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A gut triumvirate rules homeostasis

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Abstract

IgA regulates intestinal homeostasis by maintaining appropriate communities of bacteria within the gut. A new study shows that intestinal bacteria regulate metabolism via IgA (pages 1585–1593).

The gut ecosystem includes complex communities of commensal bacteria that confer many defensive and metabolic capabilities, including the ability to break down indigestible carbohydrates, generate essential vitamins and fill a niche that would otherwise be accessible to pathogens. The intestinal microbiota also educate local immune cells to generate a homeostatic balance characterized by active immune readiness against pathogens and hyporesponsiveness against commensals. This homeostatic balance involves the sensing of bacteria by intestinal epithelial cells (IECs)¹.

A key component of intestinal homeostasis is IgA, the most abundant antibody isotype in mucosal secretions². Intestinal B cells produce IgA to exclude commensals from the mucosal surface by inducing bacterial agglutination, masking bacterial proteins involved in epithelial attachment and anchoring bacterial cells to mucus^{2–4}. But IgA also decreases the inflammatory tone of the intestine by maintaining appropriate bacterial communities within specific mucosal segments^{5–7}. Thus, the lack of IgA causes changes in the composition of the intestinal microbiota that can cause hyperactivation of the immune system and inflammation^{5–7}. Despite recent advances², how IgA generates intestinal immunity without causing inflammation is not well understood. An integrated view of the mechanisms by which IgA-coated commensals influence health and disease states is also lacking. In this issue of *Nature Medicine*, Shulzhenko *et al.*⁸ show that, in the absence of B cells or IgA, commensal bacteria favor the expression of genes controlling immunity in IECs over those regulating metabolism (Fig. 1). This finding may explain why individuals with certain immunodeficiencies show defective lipid absorption.

Commensal bacteria enhance the development of the intestinal immune system, including the generation of IgA-producing B cells, by establishing an intimate dialog with IECs and dendritic cells beginning shortly after birth^{2–4,9,10}. In addition to forming a physical barrier between the lumen and the sterile milieu of our body, IECs recognize microbial signatures through different innate sensors that inform the immune system about the composition of the

gut microbiota¹. Conversely, the immune system shapes the composition of the gut microbiota through the production of bacteria-reactive IgA by B cells³⁻⁷.

This relationship between the host and commensals may influence not only immunity and homeostasis but also metabolism. Shulzhenko *et al.*⁸ now provide new insights into how B cells regulate metabolism. The authors found that IECs from mice lacking B cells upregulated the expression of interferon-regulated genes involved in immune defense at the expense of the expression of Gata4-regulated genes activating lipid metabolism (Fig. 1). *In silico* reconstruction of gene expression networks led to the identification of distinct immune and metabolic networks in IECs and showed that these networks were functionally interconnected but were inversely regulated⁸. Whereas IECs upregulated the expression of interferon-regulated immune genes, they downregulated the expression of Gata4-regulated metabolic genes after exposure to interferon⁸.

IECs from mice lacking B cells or epithelial Gata4 showed a comparable inactivation of genes involved in fat uptake and deposition⁸. These genes included *Slc27a2*, *Osbpl3* and the group of genes containing *Acaa1b*, *Clps*, *Agmo* and *Apoc3*, which encode a fatty acid transporter, an intracellular lipid receptor and a group of regulators of lipid oxidation, hydroxylation or catabolism⁸, respectively. Downregulation of Gata4-dependent gene expression correlated with systemic alterations of lipid metabolism, for example, decreased serum concentrations of the metabolic hormone leptin and reduced body accumulation of fat⁸. The authors further showed that IECs from B cell-sufficient mice lacking IgA had an IEC gene expression profile similar to that of B cell-deficient mice⁸. They obtained similar findings in B cell-sufficient mice lacking Ig secretion and activation-induced cytidine deaminase⁸, an enzyme that is essential for B cells to improve the affinity of Igs for antigen and to switch from IgM to other Ig classes, including IgA^{2,6,7}. Overall, these findings indicate that B cells regulate metabolism by influencing IEC expression of Gata4-regulated genes through a mechanism involving IgA.

Under germ-free conditions, B cell-deficient mice showed an IEC gene expression profile comparable to that of wild-type mice⁸, indicating that intestinal bacteria have a key role in the metabolic alterations brought about by B cell or IgA deficiency. Accordingly, the gene expression profile of IECs from B cell-deficient mice was recapitulated *in vitro* by exposing IECs to intestinal bacteria such as *Escherichia coli* or microbial products such as lipopolysaccharide⁸.

Similar to IECs from B cell-deficient mice, gut tissue from individuals with common variable immunodeficiency, a primary B cell disorder associated with impaired intestinal IgA production, showed an upregulation of *OAS2*, *IFI44*, *IFITM*, *TNFSF10*, *CD5*, *CD8A* and *MHC*, which encode antimicrobial and immunostimulating factors, but a down-regulation of *APOC3*, *PDK4*, *HPGD* and *FBP1*, which encode regulators of lipid and carbohydrate metabolism⁸. This gene signature correlated with the development of lipid malabsorption⁸, a clinical manifestation frequently associated with primary B cell deficiencies¹¹. Altogether, these findings indicate that IgA shapes the metabolic features of IECs and that this function depends on the presence of intestinal bacteria.

Consistent with this interpretation, mice lacking Toll-like receptor 5 (TLR5), a microbial sensor that recognizes the protein flagellin on commensal bacteria, develop hyperlipidemia, hypertension and insulin resistance and show increased body fat deposition¹². This complex metabolic syndrome originates from an alteration of the specific composition of the intestinal microbiota¹², which could emerge from a concomitant perturbation of the intestinal IgA response. Accordingly, certain dendritic cells have been shown to stimulate

intestinal IgA production by releasing B cell stimulating factors after recognizing flagellin through TLR5 (refs. 2,9,10,13).

Growing evidence points to the key role of commensals in the development of auto-immune disorders such as rheumatoid arthritis, as well as inflammatory disorders such as Crohn's disease and ulcerative colitis¹⁴. The present study suggests that commensals also modulate metabolism through a mechanism involving IgA⁸. In the absence of IgA, commensals may undergo functional changes that alter the metabolic response of IECs. Consistent with this interpretation, IgA seems to exert a genetic pressure that shapes the fitness of commensals through the modulation of specific microbial surface epitopes⁵.

In general, the results of the study by Shulzhenko *et al.*⁸ support the idea that the pathogenicity of the intestinal microbiota is not necessarily an intrinsic property of bacteria. Mutualistic and pathogenic functions of bacteria may depend on the context in which the bacteria interact with the host. In individuals with IgA deficiency, commensals could acquire pathogenic properties as a result of their adjustment to immune forces that shift the homeostatic balance of IECs toward immunity at the expense of metabolism. This shift would cause metabolic disorders that arise from malabsorption but may also enhance inflammation.

Understanding how commensals, IECs and IgA promote an intestinal balance between immunity and metabolism provides a conceptual framework to better understand the pathogenesis of metabolic and inflammatory disorders arising in individuals with immunodeficiency¹¹. According to a 2005 survey sponsored by the Immune Deficiency Foundation, about 1 in 1,200 individuals in the United States has been diagnosed with a primary immunodeficiency disease. The most prevalent primary immunodeficiencies include selective IgA deficiency and common variable immunodeficiency, two B cell disorders that frequently cause inflammatory bowel disease and malabsorption, in addition to mucosal infections¹¹.

Similar inflammatory and metabolic disorders emerge in individuals infected with human immunodeficiency virus who have acquired immunodeficiency syndrome, which is typically associated with profound alterations of intestinal B cell responses¹⁵. Shulzhenko *et al.*⁸ found that gut tissue from these individuals showed metabolic alterations similar to those detected in people with common variable immunodeficiency. Thus, it is conceivable that individuals with either primary or acquired IgA deficiency may benefit from supplemental therapy with pooled IgA molecules resistant to intestinal degradation. By shifting the balance of IEC gene networks toward metabolism, this approach may normalize lipid absorption and attenuate inflammation.

These new findings show an unexpected link between commensals, IgA and metabolism. More studies are needed to identify the microbial determinants that are targeted by IgA to regulate intestinal metabolic functions and the precise molecular mechanisms governing the interaction between interferon-controlled immune pathways and Gata4-controlled metabolic pathways in IECs. Given that infections by pathogens can be a major complication of immune disorders associated with IgA deficiency, further work is also needed to verify whether pathogens alter metabolism through a mechanism similar to that used by commensal bacteria.

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Figure 1.

Intestinal bacteria regulate metabolism and immunity through an IgA-dependent mechanism. In healthy individuals (left), B cell-derived plasma cells release IgA onto the mucosal surface, where IgA binds to commensal bacteria. IgA-coated bacteria regulate intestinal immunity and homeostasis by delivering signals through microbial sensors on IECs. Shulzhenko *et al.*⁸ show that in addition to enhancing protection through immune pathways controlled by the cytokine interferon (IFN), these signals also regulate the intake of food lipids through metabolic pathways controlled by the transcription factor Gata4. In IgA-deficient individuals (right), IECs upregulate the expression of IFN-dependent genes to compensate for the lack of adaptive humoral immunity. This upregulation leads to a downregulation of the expression of genes regulated by Gata4. The resulting gene imbalance impairs the absorption of lipids, such as cholesterol, by IECs, resulting in metabolic disorders.