REVIEW ARTICLE

The antibody/microbiota interface in health and disease

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The human intestine is densely colonized with commensal microbes that stimulate the immune system. While secretory Immunoglobulin (Ig) A is known to play a crucial role in gut microbiota compartmentalization, secretory IgM, and systemic IgG have recently been highlighted in host-microbiota interactions as well. In this review, we discuss important aspects of secretory IgA biology, but rather than focusing on mechanistic aspects of IgA impact on microbiota, we stress the current knowledge of systemic antibody responses to whole gut microbiota, in particular their generation, specificities, and function. We also provide a comprehensive picture of secretory IgM biology. Finally, therapeutic and diagnostic implications of these novel findings for the treatment of various diseases are outlined.

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INTRODUCTION

Humoral immunity, in particular antibody-mediated responses, plays a key role in the host defense against extracellular pathogens. Notably, the function of secretory Immunoglobulin (Ig) A, given its mucosal localization, has been considered for a long time to be restricted to immune exclusion, i.e., neutralization of luminal pathogens prevention of host invasion. In the past decade, with the advent of microbial metagenomics and the improvement of bacterial flow cytometry, murine and human studies have shed new light on IgA/microbiota commensalism. IgA is now viewed as playing a pivotal role in supporting the establishment, selection, diversification, and long-term maintenance of a healthy commensal gut microbiota.

Novel functions have also been ascribed, albeit putatively, to IgM and IgG at the gut-microbial interface. Whereas early studies have shown the presence of IgM plasmocytes in gut biopsies of IgA-deficient patients (IgAd),^{1,2} more recent studies provide evidence that secretory IgM (sIgM) binds a fraction of commensal microbiota in IgA deficiency thereby enhancing bacterial diversity.³ Moreover, sIgM in healthy humans seem to bind a very restricted fraction of gut microbiota along with secretory IgA.⁴ The functional consequences of these observations are unclear, but could be clinically relevant as it is well established that patients selectively lacking IgA rarely develop inflammatory bowel diseases (IBD), which is instead more common and severe in those lacking both IgA and IgM.^{5,6} Finally, systemic IgG responses targeting gut-microbial communities were initially described in IBD and considered merely secondary to bacterial translocations in relation with gut barrier defects. However, it has been reported recently that IgG targeting either bacterial antigens, whole bacterial cells, or whole microbial consortia, can also be retrieved from healthy subjects.

Here, we review recent murine and human studies in an attempt to provide a comprehensive picture of our current knowledge of the interplay between gut antibodies and microbiota.

SECRETORY IGA BIND A WIDE RANGE OF COMMENSALS

Early studies of gut microbiota revealed that secretory IgA coat only a fraction of human and murine microbiota.^{7,8} Recently, a combination of bacterial flow cytometry with high-throughput 16S gene sequencing offered an opportunity to identify IgA-coated bacteria *ex vivo*. Several such IgAseq studies have independently described IgA⁺ communities in mice^{9–14} and in humans.^{3,4,15–18} Table 1 gathers bacterial taxa that are significantly targeted by IgA in healthy individuals. Despite some variations, core features of the IgA-coated subset emerge from these data. First, IgA bound a highly diverse fraction of microbiota, including numerous rare genera (generally <1% in frequency). Second, the four major phyla, namely *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* were detected in IgA-coated microbiota. Consistently, most microbes, irrespective of their microbial phylogeny, can induce specific IgA in monoclonized gnotobiotic mice.^{19,20} Of note, multiple taxa of the phylum *Firmicutes*, in particular those belonging to the family *Lachnospiraceae*, are significantly enriched within the IgA⁺ fraction whatever the human cohort (Table 1). The relatively high frequency of these organisms in the human colon might account for their prevalence in IgA⁺ fractions. This observation supports earlier studies showing that *Lachnospiraceae* members are able to elicit innate immune responses and modulate adaptive immune responses in the gut.^{21–23}

While it was concluded from each of the above mentioned studies that IgA preferentially binds a taxonomically distinct subset of the whole microbiota, it remains difficult to define a core sIgA-coated community in healthy individuals. A similar observation has been made in uniform patient groups. One likely reason is that interstudy variability might not only result from technical factors, but also from different strategies to define the sIgA-coated microbiota. Key variations in immunostaining protocols, such as the use of either monoclonal^{4,24} or polyclonal anti-IgA antibody,^{3,9,15,16,18} have a substantial impact on background staining.

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Table 1. IgA-coated bacteria in humans

Study	Cohort	Sequencing method	Family	Genera	Species
D'Auria et al, 2013, Sci Rep (18)	6 healthy adults	16S gene sequencing	Bacteroidaceae	ND	ND
			Ruminococcaceae		
			Enterococcaceae		
			Lachnospiraceae		
			Nocardiaceae		
			Pseudomonaceae		
			Comamonadaceae		
			Sphingomonadaceae ud-Sphingomonadales		
Palm et al, 2014, Cell (24)	20 healthy adults	16S gene sequencing	Actinomycetaceae	Actinomyces	spp.
			Bifidobacteriaceae	Bifidobacterium	ND
			Erysipelotrichaceae	Erysipelotrichaceae	ND
			Lachnospiraceae	Dorea	spp.
			Lachnospiraceae	Ruminococcus	torques
			Verrucomicrobiaceae	Akkermansia	muciniphila
Kau et al, 2015, Sci Transl Med (15)	11 healthy children	16S gene sequencing	Clostridiaceae	ND	ND
			Streptococcaceae	Streptococcus	salivarius
			Enterobacteriaceae	Escherichia/Shigella	ND
			Verrucomicrobiaceae	Akkermansia	muciniphila
Planer et al, 2016, Nature (16)	82 twins, 2 year-old	16S gene sequencing	Bifidobacteriaceae	Bifidobacterium	bifidum
			Clostridiaceae	Clostridium	nexile
			Clostridiaceae	Clostridium	spiroforme
			Lachnospiraceae	Ruminococcus	torques
			Lachnospiraceae	Ruminococcus	gnavus
			Enterobacteriaceae	Escherichia/Shigella	ND
Dzidic et al, 2016, J Allergy Clin Immunol (17)	28 healthy children 1 year-old	16S gene sequencing	Bacteroidaceae	Bacteroides	ND
			Clostridiaceae	ND	ND
			Clostridiales Familie XI	ND	ND
			Erysipelotrichaceae	ND	ND
			Erysipelotrichaceae	ND	ND
			Lachnospiraceae	Roseburia	ND
Magri et al, 2017, Immunity (4)	5 healthy adults Mucus-embedded microbiota	16S gene sequencing	Bacteroidaceae	Bacteroides	ND
			Barnesiellaceae	ND	ND
			Erysipelotrichaceae	ND	ND
			Lachnospiraceae	ND	ND
			Lachnospiraceae	Roseburia	ND
			Lachnospiraceae	Blautia	ND
			Lachnospiraceae	Ruminococcus	ND
			Lachnospiraceae	Ruminococcus	gnavus
			Ruminococcaceae	ND	ND
			Ruminococcaceae	Ruminococcus	ND

Taxa belonging to Actinobacteria are colored in pink, Bacteroidetes in green, Proteobacteria in blue, Verrucomicrobia in purple, and Firmicutes in orange

Differences in sequencing methods may also explain the variations observed between reports. IgA⁺ bacterial identification usually relies on 16S gene sequencing,^{4,15–18,24} yet 16S-based classifications cannot discriminate among strains, or even species, within the same bacterial genera, which may substantially differ in terms of immunogenicity.^{25,26} Indeed, Geva-Zatorsky et al. found that two related species of *Bacteroides* (*B. thetaiotaomicron* and *B. vulgatus*) displayed differential IgA induction potential in mono-colonized gnotobiotic mice.¹⁹ By contrast, whole genome shotgun sequencing has extended taxonomic classification at both species and strain level,²⁷ thereby revealing IgA predilections at lower taxonomic levels. In addition, whereas some authors focused their analysis on the IgA^{high} population,^{3,4,24} other studies included both IgA^{high} and IgA^{dim} populations^{9,17} in the definition of IgA⁺ microbiota. Beyond these practical issues, interstudy variations also reflect the considerable diversity of human gut microbiota.^{28,29} Numerous factors such as age, diet, antibiotics, and genetic background impact gut microbiota composition.^{30–33} Interestingly, environmental factors have also been shown to influence IgA responses to bacteria. For instance, antibiotic exposure is associated with increased IgA coating of *Enterococcus* sp and *Lactobacillales*³⁴ and it is therefore expected that each individual harbors a distinct IgA-coated bacterial repertoire. Another potential challenge for IgAseq studies is that enchainment growth, driven by high-affinity IgA, can exert a negative selective pressure.³⁵ Enchainment growth can also contribute to an

environment with lower levels of temperate phage reactivation.³⁶ It is therefore expected that bacteria persisting in the gut in the presence of IgA have evolved traits to avoid, evade or benefit from enchainment growth (such as large capsules preventing cross-linking and protect from phage predation, or enchainment growth-induced microcolony deep mucus settling^{36,37}). Strains that are susceptible to IgA-mediated enchainment growth are expected to be absent from IgAseq data, and are logically extremely difficult to identify by IgAseq alone. We also need to take care in interpreting species presence/absence data in terms of function: the microbiota is a complex ecosystem and minor shifts in the abundance or function of one species can have chaotic effects on the rest of the consortium.

ANALYSIS OF IGA-COATED BACTERIAL COMMUNITIES TO UNRAVEL IGA FUNCTION

The identification of IgA-coated bacteria has provided new insights in our understanding of the role of secretory IgA in mucosal homeostasis. The contribution of human studies to describe functions of IgA will be discussed below, while other important roles of secretory IgA are reviewed elsewhere in this issue.

The work published by Palm et al. suggests that IgA could coat a group of disease-prone intestinal bacteria in humans.²⁴ This conclusion is based on human IgA⁺ microbiota transfer to murine

disease models. The latter view proposing that IgA would not induce bacterial clearance, but instead might minimize inflammatory effects of targeted bacteria, has been confirmed in other studies in mice. In *B. thetaiotaomicron* monocolonized mice, Peterson et al. showed that specific IgA selects against a specific phase-variable capsular polysaccharide associated with reduced intestinal innate immune activation.³⁸ Affinity-matured IgA appear also necessary for SFB (*Segmented Filamentous Bacteria*) pathobiont control, since AID- and IgA-deficient mice suffer from SFB overgrowth and intestinal inflammation.^{39,40} Thus, the selective and/or neutralizing effects of IgA could modulate bacterial fitness toward a noninflammatory profile. Another interpretation is that bacteria with a better grafting potential in mice have a more pronounced impact on the immune system and therefore are more likely to induce a strong IgA response. These two effects likely coexist in vivo.

These observations notwithstanding, it is also possible that IgA might be beneficial for commensal growth and therefore could play a protective role in commensal ecology. In line with this idea, we observed that bacterial species known to be IgA-coated in human samples are more likely to be underrepresented than overrepresented in fecal microbiota from slgAd patients.³ Therefore, IgA do not necessarily inhibit bacterial growth, since bacteria such as *Coprococcus comes*, *Dorea sp.*, and *Clostridium sp.* thrive in the presence of IgA.^{3,35} This promicrobial effect of IgA has also been shown using an in vitro system, in which human IgA facilitate biofilm formation and enteric bacteria proliferation.⁴¹ Interestingly, Donaldson et al. demonstrated that IgA binding to *Bacteroides fragilis* facilitated adherence to intestinal epithelial cells by modulating surface epitopes³⁷ promoting long-term maintenance of this species in the gut microbiota. Furthermore, Nakajima et al. showed that IgA interacts with *B. thetaiotaomicron* via the O- and N-glycans that extensively decorate its secretory component and hinge regions.⁴² The latter results also raise the important issue of the relative importance of Fab- (i.e., canonical binding) versus Fc- or glycan-bound (i.e., noncanonical bonding) consortia, which are not currently distinguished in most IgAseq studies.

IGA AS A REGULATOR OF BACTERIAL NETWORKS

An attractive hypothesis is that IgA might support bacterial symbiosis by facilitating or modifying bacterial networks. Bacterial symbiosis implies that some bacteria depend on other bacteria for their persistence. Within such interdependence, a bacterium, called “satellite”, never inhabits independently of another, named “host”, in a given microbiota. In slgAd patients, substantial links were found to be lost between satellites and hosts meaning that bacterial networks are altered in the absence of IgA.³ One could consider the possibility that IgA, bound noncanonically or displaying cross-species reactivity, might favor incorporation into symbiotic networks as an ecological extension of their ability to agglutinate pathogens. Despite these exciting insights into the role of IgA in microbiota homeostasis, studies in human patients who lack IgA share a main weak spot: such patients were recruited from hospital and therefore may not be representative of the majority of slgAd individuals who are asymptomatic. To better understand the physiological role of IgA in humans, a major challenge will be to explore a large number of asymptomatic slgAd individuals and to design interventional studies in symptomatic patients. Longitudinal studies would also be relevant to look at the effect of IgA on strain stability over time.

TOWARD THE DEFINITION OF IGA DEFICIENCIES AT FUNCTIONAL LEVEL

The impressive development of knowledge surrounding IgA-coated bacterial repertoires may lead to the definition of novel

immunopathologic conditions characterized by aberrant patterns of IgA coating. Although such perturbations have already been described in humans, their clinical consequences need to be investigated. Initially, Dzidic et al. reported that low proportions of IgA-coated gut-derived bacteria in infants at 12 months of age preceded the development of allergic asthma. Furthermore, IgA⁺ repertoires remarkably differed between healthy and allergic children.¹⁷ Although these results remain correlative, one could speculate that overall reduction of IgA coating might reflect weaker stimulation of the mucosal immune system in allergic children. It will be interesting to follow up whether this is due to the presence of less invasive species, or an altered handling by the immune system of very young children at high risk of atopy. Furthermore, fluctuations of IgA⁺ fraction were measured in multiple sclerosis fecal microbiota depending on disease status (e.g., remission or relapse). The IgA-coated subset tended to increase during remission, whereas significant decrease of IgA-coated bacteria have been found in active patients. Beyond IgA on their own, the authors discovered that IgA-secreting cells travel from the gut to the brain to attenuate neuroinflammation in an interleukin-10 dependent manner. Translating this result from mice to humans, the authors speculated that a reduction in IgA-bound bacteria might be due to egress of IgA-secreting cells out of the gut.⁴³ Aberrant patterns of IgA coating have also been analyzed at the bacterial family level in undernourished children. Gordon et al. reported that Enterobacteriaceae IgA coating discriminated healthy from undernourished children, suggesting an interrelationship between IgA responses and nutritional status.¹⁵ Further work should investigate whether these changes in IgA coating emerge as a consequence of the disease, or play a causative role.

SECRETORY IGM REINFORCES THE ROLE OF SECRETORY IGA

In addition to IgA-secreting cells, the gut mucosa also contains IgM-secreting cells that coexist with clonally related IgM-memory B cells in humans, but not in mice.⁴ These newly described IgM-memory B cells harbor a gene signature distinct from splenic marginal zone B cells, yet reflecting antigen experience. Both IgM-secreting- and IgM-memory B cells arise as early as 1.5 months after birth. Numbers of IgM-memory B cells remain stable over time, while IgM-secreting cells accumulate over the first 10 years of life.⁴ IgM-secreting cells release slgM into the gut lumen through the polymeric Ig Receptor (plgR). While pentameric IgM shows higher affinity for plgR, export of dimeric IgA is favored by a factor 5. This is likely due to the large size of IgM limiting its diffusion through the stroma and its access to the plgR.⁴⁴ In contrast to slgA, the extracellular receptor part (secretory component, SC) is noncovalently incorporated to pentameric IgM, which explains why slgM is not as resistant as slgA to proteolytic degradation in the gut. Importantly, free SC that is released from excess of unoccupied plgR in most secretions, cooperates with bound SC to stabilize the quaternary structure of slgM.^{45,46}

Several studies established that slgM play a protective role in gastrointestinal infections. While immune exclusion is mainly performed by slgA, slgM can efficiently bind certain pathogens such as *Salmonella enterica* Typhimurium and limit their entry into Peyer's patches.⁴⁷ In an experimental *Shigella flexneri* mouse model, slgM also displayed the ability to modulate the expression of bacterial virulence factors, thereby preserving epithelial surface homeostasis.⁴⁸ Unlike slgA, slgM can activate the complement system, facilitating pathogen killing through the classical pathway and leading to membrane attack complex formation or opsonisation for phagocytosis. Kirkland et al. demonstrated that slgM- and complement-deficiency are associated with a worse disease course of DSS-induced colitis,

supporting a role for IgM in intestinal homeostasis. However, variations of microbiota in WT versus mutant mice were not studied in these immunodeficient animals.⁴⁹ The protective role of sIgM is further illustrated in patients with primary selective IgM deficiency that present increased susceptibility to mucosal infections.⁵⁰

For years, the production of sIgM has been considered to function as a compensatory mechanism in patients lacking IgA, explaining the mild phenotype in the latter. Numerous IgM-producing cells were indeed detected in mucosal samples from sIgAd patients compared with healthy donors.^{1,2} Consistently, we found substantial IgM binding to commensals in sIgAd fecal samples and higher free fecal IgM levels compared with healthy donors. However, unlike sIgA, sIgM was found to poorly bind bacteria belonging to *Enterobacteriaceae* family, which indeed overgrew in sIgAd microbiota. These observations could explain the susceptibility to enteropathogens in sIgAd patients.^{3,51} We also observed that sIgM binding preserves Actinobacteria diversity, which, strikingly decreased dramatically in patients with common variable immunodeficiency (CVID) patients, lacking both IgA and IgM,^{3,52} thus highlighting a new role of sIgM in supporting gut microbiota diversity. IgM function is unlikely to be restricted to a particular disease state in humans. Magri et al. indeed profiled mucus-embedded bacteria from ileum and colon of healthy individuals and detected significant IgM-bound commensals.⁴ A greater bacterial diversity has been found in IgM-coated communities, corroborating the notion that sIgM optimize microbiota diversity and likely to maximize mucus retention of specific bacterial communities with putative beneficial effects. Accordingly, the microbiota of CVID patients is characterized by a drastic reduction in bacterial diversity and a high dysbiosis index, as compared with sIgAd microbiota.^{52,53} Moreover, the prevalence of IBD is higher in CVID patients than in sIgAd patients.⁵ Altogether, sIgM appear to play a dual role in the intestine, on one hand providing protection from pathogens and on the other hand preserving gut microbiota diversity and intestinal homeostasis, particularly in the case of barrier- or IgA insufficiency.

SPATIAL HETEROGENEITY OF SECRETORY IG

Profiling of Ig-bound commensals enabled by bacterial flow cytometry provides a valuable picture of the spatial heterogeneity of bacterial communities and secretory antibodies abundance. For instance, Ig-bound bacteria are more frequent in ileum than in colon and in mucus compared with central gut lumen.^{3,4,9,15,24} The mucus layer is thin in the small intestine but divided in two distinct layers in colon with an inner, attached layer and an outer, loose mucus layer. Swab samples or colon biopsy were used to profile mucus-associated bacteria, while fecal content served as central gut lumen representative.^{54–56} In the mucus layer, healthy microbiota can be divided into three fractions: sIgA⁺sIgM⁺, sIgA⁺sIgM[−], and sIgA[−]sIgM[−] commensals although in central gut lumen sIgM coated bacteria have not been detected in healthy donors. Thus, only two fractions can be discriminated: sIgA⁺sIgM[−] and sIgA[−]sIgM[−] bacteria (Fig. 1).^{3,4} One could speculate that sIgM cannot be detected in the central gut lumen due to its slow, size-dependent diffusion through mucus and rapid proteolysis, although this remains to be demonstrated in vivo. The existence of an antibody gradient from epithelium to central gut lumen and from proximal to distal compartments could complicate our understanding of secretory Ig function. Secretory Ig may operate differently depending on bacterial density, antibody concentration, and an enriched glycoprotein mucus environment. One study revealed that bacterial density determines how sIgA clump bacteria.³⁵ At high pathogen densities, IgA efficiently agglutinates pathogens as they randomly collide in intestinal compartment. However, at lower densities, pathogen collisions are too rare and IgA-mediated clumping can only occur by enchainning growing bacteria (which are necessarily in close proximity³⁵). Because location will also influence bacterial growth rates, future work should determine how biogeography might have implications for secretory Ig functions.

SYSTEMIC IGG RESPONSES TO MICROBIOTA

The initial observation that patients with IBD presented high titers of serum IgG against intestinal commensal bacteria was thought

Fig. 1 Secretory and systemic Ig work in concert to control gut microbiota. sIgA, sIgM, and serum IgG converge toward the same microbial targets.^{4,62} sIgA and sIgMs are present in decreasing concentrations from mucus to lumen.^{3,4,9,15,24} Although IgG are absent from the healthy human gut, IgG plasmocytes are found in the lamina propria⁷⁰ and likely contribute to systemic anti-commensal IgG pools, whose main origin remains unclear

to reflect a leaky epithelial barrier in these patients.^{57,58} However, several recent studies have demonstrated that robust levels of serum IgG capable of binding symbiotic bacteria are also detectable in healthy humans.^{59–62} Similarly, peripheral CD4⁺ T cells specific for intestinal are present in healthy donors.^{63,64} Using novel sensitive assays, such as microbial protein arrays and bacterial flow cytometry, it has been shown that serum IgG levels with measurable affinity for commensals arise by 6 months of age, increase from 12 to 24 months of age and remain stable in adulthood.^{61,62} This timing correlates well with the pattern of gut colonization at birth, diversification of the microbiota after weaning, and microbiota stabilization during adulthood.^{65,66} Longitudinal analysis within a time frame of 5–6 years showed that commensal-binding antibody responses do not significantly change over time in humans.⁵⁹ In line with these data, anti-commensal IgG antibodies have been found in naïve mice housed under steady state conditions.^{12,67} In addition, an elegant model of reversible *Escherichia coli* colonization unequivocally demonstrated that intestinally restrained bacteria are able to induce persistent levels of specific IgG in periphery.^{68,69}

Early studies using bacterial flow cytometry showed that systemic IgG bound a wide range of commensal bacteria (*E. coli*, *Enterococcus faecalis*, and *B. fragilis*), as well as certain commensal fungi such as *Candida albicans*.⁵⁹ We recently reported that about 1% of the gut microbiota of healthy individuals can be bound by serum IgG. Strikingly, serum IgG converge with secretory IgA toward the same bacterial targets with each subject exhibiting a private set of preferred IgG-targeted commensals. However, a “core” IgG repertoire to particular commensals emerged, genera belonging to Proteobacteria (*Serratia*, *Achromobacter* and *Delftia* for instance) being preferentially enriched in the IgG-targeted fraction of the microbiota.⁶² Of note, multiple taxa of the phylum Proteobacteria have been previously described as secretory IgA targets in several human, as well as murine studies.^{9,14,16} Together, these observations suggest that serum IgG coat a particular subset of microbiota, including a broad range of bacteria, enriched in Proteobacteria. Because 16S sequencing analysis cannot resolve species and substrains variations that directly modulate IgG responses, Christmann et al. developed an alternative approach to decipher bacterial determinants of IgG responses using printing slides with a panel of known antigens from the gut microbiota.⁶¹ Using this technique, IgG reactivity to different bacterial components, both extracellular and intracellular, from the three most prominent phyla of the human gut microbiota has been uncovered. Four antigens were found to be universally recognized among the cohort. It remains to be shown whether this is due to cross-reactivity with yet unidentified common pathogen antigens, or whether the intriguing hypothesis that postulates the existence of a core microbiota-binding IgG reactivity can be validated. The results of a recent study supported the idea of cross-reactivity of microbiota-binding IgG by showing that monoclonal antibodies specific for the Klebsiella O3 O-antigen, a mannose polymer, also bind yeast and mammalian-derived mannose-containing glycans. Such antibodies were shown to bind an array of commensals, likely sharing mannose-containing surface structures.⁷⁰ The potential role of such specificities in anti-commensal and cross-reactive autoimmunity is extensively reviewed elsewhere.

THE ORIGIN OF SYSTEMIC ANTI-MICROBIOTA IGG

Several studies explored commensal-binding IgG in mice and humans yet it remains unclear how this systemic response to gut microbiota develops. It likely reflects episodic exposure to gut commensals that breach the intestinal barrier. Increased gut permeability has been observed in human after high-fat meals, alcohol binging or the use of proton pump inhibitors, and nonsteroidal anti-inflammatory drugs absorption. Various intestinal pathogens, including bacteria and viruses, are also able to disrupt the intestinal epithelial barrier.^{71,72} In such conditions,

commensal translocation take place in an inflammatory context, likely in the presence of cytokines promoting the production of IgG, instead of IgA, in the lamina propria. It is of note that Ig gene sequence analysis has revealed that gut IgG- and IgA-secreting cells are not clonally related and therefore originate from independent precursors.⁷³ Consistently, direct switching from IgM to IgA1 or IgA2 predominates in colonic mucosa, in contrast to the rare sequential event during which IgM switches to IgA2 via IgG2,⁷⁴ reinforcing the idea that microbiota-specific IgA and IgG B cells arise via independent mechanisms. Experimental data in mouse models have detailed the ontogeny of anti-commensal IgG B cells showing that many commensal-binding antibodies are generated in a T-independent manner dependent on TLR signaling in B cells. These B cells might derive from B1 cells in mice, although the relevance of this finding for human biology remains unclear.^{12,75} The microbiota also nonspecifically supports systemic antibody production through the production of short-chain fatty acids (SCFAs), the major microbial metabolites of dietary fiber fermentation. SCFAs promote B cell differentiation into antibody-secreting cells and boost B cell metabolism resulting in antibody production.⁷⁶

Gut-associated lymphoid tissue (GALT) is the primary site of IgA induction.⁷⁷ By contrast, the extent to which GALT contributes to the IgG repertoire remains still to be determined. Although the intestinal B cell pool is highly dominated by IgA-producing cells, 3–4% of intestinal antibody-secreting cells express IgG at steady state in humans. About two thirds of monoclonal antibodies derived from intestinal IgG⁺ plasmablasts react with common gut bacteria.^{71–73} Moreover, the majority of anti-commensal IgG antibodies were of the IgG2 subclass and IgG2-secreting cells have been detected in the lamina propria throughout the intestine.⁶² In addition, higher serum anti-*E. coli* IgG levels in patients with IBD were associated with a substantial increase of gut IgG⁺ B cells.⁷³ In mice, mesenteric lymph nodes have also been implicated in generating systemic IgG responses to invasive bacteria.⁷⁸

Together, these data suggest that intestinal IgG⁺ B cells might contribute to the serum IgG repertoire in humans (Fig. 1). Recently, Wilmore et al. demonstrated that members of the gut microbiota enhance serum IgA levels and induce large numbers of IgA-secreting cells in the bone marrow.¹⁴ However, the existence of such a gut/bone marrow axis supporting the production of anti-commensal IgG remains to be proved both in humans and in mice.

A RAISON D'ÊTRE FOR ANTI-COMMENSAL IGG

The functional relevance of systemic anti-commensal IgG has been first revealed by producing evidence for their protective role in gastrointestinal and systemic infections. Mice lacking the innate immune signaling components MyD88 and TRIF spontaneously produce very high levels of microbiota-targeting IgG. Gnotobiotic colonization demonstrated that these responses were T cell-dependent and, at least partly, capable of providing protection from sepsis.^{67,79} The clinical relevance of anti-microbiota IgG is consistent with observations that patients with CVID, lacking circulating IgG, but not intestinal IgA, nevertheless suffer from gastrointestinal infections and lymphoproliferative disorders.^{6,80}

Anti-commensal IgG also play a role in early life in modulating the development of the neonatal immune system, with both stimulatory and regulatory effects. Maternal IgG is transported to the neonate across the placenta via the neonatal Fc receptor⁸¹ that also mediates neonatal uptake of maternal milk-ingested IgG into the small intestine.^{82,83} Transfer of IgG during gestation drives the development of intestinal NKp46⁺ innate lymphoid cells (ILC3) and causes changes in the intestinal gene expression profile, in particular genes involved in mucus secretion and metabolism of sugar or dietary xenobiotics whose expression is upregulated in an

antibody-dependent manner. Moreover, the study of Gomez de Agüero et al. indicated that microbial products from the maternal microbiota, likely bound by IgG, were transferred to the neonate before birth. Thus, IgG appear to prepare the neonate in utero to the massive bacterial colonization occurring after birth.⁶⁸ The specificity of these IgG transferred to the neonate remains to be defined, but it is tempting to speculate that anti-commensal IgG is an important component.

Anti-commensal IgG ingested from maternal milk, have also been found to have regulatory effects on the neonatal immune system. Maternal milk contains both secretory IgA and IgG that cooperate to discourage bacterial translocation and thereby limiting mucosal T cell responses. In mice lacking maternal antibodies, an increased frequency of T follicular helper cells and germinal center B cells has been described, resulting in an increased antibody production aimed to restore homeostasis. The absence of either IgA or IgG during suckling is sufficient to fuel aberrant immune responses in gut mucosa.¹²

In summary, systemic anti-commensal IgG (i) provide a preexisting set of antibodies against a variety of pathogens and (ii) might play a critical role in modulating immune system development in early life. Although these findings raise exciting possibilities in terms of novel therapeutic strategies, human data are still lacking. At present, multiple clinical trials have failed to demonstrate consistent beneficial effects of pooled human IgG (IVIGs) in sepsis, suggesting that IVIGs do not contain the appropriate specificities.⁸⁴

ANTI-COMMENSAL IGG AND CANCER

Current evidence supports a model in which some (potentially invasive) commensals are able to induce IgG responses in the context of a healthy microbiota and an intact intestinal barrier. Other microbes however, might only induce systemic responses in the context of dysbiosis or intestinal barrier disorders. This hypothesis has been extensively studied in IBD patients who presented elevated and biased serum anti-commensal IgG responses.^{57,58,85,86} More recently, we reported that sIgAd patients have a higher level of anti-commensal IgG, suggesting that bacterial translocation may occur more frequently in the absence of secretory IgA. Moreover, sIgAd patients (sIgAd) harbor a different set of anti-commensal IgG, as compared with healthy donors, which is consistent with the presence of a mild dysbiosis.³ Greater alterations of gut microbiota composition and diversity have been described in fecal samples from CVID patients, lacking both IgA and IgG.⁵² In line with these findings, pooled IgG from healthy donors (IVIGs) poorly bound to fecal bacteria from CVID patients, meaning that these antibodies do not contain appropriate specificities of anti-commensal IgG for the treatment of dysbiotic patients.⁶²

In colorectal cancer (CRC), changes in the intestinal tissue result in a leaky gut, with potential aberrant bacterial excursions.⁸⁷ It has also been reported that colorectal CRC is associated with increased prevalence of *Fusobacterium nucleatum*, a bacteria species with oncogenic potential.^{88–90} A prospective study recently associated a commensal candidate, *Streptococcus gallolyticus subspecies gallolyticus* (SGG) with the risk to develop CRC, since anti-SGG IgG were more frequently present in individuals who developed cancer later in life (Table 2).⁹¹

Although a causative link between the presence of such species and CRC has not been demonstrated, certain anti-commensal IgA⁹² or IgG⁹¹ reactivities might constitute potential diagnostic biomarkers for CRC. The detection of anti-commensal IgG might also offer novel opportunities for predicting immunotherapy efficacy in the treatment of cancers. The dominance of distinct commensal species in gut microbiota such as *Akkermansia muciniphila* and *Enterococcus hirae*, has been shown to drive immunological changes that influence the anti-cancer efficacy of blockade of the PD1/PDL1 pathway in epithelial tumors.⁹³ Screening IgG against these specific microbes before treatment could be more convenient than an extensive analysis of stool composition in an attempt to predict resistance to these and other immune checkpoint inhibitors.

ANTI-COMMENSAL IGG AND AUTOIMMUNITY

For years, the molecular mimicry theory has supported the view that homologies between microbial components and human proteins are likely to take part in the development of autoimmune diseases. This dogma was first supported by studies showing associations between pathogens and the risk to develop autoimmunity, such as *Campylobacter jejuni* and Guillain-Barré syndrome or *Streptococcus pyogenes* and juvenile dermatomyositis.^{94–96} A few recently published studies also aimed at linking the presence of commensals and anti-commensal IgG with the development of certain autoimmune diseases. Recently, Azzouz et al. found that active SLE patients displayed a fecal expansion of *Ruminococcus gnavus* strain associated with high and specific systemic IgG responses toward this species, suggesting that some specific components of *R. gnavus* are nephritogenic by molecular mimicry (Table 2).⁹⁷ The magnitude of serum antibodies titers directed against *Enterococcus gallinarum* was correlated with that of anti-RNA antibodies in serum from patients with systemic lupus erythematosus.⁹⁸ Greiling et al. also proposed that commensal bacteria expressing Ro60 orthologs might induce hRo60 cross-reactive antibodies and therefore trigger autoimmunity in lupus.⁹⁹ To test this hypothesis, the authors monocolonized lupus-prone mice with Ro60-expressing bacteria i.e., *Bacteroides thetaiotaomicron* and observed increased

Table 2. Anti-commensal IgG responses are altered in various diseases

Disease	Whole anti-commensal IgG response	Commensal candidates	References
Selective IgA deficiency	↗	ND	62
Colorectal cancer	ND	<i>Streptococcus gallolyticus subspecies gallolyticus</i> (SGG)	87
Systemic lupus erythematosus	ND	<i>Enterococcus gallinarum</i> <i>Bacteroides thetaiotaomicron</i> <i>Ruminococcus gnavus</i>	97,98,99
Inflammatory bowel diseases	↗	<i>E. coli</i> <i>E. coli</i> , <i>B. fragilis</i> , <i>C. perfringens</i> <i>E. coli</i> CBir1 flagellin	57,58,60,86
Allergy	↘ During infancy	ND	61

ND not determined

autoantibody production and lupus-like nephritis. However, most microbes can induce strong immune responses in mono-colonized gnotobiotic mice,¹⁹ likely representing an effect of monocolonization due to overabundance of a single species, or immaturity of the germ-free mucosal system on initial encounter with the microbe. Moreover, autoimmune prone nonobese-diabetic mice that were monocolonized with *B. theta* actually carried hRo60 cross-reactive antibodies but did not develop autoimmune symptoms, indicating that triggering autoimmunity might be the consequence of a much more complex interplay between commensals, host genetics and environmental factors.

Another paradigm, that links anti-commensal IgG responses and immune-mediated diseases is represented by the so-called hygiene hypothesis.^{100–102} Christmann et al. associated lower anti-commensal IgG levels during infancy with the risk to later on eventually develop allergy, suggesting that strong early life anti-microbiota immune responses might be protective against the subsequent development of immune-mediated diseases (Table 2).⁶¹ Likewise, early colonization by microbes, like *Bacteroides* sp., that potentially activate immune pathways plays an important role in immune education and decreased incidence of autoimmune diseases.¹⁰³ Of note, such induced beneficial immune deviation effects would not be mediated predominantly by pathogens, but rather result from exposure to diverse commensal consortia.^{104,105}

OUTLOOK

The sequencing of immunoglobulin-bound microbiota fractions from both healthy humans and patient populations has provided insight in the nature of bacterial interactions with the host immune system. We and others have noted interesting overlaps and distinctions between IgA, IgM, and IgG reactivities, which may hint at both differential induction pathways and differential functions. For example, bacterial strains showing strong reactivity with all three isotypes in healthy donors may be particularly strong inducers of humoral immunity. However, in patients with sIgAd there is a counterintuitive (paradoxical) absence of compensatory sIgM directed against Gammaproteobacteria, despite evident overgrowth of this gram-negative class of bacteria, suggesting an, as yet, unknown requirement for the induction of sIgM. Another challenge remains in interpreting these results with respect to microbiota control. The mechanisms by which IgA can selectively disadvantage a bacterial species in the gut lumen are well defined, but while a range of hypotheses exist, there is still limited evidence for procolonization mechanisms. Suggestions currently include the generation of mucus-embedded microcolonies or altered bacterial metabolism. Highly relevant questions also remain regarding the function of anti-commensal Ig in health and disease. Currently, the relatively mild clinical phenotype associated with IgA deficiency is difficult to reconcile with the critical role played by IgA in disease protection in many animal models.^{47,106–108} Further, microbiota robustness is emerging as an important parameter for health, in which secretory antibodies could play both beneficial and deleterious roles. Perturbation/recovery studies, as well as hypothesis-driven research in experimental model systems, will be required to address these major questions. We would propose these as priorities, necessary to open up the major untapped potential of secretory antibodies in modulating microbiota for diagnostic and therapeutic purposes.

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ADDITIONAL INFORMATION

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