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RESEARCH HIGHLIGHT

Intimate gut interactions: helminths and the microbiota

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Changing exposure to intestinal helminths, or alterations in our intestinal microbiome, have been independently proposed to underlie the increasing incidence of chronic inflammatory diseases including allergy, autoimmunity and inflammatory bowel disease (IBD) observed in developed nations. A recent study in *Science* links these findings by showing that intestinal helminth infection can prevent the outgrowth of a common intestinal bacterium that causes IBD in genetically susceptible mice.

The intestine harbors a complex and dense population of bacteria, typically referred to as the microbiome, that normally lives in harmony with the host and can even benefit health. Breakdown of this mutually beneficial relationship induces chronic inflammation, resulting in inflammatory bowel disease (IBD). Environmental and genetic factors contribute to IBD with one of the most striking gene polymorphisms associated with this human disease located in the gene encoding nucleotide-binding oligomerization domain 2 (NOD2) [1]. NOD2 helps the immune system recognize and respond to bacteria, yet paradoxically mice deficient in the *Nod2* gene (*Nod2*$^{-/-}$ mice) develop excessive immune responses that lead to intestinal inflammation. Ramanan *et al*. [2] helped resolve this paradox several years ago by showing that *Nod2*$^{-/-}$ mice harbor an abnormally high number of the intestinal bacterium *Bacteriodes vulgatus*, which is responsible for driving the inflammatory response. *Nod2*$^{-/-}$ mice also had an abnormally low number of intestinal goblet cells, specialized epithelial cells responsible for producing the mucous that normally separates the intestinal tissue from luminal bacteria, thus preventing inflammation.

In a follow-up study recently published in *Science*, Ramanan *et al*. [3] now show that intestinal helminth infection can restore goblet cell numbers in *Nod2*$^{-/-}$ mice, prevent *Bacteriodes vulgatus* outgrowth and protect mice against intestinal inflammation (Figure 1). These findings are important as it has long been postulated that the eradication of intestinal helminths underlies the increasing prevalence of allergic and inflammatory diseases in developed societies [4], and helminth-based therapies are being trialed in numerous diseases [5]. The study by Ramanan *et al*. [3] provides new insight into these observations by showing that helminth infection can alter IBD by altering the intestinal microbiome. They further reveal that helminth-mediated prevention of *Bacteriodes vulgatus* outgrowth requires an intact type 2 immune response that leads to the expansion of intestinal bacteria belonging to the Clostridiales family (Figure 1). The idea that helminth infection protects against intestinal inflammation by altering the intestinal microbiome was further supported by experiments in which oral delivery of a 'probiotic' cocktail containing Clostridiales species prevented the outgrowth of *Bacteriodes vulgatus* and consequent inflammation in *Nod2*$^{-/-}$ mice. Although not formally demonstrated by the authors, it is likely that helminth infection impacted the intestinal microbiome by increasing mucous production as addition of porcine mucous to Clostridiales spps cultured in the laboratory resulted in improved bacterial growth.

The new concept brought forward by this work is that helminth infection can modulate inflammation by impacting microbial communities. The unveiling of host immunity, and potentially mucous production, as one pathway by which helminth infection alters microbial communities represents an exciting advance for the field. But where does this work leave us now? We still have much to learn about the impact of helminth infection on mucous and the role of mucous in altering bacterial growth. Mucous provides a physical layer between mucosal tissues and the environment, contains antimicrobial peptides, can dampen inflammation and can be used as an energy source by bacteria. Yet mucous is a complex structure built from glycoproteins (proteins coated with sugars) called mucins that form gels by trapping water. Mucins are encoded by a large gene family and can exist in secreted or membrane (cell surface)-associated forms. The exact combination of mucins present depends on the tissue (intestine, respiratory tract, nasal cavity, and genital tract) and infection status, with helminth infection leading to striking alterations in both total quantity and composition of mucous [6]. Thus, it will be imperative to know whether, and how, mucous production elicited by helminth infection could modulate the growth of bacteria species present in the intestinal microbiome.

The central protective role of the intestinal microbiome identified by the authors strengthens the idea that probiotic use may represent an effective strategy for treating IBD. Yet many questions remain. Do similar changes

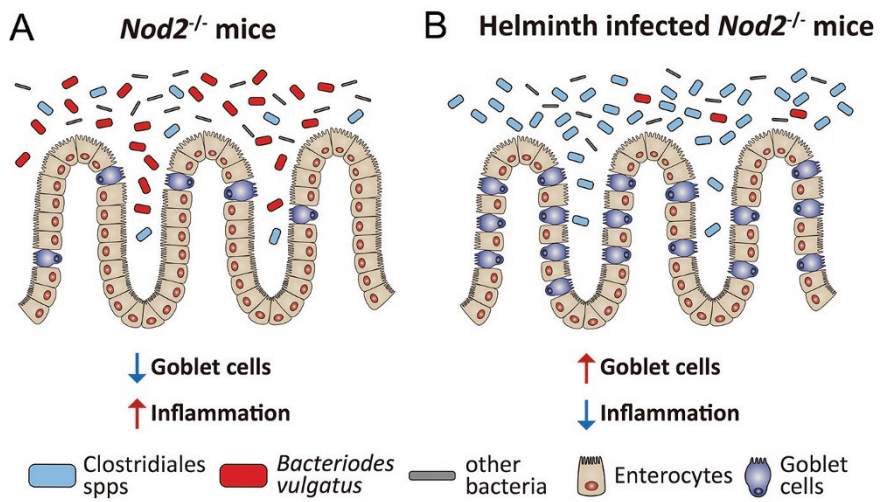

Figure 1 (A) *Nod2*$^{-/-}$ mice exhibit low goblet cell numbers and an outgrowth of the intestinal bacterium *Bacteriodes vulgatus*, and develop intestinal inflammation. **(B)** Infection of *Nod2*$^{-/-}$ mice with an intestinal helminth (*Trichuris muris* or *Heligmosomoides polygyrus*) elicits host type 2 immunity, leading to increased goblet cell numbers, mucous production and an expansion of intestinal bacteria belonging to the Clostridiales family. The outgrowth of Clostridiales species in turn suppresses the growth of *Bacteriodes vulgatus* and prevents intestinal inflammation.

in bacterial communities alter IBD in genetically susceptible humans? Can helminth infection, or delivery of the correct mix of probiotics, improve disease in individuals already suffering from IBD? Recent estimates indicate that up to half of IBD patients also exhibit respiratory symptoms associated with low-grade inflammation in the lung and airways [7], an observation that fits the concept of a common mucosal immune system, first proposed in 1978 by Bienenstock *et al*. [8]. As mentioned earlier, intestinal helminth infection is well known to protect against allergic airway inflammation in mice, and helminth-microbial interactions were recently demonstrated to play a role in this process [9]. Alterations in airway microbial communities are associated with a number of respiratory diseases [10], thus it would be of great interest to examine whether intestinal helminth infection also alters mucous production within the lung, and if so, whether this could impact local microbial communities and disease development.

Nicola L Harris[1]

[1]*Global Health Institute, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), station 19, 1015 Lausanne, Switzerland*
Correspondence: Nicola L Harris
E-mail: nicola.harris@epfl.ch

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