**Trichuris muris** and comorbidities – within a mouse model context

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**Abstract**

*Trichuris muris* is a mouse intestinal parasitic nematode that inhabits the large intestine of its host and induces a strong immune response. The effects of this strong anti-parasite response can be found locally within the intestinal niche and also systemically, having effects on multiple organs. Additionally, the anti-parasite response can have multiple effects on infectious organisms and on microbiota that the host is harbouring. It has been shown that Th1 responses induced by *T. muris* can affect progression of bowel inflammation, cause colitic-like intestinal inflammation, reduce barrier function and intestinal mucosal responses. In the brain, *T. muris* can exacerbate stroke outcome and other neurological conditions. In the lung, *T. muris* can suppress airway inflammation and alter immune responses to other parasites. Additionally, *T. muris* induced responses can inhibit anti-tumour immunity. Although this parasite maintains a localized niche in the large intestine, its effects can be far-reaching and substantially impact other infections through modulation of bystander immune responses.

**Introduction**

*Trichuris muris* is a mouse intestinal parasitic nematode used as an experimental model for the human counterpart, *T. trichiura*. This nematode is one of the four major soil-transmitted helminths that infect 1.5 billion people worldwide causing significant morbidity (WHO, 2020). These diseases bear a huge impact on the quality of life of infected people and on the economic growth of infected communities (Hotez et al., 2014).

*T. muris* inhabits the large intestine and caecum of the host, with adult parasites living with their anterior half tunneled into the host epithelium and their posterior free in the lumen to facilitate egg deposition (Cliffe and Grencis, 2004). The immune response to *T. muris* in mice is very well characterized and there is a distinct polarization of immune response in resistant and susceptible strains of mouse (Else and Grencis, 1991; Else et al., 1992). Resistant animals produce high levels of interleukin 13 (IL-13) and associated Th2 cytokines in response to infection (Fig. 1), which are essential for parasite expulsion via mechanisms such as epithelial cell turnover and mucin production and muscle contraction (Khan et al., 2003; Cliffe et al., 2005; Hasnain et al., 2010; Chen et al., 2021). However, a susceptible animal produces high amounts of interferon-γ (IFN-γ) and Th1 associated cytokines (Fig. 1) that leads to chronic infection, enabling the parasite to establish to maturity within the large intestine and release eggs into the environment, thereby perpetuating infection. Trickle infections can also be used to more closely mimic a natural infection of repeated low-dose exposures. Weekly trickle infections promote an initial Th1 response but this changes to a dominant Th2 response after 9 weeks (Fig. 1), which prevents any further establishment of worms (Glover et al., 2019). Chronic infection, either in genetically susceptible mice or due to a low-dose infection and its associated Th1 response, are associated with dysregulation within the gut, such as crypt hyperplasia and apoptosis (Cliffe et al., 2007) together with a regulatory response that is required to limit worm-driven pathology (D’Elia et al., 2009; Grencis et al., 2014; Duque-Correa et al., 2019). Interestingly, reducing T regulatory (Treg) cells early on during a low-dose infection does have a small but significant effect on the capacity to expel parasites and subsequently intestinal pathology is reduced, suggesting that this induced Treg response is of benefit to both the host and to the parasite (Sawant et al., 2014). However, this effect on parasite expulsion was lost if Tregs were depleted once infection had become established (Sawant et al., 2014). A key cytokine produced by CD4+ T cells IL-10, is critical in host survival during *T. muris* infection (Schoepf et al., 2002) although whether Tregs are the major source of IL-10 during *T. muris* infection is unclear. TGF-β is another regulatory cytokine that is produced during *T. muris* infection that can dampen CD4+ T cell responses (Li and Flavell, 2008). As with the effects of an early reduction in Tregs, early ablation of TGF-β during a low-dose infection again caused a significant, although partial, reduction in worm numbers (Worthington et al., 2013). When the ability of dendritic cells to induce TGF-β was prevented, mice were able to clear a low-dose infection efficiently although this did not seem to be dependent upon the generation of Tregs (Worthington et al., 2013). Thus, it appears that the regulatory response generated by *T. muris* is complex and involves CD4+ T cells, Tregs, IL-10 and TGF-β contributing to the net result of a chronic infection.
with controlled intestinal inflammation. This review will discuss the differing effects that either low-dose or high-dose intestinal *T. muris* infection can have on both enteral and systemic responses in the host (Fig. 1).

**Intestinal inflammation**

Inflammatory bowel disease (IBD) in humans represents broadly two distinct immunological conditions; Crohn’s disease and ulcerative colitis. Disease onset is prompted in genetically susceptible individuals by atypical responses to microbiota or environmental cues such as diet and stress (Guan, 2019). The influence of human trichuriasis upon IBD has received little attention, with notable exceptions (Broadhurst et al., 2010). This study followed pathological and immunological changes in an individual with ulcerative colitis prior to and following self-treatment with *T. trichiura*. The data supported a modulatory role for whipworm infection upon disease severity with infection associated with disease remission. Due to the intestinal niche that *Trichuris* species inhabit, an effect upon inflammatory disease of the large intestine in the host might be expected. Mechanistically this can be explored in the mouse using *T. muris* together with murine models of IBD. It is plausible that *T. muris* infection may cause IBD symptoms while the host immune response to the parasitic infection could have implications on progression of intestinal inflammation. Specifically, it is known that a low-dose infection of ∼20 *T. muris* eggs will proceed to chronicity (Fig. 1), even in normally resistant strains of mouse, leading to an IFN-γ/Th17-driven disease (Levison et al., 2010) that is controlled by a concomitant IL-10 response (Grencis et al., 2014). Indeed, IL-10 knock-out (KO) and IL-10R KO mice develop severe pathology in response to *T. muris* infection (Schopf et al., 2002; Duque-Correa et al., 2019). This low-dose infection regime can be used to mimic colitis, leading to both phenotypic and transcriptional similarities to other widely used models of IBD (Levison et al., 2010; Foth et al., 2014). Of 32 genes that are known to be transcriptionally different during IBD, 30 are also found to be upregulated in the CD4+CD45RB T cell transfer model of colitis (te Velde et al., 2007). Nineteen of these 30 genes, including IFN-γ, were also found to be upregulated in chronic *T. muris* infection (Levison et al., 2010). Indeed, chronic *T. muris* infection shows a degree of similarity to all mouse models of Th1-driven colitis, both phenotypically and transcriptionally, though the degree of similarity does vary from model to model (Levison et al., 2010). Additionally, it has been shown that *T. muris* pathology and Crohn’s disease have overlapping QTL regions – overlapping regions of DNA suggesting common genetic parameters (Levison et al., 2013). To exemplify this, the role of two different cytokines have been shown to be important in both *T. muris* and colitis, IL-27 and IL-13. IL-27 is a potent stimulator of Th1 responses (Pflanz et al., 2002) and is more highly expressed in patients with IBD (Nemeth et al., 2017). However, IL-27 is also known to regulate Th17 responses and to stimulate IL-10 production and Treg generation (Awasthi

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**Fig. 1.** The whipworm *T. muris*, though caecal dwelling, can affect many other systems in the body. The immune response to *T. muris* is dose-dependent with different cytokines being produced in response to the different doses of eggs given which can lead to chronic infection (Th1) or expulsion (Th2). Each of the immune responses to the differing doses of eggs can impact different systems in the body as depicted by the arrows. As pictured, tumours are increased in size and number in a cancer model with chronic *T. muris*, pathology is increased in chronic infection and shows similarity to IBD, and hippocampus RANTES expression is increased with chronic *T. muris* infection. Changes in microbiota, lung effects and effects on other infections are also apparent with *T. muris* infection. (Created with BioRender.com)
Sulphate sodium (DSS)-induced colitis, which is Th1 driven, as decreased morbidity and mortality as compared to IL10 KO infection in IL-10 KO mice has been used to highlight the importance of IL-13 in controlling T. muris-induced pathology. IL-13Rα2 is the decoy receptor for IL-13 and reduces the bio-availability of IL-13 (Minty et al., 1993) that is upregulated during an acute resolving T. muris infection (Bancroft et al., 1998). IL-13 is a potent suppressor of TH1 responses in humans (de Waal Malefyt et al., 1993; Wynn, 2015), although its role in IBD is complex. Crohn’s disease is principally a TH1 and IFN-γ driven condition whilst ulcerative colitis is associated with increased TH2 cytokines such as IL-5 and IL-13 (Fuss et al., 1996, 2004). T. muris infection in IL-10 KO mice has been used to demonstrate the protective role of IL-13. In support of this, recent studies have shown that IL-13 acts to mediate recovery and repair in the gut following dextran sulphate sodium (DSS)-induced colitis, which is TH1 driven, as disease was improved in both IL-13Rα2 KO mice and in mice treated with a neutralizing IL-13Rα2 antibody (Karmele et al., 2019). Additionally, transcripts for IL-13Rα2 have been found to be elevated in human IBD biopsies suggesting a protective role for IL-13 in these patients (Arijis et al., 2009, 2010). Similarly, patients expressing a more active variant of IL-13, with a reduced affinity to the IL-13α2 decay receptor, had a lower risk of developing Crohn’s disease (Karmele et al., 2019).

Although T. muris infection can cause varied components of intestinal inflammation, the Treg response (D’Elia et al., 2009; Worthington et al., 2013; Sawant et al., 2014; Duque-Correa et al., 2019) that it also initiates has been taken as a basis for a potential approach to treat IBD. The pig whipworm T. suis has been used in human trials for treatment of both Crohn’s disease and ulcerative colitis with resulting remission of disease in some patients in small cohort studies (Summers et al., 2005a, 2005b) although no clinical improvement was seen in a larger cohort study (Schölmerich et al., 2017). Although the exact mechanisms of action are unknown, excretory/secretory (E/S) products of T. suis on epithelial cells in vitro have been shown to elicit IL-6 and IL-10 secretion (Parthasarathy and Mansfield, 2005). Additionally, when T. suis E/S products were added to bone-marrow-derived macrophages and dendritic cells, there was a reduction in secretion of pro-inflammatory cytokines and a strong enhancement of IL-10 secretion (Leroux et al., 2018). Remission of ulcerative colitis, following self-infection with T. trichiura, was associated with a marked elevation in IL-22 (an IL-10 family member) producing T cells which were hypothesised to promote intestinal repair by increasing goblet cell numbers and mucus production (Broadhurst et al., 2010).

**Barrier function in the intestine**

During infection, T. muris is known to cause epithelial dysregulation in the large intestine (Artis et al., 1999; Cliffe et al., 2007), a process which is also observed in human IBD (Strober et al., 2007). T. muris induced TNF-α and IFN-γ production drive apoptosis within the caecal crypts of the large intestine (Artis et al., 1999), which is thought to be in response to IFN-γ-induced epithelial cell hyperproliferation that also occurs (Cliffe et al., 2007) thus leading to a perturbation in intestinal homeostasis. Infection with T. trichiura, the human whipworm, may cause trichuris dysentery syndrome (Cooper et al., 1990) in children, which is also associated with an increase in TNF-α production by mucosal macrophages (MacDonald et al., 1994). Increased intestinal apoptosis is also known to lead to a dysregulation of barrier integrity with an associated increase in epithelial permeability in IBD patients (Schulzke, 2006; Mankertz and Schulzke, 2007). During acute T. muris infection (whereby the worms are expelled before chronicity, Fig. 1), there is an accumulation of epithelial mast cells in the large intestine (Sorobeta et al., 2017). Mast cells produce mast cell protease-1 (MCP-1) (Metcalfe et al., 1997) and indeed, acute T. muris infection is associated with an increase in MCP-1 both systemically and locally in the large intestine, which is associated with a loss of barrier integrity leading to increased epithelial permeability (Sorobeta et al., 2017). T. muris infection in IL-10 KO mice is known to result in marked mortality and morbidity including a loss of Paneth cells and an absence of mucus (Schopf et al., 2002). Pathology in IL-10 KO and IL-10/IL-4 KO mice is also associated with bacterial outgrowth as broad-spectrum antibiotic treatment enhances survival (Schopf et al., 2002). Duque-Correa et al. (2019) also showed that IL-10 signalling had a protective effect on loss of barrier integrity leading to bacterial translocation. It is also known that T. suis E/S can affect barrier integrity by reducing the expression of tight junction proteins (Hemstra et al., 2014) although whether this is also a function of T. muris E/S is unknown. However, Hasnain et al. (2012) showed that adult T. muris E/S was able to degrade intestinal mucus and T. muris-induced changes in the intestinal mucus barrier have also been demonstrated that may act to increase intestinal permeability (Hasnain et al., 2010, 2011). Infection itself can lead to thickening of the glycocalyx, the glycoprotein and glycolipid covering of the intestinal epithelial cells (Linden et al., 2008) likely due to the increased production of mucus proteins. However, there is also a decreased glycoprotein content within the mucosal barrier during chronic infection that may allow increased contact of the intestinal microbiota with intestinal epithelial cells (Hasnain et al., 2011). Congruous to this, chronic T. muris infection can also alter the host intestinal microbiota (Holm et al., 2015; Houlden et al., 2015) and it is known that a modification in the composition and function of the gut microbiota can also change intestinal permeability (Gomaa, 2020).

**Microbiota changes in the intestine**

Changes in microbiota during a T. muris infection are evident from as early as only day 14 post-infection (p.i.). By the time that infection has reached latency (more than day 33 p.i.), there are significant changes in the composition and diversity of the microbiota (Fig. 1) (Holm et al., 2015; Houlden et al., 2015). There was a general shift in the microbiota to a decreased number of bacteria in the Bacteroidetes phyla and an increased number of Gram-positive Lactobacillaceae. Such changes in the microbiota appear to be of benefit to the parasite and changes were transitory and required the presence of the parasite to be maintained (White et al., 2018). In contrast, changes in microbe composition in an outbred strain of mouse with a chronic T. muris infection led to an increase in bacterial invasion of the host intestinal epithelium (Schacht et al., 2020). Interestingly, infection-induced microbiota changes can also promote resistance to damage. In a colitis-susceptible strain of mouse (NOD2 KO), it...
has been established that overgrowth of Bacteroides vulgatus leads to intestinal abnormalities (Ramanan et al., 2014). However, acute infection with T. muris, that drives a Th2 response and a mucus response, led to an increase in Clostridia strains of bacteria that inhibited B. vulgatus colonization and the resulting B. vulgatus-driven abnormalities (Ramanan et al., 2016). The microbiota of the host can also directly influence pathogenesis of T. muris as antibiotic treatment of chronically infected IL-10 KO animals, although experiencing similar pathology to control animals, had a significantly reduced mortality (Kopper et al., 2015). Chronic infection induced changes to microflora have also been shown in T. suis infected pigs (Li et al., 2012) although there is contrasting evidence as to whether the human whipworm also drives microflora changes (Cooper et al., 2013; Ramanan et al., 2016).

**Trichuris effects distal to the site of infection**

Despite its intestinal epithelial location, the effects of T. muris infection are not only restricted to the site of infection. Chronic T. muris infection can modulate responses to chemical skin sensitizers applied to the ear of the mouse. Suppression of local cellular/cytokine Th1/pro-inflammatory responses and ear pathology were observed when using a Th1-promoting compound [2,4-dinitrochlorobenzene (DNDCB)] although no depression in IL-13, or ear swelling was noted after sensitizing with the Th2-promoting compound trimelitic anhydride (TMA). Interestingly, the suppression of pathology after DNCB treatment was associated with a reduction in egress of dendritic cells (DCs) from the skin coincident with elevated IL-10 production (Cumberbatch et al., 2000).

**T. muris effects in the lungs**

Chronic T. muris infection which drives a strong Th1 response in the intestine, has also been shown to drive the production of IFN-γ (by Th1 cells) and IL-10 (myeloid cells) in the lung of the host (Fig. 1), and so has the potential to suppress the development of Type-2-driven airway inflammation (Chenery et al., 2016). The increased Th1 type response in the lung was able to reduce the lung response to both papain and house-dust mite, together with a reduced eosinophil infiltration and reduced lung mucus production. IL-17 is another cytokine known to be increased in complex asthma and may contribute to disease progression (Doe et al., 2010); additionally, IL-17 is critical for neutrophil expansion and remodelling of lung tissue and may contribute to disease progression in other chronic respiratory conditions (Gurczynski and Moore, 2018). A high-dose injection of T. muris, that induces a Th2 response (Fig. 1), can promote a mixed IL-17 and Th2-type immunity to the parasite (Wilson et al., 2011). Induction of Th2 cytokines can also be seen in the host lung following infection with a high dose of T. muris; however, this is dependent on IL-17 production and is ablated in an IL-17 KO animal (Ajendra et al., 2020). Interestingly, this IL-17-dependent suppression of IFN-γ, which allowed the promotion of type-2 immune responses, was only apparent in the host lung and was not seen in the intestine. Additionally, a secreted product from T. muris, p43, is able to bind to IL-13 in vitro and in vivo (Bancroft et al., 2019). When given to mice intranasally with IL-13, p43 reduced the percentage of RELM-β positive interstitial lung macrophages as compared to mice treated with IL-13 only. The effects of p43 are further reviewed in this special issue by Bancroft & Gencis. By-stander effects of Trichuris infection in the lung are also seen with other species of Trichuris.

**T. suis cerebrovascular and neurodegenerative disease**

It is well established that infection and systemic inflammation are risk factors for ischaemic brain damage (stroke) and can also affect the progression of some neurodegenerative disorders (He et al., 2020).

Using transient middle cerebral artery occlusion as a model of stroke it was shown that a chronic low-dose T. muris infection, which drives a Th1 response (Fig. 1), dramatically exacerbated brain damage caused by experimental stroke (Dènes et al., 2010). Infection led to an increase in pro-inflammatory mediators in the brain and surrounding tissue together with an altered Treg response. Infected mice had elevated Th1-associated cytokines and chemokines after cerebral artery occlusion however, only CCL5 (RANTES) stayed significantly increased after 48 hours post-stroke. Anti-RANTES treatment prevented the infection-driven exacerbated of stroke-induced damage. Analysis of matrix metalloproteinase 9 expression in the brain showed elevated levels after stroke and infection compared to stroke alone indicating augmented vascular injury and blood–brain barrier damage in chronically infected animals. Interestingly, an acute, resolving T. muris infection driving a Th2 response had no effect on infarct size demonstrating that it was the Th1 milieu driven by the parasite that was detrimental rather than the parasite itself (Dènes et al., 2010). The detrimental effects of infection are also very much dependent on age as infarct size was found to be significantly increased in chronically infected aged mice as compared to chronically infected young mice (Dhungana et al., 2013). Older mice experienced an increased neutrophil recruitment and upregulation of Th1 cytokines as compared to the younger mice leading to the increased pathology seen.

As well as stroke, it has also been demonstrated that chronic T. muris infection can accelerate the onset of experimental clinical prion disease – a chronic, neurodegenerative disease caused by infectious proteins (Donaldson et al., 2020). Mice were infected with a chronic T. muris infection after receiving prions, timed so that the peak of parasite-driven inflammation would coincide with known pre-clinical phases of the prion infection. T. muris infected mice had a reduced survival time which correlated with increased pro-inflammatory cytokines in the sera and increased numbers of CD8+ cells in the brain (Donaldson et al., 2020). T. muris infection can also exacerbate neuroinflammation in models of Alzheimer’s disease, a chronic neurodegenerative condition (Querfurth and LaFerla, 2010; Montacutu et al., 2017). Infection in the Alzheimer’s mouse model (3xTg-AD) led to increased levels of inflammation in the brain with increased microglia activation. Interestingly, these transgenic animals were also unable to fully expel a high-dose infection, which is normally acute and resolving (Fig. 1), together with increased Th1 cytokine levels in response to infection in the lymph node draining the large intestine (Montacutu et al., 2017). Although not addressed in any T. muris infection model, T. suis E/S effects in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS), have been assessed (Kuijk et al., 2012; Hansen et al., 2017). Intraperitoneal administration of T. suis E/S before
disease onset significantly decreased disease severity and markedly reduced systemic Th1 and Th17 responses (Hansen et al., 2017). However, T. suis ova therapy in MS clinical trials have had mixed effects (Voldsgaard et al., 2015; Fleming et al., 2019; Yordanova et al., 2021).

**Trichuris and coinfections**

Surprisingly little work has been carried on coinfections of *T. muris* and viral or bacterial infections though some work has been done with *Mycobacteria* and *Streptococcus*. Immunity to *Mycobacterium bovis* (*M. bovis*) infection has been shown to be negatively influenced by a *T. muris* coinfection. A high-dose *Mycobacterium* infection, which promotes a Th2 response, downregulated pulmonary Th1 and Treg cell responses to the bacteria (Fig. 1) (Nel et al., 2014) although this had no effect on bacterial proliferation and dissemination. However, *T. muris* E/S-treated human monocyte-derived macrophages prior to exposure to *M. tuberculosis* led to an M2-type polarization with reduced macrophage phagosome maturation and a resulting increased bacterial burden (Aira et al., 2017). In a *T. muris*-Streptococcus pneumoniae coinfection model, nematode infection was associated with an increased carriage of *S. pneumoniae*, though this did not reach significance, with a significant increase in dissemination of the bacteria to the lungs (Law et al., 2021). Anthelmintic treatment led to a smaller, though not significant, load of bacteria. This trend for a higher carriage of bacteria when coinfected with *Trichuris* was similarly seen in children harbouring *T. trichiura* (Law et al., 2021).

Protozoan infections such as *Plasmodium berghei*, *Trypanosoma brucei* and *Babesia microti* and *B. hylomysci* will all delay the expulsion of a high dose of *T. muris* infection, particularly at times of high parasitaemia suggesting that at least acute *T. muris* infections do not exert strong immunomodulatory effects on these co-infections (Phillips and Wakens, 1974; Phillips et al., 1974).

More data are available on the effect of *T. muris* infection on other helminth infections. Experimental infection of *Nematospiroids dubius* (*Heligmosomoides polygyrus* (bakerii)), which resides in the small intestine, delayed expulsion of a high dose *T. muris* infection and enhanced survival of a trickled *T. muris* infection (Behnke et al., 1984). The lung, like the gut, is a mucosal surface and many helminth parasites have evolved a migratory phase through the lungs in their life cycle (Craig and Scott, 2014). Cross-talk between the lung and intestinal mucosal surfaces in terms of host immunity is particularly evident during helminth co-infections. *Nippostrongylus brasiensis* is a rodent small intestine dwelling parasite that migrates through the host lung before reaching maturity (Bouchery et al., 2017). Intestinal infection with a high dose of *T. muris*, that promotes a Th2 response and is expelled by the host (Fig. 1), reduced the number of *N. brasiliensis* larvae found in the lung at d2 post-infection (Filbey et al., 2019). Interestingly, mice that had been given a trickle infection of *T. muris* (initially driving a Th1 response and then a protective Th2 response) and then a *N. brasiliensis* infection, after the switch to a Th2 dominated response, had an equivalent number of larvae in the lung at d3 post-infection as WT mice (Glover et al., 2019). This suggests either a resolving delay in *N. brasiliensis* migration in the lung as equivalent numbers of adults were found in the intestine (Glover et al., 2019) or a qualitative difference in the Th2 response initiated by a high dose as compared to a trickle infection.

*T. muris*-induced alteration in the lung cytokine expression has also been demonstrated in co-infection with *Schistosoma mansoni* (Bickle et al., 2008). *S. mansoni* is a trematode that causes chronic infection in mice, causing pathology in the lungs as it migrates (Boros, 1989). Chronic infection with *T. muris* led to a reduced trapping of larvae during their skin-to-lung migration associated with an altered lung cytokine expression. Interestingly, co-infected lungs had a lower expression of IFN-γ despite the *Trichuris*-driven Th1 response, and it was actually an IL-10-dominated response that appeared to limit antilarval schistosomula immunity (Bickle et al., 2008) and allowed progression of the parasite to the portal system with resulting increased egg burden and pathology in co-infected mice. Conversely, a chronic *T. muris* infection can be resolved by a *Schistosome* coinfection due to the *S. mansoni* egg-induced Th2 response (Curry et al., 1995). Additionally, *S. mansoni* and *T. muris* coinfected mice had significantly higher burden of adult *Schistosome* worms and eggs in the liver (Bickle et al., 2008) thus demonstrating that contrasting effects that the infections can have on one another.

**Trichuris and neoplasia**

Cancer is a leading cause of death in high-income countries and incidences are increasing in low-income countries. There exists a strong link between inflammation and cancer with chronic infection and the long-term exposure to inflammatory stimuli heightening the risk of neoplastic change (Wang and Wang, 2007).

Chronic *T. muris* infection at day 80 p.i. in a wild-type mouse led to the development of neoplastic change that was similar to that seen in mice that had been treated with the carcinoigen azoxymethane (Hayes et al., 2017). Intestinal crypt structure was altered alongside increased incidence of pre-adenomas which were more pronounced (in the case of aberrant crypt foci) in the infected mice as compared to the chemically treated mice. Even though *T. muris* infection can lead to increased epithelial proliferation and apoptosis in the intestine (Artis et al., 1999; Cliffe et al., 2007), both of which can lead to tumour formation (Evan and Vousden, 2001) these intestinal changes were only apparent in the caecum, the parasite niche, rather than throughout the small intestinal tract where neoplastic change was mostly observed (Hayes et al., 2017). Neoplastic change was seen in chronically infected animals even before the peak of parasite-specific cytokine responses was evident in the draining lymph node, although greater significant differences were seen as infection progressed. Infection generated a Th1-predominant response in these animals, however, this was not associated with a reduced neoplasia as might have been expected (Wang et al., 2015).

The APCmin+ tumour model in the mouse develops spontaneous adenomas throughout the GI tract (Moser et al., 1990). Chronic infection of APCmin+ mice with *T. muris* led to a significant increase in new tumour formation throughout the intestine and not just an increase in tumour size. Blockade of the CD25+ Treg response abrogated this heightened tumour formation demonstrating the role of the *T. muris*-induced Tregs in regulating the anti-tumour response in these animals (Hayes et al., 2017). Tregs have also been characterized within tumour microenvironments that can induce tumour-specific immune tolerance (Wang and Wang, 2007). Clonal expansion of tumour Tregs is thought to occur both locally and systemically and a high proportion of Tregs with one tumour microenvironment is correlative with poor prognosis in many cancer types suggestive of the suppressive role of Tregs on anti-tumour immunity (Mougiaikos, 2011; Fridman et al., 2012; Ahmadzadeh et al., 2019). Interestingly *T. suis* E/S proteins are capable of stimulating the secretion of IL-10 from macrophages though failed to induce CD25+Foxp3+ T cells unlike *T. muris* E/S which was able to do this (D’Elia et al., 2010; Leroux et al., 2018). Additionally, increased mucosal T cell activation production of IL-10, TGF-β and FoxP3 were found in the colon of an individual with ulcerative colitis who self-infected with *T. trichiura* (Dige et al., 2017). Tregs are known to play a role in both pathology and immunity early on following chronic *T. muris* infection as are TGF-β and IL-10.
T. muris is an intestinal dwelling nematode parasite that can have far-reaching consequences in the host (Fig. 1). Within the intestine itself, chronic T. muris in susceptible strains can have pathological consequences that show a degree of similarity to symptoms of IBD. Indeed, several genes upregulated during a chronic T. muris infection are also found to be upregulated in IBD patients. Paradoxically, T. muris infections can also help modulate IBD symptoms and pathologies due to the parasite-specific Th2 response driven by infection. T. muris also drives microbiota changes in the host, beneficial to its survival, that have consequences for the host due to the impact that these changes can have on mucus constituents and intestinal permeability. Distal from the site of infection, T. muris infections can have an impact on immune responses to chemical sensitizers in the ear. In this case, a chronic T. muris driven IL-10 production preventing the egress of DCs from the ear. Chronic T. muris infection can also modulate immune responses in the lung to airway allergens which was also associated with an increased IL-10 response. T. muris infection can also influence immune responses in the brain and it has been demonstrated that an on-going T. muris-driven Th1 response will worsen the damage caused by experimental stroke, a process driven by an elevated and sustained RANTES production. Additionally, T. muris can have an effect on other brain inflammations with papers reporting changes in prion diseases and Alzheimer’s progression. Although relatively little work has addressed the effects of T. muris on other parasites, viral and microbial infections, altered immunity to mycobacteria, pneumococcus, *N. brasiliensis*, *H. bakerii* and *S. mansoni* have been reported. Finally, effects of T. muris infection on cancer progression establish that the T. muris-driven Treg response plays an important role in inhibiting host immunity to adenoma progression in the intestine leading to development of more tumours. Additionally, two other regulatory cytokines, IL-35 and IL-31, induced by T. muris infection are able to modulate tumour immunity. In light of this, the importance of T. muris infections on other diseases and other body systems is profound and warrants further research and investigation, especially considering the widespread nature of this parasite in the human population.

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Parasitology


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