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A role for IL-22 in the relationship between intestinal helminths, gut microbiota and mucosal immunity

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Abstract

The intestinal tract is home to nematodes as well as commensal bacteria (microbiota), which have coevolved with the mammalian host. The mucosal immune system must balance between an appropriate response to dangerous pathogens and an inappropriate response to commensal microbiota that may breach the epithelial barrier, in order to maintain intestinal homeostasis. IL-22 has been shown to play a critical role in maintaining barrier homeostasis against intestinal pathogens and commensal bacteria. Here we review the advances in our understanding of the role of IL-22 in helminth infections, as well as in response to commensal and pathogenic bacteria of the intestinal tract. We then consider the relationship between intestinal helminths and gut microbiota and hypothesize that this relationship may explain how helminths may improve symptoms of inflammatory bowel diseases. We propose that by inducing an immune response that includes IL-22, intestinal helminths may enhance the mucosal barrier function of the intestinal epithelium. This may restore the mucosal microbiota populations from dysbiosis associated with colitis and improve intestinal homeostasis.

Keywords

Helminth therapy; Microbiota; IL-22; Inflammatory bowel diseases; Mucosal Immunity

1. Introduction

Our mucosal immune system plays an essential role in maintaining intestinal homeostasis with commensal bacteria and other organisms. Gastrointestinal helminths have coevolved with the mammalian immune system similarly to the gut microbiota. Just as commensal bacteria can shape mammalian immunity, helminths exert immune regulatory effects on their mammalian hosts. However, the relationship between helminths and gut microbiota is still unclear. This relationship becomes particularly important in the context of inflammatory bowel disease (IBD), which is generally considered to result from an aberrant response of the mucosal immune response against gut microbiota and is associated with microbial dysbiosis. Treatment with helminths is now in clinical trials for IBD but the mechanism by which they may improve the symptoms of IBD is not well understood. Recent evidence has suggested a role for the cytokine, IL-22, during helminth infection and in maintaining

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mucosal barrier function. IL-22 may therefore play an important role in the relationship between the mammalian immune response, gut microbiota and helminth infections.

2. IL-22 regulates barrier immunity and intestinal injury

IL-22 is a member of the IL-10 cytokine family which also includes IL-19, IL-20, IL-24 and IL-26 (Pestka et al., 2004). IL-22 signals through a heterodimeric receptor complex consisting of two subunits, IL-22R1 and IL-10R2 (Witte et al., 2010; Sonnenberg et al., 2011; Zenewicz and Flavell, 2011; Mizoguchi, 2012). While IL-10R2 is ubiquitously expressed on virtually all cell types, IL-22R1 expression is limited to the surfaces of non-hematopoietic cells such as epithelial cells, hepatocytes and keratinocytes (Witte et al., 2010; Sonnenberg et al., 2011; Zenewicz and Flavell, 2011; Mizoguchi, 2012). This restricted expression of IL-22R1 on non-hematopoietic cells thus allows IL-22 to specifically target innate cell populations within such tissues as the gastrointestinal tract, liver, skin, kidneys and lungs (Tachiiri et al., 2003; Wolk et al., 2004).

IL-22 can be produced by a wide variety of innate and adaptive immune cells including CD4+ T cells, most notably T_H17 and T_H22 cells, CD8+ T cells, natural killer (NK) cells, γδ T cells, lymphoid tissue inducer (LTi) cells and innate lymphoid cells (ILCs) (Wolk et al., 2010; Zenewicz and Flavell, 2011). Upon binding to the IL-22R1 and IL-10R2 receptor complex, IL-22 produced from these cells activates the receptor-associated Janus kinases, Jak1 and Tyk2, resulting in tyrosine phosphorylation of STAT3 and to a lesser extent STAT1 and STAT5 (Nagalakshmi et al., 2004; Pestka et al., 2004). This in turn allows IL-22 to induce various tissue-specific genes including those encoding proteins involved in antimicrobial defense, cellular differentiation and mucin production (Wolk et al., 2006; Zenewicz and Flavell, 2011).

These effects of IL-22 are particularly important in regulating inflammatory responses within the intestine through the production of antimicrobial peptides, the enhancement of epithelial regeneration and the regulation of wound repair. Recent studies have thus looked at possible protective roles for IL-22 in IBD using several mouse models of colitis induced by dextran sulfate sodium (DSS) as well as T_H1- and T_H2-mediated colitis. In DSS-induced colitis, DSS given in the drinking water of mice causes disruption of the intestinal epithelial layer, leading to inflammation and colitis within 1 week (Strober et al., 2002). IL-22 knockout mice or wild-type (WT) mice treated with neutralizing anti-IL-22 antibodies exhibit increased epithelial damage and inflammation in the colon, more severe weight loss and impaired recovery from DSS-induced acute colonic injury (Sugimoto et al., 2008; Zenewicz et al., 2008; Pickert et al., 2009; Neufert et al., 2010).

In a T_H1 cytokine-mediated model of colitis, IL-22 expression by CD4+ T cells was shown to be critical for limiting disease severity (Zenewicz et al., 2008). Sugimoto et al. (2008) used a model of T_H2-mediated chronic colitis and found that the severity of colitis was attenuated in the colons of mice receiving supplemental IL-22. IL-22 gene delivery mediated STAT3 activation specifically within colonic epithelial cells and enhanced mucus production and goblet cell restitution, thus reinforcing the mucus barrier function within the intestine. These mouse models of IBD indicate that IL-22 plays a protective role in IBD through its ability to enhance innate epithelial defenses and mucosal barrier integrity.

3. IL-22 responses to bacterial pathogens and the gut microbiota

In addition to maintaining the mucosal barrier function in the gastrointestinal tract, IL-22 induces genes that encode proteins involved in antimicrobial defense, thus suggesting a role for IL-22 in the innate immunity against extracellular bacteria. IL-22 has been shown to regulate the expression of antimicrobial peptides such as the β -defensin family proteins (β -

defensins BD2 and BD3), S100 family proteins (S100A7, S100A8 and S100A9), the Reg family proteins (RegIII α, RegIII β and RegIIIγ) and lipocalin-2 (Aggarwal et al., 2001; Wolk et al., 2004, 2006; Zheng et al., 2008). IL-22 serves as a protective and proinflammatory mediator in the host's inflammatory response against intestinal bacterial infections; however, this seems to be dependent upon the specific type of pathogen.

Zheng et al. (2008) showed that IL-22 was essential for host protective immunity against infection with the Gram-negative enteric bacteria, *Citrobacter rodentium*, as infected IL-22 knockout mice had increased bacterial burden, intestinal epithelial damage and mortality due to a defective induction of the Reg family proteins. IL-22 also plays a protective role in systemic infection with *Salmonella enterica*. IL-23-dependent IL-22 was required for both liver cell survival and pathogen defense against systemic *Salmonella* infection in mice, especially when coupled with a diminished production of IL-12 (Schulz et al., 2008). In addition to protecting against intestinal bacterial pathogens, IL-22 serves a protective role in intestinal fungal infections with *Candida albicans*. IL-22 knockout mice infected with *C. albicans* hyphae intragastrically had an increased fungal burden and showed signs of mucosal hyperplasia in the stomach and colon compared with infected WT mice (De Luca et al., 2010). Hence IL-22 serves as a protective mediator in regulating inflammatory responses and mucosal barrier integrity in a variety of intestinal infections.

However, IL-22 seems to promote intestinal inflammation after oral infection with *Toxoplasma gondii* (Munoz et al., 2009; Wilson et al., 2010). Infected IL-22 knockout mice and mice whose IL-22 was neutralized with an anti-IL-22 monoclonal antibody developed significantly less intestinal pathology and had reduced weight loss and mortality, despite having similar parasite burdens to those of infected WT mice. Perhaps the strongly biased T_H1 cytokine environment of *T. gondii* infection may explain this difference.

As noted above, IL-22 is produced by T_H17 cells which are regulated by the intestinal microbiota. In contrast to IL-17, which induces neutrophil responses at inflammatory sites (Korn et al., 2009), IL-22 may be more important in tissue repair during mucosal immunity. Regardless, there is a close relationship between the gut microbiota and IL-22 producing cells. Most notably, it was recently shown that IL-22 producing innate lymphocytes were important in preventing the systemic dissemination of a commensal bacteria that could cause systemic inflammation (Sonnenberg et al., 2012). When Sonnenberg et al. (2012) treated Rag1−/ − mice with a neutralizing antibody to IL-22, bacteria could be cultured from the spleen and the liver of these mice, together with signs of systemic inflammation and increased levels of lipopolysaccharide (LPS). The disseminating commensal bacteria was then identified to be *Alcaligenes* sp. Hence, IL-22 plays an important role in the mucosal firewall separating our intestinal tract from our gut microbiota, which would be consistent with a protective role against IBD. Under homeostatic conditions, live bacteria are sampled by dendritic cells that carry them to the mesenteric lymph nodes, but do not disseminate systemically to secondary lymphoid tissues (Hooper, 2012) indicating that a mesenteric firewall may act in concert with a mucosal firewall to compartmentalize gut bacteria.

4. IL-22 during helminth infection and treatment of intestinal diseases

IL-22 has been shown to be upregulated within the gastrointestinal tract following infection with certain intestinal nematodes. Broadhurst et al. (2010) described a case study of an individual who was self-infected with the whipworm, *Trichuris trichuria*, in order to treat his symptoms of ulcerative colitis. Infection with *T. trichuria* ameliorated the patient's disease activity and this effect was associated with an increased expression of IL-22 and T_H2 cytokines within the gastrointestinal tract. It was hypothesized that the activation of a T_H2 and IL-22 response by *T. trichuria* allowed for the expulsion of this parasite through the

increased turnover of intestinal epithelial cells, mucus hypersecretion and goblet cell hyperplasia (Finkelman et al., 2004; Artis and Grencis, 2008; Sonnenberg et al., 2011).

Additional evidence that IL-22 is induced in the human intestinal mucosa by helminth infection comes from celiac disease trials with the hookworm, *Necator americanus*, in Queensland, Australia (Daveson, 2011; McSorley, 2011; Gaze, 2012). McSorley et al. (2011) showed that intestinal biopsies from patients infected with *N. americanus* larvae showed upregulation of IL-22 mRNA levels after restimulation with *N. americanus* excretory/secretory proteins (NaES) in vitro. Intestinal biopsies taken prior to hookworm infection did not show increased IL-22 expression upon NaES stimulation. However, the mechanisms underlying these IL-22 responses have not been further examined in clinical studies. Thus, even though helminth infections have the ability to induce IL-22 producing cells in humans, there is still no direct evidence that IL-22 is functionally important during helminth infection and a putative role for IL-22 in humans is based on correlative evidence only.

A more direct causal role for IL-22 in helminth induced immune regulation would have to be determined in mouse models. In mouse models however, whereby the activity of IL-22 can be eliminated through the use of IL-22 deficient animals and through neutralizing antibodies to IL-22, infection with the tissue dwelling helminth, *Schistosoma mansoni*, led to a similar phenotype as control animals (Wilson et al., 2010). There were similar worm and tissue egg burdens in IL-22−/− mice as that of infected WT mice. Both groups also developed nearly identical hepatic and intestinal granulomas and succumbed to similar weight loss and survival rates, suggesting that IL-22 played little to no role in the pathogenesis of schistosomiasis. While blocking IL-22 has no effect on schistosome pathogenesis, helminth infections that colonize the gastrointestinal tract have not been investigated using these mouse models.

5. Gut microbiota and inflammatory bowel diseases

The IBD, Crohn's disease and ulcerative colitis, are thought to be driven by an abnormal inflammatory response to the intestinal microbiota (Kaser et al., 2010). However, since dysbiosis of the microbiota is also a feature of IBD, it is quite difficult to determine whether there is an inflammatory response to abnormal bacteria, or if an abnormal inflammatory response is altering the microbial communities. As an environmental factor, gut microbiota could be linked to genetic predispositions that alter the interactions between our microbial communities and ourselves. The first major susceptibility gene for Crohn's disease is a receptor for bacterial peptidoglycan, known as NOD2 (or CARD15) (Hugot et al., 2001; Ogura et al., 2001) and another susceptibility gene, ATG16L1, is critical for autophagy (Hampe et al., 2007). The intestinal microbiota may also lead to a dysregulation of intestinal lymphoid cell subsets such as T_H17 cells and innate lymphocytes which are important in regulating mucosal immunity.

While there have been numerous studies investigating stool samples and mucosa associated bacteria in IBD patients, there has been a lack of consensus and reproducibility between studies (Sun et al., 2011). While broad changes, such as the expansion of the *Proteobacteria* phylum in IBD patients, have been observed (Mukhopadhya et al., 2012), more specific associations that are reproducibly identified have been few. While the identification of causative microbiota species that can trigger IBD is underway, a generalizable theme that has emerged to date is that the diversity of microbial communities is significantly reduced in IBD (Cho and Blaser, 2012). There have also been repeated observations that specific bacterial taxa are depleted in IBD patients, most notably that *Faecalibacterium prausnitzii*, a

member of the *Lachnospiraceae* family, is reduced in the intestinal mucosa (Sun et al., 2011).

6. Effects of helminth infections on the gut microbiota

While we now have an in-depth understanding of the healthy human microbiota from individuals of the developed world, the fecal microbial communities of residents of developing countries are extremely different to residents from the developed world (De Filippo et al., 2010; Yatsunenko et al., 2012). The genus *Prevotella* was found to be more common in the fecal microbiota of children in developing countries compared with Europe and the USA (De Filippo et al., 2010). Notably, the helminth infection status of the individuals sampled in the developing countries was not discussed in these studies. While the assumption is that diet contributes most significantly to differences between the developing and developed worlds, it is conceivable that helminth infections may also have a substantial impact on the human microbiome. There is certainly evidence from animal studies that helminths can alter the gut microbiota.

In mice the nematode parasite, *Heligmosomoides polygyrus,* was found to alter gut microbiota of healthy mice (Walk et al., 2010). *Heligmosomoides polygyrus* typically establishes a chronic infection in the intestinal lumen during primary infection (Anthony et al., 2007), which has been shown to inhibit colitis (Elliott et al., 2004; Hang et al., 2010). Notably, members of the *Lactobacillaceae* family were increased after infection in two independent experiments (Walk et al., 2010). Interestingly, early experiments with germ-free mice had found that fewer adult worms were recovered from these mice, which was associated with increased eosinophilia, granulomas and thickening of the small intestinal wall (Wescott, 1968). It is possible that commensal bacteria help to reduce the inflammatory response against the worms, or that *H. polygyrus* requires commensal bacteria to develop appropriately. Another example of such a synergistic relationship was shown recently for another nematode, *Trichuris muris*, which utilizes the cecal microbiota to provide the right environmental cues for it to remove the plugs from its ova and enable hatching and exit of the larvae (Hayes et al., 2010). Whether or not *T. muris* also alters the intestinal microbiota to promote expansion of bacterial taxa that can enable hatching and in order to promote mating opportunities will be interesting to determine.

Trichuris suis ova (TSO) have been used in clinical trials to treat IBD patients (Elliott and Weinstock, 2011; Wolff et al., 2012). While the effects of TSO on the human intestinal microbiota has yet to be characterized, a recent study investigated the effects of *T. suis* infection on the intestinal microbiota of pigs (Li et al., 2012) and another study investigated the relationship between the mucosal immune response, worm burden and alterations in microbial compositions (Wu et al., 2012). *Mucispirillum* bacteria, which colonizes mucus, were substantially increased in infected animals (Li et al., 2012). Interestingly, shotgun sequencing indicated that *T. suis* infection reduces carbohydrate metabolism, coinciding with reductions in *Ruminococcus* bacterium that are cellulolytic (Li et al., 2012). Pigs analyzed at a later time point (53 days) also had reduced *Ruminococcus* (and *Fibrobacter*) (Wu et al., 2012). At this time point, some pigs were cleared of adult worms, whereas others were still colonized, enabling the comparison of infected pigs that retained worms with pigs that had cleared worms (Wu et al., 2012). The presence of a heavy parasite burden was associated with increased expression of inflammatory genes, *arg1, cxcr2, c3ar1, il6, muc5ac* and *ptgs2*, although significant changes in the microbiota occurred regardless of worm status (Wu et al., 2012). It was suggested that persistent changes of the microbiota occurred from the initial infection (Wu et al., 2012). Of note, *Campylobacter* was much more common in worm bearing pigs, consistent with previous studies showing that *T. suis* is associated with exacerbation of campylobacteriosis (Mansfield et al., 2003). The effects of a nematode

parasite, *Ostertagia ostertagi*, on cattle has also been investigated but in that case infection led to minimal changes to the microbiota (Li et al., 2011). However, this parasite infects the abomasum, which has a very low pH environment compared with the colon and it is possible that the abomasal microbiota are less sensitive to the mucosal immune responses elicited by these helminths. The assumption here would be that the mucosal immune responses to helminth infections are responsible for these alterations of the microbiota, which has still not been clearly demonstrated.

7. Treatment of autoimmune diseases through acute versus chronic helminth infections

Helminth infections generally trigger a T_H2 type immune response, which can be protective in terms of parasite expulsion (Anthony et al., 2007; Patel et al., 2009) as well as protective against tissue damage to the host (Allen and Wynn, 2011). However, many helminths are able to establish persistent and chronic infections in their hosts and evade expulsion, in which case they establish an immune regulatory network that reduces inflammatory damage to both the host and parasite (van Riet et al., 2007; Taylor et al., 2012). This immune regulatory network has been suggested to be a major mechanism acting in the context of a therapeutic helminth infection; however it should only be established during chronic infection and not acute infection. Nonetheless, acute infections could also lead to long lasting effects such as persistent alterations in the microbiota (Wu et al., 2012). A detailed characterization of the glycoconjugate components during acute and chronic *T. muris* infection revealed a striking increase in thickness of the glycocalyx, especially during acute infection (Hasnain et al., 2011). This likely has profound effects on the mucosa-associated microbiota, which has yet to be investigated. It is therefore conceivable that repeated acute infections might also lead to the establishment of a microbiota associated immune regulatory network similar to a chronic infection.

This distinction between the effects of acute versus chronic infection has implications for the utilization of TSO as a therapeutic agent. The advantage of not infecting human subjects with *T. suis* and establishing patency also means that chronic infection is never established. While TSO has been shown to be efficacious in the treatment of patients with IBD, the mechanism of action is still unclear. The large doses (2,500 eggs) typically given to patients in clinical trials should elicit an acute response that is generally repeated every 2 weeks. While a T_H2 response is clearly elicited in terms of an increased eosinophilia in the blood (Bager et al., 2010; Fleming et al., 2011), there is less evidence for increased numbers of CD4+Foxp3+ regulatory T cells (Fleming et al., 2011). Nonetheless, systemic effects of TSO were implicated in a small study showing that in multiple sclerosis patients, there is a decrease in the number of magnetic resonance imaging (MRI)-detected lesions after 3 months of treatment, followed by an increase in lesions 2 months after treatment had ended (Fleming et al., 2011). This indicates that a protective immune regulatory network may be established despite the lack of a chronic infection. Since TSO is given every 2 weeks, the repeated infections may be equivalent to a chronic infection in terms of establishing an immune regulatory network. It will be interesting to determine in the future whether long term TSO treated patients will mimic the effects of chronic infection in endemic populations that have a well characterized depressed immune reactivity to parasite antigens in peripheral T cell responses.

Several other clinical trials are now under way for a number of clinical indications that should inform whether the effects of TSO will be limited to the intestinal tract or may influence multiple other organ systems (Jouvin and Kinet, 2012; Wolff et al., 2012). One strong possibility could be that TSO may have different immunological effects on different people, just as there is a tremendous diversity of parasite burdens (and associated

pathologies) in an endemic population that is heavily exposed to helminth infections (Hotez et al., 2008). Different people will also have very different microbial communities. The identification of biomarkers that provide indicators to the responsiveness of individuals to helminth treatment or infections would be a powerful tool to target TSO treatment to those most likely to respond, as well as to identify individuals in an endemic community that would be most at risk for developing severe pathologies from a heavy parasite burden.

8. Could protective immunity triggered by intestinal helminths treat colitis by reversing dysbiosis of the gut microbiota?

We recently proposed a model whereby *Trichuris* infection/treatment activates T_H2 responses and IL-22 production, which could then alter the intestinal epithelium, goblet cells and mucus layer. This could in turn change the composition of the mucosal microbiota, leading to protection against IBD (Wolff et al., 2012). In support of this model, we have recent data (Broadhurst, et al., In Press) from macaques suffering from idiopathic colitis. By characterizing the mucosal microbiota in these monkeys, we found that there was reduced diversity and an increased proportion of bacteria from the phyla *Cyanobacteria* and *Proteobacteria*, consistent with IBD patients. After infection with *T. trichiura*, the diversity of the mucosal microbiota was restored and microbial communities were more similar to control unaffected animals. We are currently embarking on an interventional trial on ulcerative colitis patients to determine whether this hypothesis will be supported by data from human subjects.

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Highlights

- IL-22 helps maintain barrier homeostasis against intestinal pathogens and commensal bacteria.
- The role of IL-22 in helminth infections and in response to commensal and pathogenic bacteria is reviewed.
- The relationship between intestinal helminths, gut microbiota and inflammatory bowel diseases is explored.
- IL-22 induced by helminths may enhance mucosal barrier function and restore the microbiota populations from dysbiosis.

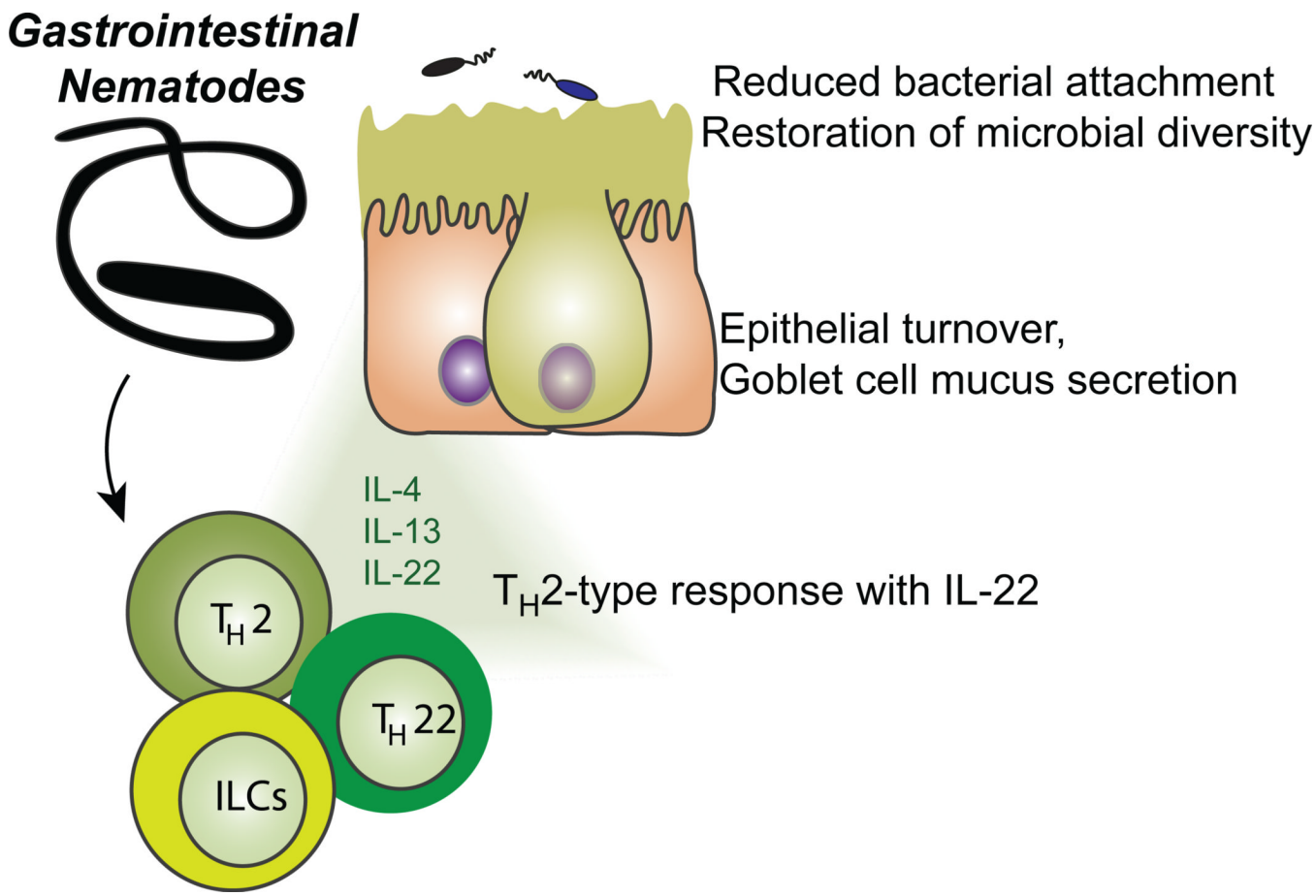

Fig. 1.

A model for gastrointestinal helminth infection stimulating the production of IL-22 by innate lymphoid cells (ILCs) and T_H22 cells, in combination with the T_H2 cytokines, IL-4 and IL-13, which will stimulate the increased turnover and proliferation of intestinal epithelial cells as well as mucus production by goblet cells. This will reduce the attachment of bacteria to the epithelial cells, especially from the phylum *Proteobacteria*, and restore the microbial community diversity that was reduced as a result of dysbiosis during intestinal inflammation.