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Can helminth infection reverse microbial dysbiosis?

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Abstract

There is growing interest in treating inflammatory conditions with helminth infection. Recently, Loukas and colleagues have reported promising results from using experimental hookworm infection to reduce gluten sensitivity in celiac disease patients. Analysis of microbiota samples from the trial is contributing to our understanding of the complexity underlying helminth-microbiota-host relationships.

The concept that parasitic intestinal helminths can be used to treat gastrointestinal diseases was first proposed by Joel Weinstock and his colleagues at the University of Iowa around the turn of the millennia [1]. They then embarked on a series of clinical studies utilizing the pig whipworm *Trichuris suis* to treat inflammatory bowel disease (IBD) patients [1]. The promising results that they reported sparked considerable interest among IBD patients, some biopharmaceutical companies as well as helminthologists, who have long been fascinated by the amazing abilities of helminths to suppress the immune response of their hosts. *Trichuris suis* drew interest from industry, who developed Good Manufacturing Processes (GMP) to produce clinical grade material for FDA regulated clinical trials. At the same time, David Pritchard and colleagues at the University of Nottingham began experimental human infections with the hookworm, *Necator americanus* on healthy volunteers and asthma patients [2].

Investigators in Australia, led by John Croese and Alex Loukas also began to investigate the use of hookworm for the treatment of gastrointestinal diseases, including Crohn's Disease and celiac disease (CeD). In their first randomized double blinded placebo controlled trial for CeD patients, infection with hookworm did not protect against a five day oral wheat challenge equivalent to 16 g of gluten per day [3]. However, they then embarked on a second study with an important modification [4]. This time, after hookworm infection was established, CeD patients were 'tolerized' with gluten microchallenges (escalating from 10 mg), before being challenged with 3 g daily for 2 weeks [4]. This challenge protocol is well established to be toxic to diet managed CeD patients, but the expected pathologies were not observed in the hookworm-infected participants [4]. Unfortunately, this study lacked a

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placebo arm of uninfected CeD patients also tolerized with gluten microchallenges, but nonetheless based on historical data, the results were very promising.

Giacomin and colleagues [5] have now reported what happens to the gut microbiota of these CeD patients as they underwent this experimental hookworm infection and escalating gluten challenge protocol. Over the last few years, our appreciation of how important gut bacteria are to mammalian physiology has increased exponentially and since they occupy the same environmental niche as intestinal helminths, the two must interact in ways that are only beginning to be characterized. Here is a unique set of longitudinal samples that inform us about what happens to developed country individuals when they are infected with hookworm, although this is in the complicated context of gluten challenge in CeD patients. Unfortunately, there is not a matched set of healthy volunteers experimentally infected with hookworm alone to be able to segregate the effects of infection and CeD in the context of gluten challenge. The sequencing depth based on 454 technology is also relatively shallow (fewer reads per sample) compared to Illumina based approaches.

The most interesting observation made by Giacomin *et al.* is that microbial richness was significantly increased in the trial participants during the course of the study [5]. This is notable because reduced microbial diversity is a hallmark of dysbiosis, or dysregulation of bacterial communities, which is well described for numerous inflammatory diseases. Hence, hookworm infection may be having the opposite effect of promoting a more diverse bacterial community in the gut that could be beneficial for intestinal homeostasis. Indeed, we have previously found that indigenous (Orang Asli) communities in peninsular Malaysia who are naturally infected with intestinal helminths harbored increased bacterial species richness compared to uninfected individuals in the same communities [6]. A study of gut microbiota in wild rodents infected with helminths similarly reported that helminths were associated with greater microbial diversity [7]. We had also previously observed that the dysbiosis of juvenile rhesus macaques suffering from chronic idiopathic colitis could be reversed by experimental whipworm (*Trichuris trichiura*) infection [8]. In sum, the evidence that helminths could potentially shift bacterial communities to increase species richness is increasing.

One caveat is that it is unclear from the report how the increased microbial richness compares with otherwise healthy individuals. The effect is certainly not very large [5], as was the case in our study in Malaysia [6]; hence this is likely within the range of normal individuals. The variation in species richness between individuals is still much greater than any increase in richness within an infected individual. Importantly, the significant increase in species richness post hookworm infection was not observed in their first (unsuccessful) clinical trial. Giacomin *et al.* [5] speculated that the hookworms have to establish a chronic infection in the context of inflammatory stimuli (e.g. gluten microchallenge) to have a significant effect on the microbiota.

It is also important to note that other studies have reported no associations between the microbiota and helminth infections [9]. In lab based C57BL/6 mouse experimental infections with *Trichuris muris*, microbial diversity actually decreases during chronic

infection [10]. Hence, the finding of increased microbial richness during helminth infection could still be considered a context dependent phenomenon.

Enthusiasm for *Trichuris suis* ova (TSO) has waned because it has failed to show efficacy in recent randomized placebo-controlled trials and it is no longer under clinical development by biopharmaceutical companies. Human (rather than pig) intestinal helminths that can establish chronic infections may have to be tested for efficacy instead, although (apart from hookworm) GMP processes are not yet established to prepare clinical grade material for use in human trials. As illustrated by the experience of Croese and colleagues [4], careful design coupled with analysis of samples collected during trials may improve the efficacy of the therapeutic potential of helminth infections, as well as improve our basic understanding of helminth-microbiota-host relationships. Clearly helminth infection is not a simple cure-all for inflammatory conditions and careful pairing of the appropriate helminth, dosage, protocol and perhaps subsets of patients (based on genetics or biomarkers) is essential for making progress in this area. Just as we are only beginning to characterize the heterogeneity of microbial dysbiosis phenotypes in human inflammatory diseases, we can only hypothesize that helminths may be able to reverse dysbiosis in specific subsets of patients.

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