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IMMUNOLOGY AND HOST-PARASITE INTERACTIONS - REVIEW

Helminths protect against type 1 diabetes: effects and mechanisms

Chun-lian Tang[1] · Jie-ning Zou[1] · Rong-hui Zhang[1] · Zhi-ming Liu[1] · Cun-lan Mao[2]

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease in which cells of the immune system destroy pancreatic β cells, which secrete insulin. The high prevalence of T1D in developed societies may be explained by environmental changes, including lower exposure to helminths. Indeed, infection by helminths such as *Schistosoma*, *Filaria*, and *Heligmosomoides polygyrus* and their by-products has been reported to ameliorate or prevent the development of T1D in human and animal models. Helminths can trigger distinct immune regulatory pathways, often involving adaptive immune cells that include T helper 2 (Th2) cells and regulatory T cells (Tregs) and innate immune cells that include dendritic cells, macrophages, and invariant natural killer T cells, which may act synergistically to induce Tregs in a Toll-like receptor-dependent manner. Cytokines such as interleukin (IL)-4, IL-10, and transforming growth factor (TGF)-β also play an important role in protection from T1D. Herein, we provide a comprehensive review of the effects and mechanisms underlying protection against T1D by helminths.

Keywords Helminths · Type 1 diabetes · Th2 · Regulatory T cells

Introduction

Type 1 diabetes (T1D) is an autoimmune disease in which cells of the immune system destroy pancreatic β cells, which secrete insulin (Xiang et al. 2018; Pugliese 2016). There is no cure for T1D, and the established treatment protocol involves controlling blood sugar levels by either daily injections of insulin or continuous subcutaneous insulin infusion. In recent decades, the prevalence of T1D has increased markedly. Genetic and environmental factors may play important roles in determining susceptibility to T1D (Jakobsen and Szereday 2018). Currently, the incidence of T1D is increasing more rapidly than genetic changes are occurring, suggesting the impact of environmental factors (Precechtelova et al. 2014). For example, the incidence of T1D in the Finnish Karelia was sixfold higher than in the Karelian Republic (Russia) with a similar genetic background (Kondrashova et al. 2005). The tremendous changes in sanitation and economic conditions in developed countries have led to reduced exposure to various helminths, which have lived symbiotically with prior generations of humans for millions of years and interact with the host immune system (Weinstock and Elliott 2014). Decreased exposure to helminths may be the reason for the increased incidence of T1D. The above conclusion is based on the hygiene hypothesis, which initially postulated to explain the inverse relationship between allergies and in early childhood (Strachan 1989). Subsequently, the hygiene hypothesis has been extended to autoimmune disease and helminth-mediated immunoregulation protected against autoimmune disease such as T1D in human as well as animal studies (Maizels et al. 2014). Indeed, several animal models of T1D support this possibility. Substantial effort has been dedicated to explain the mechanism whereby helminth infection protects against T1D. The mechanisms of T1D protection induced by helminths are complex, and regulatory T cells (Tregs), T helper 2 (Th2) cells, or both might be systemically involved in the anti-hyperglycemic effect of helminths.

Chun-lian Tang and Jie-ling Zhou contributed equally to this work.

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✉ Zhi-ming Liu
m13419550695@163.com

✉ Cun-lan Mao
CunlanMao@163.com

[1] Wuchang Hospital affiliated to Wuhan University of Science and Technology, Wuhan 430063, China

[2] Department of Obstetrics and Gynecology, People's Hospital of Songzi City, Songzi 434200, Hubei, China

An inverse relationship between helminths and T1D

Epidemiological studies suggest that the rate of T1D has increased as the frequency of helminth infections has decreased; the latter is a consequence of globalization and urbanization (Allender et al. 2008). Epidemiological data from the World Health Organization (WHO) shows reduced rates of autoimmune inflammation, such as T1D, in most populations in Africa and Asia, which increase conspicuously when these same populations migrate to a developed area or adopt a different lifestyle (Zaccone et al. 2006). Accordingly, individuals infected with helminths show a significantly lower incidence of T1D (Espinoza-Jiménez et al. 2010). In Europe, the more developed the agricultural economy is, the lower the incidence of T1D (Pazzagli et al. 2017). This finding hints that exposure to a pathogen transmitted by animals may be a factor in the prevention of T1D, which was further confirmed by the EURODIAB ACE Study Group (2000). Compared with that in individuals with T1D (0%), the prevalence of lymphatic filariasis was significantly higher in healthy glucose-tolerant individuals in Southern India, and there was an obvious inverse relationship between the prevalence rates of lymphatic filariasis and T1D (Aravindhan et al. 2010). An epidemiological study demonstrated that decreasing rates of infection with pinworms or *Strongyloides stercoralis* in humans were correlated with an increased prevalence of T1D (Gale 2002). These observations suggest the potential for the application of helminths in the treatment or prevention of T1D.

Protection against T1D conferred by helminths

Some autoimmune diseases, such as arthritis (Eissa et al. 2016), Graves' hyperthyroidism (Nagayama et al. 2004), autoimmune encephalomyelitis (Reyes et al. 2011), and inflammatory bowel disease (Ruyssers et al. 2010), can be ameliorated or prevented by helminth infection or helminth products. T1D occurs spontaneously in autoimmune-prone non-obese diabetic (NOD) mice or can be induced by the continuous injection of a low dose of streptozotocin or cyclophosphamide in BALB/c and other strains of mice. In recent decades, several parasitic helminths and their by-products, including *Schistosoma*, *Filaria*, and *Heligmosomoides polygyrus*, have been reported to prevent or ameliorate T1D. However, the mechanisms of protection are not yet clear and may differ between species.

Schistosoma

Schistosoma mansoni is a trematode worm of genus *Schistosoma* that has developed several strategies to manipulate the host immune system to survive and is reported to inhibit and prevent autoimmune disease. Our recent study demonstrated that *Schistosoma* infection and *Schistosoma*-derived products modulate the immune responses associated with protection against type 2 diabetes (Tang et al. 2018); the mechanism may be related to Tregs (Tang et al. 2017a). Cooke et al. (1999) first reported that *Schistosoma mansoni* infection and eggs prevented T1D in NOD mice, which was related to a switch from a Th1 to a Th2 response. The same result was obtained in streptozotocin-induced diabetic mice infected with *S. mansoni* (Thabet et al. 2008); in this context, egg deposition from *S. mansoni* led to a shift from a Th1 to a Th2 response by 8 weeks post-infection (El-Wakil et al. 2002). *Schistosoma*-derived products prevent but do not ameliorate T1D. Soluble worm and egg antigen can completely prevent the onset of T1D only if injections are initiated at 4 weeks of age, which increases the numbers of natural killer cells in NOD mice (Zaccone et al. 2003).

Filaria

Filariasis is a tropical disease caused by parasitic nematodes such as *Litomosoides sigmodontis*, *Brugia malayi*, and *Dirofilaria immitis*. Some studies have provided evidence for the use of filarial nematodes and filarial proteins as a novel antidiabetic therapy. Six-week-old NOD mice infected with either *L. sigmodontis* L3 larvae, adult male and female worms, or crude worm antigen were found to be fully or partially protected from the onset of diabetes (Hübner et al. 2009). Ajendra et al. (2016) observed that combined treatment with *L. sigmodontis* antigen and intranasal pro-insulin could prevent and treat diabetes in NOD mice. After treatment with the recombinant abundant larval transcript protein of *B. malayi*, 28% of streptozotocin-induced T1D mice became nondiabetic by the end of the second week of treatment, and none of them were diabetic by the end of the fifth week, which was linked to increased titers of IgG1 antibodies and decreased titers of IgG2a antibodies (Reddy et al. 2017). Pre-treatment with *B. malayi* antigens before or after the initiation of diabetes led to reduced blood glucose levels with as many as 57.5–62.5% and 62.5–71.5% of mice remaining nondiabetic, respectively, which was associated with decreased interferon (IFN)-γ and increased interleukin (IL)-10 levels (Amdare et al. 2015). A similar result was obtained using *B. malayi*-abundant larval transcript 2 in streptozotocin-induced T1D in mice (Amdare et al. 2017). For *D. immitis*, administration of recombinant antigen completely prevented insulitis in NOD mice (Imai et al. 2001).

The mechanism of filarial nematodes in the prevention or amelioration of T1D is unclear and also related to the type of filarial worm. In general, it is correlated with Th2-type immune response and Tregs. By contrast, IL-4-deficient NOD mice failed to develop a Th2-type shift but still showed resistance to diabetes after infection with *L. sigmodontis* because of transforming growth factor (TGF)-β-dependent bioactivity (Hübner et al. 2012).

Heligmosomoides polygyrus

H. polygyrus is an intestinal nematode that naturally infects rodents as its definitive host. In the streptozotocin-induced T1D mouse model, *H. polygyrus* infection affords protection against hyperglycemia and reduced pancreatic islet size. It exerts these effects via IL-10- and STAT6-independent mechanisms (Osada et al. 2013). *H. polygyrus* inoculation at 5 or 12 weeks of age in NOD mice with cyclophosphamide-induced T1D prevented hyperglycemia and pancreatic insulitis via CD25- and IL-10-independent mechanisms (Liu et al. 2009). Infection with *H. polygyrus* or *Trichinella spiralis* could also prevent T1D development in NOD mice and induce a type 2 immune response (Saunders et al. 2007).

Others

Other types of helminths, such as *Fasciola hepatica*, *Taenia crassiceps*, and *Strongyloides venezuelensis*, also exert therapeutic and preventive effects on T1D. At 30 weeks of age, 84% of NOD mice remained normoglycemic and insulitis-free after intraperitoneal injection of excretory/secretory products from *F. hepatica* (Lund et al. 2014). Disease prevention was associated with M2 macrophages, TGF-β, and PD-L1, which induced the expansion of Tregs from splenocytes. Compared with the uninfected group (100%), fewer streptozotocin-induced diabetic mice infected with *T. crassiceps* (40%) developed T1D, which was correlated with increased levels of IL-4 and decreased amounts of tumor necrosis factor (TNF)-α (Espinoza-Jiménez et al. 2010). *T. crassiceps*-derived products such as soluble (TcS) or excreted/secreted (TcES) antigens also have beneficial influence on the development of experimental T1D along with recruitment of alternatively activated macrophages (Espinoza-Jiménez et al. 2017). Immunization with soluble *S. venezuelensis* antigen prevented the development of streptozotocin-induced T1D by inducing a Th2 response (Peres et al. 2013).

Mechanisms of helminth-dependent protection against T1D

Even though the pathogenesis of T1D and T2D is distinct, the immune system is actively involved in both forms of the disease (Surendar et al. 2017). The characteristic immune response of helminth infections that can protect against T1D includes the following factors: decrease in IFN-γ and IL-17 and increase in IL-4, Tregs, IL-10, TGF-β, macrophages, dendritic cells (DCs), and natural killer T (NKT) cells (Elliott and Weinstock 2012). Th1 cells participate in cell-mediated immunity and phagocyte-dependent protective responses, which can destroy the islet β cells and accelerate the course of T1D by producing IFN-γ (Kikodze et al. 2013). According to one study, therapeutic agents targeting IL-17 or inhibiting IL-17-producing cells regulate T1D, suggesting IL-17 involvement in the pathogenesis of T1D (Lee et al. 2013). Since T1D is a Th1-mediated disease, it was hypothesized that skewing the immune response to suppress Th1-type immune response may suppress the T1D. We focus on describing Th2 cells, Tregs, and innate immune responses.

Th2

Th2 cells are best known for their production of IL-4, IL-5, and IL-13 as well as IL-9 and IL-10 (Lin et al. 2011). Some of the regulatory immune responses induced by chronic helminth infections are dependent of the initial type 2 responses (Cooke 2009). Parasitic helminths regulate the host's immune system and induce type 2 as well as regulatory immune responses, which may prevent the onset of diabetes (Berbudi et al. 2016). Hurdayal et al. (2017) reveal a central role for B cell–derived IL-4 and IL-4Rα in the optimal induction of the susceptible type 2 phenotype to *L. major* infection, which are essential for regulating and assisting the early T helper dichotomy toward Th2 responses. In transgenic NOD IL-4 recipient mice, expression of IL-4 by pancreatic β cells prevents the onset of autoimmune diabetes and insulitis (Ruffner and Robbins 2010). It has been speculated that the immune response to Th2 and regulatory axes can inhibit the Th1 response in diabetes. By contrast, *H. polygyrus* infection protected NOD IL-4$^{-/-}$ mice from diabetes by IL-10 and not STAT6 signaling (Mishra et al. 2013). *S. mansoni* infection also partially prevents the degradation of pancreatic islets and hyperglycemia in streptozotocin-induced mice by augmented expression of Arg-1 and Ym1 and not via Treg/IL-4/IL-13/IL-10-dependent mechanisms (Osada et al. 2017). Several of these mechanisms appear to operate both simultaneously and independently of each other. Therefore, the loss of any one regulatory pathway does not necessarily prevent protection from T1D; ultimately, the protective mechanism of helminths against T1D is complex. Th2 cells may participate in the anti-hyperglycemic effects of helminths, as described in Table 1.

Table 1 Infection with helminths or their by-products and prevention or inhibition of T1D in animal models

Helminth infection or by-products	Effect	Putative mechanism	Model	References
Schistosoma mansoni infection	Prevention	Th2	NOD mice	Cooke et al. (1999)
Schistosoma mansoni eggs	Prevention	Th2	NOD mice	Cooke et al. (1999)
Schistosoma mansoni infection	Prevention	Th2	STZ mice	El-wakil et al. (2002)
Litomosoides sigmodontis infection, L3 larvae, adult female worm, adult male worm	Prevention	Th2	NOD mice	Hübner et al. (2009)
Litomosoides sigmodontis worm antigen	Prevention	Th2	NOD mice	Hübner et al. (2009)
Litomosoides sigmodontis antigen	Prevention	Th2	STZ mice	Ajendra et al. (2016)
Brugia malayi antigen	Amelioration	Th2	STZ mice	Reddy et al. (2017)
Brugia malayi L2	Cure	Th2	STZ mice	Amdare et al. (2017)
Brugia malayi antigen	Amelioration	Th2	STZ mice	Amdare et al. (2015)
Wuchereria bancrofti L2	Cure	Th2	STZ mice	Amdare et al. (2017)
Dirofilaria immitis recombinant antigen	Prevention	Th2	NOD mice	Imai et al. (2001)
Heligmosomoides polygyrus	Inhibition	Th2	NOD mice	Saunders et al. (2007)
Trichinella helminths	Inhibition	Th2	NOD mice	Saunders et al. (2007)
Fasciola hepatica excretory/secretory products	Inhibition	Th2	NOD mice	Lund et al. (2014)
Taenia crassiceps infection	Inhibition	Th2	STZ mice	Espinoza-Jiménez et al. (2010)
Strongyloides venezuelensis infection	Inhibition	Th2	STZ mice	Peres et al. (2013)

Tregs

Tregs were first described by Sakaguchi et al. in 1995 and are essential for immune homeostasis (Wan and Flavell 2007). Helminth infections and helminth products are potent stimuli for the generation of Tregs, a cell type that is known to modulate the host immune responses. Cellular immune hyporesponsiveness in helminth-infected individuals was first observed in the 1970s, as lymphocytes exhibited a diminished proliferative response upon stimulation with *Schistosoma* antigens (Ottesen et al. 1978). In a murine *L. sigmodontis* model, the rapid recruitment of Tregs was shown to play a role in suppressing host immunity (Taylor et al. 2009). Additionally, immunomodulation by Tregs is a key factor in *F. hepatica* infection (Escamilla et al. 2016). Tregs can modulate immune responses by inhibiting effector T cell responses or secreting the cytokines IL-10 and TGF-β to generate immune tolerance (Palomares et al. 2014). Bluestone et al. (2015) conducted a phase 1 dose escalation immunotherapy trial for adult T1D patients by administering autologous polyclonal Tregs to adult recent-onset T1D patients. In NOD mice, a loss of Tregs or impaired suppressive function of Tregs may contribute to the pathogenesis of diabetes (Tritt et al. 2008), whereas the transfer of antigen-specific Tregs can delay and even reverse T1D (Johnson et al. 2013). IL-10 has also been shown to delay the onset of disease and significantly reduce the incidence of diabetes when administered daily and subcutaneously to NOD mice (Li et al. 2016). Compared with those in healthy controls, serum TGF-β levels in T1D patients are reduced, and autocrine/paracrine TGF-β signaling in diabetogenic $CD4^+$ T cells is essential for controlling the development of T1D (Ishigame et al. 2013). Helminth-induced generation of Tregs and the production of IL-10 and TGF-β may further contribute to the protective effect against the onset of diabetes (Zhou et al. 2011). *S. mansoni* soluble egg antigen (SEA) treatment increased Tregs in a TGF-β-dependent manner in the pancreas, a process that requires the presence of DCs (Zaccone et al. 2009); ω-1 is the main component of *S. mansoni* SEA that can induce Tregs in NOD mice (Zaccone et al. 2011). Tregs may participate in the anti-hyperglycemic effects of helminths, as described in Table 2.

The innate immune system

The development of T1D involves complex interactions between pancreatic β cells and cells of the innate immune system (Lehuen et al. 2010). The NOD mouse is deficient in NKT cells (Blumenfeld et al. 2011), and SEA and soluble worm antigen (SWA) can stimulate an increase in the number of $V_\alpha 14i$ NKT cells and prevent T1D development. In NOD mice, SEA induces functional and phenotypic changes in DCs, creating ideal conditions for Treg cell expansion (Zaccone et al. 2010), which are reduced in T1D patients and transfer Tregs prevents disease

Table 2 Infection with helminths or their by-products and prevention or inhibition of T1D in animal models

Helminth infection or by-products	Effect	Putative mechanism	Model	References
Litomosoides sigmodontis infection, L3 larvae, adult female worm, adult male worm	Prevention	Tregs	NOD mice	Hübner et al. (2009)
Litomosoides sigmodontis worm antigen	Prevention	Tregs	NOD mice	Hübner et al. (2009)
Litomosoides sigmodontis antigen	Prevention	Tregs	STZ mice	Ajendra et al. (2016)
Schistosoma mansoni egg antigens	Prevention	Tregs	NOD mice	Zaccone et al. (2009)
Fasciola hepatica excretory/secretory products	Inhibition	Tregs	NOD mice	Lund et al. (2014)
S. mansoni glycoprotein ω-1	Inhibition	Tregs	NOD mice	Zaccone et al. (2011)
Taenia crassiceps infection	Attenuate	Tregs	STZ mice	Espinoza-Jiménez et al. (2010)

progression by cytokines of IL-10 and TGF-β (Sgouroudis and Piccirillo 2009). Further studies established that SEA can enhance TGF-β activity in response to TLR2 ligand stimulation (Burton et al. 2010). Mouse and human islet cells express TLRs that trigger increased secretion of pro-inflammatory chemokines, such as CXCL-10. The latter can attract T cells, macrophages, and DCs into the pancreatic islets. A recent study demonstrated that SEA promotes macrophage differentiation into the M2 phenotype (Tang et al. 2017b), which can be used to prevent T1D in NOD mice (Parsa et al. 2012). Taking SEA as an example, Fig. 1 provides an overview of the different mechanisms that upon helminth may affect T1D development and/or progression.

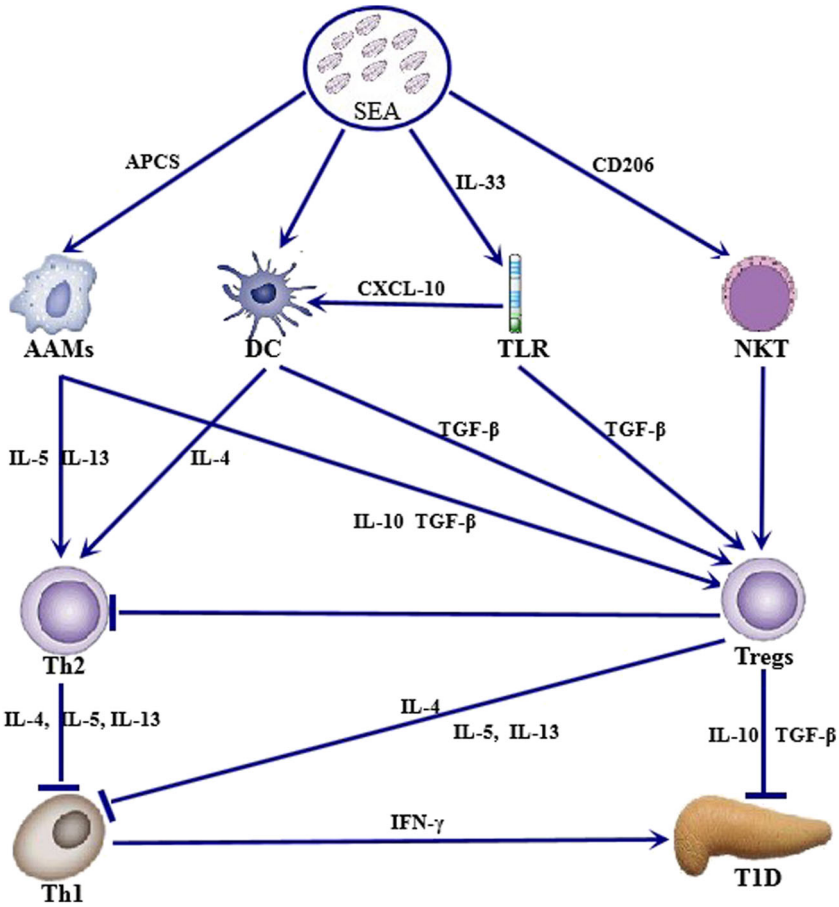

Fig. 1 Possible mechanisms of SEA protection against T1D. SEA might inhibit Th1-type inflammatory responses in T1D via the induction of Th2 and Tregs. Th2 T helper 2, Treg T regulatory cell, Th1 T helper 1, DC dendritic cell, AAMs alternatively activated macrophages, NKT natural killer T cells, SEA soluble egg antigen, T1D type 1 diabetes

Conclusions

Abundant evidence indicates that helminths and their by-products can exert immunomodulatory effects that prevent or delay the onset of T1D. Although helminths are mainly considered beneficial in specific disease scenarios of T1D, it is important to remember that they cause several diseases. Helminth infection also affects the physiology of the host. Despite the involvement of helminths in infectious diseases, the development of helminth-derived immunomodulatory products mimicking the beneficial immunoregulatory effects stimulated by helminth infections has introduced a potential avenue for identifying new T1D treatment strategies (Maizels 2016). Several studies are underway to identify bioactive helminth-derived molecules to guide the development of novel therapeutic agents that could potentially cure or help prevent T1D.

The mechanism that delays the onset of T1D remains to be fully elucidated but may be correlated with innate immune and adaptive immune response. Helminths were expected to possess the capacity to simultaneously, selectively, and/or sequentially modulate various immune regulatory pathways. Further research into the mechanisms whereby helminth infections and their by-products alter the pathogenesis of T1D will enable the identification of new drug targets. Furthermore, despite compelling evidence from animal models supporting the potential of helminth products to modulate the course of T1D, clinical translation of these findings is slow, and many obstacles remain. Firstly, the highly purified products of helminths would not have untoward side effects and physicians must balance their interests and risk of any treatment. Secondly, the route of administration is also important, with oral medication more acceptable to patients. Our preliminary findings confirmed that oral *Schistosoma japonicum* SEA can be used in the treatment of T1D (in preparation). In the future, helminth-derived supplements may be included as part of a modern balanced diet.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict interest.

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