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Review

Cooperativity among secretory IgA, the polymeric immunoglobulin receptor, and the gut microbiota promotes host–microbial mutualism

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ABSTRACT

Secretory IgA (SIgA) antibodies in the intestinal tract form the first line of antigen-specific immune defense, preventing access of pathogens as well as commensal microbes to the body proper. SIgA is transported into external secretions by the polymeric immunoglobulin receptor (pIgR). Evidence is reported here that the gut microbiota regulates production of SIgA and pIgR, which act together to regulate the composition and activity of the microbiota. SIgA in the intestinal mucus layer helps to maintain spatial segregation between the microbiota and the epithelial surface without compromising the metabolic activity of the microbes. Products shed by members of the microbial community promote production of SIgA and pIgR by activating pattern recognition receptors on host epithelial and immune cells. Maternal SIgA in breast milk provides protection to newborn mammals until the developing intestinal immune system begins to produce its own SIgA. Disruption of the SIgA-pIgR-microbial triad can increase the risk of infectious, allergic and inflammatory diseases of the intestine.

1. Introduction

The mucosal surfaces of the human body are home to some 100 trillion microorganisms, tenfold more than the total number of host cells throughout the body [1]. The highest concentrations of microbes are found in the intestinal tract, particularly in the colon. The mucosal immune system in the gut faces the challenge of eliminating potential pathogens while maintaining a mutually beneficial relationship with the commensal microbiota. Secretory antibodies of the IgA class (SIgA) represent the first line of antigen-specific immune defense in the gut lumen [2,3]. The majority of the IgA antibodies in gut secretions are germline encoded, low affinity and cross-reactive against redundant microbial antigens; however, when challenged, the mucosal B cell system can generate high-affinity, somatically mutated IgA antibodies with unique specificities [4–10]. SIgA antibodies allow beneficial microbes to thrive within the gut lumen while preventing their access to the body proper. When pathogenic microbes threaten to breach the epithelial barrier, SIgA antibodies can cooperate with other elements of the immune system to kill the invading pathogens, albeit at the cost of inflammatory damage to host tissues.

In healthy humans, up to 3 g/day of SIgA is delivered into intestinal secretions [11,12]. In the intestine, tight junctions between adjacent epithelial cells maintain a highly selective barrier, which prevents paracellular leakage of luminal contents as well as passive diffusion of antibodies from their site of synthesis by plasma cells in the *lamina propria* into the gut lumen. Transport of locally synthesized IgA across glandular and mucosal epithelial cells into external secretions is mediated by the polymeric immunoglobulin receptor (pIgR) [13–15] (Fig. 1). Proteolytic cleavage of pIgR at the apical surface of epithelial cells releases a complex of IgA covalently bound to secretory component (SC), the extracellular domain of pIgR. This complex is designated SIgA to distinguish it from IgA devoid of SC, the major form of IgA in the blood circulation. The SC moiety protects SIgA from degradation by host and bacterial proteases in the intestinal tract [16–18], promotes glycan-dependent adherence of SIgA to bacteria [19] and neutralizes inflammatory host factors, such as IL-8 [20,21]. Thus, pIgR-mediated epithelial

Abbreviations: AID, activation-induced (cytidine) deaminase; Ag, antigen; ERK, extracellular receptor kinase; IgA, immunoglobulin A; IBD, inflammatory bowel disease; IFN, interferon; IRF, interferon regulatory factor; IL, interleukin; JAK, Janus kinase; LPS, lipopolysaccharide; LT, lymphotoxin; MAMPs, microbe-associated molecular patterns; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappaB; PRR, pattern recognition receptor; pIgA, polymeric IgA; pIgR, polymeric immunoglobulin receptor; RAG, recombination activating gene; SC, secretory component; SIgA, secretory IgA; SFB, segmented filamentous bacteria; scid, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; siRNA, small inhibitory RNA; TCR, T cell receptor; TJ, tight junction; TLR, Toll-like receptor; TNF, tumor necrosis factor.

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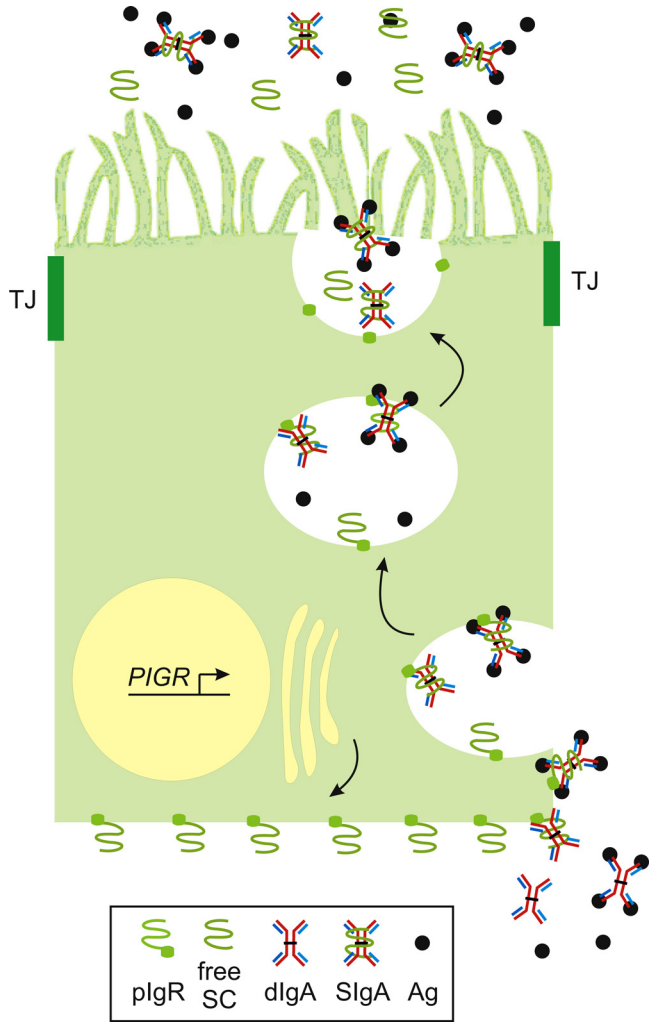

Fig. 1. Transcytosis of SIgA through a polarized epithelial cell. A polarized columnar epithelial cell is illustrated, with the apical surface at the top and the basolateral surface at the bottom and sides, separated by tight junctions (TJ) with adjacent epithelial cells. Transcription of the *PIGR* gene is induced by host cytokines and microbial factors. Newly synthesized pIgR is targeted to the basolateral surface, where it binds polymeric Ig (pIg), illustrated here as dimeric (d)IgA, with or without bound antigen (Ag). Following receptor-mediated endocytosis, pIg-bound and unoccupied pIgR molecules are transported through a series of intracellular vesicles to the apical surface. Proteolytic cleavage of pIgR at the extracellular face of the plasma membrane releases free secretory component (SC) and secretory (S)Ig (illustrated here as SIgA).

transcytosis is crucial for the immune and anti-inflammatory functions of SIgA. The discovery that polymorphisms in the *PIGR* gene locus are linked to increased susceptibility to inflammatory bowel diseases in humans [22,23] highlights the clinical relevance of this pathway. This review will focus on the mechanisms through which epithelial–microbial cross-talk regulates the transport and homeostatic functions of SIgA in the intestine.

2. Intestinal SIgA promotes host–microbial mutualism

It has long been appreciated that commensal microbes induce IgA responses in the intestine, and more recent evidence demonstrates that SIgA regulates the composition and function of the commensal microbiota. The experimental evidence for SIgA-microbial reciprocity will be discussed here (Table 1). The cellular and molecular mechanisms that mediate this reciprocal relationship between IgA and the gut microbiota have been discussed in detail in recent reviews [1–3,24–27].

Table 1
Evidence that intestinal SIgA promotes host–commensal mutualism.

Evidence	References
Colonization of germ-free mice with commensal bacteria induces intestinal IgA responses	[29–31]
Repeated oral administration of commensal bacteria to conventional mice induces specific SIgA responses that prevent bacterial invasion intro draining lymph nodes	[33]
Treatment of humans with prebiotic oligosaccharides changes the composition of the gut microbiota and increases fecal SIgA levels	[34]
Fecal bacteria in humans and mice are coated with SIgA	[32,35,37]
IgA-deficient mice exhibit overgrowth of certain types of gut bacteria, which can be reversed by restoration of IgA	[38]
Introduction of bacteria-specific IgA into antibody-deficient mice reduces host inflammatory responses	[40]
Proteobacteria-specific IgA regulates maturation of the intestinal microbiota	[32]
pIgR-deficient mice (which lack SIgA in the intestinal lumen) exhibit altered gut microbiota and intestinal epithelial gene expression	[19,42]
SIgA protects the intestinal epithelium by associating with gut microbes in the outer mucus layer	[48]

2.1. Commensal microbes induce intestinal IgA responses

Four decades ago, the observation was made that SIgA levels were extremely low in the intestinal contents of germ-free mice (devoid of commensal microorganisms) compared to mice with a normal microbiota [28], suggesting that microbial colonization of the intestine after birth provides the antigenic stimulus for development of IgA responses. Formal proof of this concept was provided by the demonstration that mono-colonization of formerly germ-free mice with various strains of normal gut bacteria resulted in hypertrophy of Peyer's patches and population of the intestinal *lamina propria* with IgA-secreting plasma cells [29,30]. More recently, using a model of reversible colonization of germ-free mice with a non-dividing mutant of *Escherichia coli*, a long-lived SIgA response was observed that was specific for the inducing bacterial strain [31] However, exposure of *E. coli*-colonized mice to other bacteria limited the duration of the SIgA response against the original colonizer, suggesting that the SIgA response adapts to the dominating members of the microbiota. In another study, antigen-specific fecal SIgA was induced by colonization of adult germ-free mice with the microbiota of infant conventional mice, which was dominated by Proteobacteria of the family Enterobacteriaceae [32]. By contrast, these investigators found no specific increase in fecal SIgA antibodies following colonization of adult germ-free mice with a more diverse microbiota from adult conventional mice. However, other investigators reported that specific SIgA responses could be generated in adult conventional mice after repeated oral administration of high doses of individual commensal bacterial strains [33]. Although it can be challenging to demonstrate specific effects of the commensal microbiota on IgA responses in humans, a recent study demonstrated that treatment of adult volunteers with prebiotic oligosaccharides altered the composition of the gut microbiota and was correlated with an increase in fecal SIgA levels [34]. Taken together, this evidence suggests that intestinal IgA responses continually adapt to the composition of the resident microbiota, allowing dynamic host–microbial mutualism.

2.2. Intestinal SIgA regulates the composition and activity of the commensal microbiota

If the commensal microbiota is the main driving force for intestinal IgA responses, how then do these vast quantities of SIgA antibodies affect the composition and activity of the microbiota?