

Gut motor function: immunological control in enteric infection and inflammation

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Summary

Alteration in gastrointestinal (GI) motility occurs in a variety of clinical settings which include acute enteritis, inflammatory bowel disease, intestinal pseudo-obstruction and irritable bowel syndrome (IBS). Most disorders affecting the GI tract arise as a result of noxious stimulation from the lumen via either microbes or chemicals. However, it is not clear how injurious processes initiated in the mucosa alter function in the deeper motor apparatus of the gut wall. Activation of immune cells may lead to changes in motor-sensory function in the gut resulting in the development of an efficient defence force which assists in the eviction of the noxious agent from the intestinal lumen. This review addresses the interface between immune and motor system in the context of host resistance based on the studies in murine model of enteric nematode parasite infection. These studies clearly demonstrate that the infection-induced T helper 2 type immune response is critical in producing the alterations of infection-induced intestinal muscle function in this infection and that this immune-mediated alteration in muscle function is associated with host defence mechanisms. In addition, by manipulating the host immune response, it is possible to modulate the accompanying muscle function, and this may have clinical relevance. These observations not only provide valuable information on the immunological control of gut motor function and its role in host defence in enteric infection, but also provide a basis for understanding pathophysiology of gastrointestinal motility disorders such as in IBS.

Keywords: Gut motility, infection, inflammation, immune response, smooth muscle

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Introduction

The majority of disorders afflicting the gastrointestinal (GI) tract arise as a result of noxious stimulation from the lumen, via either microbes or chemical. Conditions ranging from infective acute enteritis or colitis to chronic inflammatory bowel diseases (IBDs) and functional disorders such as irritable bowel syndrome (IBS) are accompanied by altered motility. However, in the absence of any major structural abnormality such as an obstruction or deep ulceration, it is unclear how injurious processes initiated in the mucosa change function and/or structure in the deeper neuromuscular layers. For the most part, overt responses to noxious stimuli result in an inflammatory response that is usually limited to the mucosal compartment and may result in

innate and adaptive immune responses. Interaction between adaptive and innate components of immune response is required to play an effective total response against any invading agent. Activation of immune cells may lead to changes in motor-sensory function in the GI tract resulting in the development of an efficient defence force which assist in the eviction of the noxious agent from the intestinal lumen. This review will address the studies on immunological basis of altered GI motor function in the context of host resistance in enteric infection, providing linkage between a variety of clinically relevant pathophysiological processes and the development of various symptoms reflecting changes in the neuro-muscular tissues of the gut wall such as pain, bloating, distension, vomiting, diarrhoea, and constipation. These studies have been performed using animal models to

generate new concepts regarding the relationship between immune system and neuromuscular tissues, and to develop models reminiscent of several important functional GI disorders.

Clinical point of view

Among the GI illness, functional disorders are the most common category which consists of entities like IBS and functional dyspepsia. They are characterized by disorders of function with preservation of the structural integrity of the GI tract. This definition does not, however, rule out subtle quantitative or qualitative changes in the cellularity of the lamina propria or, indeed, in the deeper neuromuscular tissues that are seldom, if ever, accessed through biopsies. IBS is a very common condition, and is as likely to be heterogeneous in its pathogenesis as it is in its clinical presentation. Two major mechanisms may interact in this disorder: altered GI motility and increased sensitivity [1,2]. Altered motility in IBS includes changes in whole gut transit, colonic propagating contractions, and ascending and transverse colon emptying [3]. Recent work has emphasized the role of acute gastroenteritis as a precipitating factor in the development of a chronic IBS-like syndrome termed postinfective IBS [4,5]. It has been suggested based on retrospective analysis that up to one-third of all IBS patients may have had an acute infection to precipitate their symptoms. In addition, there is evidence of subclinical inflammation and immune activation in the mucosa of some patients with IBS, and this is not necessarily restricted to those patients with an infective aetiology [6]. In overt inflammatory conditions of the bowel, such as Crohn's disease and ulcerative colitis, there have been longstanding observations of altered motility and intestinal muscle contractility [7,8]. Chronic intestinal pseudo-obstruction is another GI illness represented by chronic intestinal dilatation and dysmotility in the absence of mechanical obstruction or inflammatory disease [9,10].

Under normal circumstances, inflammatory or immune cells are found infrequently in the neuromuscular tissues of gut. Yet, it is evident that in conditions associated with overt inflammation (Crohn's disease or ulcerative colitis), in pseudo-obstruction and in cases of severe IBS, these tissues become infiltrated to varying degrees, by immune cells with a particular predilection, it appears, for lymphocytes. The remainder of this review will address the findings obtained from the studies in animal model on the influence of immune cells in the context of host resistance.

Experimental studies

Models of nematode parasite infection are of considerable importance in exploring the pathophysiology of many GI disorders and over the past decade our laboratory has used primary infection of rats or mice with the nematode

Table 1. Advantages of animal model of *T. spiralis*.

Widely used nematode model for understanding inflammatory changes and host defence.
Biology and host immunity well defined.
Presence of natural biological end point in the eviction of parasites from the gut.
Distinct Th2 type immune response is useful to understand the immune regulation of gut physiological changes.
Altered motility is associated with the primary infection.

Trichinella spiralis as a model to study the interface between the immune and motor systems. The choice of this model is based on the existence of an extensive literature regarding the inflammatory and immune responses to this parasite (Table 1), and by the fact that many of the ingested parasites in this model are eventually evicted from the gut. That is, they retain their viability and fecundity. Thus, in large part, a process of expulsion occurs and this forces attention on the role of the motor system in promoting the expulsion of these parasites from the intestine. Indeed, earlier studies showed that in segments of extrinsically denervated intestine taken from animals with a primary infection with the nematode parasite *T. spiralis*, when examined *ex vivo* following extrinsic denervation, demonstrated clear-cut and enhanced propulsive motor activity [11]. This finding showed that the enhanced propulsive power of the motility apparatus has its origin, at least in part, in the tissues intrinsic to the gut wall, thus implicating enteric nerves and muscle. These observations provided the platform for embarking on a series of *in vitro* experiments designed at understanding the interface between activation of the mucosal immune system by this parasite, and the resulting changes in enteric muscle function.

The measurement of muscle contraction as a surrogate marker of intestinal motility

The final common pathway in the regulation of intestinal motility is the contractility of intestinal muscle. This can be easily evaluated *in vitro* using a longstanding tissue bath approach. Intestinal muscle strips are suspended along a longitudinal axis in an organ bath containing oxygenated Krebs buffer. The strips are attached at one end to a force transducer and responses are recorded on a polygraph. By incremental increase in the stretch applied in the longitudinal axis of the muscle, the optimum tension of contractile studies is determined and the tissue is then exposed to various agonists or antagonists and isometric contraction assessed. Clearly, changes in contractility observed *in vitro* cannot be extrapolated directed into the *in vivo* situation. Consideration must be made of the influences of enteric nerves, the interstitial cells of Cajal, and endocrine factors. In addition, the roles of circular and longitudinal muscle differ in terms of their contribution to peristaltic activity. Nevertheless, muscle contractility is an acceptable and convenient method of assessing

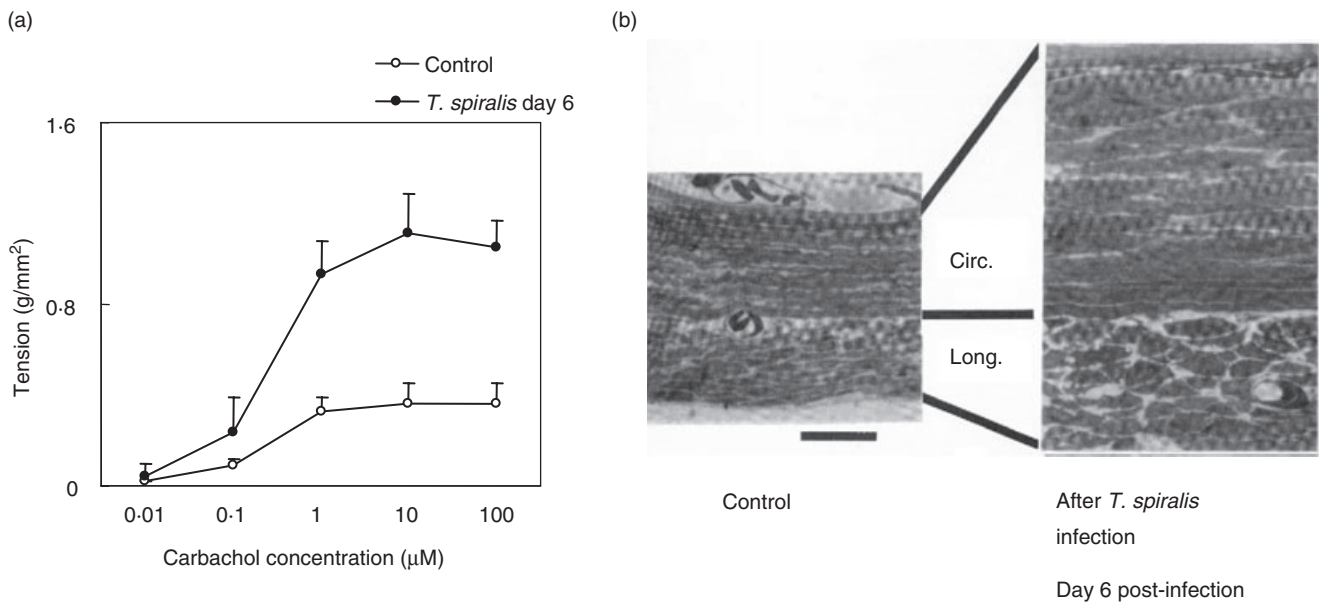


Fig. 1. Response of intestinal muscle from control and *T. spiralis* infected rats. (a) Dose–response relationships for carbachol-induced tension generation by intestinal muscle from control non-infected (\circ) and *T. spiralis* infected (\bullet) rats. Rats were infected orally with *T. spiralis* and killed at day 6 postinfection [12]. (b) Light micrographs of cross sections of *muscularis externa* of rat jejunum before and after *T. spiralis* infection, showing increased size of longitudinal and circular smooth muscle layers in the inflamed jejunum [14].

how inflammatory and immune cells alter this component of intestinal motility.

Initial studies by Vermillion & Collins [12] from our laboratory clearly show a significant enhancement in intestinal muscle contractility in response to carbachol during primary infection of rats with *T. spiralis* (Fig. 1). Subsequent studies in mice also revealed a significant increase in intestinal muscle contractility following *T. spiralis* infection [13]. In applying this technique to studies on infection-induced changes in contractility, notice is taken of the hyperplasia and hypertrophy of muscle seen in this model [14]. Thus, force generation is expressed by unit cross-sectional area of the muscle along the axis of the contraction.

Relationship between inflammatory response and alteration in intestinal muscle contractility

To address the question of whether the alterations in muscle contractility during infection occur as a result of the presence of parasites in the gut or the host's inflammatory response to them, *T. spiralis* infected rats were treated with corticosteroid and the myeloperoxidase (MPO) activity was investigated to evaluate the inflammatory response in the mucosa. MPO is an enzyme contained in the azurophilic granules of neutrophils and other myeloid cells and is commonly used as an index of neutrophil infiltration and acute inflammation [15]. Treatment with corticosteroid inhibited the increase of MPO activity following infection and this was accompanied by an attenuation of intestinal muscle contractility [16]. This study implicates that the inflammatory

process rather than the parasite as the cause of altered intestinal muscle contractility.

Immunological basis for altered intestinal muscle function

Role of innate immune response

Macrophages

Macrophages are the sentinels of the immune system. These cells perform a key role in innate defence against foreign invaders and modulate adaptive immune responses. In addition, macrophages produce a number of cytokines (low molecular weight proteins secreted from various cells which regulate the immune response) like interleukin (IL)-1, IL-6 and TNF- α , which play a variety of roles in nonspecific body defence. Macrophages infiltrate the gut including the neuromuscular layers during *T. spiralis* infection in mice and there is increased expression of pro-inflammatory cytokines IL-1 β , TNF- α and IL-6.

To determine the role of macrophages in the induction of muscle hyper-contractility, the experimental strategy was to deplete intestinal macrophages and observe whether this affected the generation of muscle hyper-contractility in infected mice. Liposomes (artificially prepared lipid vesicles) were used to encapsulate dichloromethylene diphosphate (clodronate, Cl2MDP), which induces the apoptosis of macrophages [17]. Treatment of mice with clodronate containing liposomes effectively depleted macrophages and

attenuated the inflammatory response to *T. spiralis* infection. However, muscle hyper-contraction was unaffected, implying that macrophages are not critical for the change in muscle contraction [18].

NK T cells

NK T cells are an unusual population of T cells, which coexpress receptors for T and NK cells, and these cells are considered to be a source of early IL-4 [19]. Murine CD1d1 has been implicated in the development and function of NK T cells [20]. Recently we have investigated the intestinal muscle contractility and host protective immunity during *T. spiralis* infection in CD1d1 mutant mice, which are deficient of NK T cells. Preliminary data suggest that absence of NK T cells in CD1d1^{-/-} mice is associated with the reduction of infection-induced muscle hypercontractility and IL-4 in the early stage of this nematode infection [21].

Role of adaptive immune response

T cells

T lymphocytes are crucial in many immune responses, including those associated with intestinal nematode infection. Previous studies have demonstrated the infiltration of muscle layers by T lymphocytes during *T. spiralis* infection and ultrastructural analysis revealed close communication between lymphocytes and muscle cells indicating the possibility of a direct interaction between these cell types [22].

To investigate the role of T cells, we used mice that were either deficient in T cells (athymic mice), or in T helper cells (CD8⁺ or CD4⁺ cell deficient mice) or where incapable of T cell activation by virtue of the absence of the major histocompatibility complex II (MHC II) [23,24]. Infection induced intestinal muscle hypercontractility is T cell dependent because changes were attenuated from infected athymic mice and this was accompanied by reduced parasite expulsion, indicating the presence of a common immunological basis in muscle function and worm expulsion in this model. The role of CD8⁺ T cells seems to be not significant as there was no difference in the development of infection induced intestinal muscle hypercontractility and in worm expulsion between CD8 deficient and wild type mice. However, CD4⁺ T cells appeared to play a role, since CD4 deficient mice exhibited reduced muscle contractility. MHC II deficient mice showed greatest attenuation in the development of muscle contractility and also exhibited noticeably delayed worm expulsion. Reconstitution of T cell function in athymic mice by injecting splenic lymphocytes from euthymic mice prior to infection with *T. spiralis* restored intestinal muscle hypercontractility and normal worm expulsion from the gut. To examine the role of CD4⁺ cells further, MHC II deficient mice were reconstituted with purified CD4⁺ T cells and the effect on intestinal muscle contractility was assessed

following infection. The partial restoration of muscle hypercontractility during subsequent infection identified a role for T helper cells.

Th1/Th2 cells

In association with MHC II molecules, antigen presenting cells (APC) present antigens to CD4⁺ T helper (Th) cells. Th cell-dependent immune responses are generally divided into two major subsets, Th1 and Th2 [25]. Th1 cells predominantly produce IFN- γ and IL-2, while Th2 cells produce IL-4, IL-5, IL-9, and IL-13. Th1 and Th2 cross regulate one another. IFN- γ secreted by Th1 cells directly suppresses IL-4 production and thus inhibits the differentiation of naïve Th cells into Th2 cells. In contrast, IL-4 and IL-10 inhibit the secretion of IL-12 and IFN- γ , blocking the polarization into Th1 cells. Th2 type of immune response is predominantly associated with protective immunity in nematode infection. Although IL-4 is the key cytokine in the development of Th2 type immune responses, recent studies suggest the involvement of another closely related cytokine, IL-13 [26]. IL-4, and IL-13 share the alpha chain of IL-4 receptor and occupation of this receptor results in the activation of signalling pathway involving the activation of signal transducer and activator of transcription factor 6 (Stat6) through phosphorylation by Janus kinases 1 and 3 [27]. Once activated, Stat6 proteins form homodimers, translocate to the nucleus, and bind to promoter regions to regulate gene transcription. Studies using Stat6 deficient (Stat6^{-/-}) mice clearly indicate that the Stat6 pathway is critical in the differentiation of Th cells towards Th2 phenotype [28]. To determine whether a similar pathway is involved in mediating muscle hypercontractility in this model, we studied Stat6^{-/-} mice to investigate *T. spiralis*-induced muscle contractility. We observed marked attenuation in infection-induced intestinal muscle contractility in Stat6^{-/-} mice compared with the wild type mice (Fig. 2) and this was accompanied by delayed worm expulsion from the intestine [29]. We were also able to demonstrate the presence of IL-4 and IL-13 in the muscularis externa layer during the primary infection with *T. spiralis* and IL-4R alpha in the dispersed intestinal muscle cells [29,30]. These observations indicated that Th2 cytokines, IL-4 and IL-13, acting via Stat6, mediate the development of nematode infection induced intestinal muscle hypercontractility and that this, in turn contributes to the worm expulsion process.

Very recently it has been reported that IL-4 and IL-13 play an important role in the generation of intestinal muscle contractility in mice infected with *N. brasiliensis* and *Heligossomoides polygyrus* [31] further supporting our hypothesis that Th2 responses mediate muscle contractility in nematode infection.

To evaluate the role of another Th2 cytokine, IL-9, we used the strategy of immunoneutralization. We observed that although administration of exogenous IL-9 improved

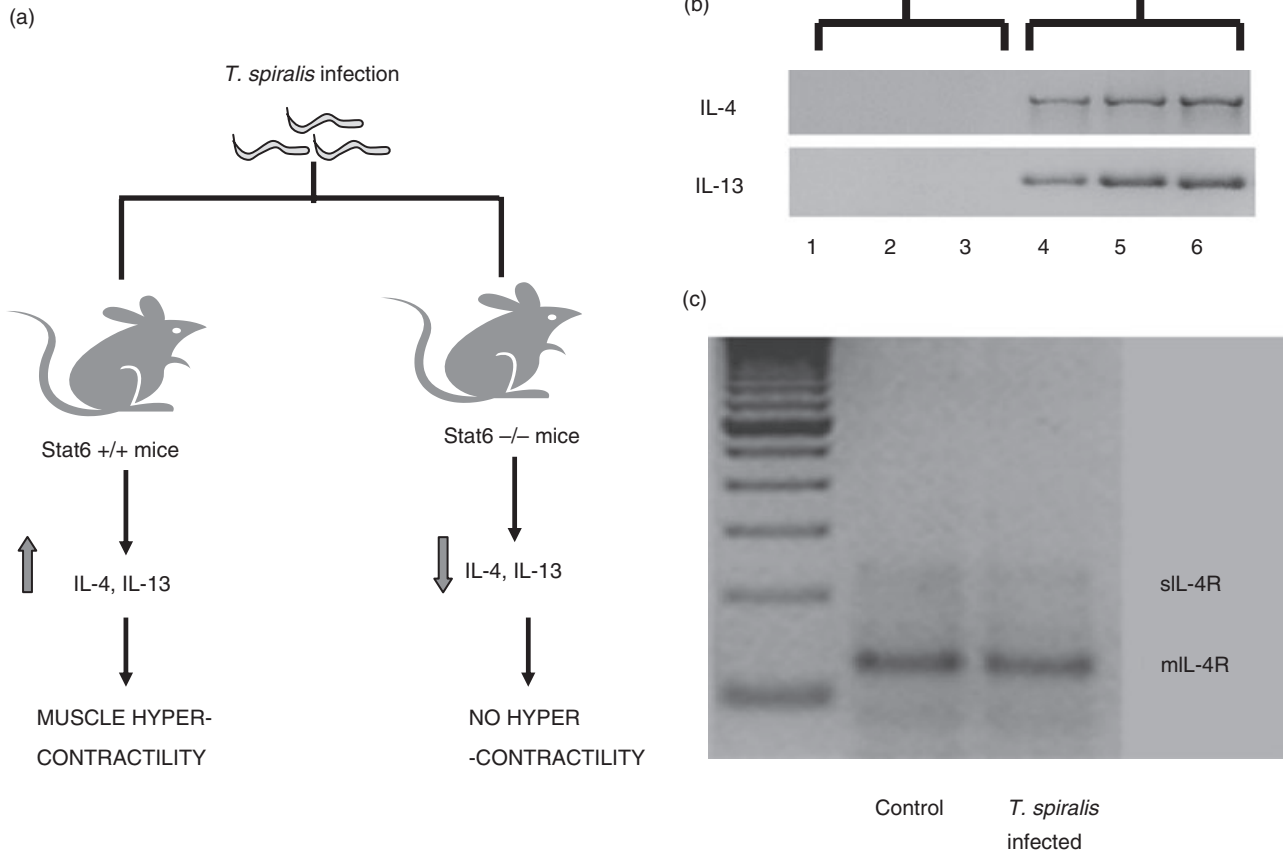


Fig. 2. (a) Intestinal muscle contraction and cytokine response in *T. spiralis* infected Stat6 deficient (Stat6 $-/-$) and wild type (Stat6 $+/+$) mice [29]. (b) Cytokines gene expression in muscularis externa of uninfected control (lanes 1–3) and *T. spiralis*-infected (lanes 4–6) mice. C57BL/6 mice were infected with *T. spiralis* orally and killed on day 6 p.i. to investigate expression of the IL-4, IL-13, and IFN- γ genes [29]. (c) IL-4 receptor (IL-4R) mRNA expression in dispersed longitudinal smooth muscle cells from control and *T. spiralis*-infected mice. sIL-4R, soluble IL-4R; mIL-4R, membrane IL-4R [30].

infection induced intestinal muscle contractility and worm expulsion in *T. spiralis* infection, neutralization of endogenous IL-9 had no significant effect on muscle contraction and worm expulsion [32]. Taken together these observations show that although a Th2 immune response is critical for the expression of muscle hypercontractility in *T. spiralis* infection, not all Th2 cytokines are involved; IL-4 and IL-13 play critical roles whereas IL-9 does not.

To further evaluate the role of Th1/Th2 in infection-induced alteration of enteric muscle function, studies were done to investigate the effect of the over expression of IL-12 on intestinal muscle contractility and on worm expulsion in *T. spiralis* infected mice. IL-12 is a key cytokine in the differentiation of CD4 $+$ Th cells toward Th1 associated responses by stimulating production of IFN- γ by Th and natural killer cells (33). It has been reasoned that if the Th2 response is critical for both the development of changes in intestinal muscle function and the expulsion of the worms, then shift of the Th2 response towards Th1 response should not only

prolong the infection but also attenuate infection-induced muscle hypercontractility. Indeed, that is the case and a shift to Th1 response by over expression of IL-12 significantly altered intestinal muscle hypercontractility in this Th2 based enteric infection (34). Recombinant adenovirus vector was used for transferring and over expressing IL-12 gene. Adenovirus vector is replication deficient vector and is highly infectious and effectively express high level of target gene. IL-12 gene transfer using a single injection of recombinant adenovirus vector expressing IL-12 (Ad5IL-12) in *T. spiralis* infected mice effectively inhibited the development of infection-induced intestinal muscle hypercontractility and prolonged worm survival in the gut. This was accompanied by up regulation of the Th1 cytokine IFN- γ and down regulation of Th2 cytokine IL-13 in the *muscularis externa* of the intestine and increased IFN- γ production and decreased IL-4 and IL-13 production from *in vitro* stimulated spleen and mesenteric lymph node cells. These findings strongly suggest that intestinal muscle hypercontractility and worm

expulsion share a common immunological basis regulated by Th2 type immune response and may be causally linked.

Role of CD40–CD40 ligand interaction

The interaction between CD40 ligand (CD40L) on T cells and CD40 on antigen presenting cells has been shown to regulate both humoral and cellular immune responses [35,36]. To understand the initial events linking infection to the development of muscle hypercontractility we recently examined the contribution of CD40–CD40L interaction in the development of intestinal muscle hypercontractility, monocyte chemoattractant protein-1 (MCP-1) production and in the Th2 response in CD40L deficient (CD40L $-/-$) mice infected with *T. spiralis*. Expulsion of intestinal worms was substantially delayed in CD40L $-/-$ mice as compared to the wild-type mice following *T. spiralis* infection. Consistent with delayed worm expulsion, there was a significant attenuation of intestinal muscle contractility in CD40L $-/-$ mice [37]. Infected CD40L $-/-$ mice also exhibited marked impairment in production of MCP-1 and Th2 cytokine production. These data suggest that the early events leading to the generation of Th2 response include CD40–CD40 ligand interaction, which subsequently influences the production of Th2 cytokines most likely via up-regulation of MCP-1. Recently it has been reported that in the MCP-1 deficient mice worm expulsion is inhibited during infection with *T. muris* and this was associated with a shift of immune response towards Th1 type from Th2 type [38]. Together these findings strongly suggest that intestinal muscle hypercontractility and worm expulsion share a common immunological basis regulated by Th2 type immune response and may be causally linked.

Role of intestinal muscle hypercontractility in host defence

Previous studies from our laboratory have shown that the inflammation-induced intestinal muscle hypercontractility is prominent in the proximal part of the intestine and that the distal parts such as the ileum and colon exhibit reduced muscle contractility [39]. Therefore, it seems very likely that the distribution of changes would create an aboral gradient in muscle tension generation during infection, enhancing aboral propulsion of luminal contents. If such forces contribute to the host defence against parasite infection, then one might expect to see a relationship between the magnitude of intestinal muscle hypercontractility and the ability of the host to evict the parasites from the gut. This is indeed the case, with strong responder to *T. spiralis* infection such as NIH Swiss mice which expel the parasite faster exhibiting the greater degree of muscle contractility and slow responders such as B10.BR mice which expel the parasite slowly exhibiting lesser degree of hypercontractility [13]. These observations strengthened the association between host defence and

changes in muscle function and prompted a closer observation of the underlying immune-mediated mechanisms involved in the alteration of intestinal muscle contractility. Studies involving Stat6 deficient mice and IL-12 gene transfer mediated switching of immune response towards Th1 type clearly demonstrate that Th2 type response is critical in the development of infection-induced intestinal muscle hypercontractility and efficient worm expulsion. It seems likely that cytokines specifically IL-4 and IL-13 from the Th2 type cells influence the second message system of muscle cells by acting either on the calcium channel or on muscarinic receptor, which subsequently alter the intestinal muscle contractility and this alteration of contractility is associated with enhanced parasite eviction. Recently we have investigated a causal link between these responses by administering opiate (buprenorphine) to attenuate muscle hypercontractility in *T. spiralis* infection, and determined whether this delayed worm expulsion without attenuating the Th2 response. Results show marked inhibition of worm expulsion and intestinal muscle hypercontractility without impairing IL-4 response, supporting our hypothesis that altered motility plays an important role in host defence in this model [40]. Taken together, these studies clearly indicate that the motor apparatus of the gut is subject to modulation by the immune system and subsequently plays an important role in host defence.

Schematic representation of the interaction among mucosal inflammation, immune activation and gut motility in the defence of gut against injurious agents has been depicted in Fig. 3. Based on these studies it can be concluded that trigger in mucosal inflammation seems to recruit physiological systems such as the motor apparatus via immune activation to assist in the host defence.

Inflammation and motility in other experimental models

In addition to the findings observed in the nematode infections there are several other experimental models which clearly show interaction between inflammation and motility. Intestinal hypomotility and delayed gastric emptying have been shown to be characteristic in a mouse model of post-operative ileus [41]. This condition is the result of intestinal inflammation due to activation of macrophages [42,43] that are triggered by bowel manipulation. Recently it has been shown that peri-operative stimulation of the vagus nerve prevented this manipulation-induced inflammation of the intestine and ameliorated postoperative ileus and this effectiveness of vagal stimulation in reducing intestinal inflammation depended on activation in macrophages in the intestinal muscularis [44]. It has been also shown that leucocyte-derived inducible nitric oxide (NO) plays an important role in the generation of intestinal inflammation and inhibits GI motility after manipulation in this model of ileus [45]. In the rat model of haemorrhagic shock it has been also

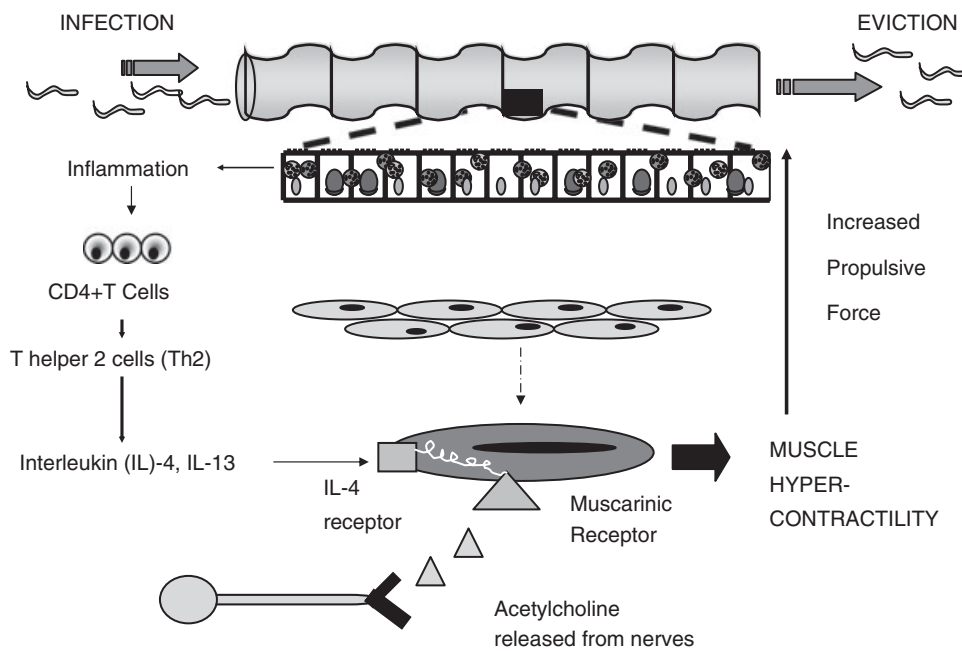


Fig. 3. Conceptual model of the interface between the immune and motor systems in the gastrointestinal (GI) tract, and the putative role of this interface in host defence. Infection produces mucosal injury and inflammation and induces an immune response. The Th2 type immune response induces changes in the intestinal muscle contractility in response to physiological stimuli such as the release of acetylcholine from the enteric nerves. The resulting increase in propulsive forces contributes to the eviction of the infective agent from the GI tract. Not shown are other components of motility apparatus including other enteric nerves, interstitial cells of Cajal and enteroendocrine cells.

shown that induced NO contributes to the inflammatory changes in the gut wall and participates in the activation of cytokine expression that regulate impaired gut motility [46]. Communication between inflammation and gut motility is also demonstrated in relation to carbon monoxide (CO), the end product of the anti-inflammatory endogenous haeme oxygenase 1 (HO-1) pathway. Inhalation of CO significantly down-regulated IL-6, IL-1 β and inducible NO response and improved post-transplant dysmotility in the syngeneic rat transplant model [47]. In hapten (2,4,6-trinitrobenzene sulphonic acid; TNBS)-mediated model of experimental colitis an attenuation of muscle contractility was observed in association with inflammation and Th1 immune response [48,49].

These observations clearly suggest that inflammation of GI tract causes significant alteration in gut motor function and the immunological profile of the inflammatory response may be an important determinant of these changes that occur in each model.

Implications

These studies have generated a number of concepts that provide insight into how the immune and motor systems of the gut interface. First, these studies clearly demonstrate that the inflammation of the mucosa causes changes in the muscle function in the GI tract. This is particularly

important when considering widespread disturbances in muscle contractility and other aspects of gut physiology occur in a variety of clinical settings associated with inflammation and immune activation which include IBS and IBD. Another concept that has emerged is that the immunological profile of the inflammatory response is an important determinant of the changes in muscle function that occur in each model. Th2 type immune response associated with enteric parasitic infection play a pivotal role in the regulation of intestinal muscle hypercontractility and this is associated with host resistance. This corroborates with the studies in asthma where Th2 cells and their cytokines are identified as critical component in the development of airway hyper reactivity in atopic and intrinsic asthmatics [50,51]. From our laboratory it has been also shown that in a model of postinfectious IBS based on primary *T. spiralis* infection changes in neuromuscular function initiated by the infection can persist long after the clearance of the infection and resolution of the inflammatory changes in the mucosal compartment [52]. It has been also demonstrated that while the initial immunological (Th2) response is required for induction of the neuromuscular changes, they are not required for the maintenance of these changes postinfection. The state of persistent dysfunction of the neuromuscular tissue is maintained by the production of mediators such as TGF- β and prostaglandin E2 by intestinal muscle [53,54]. Thus, in the postinfective or inflammatory

state, the maintenance of tissue dysfunction is maintained by production of mediators by resident cells such as muscle cells. Another concept that emerged is that manipulation of host immune response is able to modulate the accompanying motor changes, and this may have clinical relevance in the conditions associated with altered GI motility. Understanding the underlying immunological basis of altered GI motor function and its role in host defence, coupled with the ability to modulate by immune responses as depicted in our studies, may ultimately lead to new therapeutic strategies in GI functional and inflammatory disorders.

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