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Special Contribution

Helminth Infections Prevent Autoimmune Diseases through Th2-Type Immune Response

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Helminth parasites are known to elicit the immune response towards T helper 2 (Th2)-type, characterized by Th2 related cytokines, that typically include interleukin-4 (IL-4), IL-5 and IL-13. In this review we will describe the mechanisms involved in helminth induced Th2 immune response. Intestinal epithelial cells (IECs) produce thymic stromal lymphopoietin (TSLP), which is both necessary and sufficient for the initiation of Th2 cytokine-driven inflammation. IL-33 mRNA is expressed early during parasite infection and IL-33 binds ST2 receptor, both of which are associated with optimal $CD4^+$ Th2 polarization. Following innate immune cell recognition, basophils and mast cell can secrete Th2 type cytokines that are thought to contribute to $CD4^+$ Th2 differentiation. Additionaly, dendritic cell conditioned with some helminth products can promote $CD4^+$ Th2 differentiation. Alternatively activated macrophages, activated by the Th2 cytokines IL-4 and IL-13 in parasitic infections, contribute to the host protective response: control of Th1-type inflammation, wound healing and worm expulsion. Experimentally, helminths have been associated with protection against a number of autoimmune disorders, including inflammatory bowel diseases and type 1 diabetes. It may be a novel strategy to ameliorate autoimmune inflammation by expanding and activating the Th2 response originated from parasites.

Key words: alternatively activated macrophage; autoimmune disease; helminth; T helper 2; thymic stromal lymphopoietin

Helminth infections are characterized by a strong T helper 2 (Th2)-type response, which includes the combined innate and adaptive immune responses to clearly distinguish it from the adaptive Th2-cell response (Anthony et al., 2007). Th2-type responses are typically characterized by increases in the levels of Th2-type cytokines such as interleukin-4 (IL-4), IL-5, IL-13 and IL-21. In this review we will first describe the mechanism of Th2-cell response evoked by helminth parasite (Fig. 1). Second the characterization and the function of alternatively activated macrophages (AAMΦs) activated by IL-4/IL-13-dependent signal pathway will be discussed, and third we will give an overview that helminth parasites prevent the autoimmune diseases through Th2-type response.

Abbreviations: AAMΦ, alternatively activated macrophage; AMAC, alternative macrophage activation-associated CC chemokine; AMCase, acidic mammalian chitinase; CAMΦ, classically activated macrophage; CCR4, CC chemokine receptor 4; DC, dendritic cell; ERK, extracellular signal regulated kinase; ES, excretory/secretory; FcεRI, Fc receptor for IgE; IEC, intestinal epithelial cell; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; MDC, macrophage derived chemokine; SEA, schistosome egg antigen; SWA, soluble worm antigen; TARC, thymus and activation-regulated chemokine; TIMP, tissue inhibitor of metalloproteinase; TGF-β, transforming growth factor-β; Th2, T helper 2; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin

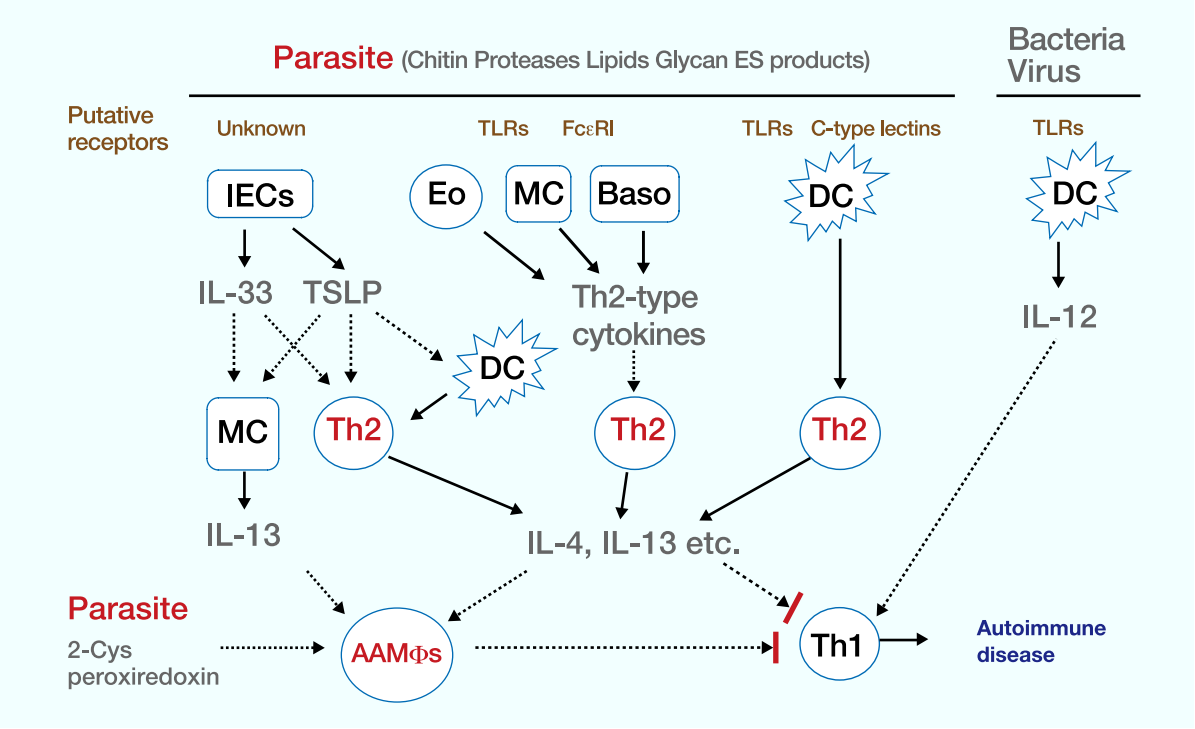

Fig. 1. The orchestration of CD4$^+$ Th2 cell differentiation following innate cell recognition and response to parasite infection and the inhibitory mechanism of Th1-dependent autoimmune diseases. Following innate cell recognition, Th2-type cytokines including IL-4, IL-13 and IL-33, or TLSP are secreted. These cytokines are thought to contribute to CD4$^+$ Th2 cell differentiation. DC conditioned with helminth products also induces Th2 cell polarizing. Th2 cytokines and AAMΦs prevent Th1-dependent autoimmune diseases. AAMΦ, alternatively activated macrophage; DC, dendritic cell; Eo, eosinophil; IEC, intestinal epithelial cell; IL, interleukin; MC, mast cell; Th, T helper; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

Th2-type response induced by helminth parasites

Innate immune responses: basophils and mast cells

Innate immune cells are essential for both the initiation and effector phases of Th2-type immune responses. Following helminth infection, basophils increase in number in the blood and tissues. In *Nippostrongylus brasiliensis* infection, IL-4-producing basophils are readily detected in the lungs, liver and spleen (Shinkai et al., 2002; Min et al., 2004). Basophils and eosinophils might be a major source of IL-4 at early stages of the Th2-cell response, suggesting that they promote the development of Th2 cells or their recruitment to sites of inflammation.

Mast cells share many characteristics with basophils, including the cell-surface expression of the high-affinity Fc receptor for IgE (FcεRI), IL-18R and the Toll-like receptors (TLRs), and IL-4/IL-13 secretion (Yoshimoto and Nakanishi, 2006). They have also been shown recently to derive from a common progenitor (Arinobu et al., 2005). However, unlike basophils, which circulate in the blood, mast cells reside in peripheral tissues and are thus well situated to respond immediately to invasive agents. Increased numbers of mucosal mast cells are often observed in affected tissues during helminth infections and this increase is dependent on Th2-type cytokines.

TSLP

Intestinal epithelial cells (IECs) are a critical cell population that maintains intestinal immune homeostasis through both barrier function and the ability to actively modulate intestinal immune re-

sponses (Zeuthen et al., 2008). One IEC-derived cytokine with immunomodulatory properties is thymic stromal lymphopoietin (TSLP). TSLP is a four-helix bundle cytokine that is expressed both in humans and mice. Despite poor sequence homology, human and mouse TSLP exhibit similar biological functions (Liu et al., 2007). Expression of TSLP is regulated by nuclear factor (NF)-κB and can be induced by exposure to viral, bacterial and parasitic pathogens, and inflammatory cytokines IL-1β and TNFα (Allakhverdi et al., 2007; Lee et al., 2007). TSLP binds to its high affinity receptor (R), a heterodimer composed of a unique TSLPR chain and the IL-7R chain, that is expressed on hematopoietic cell lineages, including B cells, T cells, mast cells and dendritic cells (DCs) (Soumelis et al., 2002; Allakhverdi et al., 2007; Chappaz et al., 2007; Liu et al., 2007).

TSLP-conditioned human DCs can promote Th2 cell responses (Soumelis et al., 2002; Ito et al., 2005; Rimoldi et al., 2005). TSLP-treated DCs exhibit reduced production of IL-12/23p40 upon TLR ligation, and the ability of DC-derived OX40L to drive Th2 cell differentiation is critically dependent on the absence of IL-12 (Soumelis et al., 2002; Ito et al., 2005; Rimoldi et al., 2005). TSLP treatment of human DCs induces expression of the chemokines CCL17 and CCL22, known ligands for CCR4, a chemokine receptor found on effector Th2 cells (Soumelis et al., 2002). More recently, TSLP has been reported to act directly on naïve mouse $CD4^+$ T cells to promote IL-4 production and to induce Th2 cell differentiation in the absence of exogenous IL-4 and antigen presenting cells in vitro (Omori and Ziegler, 2007). TSLP is both necessary and sufficient for the initiation of Th2 cytokine-driven inflammation (Ziegler and Liu, 2006; Liu et al., 2007). TSLP–TSLPR interactions are critical for immunity to the intestinal pathogen *Trichuris*. Monoclonal antibody-mediated neutralization of TSLP or deletion of the TSLPR in normally resistant mice resulted in defective expression of Th2 cytokines and persistent infection (Taylor et al., 2009). However, TSLP-TSLPR interaction has no functional impact on the development of protective Th2 immune responses after infection with 2 helminth, *Heligmosomoides polygyrus* and *N. brasiliensis* (Massacand et al., 2009).

IL-33

IL-33 is produced very early during *Trichuris muris* infection (Humphrey et al., 2008). IL-33 is structurally closely related to IL-18, requires posttranslational processing, and binds the receptor complex consisting of the orphan IL-1R family member ST2 and the IL-1R accessory protein (Acosta-Rodriguez et al., 2007). ST2 is expressed on mast cells and Th2 cells (Nakanishi et al., 2001) and has been shown to play an important role in Th2 responses (Yoshimoto and Nakanishi, 2006). IL-33 induces IgE-independent production of IL-13 from both human and mouse mast cells (Florian et al., 2006) and can operate in coordination with the epithelial cell-restricted cytokine TSLP on mast cells to maximize Th2-associated cytokines and chemokine production (Brunner et al., 2004). Likewise, IL-33 has been described as a chemoattractant of Th2 cells (Oshikawa et al., 2001). The ability of IL-33 to enhance TSLP-induced responses from mature mast cells has recently been demonstrated (Brunner et al., 2004). It is conceivable that IL-33 can act via TSLP to promote Th2-driven immunity to *T. muris* infection.

The IL-17-related cytokine IL-25 (also known as IL-17E) is also associated with the Th2-type response and can promote Th2-cell differentiation and nematode parasite expulsion (Fallon et al., 2006; Owyang et al., 2006).

The induction of Th2 responses by DCs

DCs play a central role in activating $CD4^+$ Th cells. The ability of DCs to interpret helminth-inherent signals and induce Th2 responses has been illustrated by experiments in which mice injected with DCs that have been pulsed with extracts of helminths in vitro develop Th2-biased helminth-specific responses (MacDonald et al., 2001; Balic et al., 2004; Leech et al., 2006). The Th2-polarizing

Table 1. Specially upregulated genes in alternatively activated macrophages

Marker	Alternatively activated macrophage	Reference
Pattern recognition receptors	Mannose receptor (CD206)	Stein et al., 1992
	β-glucan receptor	Goerdt and Orfanos, 1999
Other receptors	IL-4Rα	Herbert et al., 2004
	FcεRII (CD23)	Goerdt and Orfanos, 1999
L-arginine metabolism	Arginase-1	Loke et al., 2002
Tissue remodeling factors	TGF-β	Song et al., 2000
	TIMP1, TIMP2	Sandler et al., 2003
	Fibronectin	Gordon, 2003
Chemokines	MDC (CCL22)	Bonnecchi et al., 1998
	TARC (CCL17)	Imai et al., 1999
	AMAC-1 (CCL18)	Goerdt and Orfanos, 1999
Anti-inflammatory effects	IL-10	Goerdt and Orfanos, 1999
Th2 type inflammation	Ym1, FIZZ1/RELMα	Raes et al., 2002
	AMCase	Nair et al., 2005

AMAC-1, alternative macrophage activation-associated CC chemokine; AMCase, acidic mammalian chitinase; IL, interleukin; TGF-β, transforming growth factor-β; MDC: macrophage derived chemokine; TARC, thymus and activation-regulated chemokine; TIMP, tissue inhibitor of metalloproteinase.

properties of helminths appear to reflect the conditioning of DCs to induce these types of immune response, because helminth products can act as Th2 adjuvants for unrelated antigens (Holland et al., 2000; Okano et al., 2001; Gomez-Garcia et al., 2006).

The response of DCs to microbial pathogens is mediated in large part via TLRs, with input from other pattern recognition receptors such as lectins (Medzhitov 2007; van Vliet et al., 2008). A striking and significant difference between Th2 responses and Th1 responses is that the former develop normally in the absence of MyD88 (Helmby et al., 2003; Layland et al., 2005). Analyses of signalling events within the NF-κB and mitogen-activated protein kinase (MAPK) pathways have revealed significant differences between DCs exposed to helminth products and those stimulated with microbial products such as bacterial lipopolysaccharide (LPS). For example, extracellular signal regulated kinase (ERK), c-Jun N-terminal kinases (JNK) and p38 are heavily phosphorylated after exposure of DCs to LPS, but in DCs exposed to schistosome egg antigen (SEA), a soluble extract of schistosome eggs that is capable of conditioning DCs to induce strong Th2 responses, ERK and to a lesser extent p38 are phosphorylated, but JNK is not (Kane et al., 2004).

Exposure of DCs to helminth products has also been reported to stimulate NF-κB activation. For example, LNFPIII stimulates rapid, transient NF-κB nuclear translocation and activation (Thomas et al., 2005). Consistent with these findings, neither SEA nor LNFPIII-dextran pulsed NF-κB1$^{-/-}$ DCs are able to induce Th2 responses (Thomas et al., 2005; Artis et al., 2005). LNFPIII and excretory/secretory products (ES)-62, a phosphorylcholine-containing protein secreted by the nematode *Acanthocheilonema viteae*, condition DCs to induce Th2 responses through TLR4 (Thomas et al., 2003; Goodridge et al., 2005). Lysophosphatidylserine from schistosomes has been reported to trigger DC activation by binding to TLR2 in DCs (van der Kleij et al., 2002).

There has been great interest recently in the possibility that C-type lectins represent the major class of pattern recognition receptors for helminth products. N-Glycans containing fucose, expressed in multiple schistosome life stages, as possessing many of the Th2-inducing properties of SEA, as described above (Faveeuw et al., 2003; Thomas et al., 2003, 2005), and generally indicated a role for glycans in the priming of Th2 responses by helminths.

Alternatively activated macrophages in helminth infections

Recent studies suggest that macrophages, conventionally associated with IFNγ-dominant Th1-type responses to many bacteria and viruses, also play an essential role in the Th2-type inflammatory response. These macrophages are referred to as AAMΦs as they express a characteristic pattern of cell surface and secreted molecules distinct from that of classically activated macrophages (CAMΦs) associated with microbe infections.

Characterization and phenotype

The concept of AAMΦs was first introduced to distinguish specifically between the phenotype of cells "activated" in the presence of IL-4 and cells "deactivated" in the presence of IL-10 (Stein et al., 1992). Gordon (2003) later included the effects of IL-13 in the definition of alternative activation because IL-13 shares a common receptor chain with IL-4 and exerts similar effects on macrophages. Administration of recombinant peroxiredoxisin from *Fasciola hepatica* and *Schistosoma mansoni* to wild type and IL-4$^{-/-}$ and IL-13$^{-/-}$ mice induced the production of AAMΦs independently of IL-4/IL-13 signaling (Donnelly et al., 2008) (Fig. 1).

AAMΦs are observed in a variety of helminth infections, including Th2-type immune responses to *S. mansoni* (Herbert et al., 2004), *Taenia crassiceps* (Rodriguez-Sosa et al., 2002), *Trichinella spiralis* (Dzik et al., 2004), *F. hepatica* (Donnelly et al., 2005) and filarial parasites (Nair et al., 2003). A number of markers are used to identify AAMΦs (Table 1). Cell surface IL-4Rα and the mannose receptor (CD206), are readily detected using either flow cytometric (Herbert et al., 2004) or immunohistologic (Anthony et al., 2006) techniques. Arginase-1 is upregulated in AAMΦs and, due to its higher affinity for arginine, competes with inducible nitric oxide synthase (iNOS), which metabolizes arginine in CAMΦs. Then, AAMΦ fail to generate NO from arginine, and arginase-1 and its metabolic products, including urea and proline, are also indicative of AAMΦ differentiation (Loke et al., 2002).

Human AAMΦs specifically express alternative macrophage activation-associated CC chemokine-1 (AMAC-1; CCL18) (Goerdt and Orfanos, 1999), macrophage-derived chemokine (MDC; CCL22) (Bonecchi et al., 1998), and thymus and activation-regulated chemokine (TARC; CCL17) (Imai et al., 1999). These chemokines preferentially recruit Th2 cells through interaction with the CC chemokine receptor 4 (CCR4).

AAMΦs express certain chitinase and FIZZ (found in inflammatory zone) family member proteins, including: FIZZ1/RELMα, Ym1 and acidic mammalian chitinase (AMCase) (Nair et al., 2005); the Ym1 transcript shows the highest upregulation of any gene in AAMΦs during nematode infection (Raes et al., 2002) .

Control of inflammation

AAMΦs have multiple roles during helminth infection, one of which is regulation of the immune response. A dominant role for helminth-elicited AAMΦs is suggested to control the underlying Th1-type inflammatory responses that may otherwise contribute to pathogenesis. Suppressive effects of AAMΦs on T cell proliferation can occur in murine models of filarial infections. *Brugia malayi* L3 injected into the peritoneal cavity can elicit AAMΦs with potent T cell suppressive properties (Nair et al., 2005). Infection with *Litomosoides sigmodontis* also induces AAMΦs, which can suppress in vitro T cell proliferation. Further in vitro studies suggest that the mechanism of T cell suppression is independent of IL-10 and CTLA-4, but partially dependent on transforming growth factor (TGF)-β (Taylor et al., 2006). Thus, AAMΦs appear to be more important in blocking underlying Th1-type responses than promoting Th2-type responses, including Th2 cells.

Wound healing

AAMΦs can contribute to fibrosis and repair at the site of injury (Martin and Leibovich, 2005), which

Table 2. Helminth infections or products that prevent autoimmune diseases in animal models or humans

Immunological disease	Helminth	Agent or product	Reference
(a) Animal models			
Type 1 diabetes	*Schistosoma mansoni*	Infection	Cooke et al., 1999
	S. mansoni	SWA, eggs or SEA	Zaccone et al., 2003
	Trichinella spiralis	Infection	Saunders et al., 2007
	Dirofilaria immitis	Recombinant antigen	Imai et al., 2001
Experimental autoimmune encephalitis	*S. mansoni*	Infection	La Flamme et al., 2003
	S. mansoni	Eggs	Sewell et al., 2003
Collagen-induced arthritis	*Acanthocheilonema viteae*	ES-62	McInnes et al., 2003
Experimental colitis	*S. mansoni*	Infection	Smith et al., 2007
	S. mansoni	Eggs	Elliott et al., 2003
	Heligmosomoides polygyrus	Infection or transfer of MLN from infected mice	Elliott et al., 2004
	Hymenolepis diminuta	Infection	Reardon et al., 2001
	T. spiralis	Infection	Khan et al., 2002
	Trichuris suis	Infection	Summers et al., 2003
(b) Human diseases			
IBD: Crohn's disease	*T. suis*	Infection	Summers et al., 2005a
	Necator americanus	Infection	Croese et al., 2006
IBD: ulcerative colitis	*T. suis*	Infection	Summers et al., 2005b

ES-62, excretory/secretory products of 62 kDa; IBD, inflammatory bowel disease; MLN, mesenteric lymph node; SEA, soluble egg antigen; SWA, soluble worm antigen.

may be of considerable importance during helminth infection. These large metazoan parasites can cause extensive damage as they pass through tissue, releasing proteolytic enzymes that damage cells and tissues. Genes involved in tissue remodeling, including tissue inhibitors of metalloproteinases (TIMPs), are upregulated (Sandler et al., 2003). FIZZ1/RELMa has recently been implicated in wound healing (Liu et al., 2004).

Worm expulsion and resistance

Elements of the Th2-type response can control pathologic Th1-type inflammation and also marshal effective helminth resistance; for example, the Th2-type response has a demonstrated role in the expulsion of several intestinal nematode parasites (Gause et al., 2003; Finkelman et al., 2004). Clearly AAMΦs may contribute to resistance by controlling Th1-type immunity and thereby promoting a potent and polarized Th2-type response. Recently, it is becoming increasingly apparent that AAMΦs may also promote certain components of the Th2-type response important in worm expulsion. For example, AAMΦs recruit eosinophils to the lung and peritoneum during *N. brasiliensis* infection (Voehringer et al., 2007). Two candidates for eosinophil recruitment are leukotriene B_4 (Reese et al., 2007) and Ym1, a chitinase-like peptide that lacks chitinase activity (Owhashi et al., 2000). Related to Ym1, AMCase is a functional chitinase, which shows elevated gene expression during *H. polygyrus* or *B. malayi* infection (Anthony et al., 2006; Nair et al., 2005). It is tempting to speculate that AMCase may function to damage chitin-containing parasites, including developing microfilaria. If so, this would be in addition to its recently described function in augmenting Th2-type responses by stimulating production of monocyte chemotactic protein-1 and eotaxin (Zhu et al., 2004). The potential multiple roles of Ym1 and AMCase during helminth infection make these related molecules compelling subjects for future investigations of AAMΦ function.

These AAMΦ effector functions can be generally separated into three categories contributing to the host protective response: control of Th1-type inflammation, wound healing, and worm expulsion.

Prevention of autoimmune diseases by helminth

Experimentally, helminths have been associated with protection against a number of autoimmune disorders, including inflammatory bowel disease and diabetes (Table 2a). The incidence of autoimmune type 1 diabetes is on the increase in developed countries while remaining relatively uncommon in the developing world. This trend coincides with a decrease in helminth infection (Gale, 2002).

Previous studies have shown that infection with *S. mansoni*, *T. spiralis* and *H. polygyrus* can significantly inhibit or delay the development of diabetes in nonobese diabetic mice (Cooke et al., 1999). This appeared to be due to a skewing of the diabetes-associated Th1 response towards protective Th2 responses including IL-4, IL-5, IL-10 and IL-13 production (Zaccone et al., 2003). Administration of schistosome eggs has been shown to reduce the severity of experimental autoimmune encephalomyelitis (Sewell et al., 2003) as well as preventing the development of both trinitrobenzene sulfonic acid-induced colitis (Elliott et al., 2003) and diabetes in the nonobese diabetic mouse model (Cooke et al., 2004; David et al., 2004).

Inflammatory bowel disease is the most common and serious chronic inflammatory condition of the gut. Among the distinct Th cell subsets, a Th1 type response is associated predominantly with Crohn's disease while helminth infections generate a strong Th2 type response. Inflammatory bowel disease is most prevalent in developed countries but rare in countries where infections with helminths are common. Both Crohn's disease and ulcerative colitis have a prevalence range of 10 to 200 per 100,000 individuals per year in North America and Europe (Bouma et al., 2003). Inflammatory bowel disease can begin relatively early in life and persist for long periods, leading to substantial morbidity and decreased quality of life (Blumberg et al., 2001).

Previously it is shown that prior infection with the helminth parasite, *T. spiralis*, ameliorates subsequent hapten-induced colitis in mice and this was associated with a down-regulation of the Th1 response (Khan et al., 2002). This was correlated with a down-regulation of myeloperoxidase activity, IL-1 β production and inducible nitric oxide synthase (iNOS) and an up-regulation of IL-13 and TGF-β production in the colon (Motomura et al., 2008). It may be a novel strategy to ameliorate colonic inflammation with helminth antigens by expanding and activating the Th2 response.

Recent clinical studies provide evidence that *Trichuris suis* ova therapy is effective in treating both Crohn's disease and ulcerative colitis without any adverse effects (Summers et al., 2005a, 2005b) (Table 2b). The outcome of these trials supports further the concept that de-worming the population has led to the rising prevalence of inflammatory bowel disease.

The ability of TSLP to inhibit IL-12/23p40 and IFN-γ production suggests that TSLP-based biologics may also offer a novel therapeutic modality in the treatment of inflammatory bowel disease and other chronic inflammatory disorders. Consistent with this, TSLP expression was decreased in intestinal biopsies from patients with Crohn's disease, suggesting that increased TSLP expression may provide therapeutic benefits (Rimoldi et al., 2005). Thus, the TSLP–TSLPR pathway may be a novel therapeutic target for a variety of inflammatory conditions associated with the overproduction of proinflammatory cytokines.

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