



# Microbial symphony orchestrated by mucosal IgA

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The ability of an organism to handle the beauty and cruelty of existence is largely due to a complex network of molecular and cellular interactions and processes named the immune system. Important components of this network are antibodies (Abs) that have key roles in immune defense and regulation. Typical biological functions of Abs include neutralizing pathogens by blocking functionally important molecules and/or to elicit lethal effector functions by bridging the recognition of pathogens with binding to different innate immune receptors. However, Abs also promote alternative strategies known as noncanonical functions. For instance, Abs exhibit catalytic activities, act as chaperons and carriers for hormones, and regulate cell signaling.<sup>1</sup> The past decade has been marked by enormous interest in studies of mucosal Ab immune responses. This interest resulted in the discovery of various novel biological functions of secretory immunoglobulin A (SIgA). In a recent article published in *Nature*, Rollenske et al.<sup>2</sup> reveal an important biological role of intestinal SIgA, namely, the ability to shape microbial fitness by exerting in parallel a set of different functional activities on bacteria.

IgA typically exists in two forms: monomeric, which circulates in serum, and oligomeric (mostly dimeric), which is present at mucosal surfaces. The complex of an epithelial-derived glycoprotein called the secretory component (SC), two IgA molecules and the J chain is known as SIgA. One of the main tasks of SIgA is to protect the intestinal epithelium from enteric pathogens and toxins.<sup>3</sup> Hence, given the belief that everything happens for a reason, it is not surprising that IgA Abs are abundant at mucosal surfaces where two different types of humoral immunity coexist: one implicated in protection against pathogens and another required for homeostatic interactions with commensal bacteria.<sup>4</sup> SIgA evokes multiple processes for neutralization of pathogens, including (1) blocking the attachment of microbes to the epithelium by binding to receptor-binding domains and (2) immune exclusion through the induction of agglutination, entrapment or clearance of microbes.<sup>3,4</sup> Uncovering how these

pathways function is of paramount importance to obtain new insights from the evolutionary point of view as well as the treatment of enteric pathologies.

In their study, Rollenske et al.<sup>2</sup> exposed germ-free mice to the commensal bacteria *Escherichia coli* strain HA107. After a short-term bacterial exposure (21 days), the authors cloned the V region of immunoglobulin genes isolated from mucosal IgA+ plasma cells and expressed them as 91 recombinant IgG1 as well as in their original form, i.e., SIgA. Furthermore, the reactivity of these Abs was studied, and 17/91 of the Abs were found to bind to elicit bacterial strains. The *E. coli* HA107-reactive Abs had no or only a few somatic mutations in their V regions. These Abs target only the membrane fraction of bacteria. Using a high-throughput approach with mutant strains of *E. coli*, the authors identified the target antigens on the bacterial surface of different monoclonal Abs. Among the identified targets were type I fimbriae, and the outer membrane porin proteins OmpW and OmpC. Importantly, using kinetic analyses, it was estimated that two SIgAs bound to OmpC with modest but physiologically relevant affinity ( $K_D$  values of 128 and 250 nM), implying that short bacterial exposure is sufficient for rapid recruitment of specific B cells and their differentiation in plasma cells.

One of the most important and innovative aspects of the work of Rollenske et al. is the assessment of the functional activity of monoclonal SIgA targeting *E. coli*. Interestingly, the exposure of *E. coli* HA107 bacteria to recombinant SIgA resulted in changes in the expression of >9% of bacterial genes. This Ab targets the outer membrane pore OmpC, and its binding causes downregulation of the expression of genes involved in metabolic pathways and the transport of ions and carbohydrates. On the other hand, it upregulated stress-induced genes (genes induced by osmotic shock and those responsible for iron transport and storage). Moreover, the functional outcome of different SIgAs depends on the binding context given that Abs targeting the same Ag (OmpC) but not able to bind to most live bacteria did not

trigger the same effects on the microbial transcriptome induced by SIgA capable of coating live cells. Nonetheless, the effects on the microbial transcriptome were independent of the ability of SIgA to coat the bacterial surface, as different surface-binding SIgA evoked diverse modulation of gene transcription in bacteria. An important finding of this study is that different monoclonal SIgAs binding to the same protein (OmpC) but with different fine specificities caused distinct patterns of gene expression in bacteria, resulting in different functional consequences.

The capacity of some Abs to directly modulate the gene expression of microbes was demonstrated more than one decade ago. McClelland et al. discovered a new mode of action for Ab-mediated immunity by demonstrating that after binding, IgG and IgM Abs induced divergent changes in the gene expression of the pathogenic fungus *Cryptococcus neoformans*, affecting its metabolism.<sup>5</sup> Later, it was found that nonopsonic Abs that are highly protective against *Streptococcus pneumoniae* alter the expression of genes related to quorum sensing.<sup>6</sup> This alteration led to competence increases and fratricide events as consequences. Hence, the direct alteration of gene expression was proposed as another mechanism involved in Ab-mediated immunity.

In addition to SIgA-induced changes in the gene expression patterns of bacteria, Rollenske et al. showed that binding of some monoclonal Abs caused other important functional effects for bacteria, such as increased aggregation, higher resistance to bacteriophages, and increased resistance to the bactericidal effect of bile acids. These results strongly suggest that SIgA Abs regulate microbial colonization through several mechanisms that act in parallel. These concerted actions of SIgA influence microbial fitness, ultimately resulting in adaptation of the bacteria to establish mutualistic equilibrium with the host (**Figure 1**).

If we consider IgA-mediated immunity to a single microbe as a set of parallel responses with different functional outcomes, one may wonder about the effects of the binding of several

Abs with different Ag specificities to the same microbe. Will these Abs evoke synergic or antagonistic effects? Will they trigger a new pathway of signaling different from the one triggered by an individual type of Ab? The answers to these questions may provide a better perspective of the events occurring in life between SIgA and microbes, as different Abs can bind to the same microbe simultaneously. Another interesting aspect will be assessment of the effects of SIgA in the modulation of the human cell transcriptome given that this information could decipher the crosstalk between human cells and SIgA microbes in the context of their coexistence.

Certain Abs referred to as polyreactive can bind multiple structurally diverse antigens. Mucosal B cells express a higher proportion of polyreactive Abs than B cell populations in other locations in organisms, and these Abs contribute to priming the immune system for the generation of highly specific immune Abs.<sup>7,8</sup> Polyreactivity may influence antibody-mediated immunoselection of the microbiota. Rollenske and colleagues did not observe an increase in the proportion of polyreactive Abs targeting the model bacteria. Moreover, based on analysis of gene expression modulation induced by two different polyreactive monoclonal SIgAs, these researchers found that only one common gene set was upregulated/downregulated by the two polyreactive Abs. Hence, there was no consistent effect on polyreactivity per se on the transcriptome of bacteria.

In conclusion, the work of Rollenske et al. further extends our understanding of how mucosal immune responses can influence microbial fitness and result in the establishment of homeostatic relationships between hosts and microbes.<sup>9,10</sup> In addition to demonstrating novel noncanonical functions of Abs, this study paves the way for the development of novel therapeutics for modulation of the intestinal microbiome in different diseases.

## References

- 1 Dimitrov, J. D. & Lacroix-Desmazes, S. Noncanonical Functions of Antibodies.  
2 *Trends Immunol* **41**, 379-393 (2020).
- 3 Rollenske, T. *et al.* Parallelism of intestinal secretory IgA shapes functional microbial  
4 fitness. *Nature* **598**, 657-661 (2021).
- 5 Mantis, N. J., Rol, N. & Cortes, B. Secretory IgA's complex roles in immunity and  
6 mucosal homeostasis in the gut. *Mucosal Immunol* **4**, 603-611 (2011).
- 7 Macpherson, A. J., Yilmaz, B., Limenitakis, J. P. & Ganai-Vonarburg, S. C. IgA  
8 Function in Relation to the Intestinal Microbiota. *Annu Rev Immunol* **36**, 359-381  
9 (2018).
- 10 McClelland, E. E., Nicola, A. M., Prados-Rosales, R. & Casadevall, A. Ab binding  
11 alters gene expression in *Cryptococcus neoformans* and directly modulates fungal  
12 metabolism. *J Clin Invest* **120**, 1355-1361 (2010).
- 13 Yano, M., Gohil, S., Coleman, J. R., Manix, C. & Pirofski, L. A. Antibodies to  
14 *Streptococcus pneumoniae* capsular polysaccharide enhance pneumococcal quorum  
15 sensing. *mBio* **2**, doi:10.1128/mBio.00176-11 (2011).
- 16 Fransen, F. *et al.* BALB/c and C57BL/6 Mice Differ in Polyreactive IgA Abundance,  
17 which Impacts the Generation of Antigen-Specific IgA and Microbiota Diversity.  
18 *Immunity* **43**, 527-540 (2015).
- 19 Bunker, J. J. *et al.* Natural polyreactive IgA antibodies coat the intestinal microbiota.  
20 *Science* **358**, doi:10.1126/science.aan6619 (2017).
- 21 Kubinak, J. L. & Round, J. L. Do antibodies select a healthy microbiota? *Nat Rev*  
22 *Immunol* **16**, 767-774 (2016).
- 23 Donaldson, G. P. *et al.* Gut microbiota utilize immunoglobulin A for mucosal  
24 colonization. *Science* **360**, 795-800 (2018).

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161 **Figure legend.** The challenge of mice with model intestinal bacteria results in rapid  
162 recruitment of plasma cells and production of SIgA. These Abs bind to different antigens on  
163 the bacterial membrane (here denoted Ag A and Ag B), resulting in changes in gene  
164 expression and resistance to bacteriophages. Of note, binding of SIgA with different fine  
165 specificities to a single antigen resulted in differences in gene expression patterns. Ultimately,  
166 the interaction of bacteria with SIgA results in functional changes that modulate the fitness of  
167 the microbe that might be favorable for colonization of the intestine.



