David Artis: Fear no worm

As the incidence of inflammatory disease and food allergies increases in the industrialized world, David Artis wonders if something is wrong with the little friends in our guts.

Less than a decade ago, Artis moved from Manchester, UK to Philadelphia to start his own laboratory at the University of Pennsylvania. Early in his career he became fascinated with the relationship between parasitic worms and the mammalian intestines they inhabit. Over millions of years, our immune systems have evolved ways to figure out whether they should attack or ignore parasites and other microbes (1–3). And Artis' experiments in mice have shown how intestinal epithelial cells help to modulate that response (4). Among a number of related projects on inflammation he is currently exploring how we acquire intestinal commensals and how they might one day be used to treat disease (5).

"Having too few worms or other commensals may induce a state of immune-hyper-responsiveness."

KEEPING THE PEACE

What's life like for an intestinal worm?

These are elaborate, multicellular animals that have evolved mechanisms to live in the most inhospitable of places. The intestine is either acidic or alkali, it's always undergoing peristalsis, and worms have to share the gut with 10^{14} bacteria. If you're being anthropomorphic about it, it's probably the last place you would want to inhabit in a mammalian host.

Yet they live there, and isn't there some evidence that we need them, too?

There is an argument to be made that helminth parasites may have evolved as part of our normal commensal flora. In the last couple of years my laboratory has really developed an interest in how commensals may be essential for our metabolism and diet. They may also instruct or influence our immune responsiveness.

How does this relate to the hygiene hypothesis—the idea that getting rid of our inner fauna may cause our immune systems to overreact.

It is possible that our sanitized environment could be a sort of detriment for us. Having too few worms or other commensals may induce a state of immune-hyper-responsiveness. Maybe in our hyper-hygienic world we've lost those microbial-induced immunoregulatory signals. I don't think that's the only influence, but I do think it's a component of a multi-factorial picture.

What makes one person's commensals different from another's?

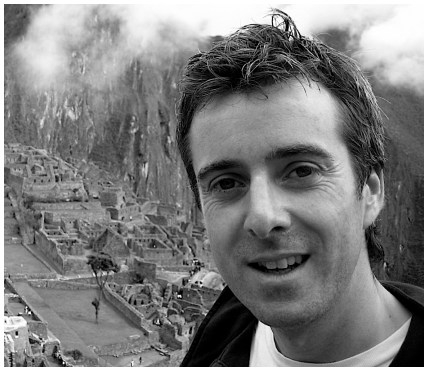
We've discovered some fundamental factors that influence the acquisition and composition of your commensal bacteria. There's quite a lot of acquisition following birth. The other major component appears to be diet. In mice, if you change their diet by very small amounts in terms of the percentage of fat or carbohydrates, it will have a dramatic outcome on the composition of commensal bacteria. It's just as if you put a mish-mash of bacteria in a culture dish rich in glucose versus one rich in fatty acids—different types of bacteria would grow on those different plates. The same thing is true with our intestine.

This could be one link between diet and inflammation. We know that there are epidemiological correlations between diet and disease susceptibilities. And it may be that your diet's influence on commensals plays some role in influencing the function of the immune system.

Do people infected by lots of gut parasites have a lower incidence of inflammatory bowel disorder (IBD) or dietary allergies?

Numerous reports say that individuals with exposure to helminth parasites have fewer allergies and are less prone to inflammatory diseases. Similarly, even in industrialized countries, children who grow up in the countryside are less prone to asthma than children growing up in urban areas.

One argument is that it's because they're rolling around in the dirt in Wisconsin more than they are in New York City. Of course, it's difficult to control for other lifestyle differences between people, but experimentally we know that helminth parasite-derived signals can limit the development of inflammation in mice.



David Artis

In one of your papers, you use the term "declared truce" to describe how cells in the gut tolerate microbes. Who's doing the declaring?

This "truce" is a little paradoxical in that we know there's this huge microbial stimulus in the gut and, at the same time, the gut is one of the most immunologically rich organs in the body. How is it that there isn't constant immunological activation?

Some of the metabolites derived from commensals limit the expression of pro-inflammatory cytokines. And another possibility is that there are discriminatory pathways in the immune system that can tell the difference between a commensal *E.coli* and an enteropathogenic *E.coli*. A fundamental question in mucosal immunology is how that discrimination occurs. Maybe in patients with inflammatory diseases, the cease fire is over. It may be that some dysregulation of commensals results in an imbalance in homeostasis that may allow for the development of pro-inflammatory diseases. It certainly appears to be the case in intestinal inflammation, like inflammatory bowel disease and Crohn's Disease, perhaps in food allergies as well.

Is there a way to treat these diseases by manipulating gut biota?

Text and Interview by Amy Maxmen
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Helminth parasites have already been proposed as treatments for inflammatory diseases. Currently, there are investigators in the US and in the European Union who are exploring clinical trials to use helminth parasites to limit things like IBD.

People willingly invite worms into their gut?
Sure. It's quaintly coined "fear factor" medicine at the moment because it's a little eighteenth century. In clinical trials, they are infecting IBD patients with low doses of *Trichuris* from pigs. And they're seeing an amelioration of their patients' symptoms. I don't think these approaches are FDA-approved yet, so you can't go to your physician and ask for a jar of *Trichuris* eggs. Although you'd be amazed at the number of people that phone me out of the blue asking for exactly that.

No kidding.
No, I'm not kidding. The Internet is an amazing thing. I have individuals from nonscientific backgrounds emailing me questions about papers we've published. It's really empowering for patients, but it's something scientists have to be responsible about.

The real challenge for parasitologists and immunologists is to identify the factors derived from helminth parasites and other commensals, and make recombinant proteins that can be quality-controlled, dosed at appropriate levels, and delivered in tissue-specific ways that may be beneficial. It's fascinating that some of our most promising anti-inflammatory agents are derived from lessons learned from ancient parasites.

HOW GUTS SEE WORMS

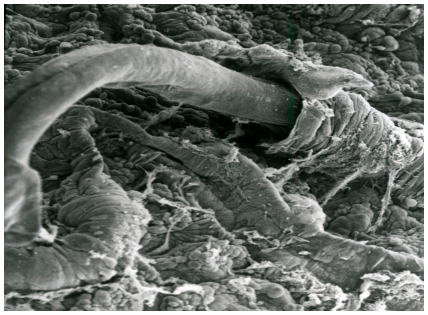
What's something that initially impressed you about parasites?
A couple of inspiring individuals exposed me to parasite biology during my career, one is Keith Vickerman. In the '50s, he was one of the first people to realize that trypanosomes [the parasite behind sleeping sickness] had specialized coats that enabled them to undergo dramatic alterations that allowed them to evade the host immune system. To me, that was a fundamental insight into how the mammalian immune system was a selective evolutionary force on the parasite, and how at the same time, parasites were probably an evolutionary pressure on the immune system.

Do worms from different phyla elicit the same intestinal response?
Generally speaking, the adaptive response that a flatworm [Platyhelminthes] or a roundworm [Nematoda] elicits is a pretty polarized Th2 cytokine response. Having said that, I think the components of the innate immune system that recognize these types of worm infections are probably very different. How the innate immune system differentially recognizes something that provokes a Th2 response versus a more classical proinflammatory response is still a black box.

If you inject a mouse with *C.elegans*, for instance, which is a nonpathogenic, free-living nematode, it will elicit a Th2 response. So there's something preserved structurally, biochemically, or genetically about worms themselves that the immune system has evolved and retained [in order to recognize helminths]. It's some sort of pattern recognition, but we don't know what that is.

TAPEWORM DIETS, DOG KISSES, AND OTHER URBAN LEGENDS

What are the first things nonscientists ask about parasitic worms and other gut biota?
People are intrigued and disgusted in equal measure. Actually, diet and commensal bacteria seem to be in the collective consciousness with all of these ads for probiotic therapies. So people are concerned about their health.



LEW TILNEY AND DAVID ARTIS

A parasitic nematode *Trichuris muris* invades the intestine of a mouse.

Can ingesting tapeworms help dieters lose weight?
No. I think that in Victorian times that was quite popular. As I understand it, however, tapeworms are not an effective way to control weight gain.

How long can a tapeworm live inside you?
Decades.

Can people get heartworms from dogs?
People can get the heartworms that dogs have, but this is very rare and in most cases the larvae of the parasite die before becoming adults. But you can get a lot of other parasites from your dog. I know someone who is testing a hypothesis that people with dogs have different commensal bacteria than people who don't have dogs…which is something that makes you even closer to that beloved family pet.

"There's something inherently attractive about all [worms], even if in the darkest of ways."

Given what you know, do you stay away from raw horsemeat or tripe?
No. If anything, I'm probably less cautious given what I know about parasite systems. I love awesome food and I'm very adventurous.

So you enjoy sushi too?
Irony of ironies, I recently developed a shellfish allergy. Now I'm off lobster, I'm off shellfish of all kinds. Another reason why we need to figure out how the intestinal immune system really works.

In your opinion, which worm is ugliest?
There's something inherently attractive about all of them, even if in the darkest of ways.

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