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Microbial symphony orchestrated by mucosal IgA

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

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

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

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

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

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

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

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

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

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

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

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

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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.

