Helminths and harmony

Mounting evidence suggests that helminths help regulate mucosal inflammation

The frequency of Crohn’s disease (CD) has increased substantially over the last 50 years. It is most prevalent in highly industrialised temperate regions. CD and ulcerative colitis (UC) are rare in less developed countries. This suggests that critical environmental factors affect the worldwide distribution of inflammatory bowel disease (IBD). The “IBD hygiene hypothesis” states that raising children in extremely hygienic environments negatively affects immune development which predisposes them to immunological diseases such as IBD. It is also postulated that the modern day lack of exposure to helminths due to our hygienic practices is an important environmental factor contributing to IBD. Until modern times, nearly all children and most adults harboured intestinal helminths. Helminths and the immune system of Homo sapiens co-evolved in close proximity over many 1000s of years. Helminths regulate their host’s immune system and prevent excessive inflammatory responses, which could underlie the mechanism of protection. Moreels and colleagues now lend further support for this hypothesis by reporting in this issue of Gut that infection with the helminth Schistosoma mansoni protects rats from trinitrobenzene sulphonic acid (TNBS) induced colitis [see page 99].

Approximately two million people in the USA and Europe have CD or UC, which usually begins during the second to third decade of life. IBD probably results from an inappropriate vigorous immune response to contents of the intestinal lumen. Evidence supporting this contention includes the effectiveness of immune suppressants at controlling the disease and experimental data derived from mice prone to IBD because of defects in immune regulation. In most of these murine models, the inflammation is driven by T helper 1 (Th1) cytokines and by substances in the intestinal lumen.

The Case for Genetics in IBD

UC and CD are disorders of complex derivation caused by the interplay of poorly defined environmental exposures and, at least in some instances, the inheritance of susceptibility genes. Often cited as evidence for genetic predisposition for IBD is the higher than expected occurrence of IBD in family members of patients with this condition and the high prevalence of the disease in Jewish populations of Western countries. Yet IBD is much less prevalent in the Jewish population of Israel with similar ethnic origin. Twin studies provide evidence of genetic predisposition for at least CD. A genetic defect in CARD15/NOD2, an intracellular protein that senses the bacterial product muramyldipeptide, leaves some people more susceptible to CD. Various other genetic alterations are proposed as IBD risk factors. Yet genetic predispositions do not explain the rapidly increasing incidence of disease.

The Case for Environment in IBD

There certainly are important environmental factors that affect the regional frequency of these diseases worldwide. Smoking is a risk factor for CD. Appendectomy for appendicitis under the age of 20 years decreases the incidence of UC. The risk for IBD varies according to geography and occupation. There is a North-South gradient of IBD in the USA and Europe, with IBD being more common in people raised in the North. US military veterans are at low risk for this disease if they were raised in the rural South, were prisoners of war, or served in combat in tropical regions. People with blue collar jobs exposing them to dirt and physical exercise are less prone to IBD. IBD is more common in urban versus rural areas. CD and UC are rare in South America, Central America, Africa and Asia with the White population of South Africa being the exception. Migration studies show that children of people from regions of low CD or UC frequency acquire a greater risk for IBD if they move to areas of high disease prevalence.

The Habitat of Helminths

Helminths are parasitic animals (worms) which, depending on species, live in locations such as the intestinal lumen, blood stream, or muscles of the host. These organisms colonise more than one third of the world population. Helminth colonisation is most common in children living in warm climates and subject to poor sanitation. The infective forms of these organisms are spread through contact with contaminated soil, food, or water. Before the 1940s, many children and adults in the USA carried helminths. Worm carriage was particularly common in rural areas of the South and in indigent populations of major cities. In the USA and Europe, helminthic colonisation has steadily declined. They are found in recent immigrants from less developed countries and in economically disadvantaged populations living in underserved regions of the USA such as some Indian reservations. These groups are at low risk for IBD. There is an inverse relationship between the frequency of worm colonisation and the prevalence of CD. There is more CD in urban versus rural populations, in northern versus southern regions of the USA and Europe, and developed versus less developed countries. The opposite is true for worm carriage.

Immune Regulation and IBD

Inflammation can generate various regulatory agents such as interleukin (IL)-10, transforming growth factor β (TGF-β), IL-4, IL-13, and prostaglandin E2 (PGE2) that help modulate immune responses and limit tissue injury at...
mucosal surfaces. IL-10 is a mediator with strong immunomodulatory actions. For instance, IL-10 inhibits macrophage and dendritic cell function and suppresses the production of important proinflammatory cytokines such as tumour necrosis factor α, IL-12, IL-1, nitric oxide, and various chemokines. Mice with a disruption of the IL-10 gene develop severe colitis showing the importance of IL-10 for mucosal immune homeostasis. TGF-β mediates highly pleiotropic immunoregulatory functions, and transgenic mice with a T cell selective blockade in TGF-β signalling develop colitis. PGE₂ is another well known factor that influences T helper 1 cell/T helper 2 cell (Th1/Th2) activation. It preferentially down-regulates IL-12 receptor expression, inhibits the differentiation of Th1 cells, blocks IL-12 production from antigen presenting cells, and more. Mice deficient in the PGE receptor EP4 are more subject to dextran sodium sulphate induced colitis suggesting that PGE₂ is important for mucosal protection.

Regulatory T cells can induce peripheral tolerance and limit mucosal reactivity. In various animal models, several regulatory T cell phenotypes have been reported. Some express CD4 while others CD8. In some systems, they are distinguished through differential expression of surface molecules, such as CD25, CD45RB, and CTLA-4. This pattern of cell surface protein expression suggests that they may be in a primed effector or memory state. These regulatory cells may mediate some of their effects through production of IL-10 and TGF-β. Described is an anergic regulatory T cell (Tr1) that produces high levels of IL-10 and TFG-β. Another cell called Th3 suppresses induction of experimental autoimmune encephalomyelitis primarily through production of TGF-β. Still others are not dependent on soluble IL-10 or TGF-β but instead express on their surface latency associated peptide, which is the amino terminal domain of the TGF-β precursor peptide. These cells can induce suppression via cell-cell contact.

Rag mice reconstituted with CD4⁺, CD45⁺ high T cells can develop severe colitis, which can be prevented by cotransfer of CD4⁺, CD45⁻ low T cells. TGF-β and IL-10 are required for protection, suggesting a role for these cytokines in the regulatory process. These studies suggest that regulatory T cells are also important in preventing IBD.

THERE IS AN IMMUNOLOGICAL BASIS FOR HELMINTHIC PROTECTION

Populations experiencing deworming also undergo other socioeconomic alterations that could affect risk for disease. These include changes in diet, housing, and sanitation among others. Yet there is an immunological basis to suspect deworming as a risk factor. People bearing helminths display dampened immune responses to unrelated concurrent antigenic exposures. These changes in immune responsiveness can persist long after elimination of these helminthic exposures. Mice colonised with helminths have blunted Th1 responses. Helminths promote Th2 responses associated with production of IL-4 and IL-13. IL-4 helps impede Th1 cell differentiation. Thus induction of IL-4 could underlie the alternations seen in host immunity. However, the mechanism of protection is not simply “Th2 suppresses Th1” as helminths also appear to protect the host from aberrant Th2 diseases such as asthma and food allergy. Interactions between these parasites and their hosts are complex and multifaceted as would be expected for such a successful co-evolutionary process that leads to “peaceful” coexistence. Helminths not only trigger Th2 responses, which help to limit worm number in the host, they also promote production of powerful immunomodulatory molecules such as IL-10 and TGF-β, and “regulatory” T cells.

HELMINTHS PROTECT

There is now substantial human epidemiological data and several animal studies supporting the hypothesis that helminths protect the host from immunological disease. For instance, people colonised with helminths have high serum levels of IL-10, which may protect them from atopy. Helminths protect mice and rats from TNBS induced colitis, experimental autoimmune encephalomyelitis, and other diseases of immunity most likely in part through induction of IL-4. They also reverse ongoing colitis in IL-10KO animals via induction of regulatory T cells (manuscript submitted). Thus natural exposure to helminths may guard people from developing IBD and other immunological diseases through induction of IL-4, IL-10, TGF-β, regulatory T cells, or perhaps by other means. In a preliminary and uncontrolled trial, we have demonstrated that oral administration of *Trichuris suis* ova to patients with active ulcerative colitis or Crohn’s disease is safe and possibly effective. Controlled clinical trials in both disorders are also being conducted and are nearing completion using a similar approach.

SUMMARY

Environmental factors affect the worldwide distribution of IBD. Supported by a growing volume of both epidemiological and experimental data, it appears plausible that exposure to helminths is a factor that protects people from IBD. As reported by Moreels and colleagues in this issue of *Gut*, helminths protect mice from experimental colitis. Many factors help initiate and maintain immunological diseases. Targeting one or just a few cytokines in most cases may not prove sufficient to permanently suppress disease activity. Helminths have broad immunoregulatory properties that evolved as part of the successful host-parasite interaction.
Studying helminths and how they alter the host's immune response could lead to new and highly effective therapeutic strategies for human IBD. Such studies may also provide new insight into the pathogenesis of CD, UC, and other emerging immunological diseases.

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