogenic organisms and toxins, and increased exposure to allergens.

Very high levels of sIgA can be found in people who have chronic infections and whose immune system is overloaded or hypersensitive.

Individuals with sIgA deficiency usually show varying degrees of nutrient malabsorption and are susceptible to food allergies.

Clinical Pearls

Secretory IgA has been shown to bind to toxin A from Clostridium difficile, preventing its interaction with the brush border of the intestines. Other studies indicate that sIgA prevents Vibrio cholera from adhering to the intestinal mucosa.

Autoimmune thyroid disease is seen individuals with sIgA deficiency.

Stress and SigA

Suppression of sIgA has been associated with the stress response. The level of sIgA measured in saliva is down-regulated during periods of chronic stress, whereas acute stress induces mobilization and results in a transient increase in sIgA.
Many studies on the effects of extreme physical and/or emotional stress in test populations, such as military personnel in basic training and competitive endurance athletes, have demonstrated that levels of sIgA become depressed following such levels of stress, whereas cortisol levels increase.

Changes in levels of sIgA and cortisol in subjects under pre- and post-examination stress have been somewhat contradictory.

The high-stress occupation of air traffic controllers did not produce low sIgA, but rather a transient elevation in sIgA and cortisol.

These results have been attributed to the acute nature of the stresses experienced by the controllers or the counter-acting effects of positive emotional engagement among controllers in the workplace.

Relaxing activities have been demonstrated to increase positive effect and sIgA, while reducing negative effect and sIgA suppression.

Combining salivary sIgA with evaluation of cortisol and DHEA is beneficial in the over-all assessment of the stress response and the management of leaky gut, food allergy inflammatory arthritities, immunogenic thyroiditis, autoimmunity and other chronic diseases.

**Testing for Secretory IgA**

In recent years functional tests have been developed to assess the strength of our secretory IgA. A simple saliva test can be used to measure SlgA levels in the mouth/throat, and a stool test can be used to measure them in the gut. Although SlgA in each area can be evaluated independently, lab testing has shown that there’s a strong correlation between antibody levels registered from the mouth/throat area and from the intestinal tract. Again, if the SlgA level measured in oral saliva is depressed, there is a high probability that it will also be low in other mucus-producing areas of the body.

**Secretory IgA; stool**

<table>
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<th>SlgA</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Reference</th>
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<td></td>
<td>213</td>
<td></td>
<td>40 - 204mg/dL</td>
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Secretory IgA is secreted by mucosal-associated lymphoid tissue and represents the first line of defense of the GI mucosa and is central to the normal function of the GI as an immune barrier. Elevated levels of sIgA are associated with an upregulated immune response.

**Secretory IgA/Gliadin - Saliva**

| Secretory IgA | 179 | mcg/mL | 102 - 471 |

**Improving First Line Immune Defense**

Any kind of infection can lower our stores of antibodies (our precious SlgA). An infection anywhere in the body, even a tooth abscess, can affect the gut by increasing stress and reducing the secretory IgA.
**Stress** reduces secretory IgA. Any kind of stress can do this. Two German studies indicate that mental relaxation procedures, such as meditation or biofeedback, can lead to increased secretion of SlgA. To promote this positive effect, stress reduction; moderate exercise such as yoga, tai chi, or Qigong; meditation; or any kind of mental relaxation are very important for a healthy digestive tract.

**Poor diet and low nutrient** levels generally also lower SlgA. It's been shown that kids in third world countries who have protein calorie malnutrition (PCM) have lower SlgA levels and therefore frequently get diarrhea because they're lacking the SlgA to protect them against it. Once you get diarrhea, you lose even more lining in the gut and it becomes a vicious cycle.

**SlgA decreases with age.** It seems that there are many more things that reduce secretory IgA than easily increase it, so you really have to be on guard.

The key influences on your primary immune function are

- genetics,
- nutrition
- stress,
- lack of breast-feeding
- age
- the integrity of the gut lining
- the health of the microflora
- the presence of infection in the gut or anywhere in the body.

Vitamin A in particular is critical in replenishing the lining of the gut and maintaining the integrity of the mucosa. Unfortunately the lack of vitamin A happens to be the most common vitamin deficiency in the entire world. Other nutrients that increase SlgA include zinc taken with vitamin A, colostrum (for people who are not dairy intolerant), and probably L-glutamine.

**Recommended products include:**

- Sialex
- Gooseberry

**Cutting Edge Details About SigA**

**Virus neutralization**

SigA antibodies neutralize viruses through several mechanisms, including inhibition of binding to cellular receptors, internalization and intracellular replication. Viral neutralization may also occur during the SC-mediated transport of plgA across epithelial cells if the vesicles interact with virus invading from the apical surface.

**Neutralization of enzymes and toxins**

The ability of IgA antibodies to inhibit enzymes or toxins have been demonstrated to be do to conformational changes in the enzyme or toxin molecule induced by antibody binding.
SigA is well adapted to functioning as an antibodies in fluids such as those in the intestines because it is to some extent protected from the proteolytic digestion by covalently bound secretory component.

**Inhibition of Antigen Uptake**

Intestinal uptake of food antigens is diminished by SigA antibodies. It also has the ability to inhibit the absorption of environmental carcinogens. IgA deficient subjects show increased absorption of food antigens and the formation of circulating immune complexes as well as statistically increased susceptibility to atopic allergies or autoimmune disease, thereby illustrating the importance of SigA mediated exclusion. The mechanism probably includes a combination of **agglutination, hydrophlicity and mucus training**.

<table>
<thead>
<tr>
<th><strong>Agglutination</strong></th>
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<tr>
<td>Agglutination is the clumping of particles (to glue to)</td>
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<tr>
<td>1. The clumping of cells such as bacteria or red blood cells in the presence of an antibody. The antibody or other molecule binds multiple particles and joins them, creating a large complex.</td>
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<td>2. The coalescing of small particles that are suspended in solution; these larger masses are then (usually) precipitated.</td>
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<tr>
<td>3. An allergic reaction type occurrence where cells become more compacted together to prevent foreign materials entering them. This is usually the result of an antigen in the vicinity of the cells.</td>
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Because of their non-inflammatory nature, IgA antibodies can form without inducing inflammatory reactions that might cause collateral damage to nearby tissues. This property of IgA may be especially important at mucosal surfaces, where the immune system continuously interacts with exogenous materials.

**Interaction with Innate Antimicrobial factors**

The secretions of most mucosal surfaces contain numerous innate defense factors that kill or inhibit microorganisms. It has been found that SigA may be able to interact synergistically with some of these systems. In fact, SigA may form complexes or act synergistically with lactoferrin. The anti-inflammatory property of IgA antibodies is of physiological significance in controlling inflammation at mucosal surfaces where IgA is abundant and where maintenance of the mucosal barrier is important

**Regulation of Cytokine Release**

A fresh area of investigation is the finding that IgA can **downregulate the release of inflammatory cytokines** and induce the production of IL-1 receptor antagonist in human monocytes stimulated with bacterial lipopolysaccharide.
SigA also appears to be effective in stimulating the degranulation of eosinophils and mediating the killing of schistosomes by eosinophils. IgA antibodies have been found to inhibit IgE-mediating hypersensitivity.

**Point of Interest and More Peer Reviewed Studies**

**Tonsils**

Clinical observations have been made that palatine, lingual and nasopharyngeal tonsil may serve as a source for precursors of IgA plasma cells found in the upper respiratory and digestive tracts. Clinical studies have shown that tonsillectomized children displayed a reduced level of SigA compared with children with intact tonsils.


**Role of secretory IgA, secretory component, and eosinophils in mucosal inflammation.**

Moteqi Y, Kita H, Kato M, Morikawa A.

Department of Pediatrics, Gunma University School of Medicine, Maebashi, Gunma, Japan. mocy@satnet.ne.jp

Eosinophils and their products are important in the pathophysiology of allergic inflammation in mucosal tissues. Secretory component (SC) bound to IgA mediates transepithelial transport of IgA. As another biological activity of SC, we have reported that secretory IgA (sIgA) and SC preferentially activate human eosinophils. When eosinophils were stimulated with immobilized sIgA, degranulation and superoxide production were greater than when stimulated with serum IgA. In contrast, neutrophils responded similarly to sIgA and serum IgA. Superoxide production by eosinophils stimulated with cytokines was enhanced synergistically by immobilized SC, while SC showed no effect on neutrophil activation. Eosinophil superoxide production stimulated with sIgA was abolished by anti-CD18 mAb, suggesting that beta2 integrins might be crucial for this reaction. There are several reports that SC and sIgA may play important roles in regulating eosinophil functions in vivo in diseases associated with mucosal eosinophilia and in various allergic diseases. It is speculated that eosinophils in the mucosa are activated by SC or sIgA, and that subsequent degranulation and superoxide production are induced. Copyright 2000 S. Karger AG, Basel.
**Secretory component: a new role in secretory IgA-mediated immune exclusion in vivo.**

**Phalipon A, Cardona A, Kraehenbuhl JP, Edelman L, Sansonetti PJ, Corthésy B.**

Unité de Pathogénie Microbienne Moléculaire, INSERM U 389, France. phalipon@pasteur.fr

Secretory immunoglobulin (Ig) A (sIgA) is essential in protecting mucosal surfaces. It is composed of at least two monomeric IgA molecules, covalently linked through the J chain, and secretory component (SC). We show here that a dimeric/polymeric IgA (IgA(d/p)) is more efficient when bound to SC in protecting mice against bacterial infection of the respiratory tract. We demonstrate that SC ensures, through its carbohydrate residues, the appropriate tissue localization of sIgA by anchoring the antibody to mucus lining the epithelial surface. This in turn impacts the localization and the subsequent clearance of bacteria. Thus, SC is directly involved in the sIgA function in vivo. Therefore, binding of IgA(d/p) to SC during the course of sIgA-mediated mucosal response constitutes a crucial step in achieving efficient protection of the epithelial barrier by immune exclusion.

**Secretory IgA induces degranulation of IL-3-primed basophils.**

**Iikura M, Yamauchi M, Fujisawa T, Miyamasu M, Takaishi T, Morita Y, Iwase T, Moro T, Yamamoto K, Hirai K.**

Department of Medicine and Physical Therapy, University of Tokyo School of Medicine, Japan.

We examined whether secretory IgA (sIgA), known to mediate eosinophil stimulation, has an effect on basophil functions. An immobilized preparation of sIgA, but not of monomeric IgA, induced histamine release (approximately 15% of total histamine contents) from human basophils in vitro. sIgA-induced basophil histamine release was totally dependent on pretreatment with IL-3. IL-5 and granulocyte-macrophage CSF also primed basophils for sIgA-mediated release. Exogenous divalent ions, i.e., Ca²⁺ and Mg²⁺, were essential for sIgA-mediated basophil degranulation, and the degranulation was completed within 45 min. A newly synthesized lipid mediator, leukotriene C₄, was also liberated from IL-3-primed, sIgA-stimulated basophils. Enzyme digestion experiments revealed that the (Fc)₂ x secretory component portion of sIgA is important for sIgA-mediated basophil activation, but the functional binding sites of sIgA on basophils were surmised to be different from FcαR. These observations reveal the novel finding that sIgA is able to stimulate basophils as well as eosinophils. Since sIgA is the most abundant Ig isotype in the secretions from mucosal tissues, and basophils are active participants in allergic late-phase reactions, sIgA-mediated basophil mediator release is potentially involved in exacerbation of the inflammation associated with allergic disorders.
The effect of secretory immunoglobulin A on the in-vitro adherence of the yeast Candida albicans to human oral epithelial cells.

Vudhichamnong K, Walker DM, Ryley HG.

Secretory immunoglobulin A (s-IgA) isolated from human breast milk inhibited the adherence of C. albicans to human oral epithelial cells. This inhibitory effect of s-IgA was maximal at 1 1/2 hours, it was concentration-dependent and was still detectable at subagglutinating antibody concentrations. The inhibitory action of s-IgA was due to its content of specific candidal antibody. Non-specifically bound s-IgA enhanced adherence of the yeast and presumably tends to impair the immune disposal of candida by specific antibody. The reduced adherence of candida pre-treated with 0.4 per cent formal saline at a concentration which kills the organism but leaves its surface antigens intact suggests that, although dead organisms may form an initial loose attachment to the epithelial surface, only viable organisms bind irreversibly. The specific-s-IgA appears to block surface sites on C. albicans involved in epithelial adherence but this action of s-IgA cannot be attributed solely to its agglutinating properties.

Milk precipitins, circulating immune complexes, and IgA deficiency.

Cunningham-Rundles C, Brandeis WE, Good RA, Day NK.

Twenty-two patients with selective IgA deficiency were studied for the presence of serum precipitins to bovine milk, bovine and fetal calf serum, and circulating immune complexes. Fifty-nine percent had circulating immune complexes, 50% had milk precipitins, 23% had precipitins to bovine serum, and 13% had precipitins to fetal calf serum. All patients with precipitating antibodies against milk or against bovine or fetal calf serum had circulating immune complexes and the precipitin titers correlated with the amount of circulating immune complexes. After one IgA-deficient patient had drunk 100 ml of milk, studies of sequential serum samples showed the presence of casein in the circulation at 60 min and the appearance of increasing amounts of immune complexes for 120 min. These findings are interpreted to indicated that in human beings the IgA system may provide a major barrier to absorption of immunogens from the gastrointestinal tract.

Reduction of intestinal carcinogen absorption by carcinogen-specific secretory immunity.

Silbart LK, Keren DF.

University of Michigan, Pathology Department, Ann Arbor, MI 48109.

A secretory immune response to the carcinogen 2-acetylaminofluorene (AAF) was elicited in rabbits by directly immunizing the small intestine with an AAF-cholera toxin conjugate. High-titer, high-affinity secretory immunoglobulin A (IgA) antibody to AAF was secreted into the intestinal lumen in response to this immureogen. Immune secretions reduced the transepithelial absorption of a 125I-labeled derivative of AAF by more than half. This reduction of absorption by hapten-specific IgA suggests that oral vaccines against carcinogens and toxicants could be developed for humans.
Anti-inflammatory activity of human IgA antibodies and their Fab alpha fragments: inhibition of IgG-mediated complement activation.

**Russell MW, Reinholdt J, Kilian M.**

Department of Oral Biology, Royal Dental College, Aarhus.

The interaction of human IgA antibodies with the classical pathway of complement activation was investigated in a homologous human system, by means of two IgA1 and three IgG1 myeloma proteins having antibody activity against a defined antigen, staphylococcal alpha-toxin. In a solid-phase antigen-dependent C3b-binding ELISA system, the monoclonal IgG antibodies were previously shown to activate the classical complement pathway synergistically, resembling polyclonal IgG antibodies, whereas IgA antibodies were unable to activate complement by either pathway. In the present study, IgA antibodies were found to inhibit significantly the activation of complement initiated by antigen-bound polyclonal or mixed monoclonal IgG antibodies, in relation to the amount of IgA antibodies applied and bound to antigen. IgA1 myeloma proteins devoid of antigen-binding activity were without effect. Inhibition was independent of the ability of the IgA antibodies to compete against the IgG antibodies in binding to antigen, and was demonstrable with physiological concentrations of antibodies. Similar results were obtained with polyclonal serum IgA having antigen-binding activity. However, the binding of C1q to antigen-complexed IgG was inhibited only by a monoclonal IgA antibody that could compete against one of the three monoclonal IgG antibodies that bound C1q synergistically. This observation implied that at least two mechanisms were involved in the inhibition of C3b fixation. Fab alpha fragments of monoclonal IgA antibodies, obtained by cleavage with IgA1 protease from Haemophilus influenzae type b, were found to have a similar inhibitory effect on C3b fixation to the intact IgA1 antibodies. This observation supports the hypothesis that IgA1 proteases contribute to the invasive pathogenicity of certain mucosal bacteria, by cleaving secretory IgA1 antibodies to antigen-binding Fab alpha fragments, which are not only defective in mucosal defense properties, but which also protect the organisms from other immune effector systems, such as complement activation.