Nematode modulation of inflammatory bowel disease

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Abstract Inflammatory bowel disease (IBD) is a chronic disease arising due to a culmination of genetic, environmental, and lifestyle-associated factors and resulting in an excessive pro-inflammatory response to bacterial populations in the gastrointestinal tract. The prevalence of IBD in developing nations is relatively low, and it has been proposed that this is directly correlated with a high incidence of helminth infections in these areas. Gastrointestinal nematodes are the most prevalent parasitic worms, and they efficiently modulate the immune system of their hosts in order to establish chronic infections. Thus, they may be capable of suppressing unrelated inflammation in disorders such as IBD. This review describes how nematodes, or their products, suppress innate and adaptive pro-inflammatory immune responses and how the mechanisms involved in the induction of anti-nematode responses regulate colitis in experimental models and clinical trials with IBD patients. We also discuss how refinement of nematode-derived therapies should ultimately result in the development of potent new therapeutics of clinical inflammatory disorders.

Keywords Inflammatory bowel disease · Crohn’s disease · Immune modulation · Gastrointestinal nematodes · Nematode therapy

Abbreviations

AAM Alternatively activated macrophage
CD Crohn’s disease
DC Dendritic cell
DSS Dextran sodium sulfate
DNBS Dinitrobenzene sulfonic acid
IBD Inflammatory bowel disease
IFN Interferon
ES Excretory/secretory
Foxp3 Forkhead box P3
IL Interleukin
mLN Mesenteric lymph node
MPO Myeloperoxidase
RELM Resistin-like molecule
TGF Transforming growth factor
Th T helper cell
TLR Toll-like receptor
TNBS Trinitrobenzenesulfonic acid
TNF Tumor necrosis factor
Treg Regulatory T cell
TSLP Thymic stromal lymphopoietin
UC Ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that manifests in a dysregulated mucosal immune response against intestinal bacteria. Human IBD can be classified into two main characteristic forms: ulcerative colitis (UC) and Crohn’s disease (CD). UC generally involves T helper cell type 2 (Th2) and Th17-driven inflammation, leading to superficial ulceration of the...
colon. CD is characterized by Th1-type-driven inflammation that leads to isolated, often transmural lesions and may involve the entire gastrointestinal tract (Xavier and Podolsky 2007). IBD patients show relapsing and remitting disease that is often lifelong.

The pathogenesis of IBD still remains incompletely understood, but the complex etiology involves multiple genetic, immunological, and environmental factors. The intestinal microbiota is central for the initiation of IBD development. Pathogenic or commensal bacteria trigger microbial sensing systems, which initiate pro-inflammatory responses by innate cells, such as dendritic cells and macrophages producing interleukin (IL)-12/23, tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, reactive oxygen species, and nitric oxide which leads to disrupted epithelial barrier function in susceptible individuals. The following activation of the adaptive immune system leads to the strong production of inflammatory cytokines (interferon gamma (IFN-γ), TNF-α, and IL-17A) by T helper (Th) cells, which constitute the dominant force driving chronic inflammation in IBD patients (Xavier and Podolsky 2007). Genetic inheritance is a strong component of IBD development; roughly 100 gene loci are currently linked to IBD susceptibility (Anderson et al. 2011), and up to a 20-fold increased risk of developing CD has been reported if a first-degree relative is already afflicted. Predisposing polymorphisms linked to IBD development have been found in genes commonly associated with immune reactions to the intestinal flora and gut homeostasis. IBD-associated polymorphisms affect pro-inflammatory and regulatory cytokines (e.g., TNF, IFNG, and IL10), their receptors (e.g., IL23R and IL1R2) as well as signaling pathways (e.g., SMAD3) and antigen presentation molecules or epithelial innate defense factors (van Heel et al. 2002; Anderson et al. 2011; Duerr et al. 2006; Franke et al. 2010). Finally, lifestyle-associated factors like diets rich in fat and animal protein as well as smoking increase the risk of developing IBD (Hou et al. 2011).

The prevalence of IBD, allergies, and autoimmune disorders is increased in industrialized nations in comparison to developing countries. This correlation has been explained by the so-called “hygiene hypothesis,” which suggests that the decreased exposure to previously common infections that have subsequently been reduced as a result of increased hygiene in the western world may result in increased incidence of autoimmune and inflammatory disorders (Strachan 1989). In line with this concept, parasitic worm infections are efficiently controlled by antihelminthic drugs and hygiene practices in developed countries, and their eradication coincides with an increase in the development of immune disorders, including IBD (Elliott et al. 2000). The vertebrate immune system has coevolved under constant attack from parasitic helminths, leading to a balance between host protective inflammatory mechanisms controlling worm infections and immune modulation conducted by the parasites (Fumagalli et al. 2009; Maizels et al. 2004). The immune system of individuals living in an environment lacking these parasites may be insufficiently trained and modified and thus develop aberrant immune reactions to common antigens or commensal bacteria. Experimental infections with helminths or treatment with immunomodulatory worm-derived components has shown that helminths can efficiently suppress unrelated immune reactivity, including colitis. While current anti-inflammatory and immunosuppressive IBD therapies may induce and maintain remission, not all patients respond to such therapies and no long-term curative drug therapy has been developed to date. Thus, studies in mouse models and human trials with IBD patients showing preventive and therapeutic effects of helminths have generated substantial interest. For the purpose of this review, we will focus on anti-colitic effects of gastrointestinal nematodes, a diverse phylum with a large body of research regarding modulation of the host’s immune response.

Immune modulation by nematodes: the diverse targets

The induction of highly skewed T helper cell type 2 (Th2) responses to nematodes is associated with the efficient control of worm infections (see Table 1). However, nematodes have coevolved efficient immune evasion mechanisms enabling their prolonged survival and reproduction in the host (see Fig. 1). The modulation of the immune response is seen as an evolutionary adaptation that is also beneficial for the host as overt immunopathology and thereby damage to the host is avoided (Maizels et al. 2004). Nematode-induced immune modulation also has the ability to suppress bystander responses to unrelated antigens, and nematode infections have also been shown to suppress unrelated inflammation such as airway hyperreactivity (Hartmann et al. 2009; Kitagaki et al. 2006; Wilson et al. 2005). It is unlikely that the potent suppression of such inflammatory processes is the consequence of one dominant modulation pathway, but rather results from the interference with multiple steps of elicited immune responses.

Indeed, live nematodes and their excretory/secretory (ES) products have been shown to modulate a plethora of innate and adaptive immune cells (see Fig. 1). Nematode infections enhance the induction of dendritic cells (DCs) supporting the outgrowth of regulatory T cell populations and production of anti-inflammatory IL-10 in the intestine and gut-draining lymph nodes (Li et al. 2011). Macro-
phages are a target of nematode modulation, acquiring a regulatory phenotype (Klotz et al. 2011; Schnoeller et al. 2008; Siracusa et al. 2008). T cell responses are suppressed in models of chronic nematode infections (Hartmann et al. 2011).
1997; Metwali et al. 2006) as well as in human patients with long-lasting or recurring infections (Doetze et al. 2000; Fujiwara et al. 2009). The latter is seen as a consequence of limited activation by innate cells and increased numbers and activation of regulatory T cell (Treg) subsets, such as forkhead box P3 (Foxp3+) expressing natural Tregs and induced Treg populations specialized for the expression of the anti-inflammatory cytokines transforming growth factor beta (TGF-β) (Th3 cells) and IL-10 (Tr1 cells) (Chaudhry et al. 2011; Doetze et al. 2000; Metenou et al. 2010). The understanding of how nematodes afflict the different immune cells of their hosts may help to specifically interfere with inflammatory disorders such as IBD.

The largest body of evidence for a preventive and curative effect of nematodes on gastrointestinal inflammation comes from commonly used murine colitis and nematode infections models (see Box 1, Tables 1 and 2). In the following section, we will focus on how nematode infections or nematode components modulate the multiple layers of immune responses and how this is connected to the control of inflammatory disorders of the gut.

Box 1: Mouse colitis models studied for nematode immunomodulation

**DNBS/TNBS model**

**Induction:** Immunological mediated model induced by the hapten di- or trinitrobenzene sulfonic acid (DNBS, TNBS) and the intestinal microbiota. Intrarectal application of chemicals in ethanol leads to disruption of epithelial layer (Scheiffele and Fuss 2002). **Initiator of inflammatory response:** IL-12/23 production by DC and macrophages, TNF-α/IL-1β/IL-6/IL-18 from macrophages (Guan et al. 2011; Neurath et al. 2000; Scheiffele and Fuss 2002). **Dependent on adaptive immunity:** Th1/17 cells drive the colitic response. Not working in T cell deficient mice (Scheiffele and Fuss 2002; Guan et al. 2011). **Interference with inflammation:** Blockade of IL-12/23 TNF-α (Neurath et al. 2000; Guan, 2011 #124) **Relevance to human IBD:** Transmural inflammatory lesions share similarity with CD. Long lasting (about 8-12 weeks in susceptible mice). Responds to current treatments of IBD (sulfasalazine, glucocorticoids, cyclosporine, anti-TNF-α antibodies).

**DSS model**

**Induction:** feeding of dextran sodium sulphate (DSS) in drinking water leads to disruption of colonic mucosal barrier. DSS is directly toxic to epithelial cells and allows translocation of intestinal bacteria driving the pro-inflammatory response. Does not work in germ-free mice. **Initiator of inflammatory response:** macrophages sensing intestinal bacteria (Dieleman et al. 1994). **Dependent on adaptive immunity:** Macrophage-driven inflammation also detected in T cell deficient mice. Repetitive cycles of DSS application lead to exacerbated inflammation driven by Th1, Th17 and Th2 cells (Hall et al. 2011). **Interference with inflammation:** Removal of microbiota by antibiotic treatment; blockade of IL-12/23, TNF-α. **Relevance to human IBD:** Early recruitment of DC, macrophages and neutrophils reflects findings in human IBD patients (Hall et al. 2011). Repetitive DSS mimic relapse and remission phases.

**IL-10−/− Model**

**Induction:** develops spontaneously in IL-10−/− mice or after transfer of IL-10−/− T cells into RAG−/− mice deficient in mature T cells. Piroxicam treatment needed for synchronized colitic response. Does not work in germ-free mice (Blum et al. 2004; Kuhn et al. 1993). **Initiator of inflammatory response:** increased IL-12/23 production in response to bacterial stimuli due to increased mucosal permeability and lack of regulatory IL-10 circuits. Overt activation of Th1/17 effector cells liberated from (Tr1/Treg?) regulation (Elliott et al. 2004). **Dependent on adaptive immunity:** Unregulated pro-inflammatory T effector responses is responsible for colitis development. **Interference with inflammation:** removal of microbiota by antibiotic treatment; blockade of IL-12; co-transfer of Treg. **Relevance to human IBD:** Model for transmural inflammation as also seen in CD patients. Reflects unregulated T cell responses due to a defect in regulatory circuits that may be involved in genetically predisposed IBD patients.

A highly conserved feature of nematode infections is the polarization towards a Th2 response and counter-regulation of Th1 responses (see Fig. 1). Thus, many studies have aimed to dissect how the nematode-induced Th2 response antagonizes pathological Th1 and Th17 responses in murine models of colitis.

Infections with *Heligmosomoides polygyrus* have potent protective effects and suppress inflammation in several models of IBD (see Table 2). Amelioriation of trinitrobenzenesulfonic acid (TNBS)-induced or piroxicam-triggered colitis in IL-10−/− mice (see Box 1) by prior infection with *H. polygyrus* coincided with increased colonic levels of Th2 cytokines, while local IL-12, IFN-γ, and TNF-α were conversely suppressed, suggesting that the preventive effect was largely due to the nematode-induced Th2 response counterbalancing Th1-driven tissue damage (Elliott et al. 2004; Setiawan et al. 2007; Sutton et al. 2008). Suppression of Th17-driven colitis by *H. polygyrus* in the IL-10−/− model has been linked to IL-4, a key Th2 cytokine. In vitro blockade of IL-4 restored the IL-17A production by T cells...
Overview of studies assessing the therapeutic effects of nematode infections and nematode-derived components in murine colitis models

| Citation         | Nematode infection model | IBD model      | Form of therapy | Analyzed parameters                                                                 | Proposed mechanism                                                                 |
|------------------|--------------------------|----------------|-----------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Elliott et al. 2004 | *H. polygyrus*            | IL-10−/− mice | Curative        | ↑ IL-13, Foxp3 expression  
↓ IL-12, IFN-γ, inflammatory score                                                  | Inhibition via induction of suppressive T cells and Th2 induction. Protection can be transferred with T cells from worm-infected donors. |
| Metwali et al. 2006  | *H. polygyrus*            | IL-10−/− T cell transfer to RAG−/− mice | Curative | ↓ histological inflammation score  
↓ IL-12, IFN-γ, inflammatory score                                                   | CD8+ Tregs required for reversal of colitis, those act independently of IL-10 or TGF-β signaling. |
| Setiawan et al. 2007 | *H. polygyrus*            | TNBS           | Preventative     | ↑ IL-4, IL-5, IL-10, IL-13  
↓ IL-12p40, IFN-γ, inflammatory score                                               | IL-10-dependent inhibition of pro-inflammatory cytokines and disease. IL-10R blockade in vitro restores IFN-γ and IL-12p40 production by mucosal cells. |
| Elliott et al. 2008  | *H. polygyrus*             | IL-10−/− mice | Curative         | ↓ IL-17, inflammatory score                                                       | *H. polygyrus* infection cures established colitis by suppressing IL-17 production. IL-4 and IL-10 together block IL-17 production by T cells. IL-10 alone is not sufficient. |
| Sutton et al. 2008  | *H. polygyrus*             | TNBS           | Preventative     | ↑ IL-4, IL-13, mucosal mast cells and resistance  
↓ IFN-γ, TNF-α, inflammatory score                                                | Reduced Th1 cytokine expression, protection may involve control of intestinal secretory function through mast cell-mediated mechanisms. |
| Hang et al. 2010    | *H. polygyrus*             | IL-10−/− T cell transfer to RAG−/− mice | Preventative | ↑ plasmacytoid Ag, CD40 on DCs  
↓ CD80 and CD86 on DCs  
↓ IFN-γ, IL-17, inflammatory score                                                | Phenotypical changes of DC correlate with protection. Modulation of innate immune cells is sufficient to suppress colitis weeks after abrogation of *H. polygyrus* infection. |
| Khan et al. 2002    | *T. spiralis*              | DNBS           | Preventative     | ↑ IL-4, IL-13  
↓ MPO activity, IL-12, IFN-γ, inflammatory score                                   | Decrease in colitis severity correlated with the induction of a Th2 response. |
| Wilson et al. 2011  | *T. muris*                 | IL-10−/− mice | Not applicable   | ↑ IL-13Rα2 (IL-13 decoy receptor), IFN-γ, IL-17, inflammation  
↓ IL-13 bioreactivity                                                           | *T. muris* induces colitis in IL-10−/− mice due to development of a Th1-dominated response. IL-13 reduces *T. muris*-associated pathology in IL-10−/− IL-13Rα2−/− mice. |
| Nematode component  |                          |                |                 |                                                                                     |                                                                                     |
| Motomura et al. 2009 | *T. spiralis* larval antigens | DNBS           | Preventative     | ↑ IL-13, MPOβ, IFN-γ, iNOS, inflammatory score                                       | Attenuation of colitis attributed to induction of Th2 and regulatory mechanisms via nematode antigens in the absence of live worm infection. |
| Du et al. 2011      | *T. spiralis* 53 kDa ES protein | TNBS           | Preventative     | ↑ IL-4, IL-13, IL-10, TGF-β, AAM  
↓ inflammatory score, IFN-γ, TNF-α, IL-6,                                         | Amelioration of colitis due to induction of Th2 and regulatory response; may involve induction of AAM. |
| Schnoeller et al. 2008 | *Acanthocheilonema viteae* cystatin | DSS           | Concomitant with DSS application | ↓ intestinal inflammatory index, (cell infiltration, goblet cell depletion, epithelial damage, crypt loss) | Amelioration of colitis by a nematode protein also capable of attenuating Th2-driven airway inflammation. |
| Cho et al. 2011     | *Anisakis simplex* MIF II | DSS           | Preventative     | ↑ IL-10, TGF-β, Treg  
↓ IFN-γ, IL-6, IL-13, weight loss, inflammatory score                               | Lower inflammatory cytokine production and higher Treg frequencies correlate with protection. *A. simplex* MIF II induced in vitro expression of IL-10 by EC, DCs, and fibroblasts and TGF-β by fibroblasts. |
| Ruysers et al. 2009 | *Ancylostoma caninum* ES | TNBS           | Curative         | ↓ MPO activity, inflammatory score                                                | Dose-dependent decrease of intestinal inflammation and MPO activity after treatment with ES. |
| Cancado et al. 2011 | *Ancylostoma ceylanicum* crude extracts and ES | DSS           | Concomitant with DSS application | ↓ Th1 and Th17 cytokines, MPO and eosinophil peroxidase activity, inflammatory score | Live worms not required; both crude extracts and ES products ameliorate the disease. |
from nematode-infected IL10−/− mice. Conversely, addition of IL-4 (and more so the combination of IL-4 and IL-10) blocked IL-17A secretion by T cells from colitic IL-10−/− mice, showing that nematode-driven Th2 effector cytokines effectively suppress pro-inflammatory responses (Elliott et al. 2008). Importantly, H. polygyrus infection not only prevented development of colitis when given to mice before administration of the colitis trigger piroxicam, but was also able to control established colitis in IL-10−/− mice (Elliott et al. 2008).

A recent publication specifically addressed the role of IL-13, a Th2 cytokine sharing many features with IL-4, and IL-13Rα2, the soluble IL-13 decoy receptor limiting the levels of bioactive IL-13 in the body, in Trichuris muris infection (Wilson et al. 2011). Infections with T. muris lead to a pathological response resembling colitis in IL-10−/− mice, which were found to express high levels of IL-13Rα2 following T. muris infection or piroxicam treatment. Using IL-10/IL-13Rα2 double knockout mice, the authors found that in the absence of the decoy receptor a subsequent increase in IL-13 bioactivity protected against IFN-γ and IL-17A-mediated colitis. An increase in IL-13 and decreased IFN-γ were also reported in Trichinella spiralis-mediated amelioration of dinitrobenzene sulfonic acid (DNBS) colitis (Khan et al. 2002). Taken together, these data suggest that the initial strong induction of Th2 responses by nematode infections counterbalances the development of colitogenic Th1 and Th17 responses and show that even fully developed colitis may be controlled by nematode treatment.

The first line of modulation: intestinal epithelial cells and tissue-derived cytokines

The integrity of the epithelial layer is of pivotal importance for the prevention of inappropriate inflammatory responses against the commensal gut microbiota (Saenz et al. 2008). Intestinal nematode infections lead to a rapid innate response that results in a bias towards the induction of an adaptive Th2 response in order to expel developing larvae or adults. Recent work has shown how the epithelial-derived cytokines thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 influence innate and adaptive responses at mucosal sites and how they are involved in promoting Th2 responses to intestinal nematode infections (Saenz et al. 2008; Humphreys et al. 2008; Price et al. 2010; Taylor et al. 2009). TSLP and IL-25 have been shown to turn off the expression of IL-12/23 p40 by DCs and thus impair their ability to drive Th1 responses (Massacand et al. 2009; Taylor et al. 2009). In the absence of TSLP, T. muris infection led to severe gut pathology coinciding with increased Th1 and Th17 responses (Taylor et al. 2009). Importantly, the same study showed that mice deficient in TSLP develop a more severe pathology in response to dextran sodium sulfate (DSS; see Box 1) treatment in the chemically induced colitis model. Biopsies from patients with active CD showed a lack of TSLP expression compared to healthy controls (Rimoldi et al. 2005). Treatment of colonic macrophages from IBD patients with the tissue-derived cytokine IL-25 restrained their synthesis of IL-12/23 and, similar to TSLP, patients with active UC or CD produced less IL-25 than healthy controls. Furthermore, application of IL-25 ameliorated experimental colitis in mice (Caruso et al. 2009). IL-33, on the other hand, is discussed as a factor driving gut inflammation, especially in Th2-related UC (Seidelin et al. 2011) and was shown to exacerbate DSS-induced experimental colitis (Imaeda et al. 2011).

Another innate effector molecule produced by the intestinal epithelium, namely goblet cells, in response to worm infections is resistin-like molecule beta (RELM-β). RELM-β is induced by IL-4/−/− produced by early innate sources and Th2 cells and is directly involved in host defense against intestinal nematodes by binding to the chemosensory apparatus of the worms (Artis et al. 2004; Herbert et al. 2009). Furthermore, it increases mucin secretion by goblet cells and ameliorates TNBS colitis in mice by strengthening the mucus layer needed for gut barrier function and immune homeostasis (Hogan et al. 2006; Krimi et al. 2008).

The early induction of TSLP and IL-25 by nematode infections permits the development of adequate mucosal Th2 responses directed against the parasite while suppressing pathogenic Th1 and Th17 responses. Thus, the increased expression of tissue-derived factors like TSLP, IL-25, and RELM-β induced by nematodes seems integral to a protective role of these parasites in colitis models. While many studies focus on these tissue-derived cytokines as targets in modulating Th2-related atopic disorders, nematode infection models may reveal how these early players in mucosal immune responses might also be targets for suppressing Th1- and Th17-related gut inflammation.

DC as nematode modulation targets

Dendritic cells (DCs) are the most potent antigen-presenting cells and critical inducers of adaptive immunity. They play a decisive role in directing the differentiation of distinct Th cell as well as T regulatory cell subsets in response to pathogens (MacDonald and Maizels 2008). In active lesions of IBD patients, increased numbers of activated DCs are detectable, expressing toll-like receptors (TLRs) essential for the recognition of microbial pathogens and commensal bacteria as well as co-stimulatory molecules needed for the activation of T cells. As to be expected, they also produce high levels of inflammatory cytokines,
including IL-12/23p40 (Niess 2008). Given the fact that the production of IL-12/23 by gut-associated DCs is essentially involved in the induction of colitogenic Th1 and Th17 responses, it is interesting to note that many in vitro and in vivo studies show that nematode infections as well as nematode products efficiently shut down the ability of DCs to produce these pro-inflammatory factors.

Treatment of DCs with ES products of parasitic nematodes selectively suppresses their production of IL-12 in response to TLR ligation by bacterial components and/or the expression of co-stimulatory molecules (such as CD80/86 and CD40) and antigen presentation molecule MHCII (Balic et al. 2009; Li et al. 2011; Segura et al. 2007). Similarly, blood monocyte-derived DCs from patients infected with the hookworm Necator americanus were impaired in their ability to induce T cell activation and proliferation (Fujiwara et al. 2009). For T. muris, it was shown that infection led to a rapid increase of immature DCs in the lamina propria of the large intestine (Cruickshank et al. 2009). The colonic DCs were shown to extend dendrites between adjacent epithelial cells into the gut lumen (Cruickshank et al. 2009). Therefore, it is conceivable that DCs are a direct target of immunomodulatory components secreted by T. muris and other intestinal nematodes and may be modulated directly in the intestine.

Divergent DC populations with pro-tolerogenic properties have been characterized, like mucosal RALDH+/CD103+ DCs or lymphoid CD205+ DCs driving the induction of regulatory T cells and plasmacytoid DCs inducing IL-10 production by T cells (Coombes and Maloy 2007; Pulendran et al. 2010; Yamazaki et al. 2008). This raised the question whether nematodes might support such pro-tolerogenic DC populations and thus prevent the development of pathological T cell responses in the gut. A recent study provides first evidence for prevention of colitis by efficient modulation of DCs and other innate immune cells by an intestinal nematode. In the IL-10−/− T cell transfer colitis model, a transient infection with H. polygyrus weeks before the IL-10−/− T cell transfer led to protection from colitis by suppressing the subsequent generation of colitogenic Th1 and Th17 effector cells. Changes in the composition of lamina propria-derived DC populations were related to the inhibition of colitis as DCs showed decreased expression of co-stimulatory molecules and IL-12/23 p40 and contained higher frequencies of plasmacytoid-like DCs known to exert a regulatory function in disease models (Hang et al. 2010).

A refined analysis of intestinal nematode-induced changes in DC populations has been carried out in the group of Rick Maizels using H. polygyrus and Nipposstrongylus brasiliensis as models for chronic and acute nematode infections. In both infections, the number of DCs expressing high levels of co-stimulatory molecules dropped dramatically in gut-draining mesenteric lymph nodes (mLN), a finding even more prevalent during chronic H. polygyrus infection (Balic et al. 2009). This coincided with an increased Th2-inducing and restrained Th1-priming capacity of mLN DCs (Balic et al. 2009). In a subsequent study, an increased frequency of DCs with a pro-tolerogenic phenotype distinct from previously described CD205+, CD103+, and plasmacytoid DCs was detected in the mLN of H. polygyrus-infected mice (Smith et al. 2011). These DCs responded poorly to TLR ligands and had a low efficiency in driving Th1 and Th17 differentiation, but were superior in driving Th2 responses and de novo induction of Foxp3+ Tregs (Smith et al. 2011).

It is thus conceivable that the reduction in pro-pathogenic DCs and the increase of pro-tolerogenic DCs found during nematode infections are largely contributing to the profound anti-inflammatory effects of these parasites seen in IBD models and clinical trials. The fact that intestinal DCs sample antigen directly from the gut lumen (Niess et al. 2005) makes them a potential target for direct modulation via ES products of nematodes. Thus, it is also conceivable that immature DCs attracted to nematode-infected intestinal sites are efficiently modulated by ES products of the parasites, either blocking their further maturation, inhibiting migration to lymphoid sites, or equipping them with pro-tolerogenic functions exerted after their arrival at sites of T cell priming.

It should also be noted that the mechanisms involved in immune modulation may vary between species of nematodes. For example, the suppression of IL-12/23 p40 expression by DCs is dependent on the tissue-derived cytokine TSLP in T. muris infection, while H. polygyrus and N. brasiliensis are able to bypass the need for TSLP, directly suppressing the expression of pro-inflammatory cytokines by DCs through ES components (Massacand et al. 2009). Therefore, for developing nematode-derived anti-colitic therapies, differences between immune response induced between nematode species must be considered.

Nematode modulation of macrophages

Intestinal macrophages are known for their contribution to IBD as effector cells driving pathology by release of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-12, and IL-23, reactive oxygen species, and nitric oxide (Qualls et al. 2006; Bar-On et al. 2011). On the other hand, they are necessary for maintenance of intestinal homeostasis via induction of Treg differentiation (Denning et al. 2007). During nematode infections, macrophages acquire a special phenotype (named alternatively activated macrophages; AAMs) in response to the Th2 cytokines IL-4 and -13 (Loke et al. 2007; Reece et al. 2008; Siracusa et al. 2008; Gordon 2003). They are characterized by the expression of...
arginase-1, RELM-α, and YM-1, effector molecules involved in wound healing and protection against nematodes (Kreider et al. 2007). Importantly, AAMs express low levels of pro-inflammatory cytokines.

While not yet studied directly in nematode infections, AAMs may play a role in amelioration of gastrointestinal inflammation as AAMs are found in higher amounts in human patients with inactive CD compared to those with active disease (Hunter et al. 2010). This finding along with the observation that nematode infections induce AAMs with wound healing and tissue remodeling properties, as well as potential T cell suppressive capabilities, (Mylonas et al. 2009; Siracusa et al. 2008) prompts the question whether AAMs might be involved in colitis prevention in nematode infection models.

Recent in vivo and in vitro data support this view: AAMs isolated ex vivo have the potential to ameliorate DSS-induced colitis after transfer (Weisser et al. 2011), and AAMs elicited by in vivo application of the Th2-associated tissue-derived cytokine IL-25 conferred protection against TNBS-induced colitis in an IL-4-, IL-13-, and TGF-β-independent manner (Rizzo et al. 2011). Helminth-derived AAMs are also found to have anti-inflammatory effects and are involved in wound healing (Loke et al. 2007). In a murine wound healing model, AAMs elicited by the filarial nematode Brugia malayi were found to be recruited to the site of injury after sham surgery of the intestine (Loke et al. 2007). In models with intestinal barrier disruption, as in the DSS model of colitis, it is easy to speculate that wound healing by AAMs induced during nematode infection could participate in the protective effect observed. AAMs generated in vitro reduced colonic inflammation in DNBS-treated mice, and similarly, a protective, anti-colitic effect mediated by tapeworm infections was reverted when intestinal macrophages were depleted (Hunter et al. 2010). Interestingly, the same study showed that patients with active colitis had reduced numbers of AAMs in intestinal biopsies, while inactive CD correlated with increased numbers of intestinal AAMs (Hunter et al. 2010). The observation that remission in CD patients is correlated with an accumulation of AAMs in the intestine coupled with the reported protective role of helminth-induced AAMs in murine models of colitis suggests that a better understanding of the role of AAMs may yield important information for the application of modulated macrophage subsets as therapy for intestinal inflammatory disorders.

Anti-inflammatory cytokines: nematodes supporting the production of IL-10 and TGF-β

IL-10 and TGF-β are canonical regulatory cytokines which are produced by a multitude of innate and adaptive immune cells as well as epithelial cells. Both play a crucial role in maintaining immune homeostasis of the gut. They suppress the production of pro-inflammatory cytokines by innate cells and the development of Th1 cells (Doligalska et al. 2006; Elliott et al. 2008; Ince et al. 2009) while supporting and inducing regulatory T cell subsets (Coombes and Maloy 2007; Murai et al. 2009). Genetically modified mice with dysfunctional TGF-β signaling (Fahlen et al. 2005; Gorelik and Flavell 2000) or lacking IL-10 expression (Asseman et al. 1999; Murai et al. 2009) succumb to severe colitis due to a dysregulated cytokine milieu with overt pro-inflammatory T cell activation. Tregs are one important source of both cytokines (Monteleone et al. 2008; Rubtsov et al. 2008), and IL-10 from intestinal macrophages has been shown to induce Foxp3+ Tregs in conjunction with retinoic acid and exogenous TGF-β (Denning et al. 2007). Macrophage-derived IL-10 also maintains Foxp3 expression in gut Tregs in the inflamed intestine (Murai et al. 2009).

Nematode infections provoke the production of IL-10 and TGF-β by T cells (indicative of a Treg phenotype, see next section) (Doetz et al. 2000; Finney et al. 2007; Rausch et al. 2008; Rausch et al. 2009; Satoguina et al. 2002; Schopf et al. 2005), and both cytokines restrain protective antiparasitic immune responses and immunopathology (Grainger et al. 2010; Specht et al. 2004). Thus, IL-10 and TGF-β are central mediators of nematode-induced protection against intestinal inflammation. H. polygyrus infection leads to an increased production of IL-10 by CD4+ T cells in the lamina propria of the lower intestine while decreasing levels of IFN-γ and IL12/23 p40 (Setiawan et al. 2007). In the TNBS model, IL-10 was proposed to be essential for disease resolution by H. polygyrus because blockade of the IL-10R restored Th1 responses and reversed the protection against colitis (Setiawan et al. 2007). More recently, the importance of TGF-β was shown in H. polygyrus-mediated suppression of intestinal inflammation (Ince et al. 2009). Control of Th1-driven colitis by H. polygyrus required intact TGF-β signaling as mice with a defective form of TGF-βRII showed no reduction in intestinal Th1 cytokine production and were not protected from colitis by H. polygyrus infection. Interestingly, this study indicated a link between TGF-β and IL-10 expression as TGF-βRII-defective mice lacked the increased intestinal IL-10 levels seen in H. polygyrus-infected wild-type mice. H. polygyrus also modulates the response of T cells to bacterial components in favor of an anti-inflammatory cytokine response. During infection, intestinal mucosal T cells were found to start expressing TLR-4, the receptor for bacterial lipopolysaccharide (LPS). Both CD4+ and CD8+ intestinal T cells from H. polygyrus-infected mice reacted with increased production of TGF-β in response to LPS stimulation (Ince et al. 2006). This mechanism may
help to maintain the mucosal integrity during intestinal worm infections and may be involved in suppressing colitic responses by nematodes.

There is increasing evidence that IL-10 from nematode-modulated DCs or T cells primed by these DCs might be important for nematode-mediated protection against colitis. DCs treated with ES products of *H. polygyrus* or the hookworm *Ancylostoma caninum* gained the ability to induce IL-10 in primed T cells (Cuellar et al. 2009; Segura et al. 2007). *H. polygyrus* infection led to an increase in IL-10-expressing DCs in mLN that supported the induction of Tregs and IL-10 production by T cells (Balic et al. 2009; Li et al. 2011).

Resident gut macrophages also serve as a source for IL-10 and TGF-β in the intestine (Gordon 2003; Murai et al. 2009), and intestinal macrophages can confer protection from T cell transfer colitis in an IL-10-dependent manner (Murai et al. 2009). It is thus tempting to speculate that nematodes might support the inherent competence for IL-10 production in resident intestinal macrophages and, at the same time, prevent damage resulting from the release of high levels of inflammatory mediators by monocytes/macrophages migrating to the gut tissue during onset or relapse of IBD. It remains to be elucidated whether this might be a mechanism centrally involved in the nematode-mediated blockade of colitis in diverse gut inflammation models.

Treg induction and activation by nematodes

Regulatory T cells (Tregs) are essential for the control of immune disorders, and their role in preventing spontaneous or induced gut inflammation has been extensively studied (Campbell and Koch 2011; Izcue et al. 2009). Mice lacking the Treg-associated lineage transcription factor Foxp3 are prone to develop fatal colitis due to a dysregulated cytokine milieu with overt pro-inflammatory T cell activation. The production of TGF-β and IL-10 by Tregs suppresses inflammation driven by effector T cells and innate cells (Chaudhry et al. 2011; Liu et al. 2006), and both cytokines are important for Treg maintenance in what appears to be a positive feedback loop (Murai et al. 2009; Fantini et al. 2004; Mucida et al. 2007).

Increased frequencies of Tregs are detected in nematode-infected mice (D’Elia et al. 2009; Finney et al. 2007; Grainger et al. 2010; McSorley et al. 2008; Rausch et al. 2008) and humans (Babu et al. 2006; Matera et al. 2008; Metenou et al. 2010; Montes et al. 2009). Our group, as well as others, has shown that *H. polygyrus*-infected mice have higher frequencies of CD4+ Tregs and that they are stronger suppressors than Tregs from naïve controls (Finney et al. 2007; Rausch et al. 2008; Rausch et al. 2009). Infection-derived Tregs had an increased expression of the αε(α±CD103)β7 integrin linked to an activated effector/memory phenotype of Foxp3+ Tregs (Huehn et al. 2004). CD103 binds to E-cadherin expressed on epithelial cells, possibly enabling prolonged retention of these Tregs in the intestine (Cepk et al. 1994). Most importantly, the depletion of Tregs during infections with *H. polygyrus* and *T. muris* increased intestinal pathology (D’Elia et al. 2009; Rausch et al. 2009). Thus, regulatory T cell populations are one focus in nematode protection against gut inflammation.

CD4+ T cells isolated from the intestines of *H. polygyrus*-infected mice efficiently blocked IFN-γ production of T cells derived from worm-free mice. Although data on their Foxp3 expression are lacking, this shows the induction of a regulatory phenotype in gut-derived CD4+ cells during *H. polygyrus* infection. The gut-derived CD4+ T cells produced large amounts of IL-10, coinciding with the blockade of TNBS colitis in *H. polygyrus*-infected mice. Blockade of IL-10 in vitro restored the suppressed IFN-γ and IL-12/23 p40 production by lamina propria cells derived from *H. polygyrus*-infected donors. In vivo, IL-10 blockade worsened TNBS colitis in *H. polygyrus*-infected mice (Setiawan et al. 2007). An earlier study linked an increased Foxp3 expression in mLN cells of *H. polygyrus*-infected mice to the protection from colitis achieved by T cell transfer from infected to naive IL-10−/− mice (Elliott et al. 2004). As transfer of IL-10−/− T cells from *H. polygyrus*-infected donors blocked colitis in IL-10−/− recipients, the suppression of intestinal inflammation exerted by regulatory T cells activated by the worm infection is not solely based on IL-10 production. Interestingly, *H. polygyrus* also induces a CD8+ Treg population. CD8+ T cells isolated from the intestines of *H. polygyrus*-infected mice were able to largely inhibit proliferation of spleen cells from naïve mice in vitro, whereas T cells isolated from naïve mice showed very little effect. The *H. polygyrus*-driven regulatory activity in CD8+ intestinal T cells was independent of IL-10 and TGF-β, but worked in a contact-dependent manner (Metwali et al. 2006).

Recently, it was shown that ES products of *H. polygyrus* (and the related nematode *Teladorsagia circumcincta*) contain a functional mimic of TGF-β able to induce Foxp3 expression in CD4+ T cells in vitro, thus potentially enhancing the suppressive natural Treg pool (Grainger et al. 2010). Importantly, the study also shows that *H. polygyrus* infection greatly enhanced the induction of Tregs specific for an irrelevant antigen in a model of oral tolerance induction. This shows that nematodes are able to induce Tregs not specific for parasite antigen and suggests that the induced Tregs may be of essential benefit in regulating dysregulated immunity or bowel inflammation driven by the microbiota.
Taken together, it is clear that Tregs exposed to nematodes or nematode antigens are highly activated and may efficiently control immune responses. However, more work is needed to elucidate the pathways involved in Treg activity in intestinal nematode infections and their contribution to the amelioration of colitis. In future studies, the Treg populations essentially involved in amelioration of colitis by nematode infections should be better characterized. It is not yet clear whether natural CD4+ Foxp3+ T cells, induced TGF-β Th3, or IL-10+ Tr1 cells are predominantly involved in suppressing colitis. The recently described IL-35 producing induced Tregs found expanded in *T. muris* infection (Collison et al. 2010) should also be evaluated as possible anti-colitic players supported by worm infections.

**Clinical trials and case studies**

The experimental work in mouse models of colitis showed that nematodes have potent immunomodulatory effects and lead to the induction of regulatory pathways. This generated interest in adapting experimental helminth application as a therapy in human disease. Clinical trials with IBD patients treated with ova from the pig specific whipworm *Trichuris suis* (see Table 3) showed an amelioration of symptoms with a decreased disease activity in nematode-treated patients (Summers et al. 2003; Summers et al. 2005). In the first *T. suis* study, small groups of ulcerative colitis and Crohn’s disease patients were given 2,500 *T. suis* ova orally, and no adverse effects were observed (Summers et al. 2003). In three of four CD patients, remission was achieved within 12 weeks of *T. suis* ova ingestion. Since *T. suis* is not adjusted to the human host, it is considered as incapable of maintaining a chronic infection, and it was proposed that *T. suis* ova should be ingested every 3 weeks after the initial dose in order to maintain remission of colitis. In the second *T. suis* trial (Summers et al. 2005), 29 CD patients were treated with this regimen, and almost 80% responded, with 73% entering remission within 24 weeks of treatment. As immune reactivity was not measured in blood or tissue biopsies from the patients, the mechanism of *T. suis*-mediated amelioration of CD/UC remains elusive.

A recent case study of an UC patient refractory to standard treatment investigated the effects of *Trichuris trichiura*, a close relative of *T. suis* infective for humans. The patient entered complete remission for 3 years after ingestion of two doses of embryoated *T. trichiura* eggs, leading to chronic infection (Broadhurst et al. 2010). Following a relapse phase, the patient ingested a third dose of *T. trichiura*, again leading to improvement of histopathological findings. The remission after reinfestation correlated with an increase of colonic and systemic Th2- and IL-22-producing CD4+ Foxp3+ T cells, induced TGF-β Th3, or IL-10+ Tr1 cells are predominantly involved in suppressing colitis. The recently described IL-35 producing induced Tregs found expanded in *T. muris* infection (Collison et al. 2010) should also be evaluated as possible anti-colitic players supported by worm infections.

### Table 3: Overview of live nematode therapies studied in human clinical trials with IBD patients

| Citation                  | Organism        | Patients | Treatment method | Clinical outcome |
|---------------------------|-----------------|----------|------------------|-----------------|
| Summers et al. 2003       | *Trichuris suis*| 4 active CD patients; 3 active UC patients | 2,500 ova 1×/2 week; 17 weeks total | 6/7 patients reached remission after therapy; however, relapse was common within 12 months. Minimal adverse effects. |
| Summers et al. 2005       | *Trichuris suis*| 29 active CD patients | 6,500 ova 5×/3 week | Extension of previous maintenance study. At 24 weeks, 80% of the patients had responded, and 73% were in remission. No placebo control included. |
| Croese et al. 2006        | *Necator americanus*| 3 active CD patients; 4 inactive CD patients | Inoculation with 25–100 infective larva; Three patients re-inoculated at week 27–30 | Effects on CD activity index unclear due to low number of patients and variability in *N. americanus* as well as concomitant standard therapies. |
| Broadhurst et al. 2010    | *Trichuris trichiura*| 1 UC patient refractory to conventional treatment | Patient ingested 500 ova and 1,000 more ova 3 months later | Initial 2 doses resulted in chronic infection and remission for 3 years. Another dose was taken after 9 months; subsequent remission was achieved in 2 of 3 patients, and a decrease in IL-17, IL-22, and IL-13αR2. |
| Daveson et al. 2011       | *Necator americanus*| 10 celiac patients in hookworm treatment group; 10 patients in saline control group | Treatment included infection with 10 infective larvae at week 0 and again at week 5. Larva at week 12 | No significant improvement in pathology. |

The remission after infestation with *T. suis* ova was evaluated to extend remission to over a year in 3 of the 4 patients offered this option. In the second *T. suis* trial (Summers et al. 2005), 29 CD patients were treated with this regimen, and almost 80% responded, with 73% entering remission within 24 weeks of treatment. As immune reactivity was not measured in blood or tissue biopsies from the patients, the mechanism of *T. suis*-mediated amelioration of CD/UC remains elusive.
producing Th cells, while frequencies of Th cells producing the pro-colic cytokines IFN-γ, IL-17, and TNF-α remained largely unchanged (Broadhurst et al. 2010). IL-22, a cytokine produced by Th17 among other cells, is known to support mucosal integrity by promoting wound healing, increasing mucus production by goblet cells, and proliferation of epithelial cells, thus increasing mucosal barrier function (Eyerich et al. 2010). It was hypothesized that the infection with T. trichiura led to the induction of Th2 and IL-22-producing cells (in order to expel the parasite infection) and that these effector cells synergize in reducing intestinal pathology as a bystander effect by increasing the mucosal integrity. Studies with more patients are clearly needed to verify this hypothesis.

**Refining and advancing nematode derived therapies**

While infection with certain species of helminthes may result in a beneficial suppression of dysregulated inflammation, it is important to consider the consequences of administering helminths to patients as they are pathogens with the potential to induce adverse effects. High-dose infections with hookworms (e.g., N. americanus) or the whipworm T. trichiura can lead to a dysentery condition, malnutrition, and anemia as well as decreased cognitive function and retarded development in school-age children (Bager et al. 2011; Croese et al. 2006; Stephenson et al. 2000). The Th2 and regulatory immune response elicited in nematode infections may also have negative consequences in terms of responses to bystander infections. Nematodes blocking inflammatory Th1 response have been shown to enhance the susceptibility of the host to gastrointestinal bacterial pathogens (Chen et al. 2005; Chen et al. 2006), tuberculosis (Potian et al. 2011), and plasmodium infection (Tetsutani et al. 2009). Therefore, infections with live nematodes adapted to humans are not the ideal option for treatment of IBD.

As depicted above, eggs from T. suis—a species maladjusted to the human host—have been used in clinical trials to treat IBD as a way to circumvent the deleterious effects of worm infection. While it is thought that T. suis ova are unable to mature into breeding adults in the human, a case study of a 16-year-old boy treated with T. suis ova for IBD found not only an adult male worm in the intestinal lumen of the boy but also suggested that the gastrointestinal inflammation present was due to a T. suis-induced Th2 inflammatory response (Kradin et al. 2006). Likewise, in a recent double-blind placebo trial, a significant increase in the number of patients reporting gastrointestinal symptoms, such as diarrhea and abdominal pain, was observed in T. suis ova-treated patients compared to the placebo-administered control group (Bager et al. 2011). The human specific hookworm N. americanus has also been administered in CD patients in an attempt to ameliorate disease activity (Croese et al. 2006). While no significant decrease in CD activity index was observed for 17 weeks, enteropathy was noted both in N. americanus-treated CD patients and in human N. americanus reservoir donors (Croese et al. 2006). More recently, in a double-blind placebo control study, infective N. americanus larvae were given to celiac disease patients. An increase in nausea, bloating, and itchiness at infective sites was observed in early colonization periods lasting up to 16 weeks (Daveson et al. 2011). At 20 weeks postinfection, patients began a 5-day gluten challenge that resulted in no significant difference between the placebo control and treatment groups in parameters such as pain, vomiting, diarrhea, bloating, headache, lethargy, and overall well-being, in response to gluten (Daveson et al. 2011).

The potential for nematode infection to induce pathology and increase susceptibility to secondary infections, as well as the lack of long-term studies regarding these therapies, must be considered when evaluating nematode therapy. Likewise, the potential psychological effects of live worm treatment in patients living in a developed culture where hygiene may be correlated with status has to our knowledge never been studied. For these reasons, it would be beneficial to develop treatments that utilize nematode immune modulation while avoiding the induction of live nematode infections. One potential method of bypassing live worm infection, while still obtaining the positive effects of nematode immune modulation, is to uncover the specific compounds produced by these parasites and reveal the manner in which they act to downregulate inflammation in the gut. As reasoned above, ES products from nematodes and other helminths are promising candidates for the development of anti-inflammatory drugs.

To date, there are limited examples of studies examining nematode-derived immune-modulating components in colitis models. One component is a filarial nematode-derived cystatin that we previously reported to have ameliorative effects in a DSS model when administered intraperitoneally (Schonemeyer et al. 2001). Cystatins are ubiquitous cysteine protease inhibitors involved in numerous processes from catabolism to regulation of immune activation. However, it appears that parasitic nematode cystatins may have evolved a secondary role and are also capable of regulating the host immune system. Since the observation that Acanthocheilonema vitae cystatin is able to inhibit T cell proliferation (Hartmann et al. 1997), several other filarial cystatins, both native (Pfaff et al. 2002) and recombinant (Schierack et al. 2003; Schonemeyer et al. 2001), have been reported to suppress T cell responses. Reduced antigen presentation and expression of costimulatory molecules by APCs has been observed when
cells were exposed to filarial nematode cystatin (Manoury et al. 2001; Murray et al. 2005; Schonemeyer et al. 2001). Macrophages exposed to filarial cystatins were shown to increase the production of anti-inflammatory IL-10, as opposed to the increased IL-12 produced by macrophages exposed to Caenorhabditis elegans cystatins, supporting the theory of converging evolutionary development of cystatins in parasitic nematodes for establishment of chronic infection in the host (Schierack et al. 2003). Our group recently revealed the mechanism by which IL-10-producing macrophages are induced by A. viteae cystatin (Klotz et al. 2011). We found that A. viteae cystatin is taken up by macrophages and activates the phosphorylation of mitogen-activated protein kinases (MAPK), resulting in the expression of IL-10 (Klotz et al. 2011). The regulation of this pathway involved the control of MAPK phosphorylation by dual-specificity phosphatases, showing that the nematode cystatin exploits activation and deactivation pathways of MAPK to induce macrophages with an IL-10-expressing phenotype (Klotz et al. 2011). We currently investigate the use of the nematode cystatin as therapeutic for IBD in more detail.

Future perspectives for nematodes in IBD therapy

While the research to date on nematode-derived immunomodulatory substances with potential benefits in IBD treatment is limited, it can be assumed that the overall anti-inflammatory effect of live worm infections may be due to more than one ES product or nematode component. Therefore, future therapies may benefit from synergistic effects of multiple nematode immunomodulatory products. It is also likely that various nematode components differ in their suppressive efficiency in individuals with different etiology or form of IBD. Genetic screening of individual IBD patients for known IBD-associated polymorphisms would be essential for developing patient-specific IBD treatment regimens, nematode derived and otherwise.

In conclusion, while there is strong evidence that nematode infections can downregulate intestinal inflammation, much more research on the responsible ES proteins or nematode components and the active mechanisms involved is required before safe treatment options can be clinically tested and marketed for routine use. Additionally, future IBD therapies developed from nematode products, as well as the currently marketed IBD therapies, might benefit from patient-specific genetic counseling to determine individual IBD phenotype and subsequent effective treatment regimen. These patient-specific therapies may involve nematode-derived treatments synergizing with the standard therapies.

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