

# immuno armour

## The Importance of a Balanced Immune System

### Review of sIgA's Major Role as a First Line of Immune Defense and New Indications Regarding Inflammation and Gut Health

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Secretory IgA

#### Introduction

Embria Health Science's dietary supplement ingredient EpiCor fermentate has been shown in multiple published human clinical trials to help strengthen the immune system through several mechanisms and modes of action. One of EpiCor's most important functions is to increase levels of secretory IgA (sIgA),<sup>1,2</sup> a vital antibody in the body's first line of defense.

sIgA is the antibody that plays a key role in mucosal immunity. Mucosal immunity refers to the portion of the immune system that provides protection to various mucous membranes against invasion by potentially pathogenic microbes. The mucous membranes are on the surface of cavities that are exposed to the external environment, such as the digestive and respiratory tracts.

Recent science shows that sIgA may also have other beneficial effects in overall immunity through reduced inflammation in the digestive tract. This paper will review sIgA's known effects on mucosal immunity and describe the emerging research that shows its beneficial impact on digestive health.



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## slgA in Mucosal Immunity

slgA is the main antibody found in mucous secretions, including tears, sweat, saliva, milk, and colostrum. More slgA is produced in mucosal linings than all other types of antibody combined; between three and five grams are secreted into the intestinal lumen each day.<sup>3</sup> Nearly 15% of the total immunoglobulin produced in the entire body is slgA.

The mucosal system's role in overall immunity is critical because it lines all bodily passages that are exposed to the environment, such as parts of the digestive and respiratory tracts. In turn, slgA plays a key role in the first line of immune defense by neutralizing toxins and viruses found in the mucosa and preventing adhesion of microbial pathogens to mucosal epithelial cells.<sup>4,5</sup> Through a process known as immune exclusion, slgA promotes the clearance of antigens and pathogenic microorganisms from the intestinal lumen by blocking access to epithelial receptors and entrapping them in mucus, thus facilitating their removal by peristaltic and mucociliary activities.

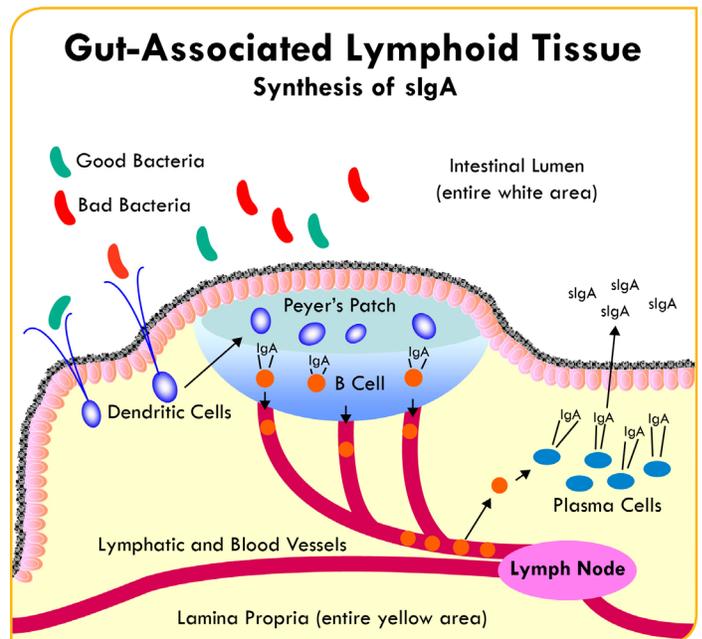
It is the unusual structure of slgA (discussed more in the following paragraph) that provides protection against microbes that multiply in bodily secretions by binding to them in the lumen of the gut, causing them to pass through harmlessly. The fact that microbes are not able to adhere to the gut wall means they cannot colonize the gut and cause infection and disease. In fact, the results from EpiCor's two human clinical trials showing reduction in cold symptoms<sup>6,7</sup> may be in part due to increased levels of slgA.

## Structure and synthesis of IgA

slgA can be produced in a variety of ways, but the predominant method is via the Peyer's Patches in the GALT (Gut Associated Lymphoid Tissue). slgA is derived from serum IgA, a monomer found throughout the body in the blood stream. There are discrete areas of the gut surface that sense the presence of foreign bacteria and respond to generate slgA through several steps.

The diagram to the right shows dendritic cells (immune cells that are part of a class of "antigen presenting cells" or APC's) sampling bacteria from the lumen. The dendritic cells then migrate to the center of the Peyer's Patch and stimulate B cells to mature and produce IgA. Monomeric IgA is transported across gut epithelial cells to the lumen by polymeric Ig receptor (plgR).<sup>8</sup> In the process, two monomers of IgA are covalently bound to form a dimer by a polypeptide called J-chain. Dimers enter the intestinal lumen and function as secretory IgA.<sup>9</sup>

The fact that the two chains are linked via their "tails" allows the slgA to cross-link bacteria, thereby preventing bacterial adhesion to the lumen wall and increasing the likelihood of the bacteria passing harmlessly through the gut. Additionally, the slgA has another protein associated with it called the secretory component, a protein derived from plgR. The secretory component protects the slgA from proteases and helps it to adhere to mucosal surfaces.



## Systemic response to localized IgA stimulation

Once IgA production has been stimulated in one region, usually via the GALT, the B cells and plasma IgA cells can travel to other parts of the lymphoid tissue, and the response can be detected in these regions.

Stimulation of mucosal-associated lymphoid tissue in the GALT allows a systemic response even from local antigenic stimulation (i.e. a response not confined to the initial stimulation site, but one that works throughout the body).

It is becoming increasingly obvious that sIgA is not only a major part of the body's first active response to infection, but is also a major part of the body's overall immune response, significantly contributing to the maintenance of a strong and balanced immune system.<sup>10</sup> Yet it should be emphasized that this will only be a part of the story of sIgA.

## Anti-inflammatory effects of sIgA

One of sIgA's important modes of action is its ability to regulate inflammation. It has been shown that sIgA can bind to pathogens such as *Shigella flexneri* resulting in a beneficial down-regulation of inflammation.<sup>8</sup> Less inflammation was reflected by lower levels of proinflammatory cytokines and by preservation of the intestinal barrier. Additionally, the authors speculate that transport of antigen-sIgA complexes may contribute to tolerance of harmless allergens. In fact, high intestinal sIgA in early life is associated with minimal intestinal inflammation and indicates reduced risk for IgE-associated allergic diseases.<sup>12</sup>

Therefore, increased sIgA may partially explain how EpiCor was able to significantly reduce certain allergy symptoms in a recent human clinical study.<sup>2</sup> Interestingly, levels of sIgA significantly increased in subjects who were also experiencing reduced allergy symptoms while on an EpiCor regimen. These results indicate that EpiCor, while helping mitigate the allergic response of allergy sufferers, continues to help maintain strong immune response through increased production of sIgA.

Moreover, one could speculate that increased sIgA may have been a contributing factor for the anti-inflammatory effects found when EpiCor was tested in two well-established animal models.<sup>13</sup>

## sIgA's regulation of homeostasis

Immune homeostasis (the body's ability to provide stable and proper immune responses in the face of constantly changing conditions) is very important for good health. The research on new roles for sIgA responses is not restricted to interactions with pathogens, but also its response to Gram-positive and negative commensal microorganisms, which helps to maintain homeostasis.<sup>11,14</sup>

For example, it is now known that sIgA can inhibit inflammatory effects in the body by inducing T-regulatory cells through interaction with commensal bacteria. The anti-inflammatory effects can be seen through elimination of Gram-negative bacteria, thereby reducing levels of LPS and production of NF- $\kappa$ B mediated pro-inflammatory cytokines, resulting in a general anti-inflammatory effect.<sup>15</sup>

sIgA's ability to maintain homeostasis may also explain EpiCor's beneficial effects in the digestive tract. In validated gut simulation models, EpiCor has been shown to act in a prebiotic-like manner. Results have shown EpiCor to alter the balance of gut bacterial populations towards the more beneficial species that positively interact with sIgA and likely down-regulate pro-inflammatory responses.<sup>16</sup>

Additionally, this research has shown EpiCor changes the resulting short chain fatty acid profile, increasing the production of butyric acid, a short chain fatty acid with known anti-inflammatory effects. Secondary trials from this work using CaCo2 cells have shown EpiCor can down-regulate the cells production of a pro-inflammatory cytokine (IL-8) when stimulated with a pro-inflammatory cocktail.



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## Conclusions

slgA is the most abundant and vital antibody in the body's first line of active defense. It not only protects mucosal areas directly exposed to airborne pathogens, but also the intestinal epithelium from pathogenic microorganisms. New research indicates that slgA plays an important role in overall immunity, including its ability to maintain homeostasis in the digestive tract and reduce inflammation.

## Key take-aways from the paper include:

- EpiCor increases levels of slgA.
- The special structure of slgA as a dimer explains its ability to prevent bacterial adhesion to the lumen wall, thereby possibly supporting healthy gut function.
- Increases in slgA may help explain EpiCor's role in reducing allergy symptoms.
- slgA produces anti-inflammatory effects by reducing bacteria-induced pro-inflammatory responses, which may help explain some beneficial effects seen in animal models.
- Even a local antigenic stimulation can result in a systemic response by slgA.
- slgA can inhibit inflammatory effects in the body through interaction with commensal bacteria.
- slgA is not only a major part of the body's first active response to infection, but is also a major part of the body's overall immune response.
- Among EpiCor's many modes and mechanisms of action that helps strengthen the immune system, its ability to increase slgA helps explain some of the multiple beneficial effects it has on human health.



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