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Parasitic Helminths as Potential Therapeutic Agents Against Autoimmune Disorders

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1. Introduction

In developed countries, the prevalence of both allergic disease (asthma) and autoimmune disorders such as Crohn's disease (CD), multiple sclerosis (MS), and type 1 diabetes (T1D) is increasing. This trend seems to be inversely correlated to prominent decreases in infectious diseases such as measles, tuberculosis, and hepatitis A (Bach, 2002). Based on such epidemiological observations, the "hygiene hypothesis", that exposure to infectious agents; i.e. bacteria, viruses, and parasites, especially in childhood, lowers the risk of later onset of immunological disorders, has attracted much attention. According to the hypothesis, a reduced exposure to infectious agents due to improved hygienic conditions in developed countries, urbanized areas, and/or a westernized lifestyle is responsible for the higher incidence of autoimmunity and allergies in modern society. A number of epidemiological and experimental studies have demonstrated the plausibility of this hypothesis. However, there is also considerable evidence that does not support or contradicts the hypothesis. In this chapter, conflicting reports are introduced and discussed.

Most studies trying to elucidate the mechanisms involved have been conducted using rodent models. In various models of autoimmune or allergic diseases, effects of bacterial, viral or parasitic infections were tested. Consequently, in many cases, preventive or ameliorating effects of infectious agents have been confirmed. In the main part of this chapter, the influence of parasitic helminths on autoimmune disorders will be introduced.

Although the mechanisms underlying the amelioration and/or prevention of immunological disorders by infectious agents have been studied extensively, they are not yet fully understood. As both Th1-polarizing (bacteria and viruses) and Th2-polarizing (parasitic helminths) infectious agents have anti-autoimmune/anti-allergic activities (Zaccone & Cooke, 2011), the "Th1/Th2 paradigm" is not enough to explain the mechanisms involved. Additionally, some autoimmune diseases have been shown to be dependent on a pathogenic T helper subset (Th17), and not on the Th1 subset. The suppressive mechanisms of infectious agents have been attributed to various regulatory/suppressive cell populations, such as Treg cells, Breg cells, NKT cells and alternatively activated macrophages (AA MΦs). In addition, the involvement of suppressive cytokines (e.g. IL-4, IL-10 or TGF-β) has been studied and demonstrated. Focusing on helminth infections, the possible involvement of regulatory cells and cytokines is discussed.

Some autoimmune diseases are being treated successfully with recently developed biological products (mainly humanized monoclonal antibodies against pro-inflammatory

cytokines). These products have outstanding therapeutic effects on autoimmune diseases (Nixon et al., 2007; Jones & Ding, 2010) compared to traditional immunomodulatory agents such as disease modifying anti-rheumatic drugs (DMARDs). However, they can cause severe adverse effects such as opportunistic infections. Helminths or their excretory/secretary products might solve the problems of monoclonal antibody therapy (Puneet et al, 2011). Therefore, at the end of this chapter, clinical trials of viable parasitic helminths for the treatment of immunological disorders are briefly introduced.

2. Evidence of the hygiene hypothesis

As described in Introduction, the prevalence of asthma, T1D, MS, and inflammatory bowel diseases (IBD) has been increasing in developed countries in an inverse relation to the declining prevalence of infectious diseases (Bach, 2002). In addition to the chronological trend, the geographical distribution of some autoimmune diseases seems to support the hygiene hypothesis. MS and T1D have a similar geographical distribution pattern known as a "North-south gradient", with a high prevalence in northern European (Scandinavian) countries (= relatively hygienic) and low prevalence in southern European countries (= relatively non-hygienic) (Bach, 2002; Shapira et al., 2010a). This pattern could be explained by the hygiene hypothesis, but also attributable to differences in genetic background. For example, the single nucleotide polymorphism (SNP) PTPN22 is associated with high risk of T1D and distributed more in the northern regions than southern regions of Europe (Shapira et al., 2010a). Another factor that might explain the "North-south gradient" of MS and T1D is the amount of sun exposure. Vitamin D, production of which is dependent on exposure to UV, has been reported to have immunomodulatory effects, and insufficient production of vitamin D might be responsible for the higher incidence of autoimmune disorders in northern European countries (Shoenfeld et al., 2009; Ponsonby et al., 2002).

There is epidemiological evidence of the importance of non-hygienic conditions in the prevention of autoimmune or atopic disorders. For instance, a significant difference in allergen-specific IgE level was reported between people of neighboring regions sharing the same ethnic background; Finland (relatively hygienic) and Russian Karelia (relatively non-hygienic) (Seiskari et al., 2007). Enteroviral infections were found to protect the children in Karelia from atopy. Moreover, there are reports that offspring of immigrants from developing countries acquire a higher incidence of autoimmune diseases, such as T1D and MS, than the population of their parents' motherland countries (Bach, 2002; Bodansky, 1992). These findings clearly indicate the importance of environmental factors (including hygienic standards) rather than genetic background in the pathogenesis of autoimmune disorders.

The "sibling effect", that children with more siblings have a lower risk of developing atopic disorders (Strachan, 1989), is the basic finding that the hygiene hypothesis comes from. The sibling effect on atopic disorders has been demonstrated in cohort studies (Benn et al., 2004; Matheson et al., 2009; Cullinan et al., 2003). A similar effect was reported in case of T1D (Cardwell et al., 2008a) and IBD (Koloski et al., 2008). From the viewpoint of the hygiene hypothesis, the decrease of the disease risk can be explained by the increased exposure to pathogens from elder siblings. Regarding atopic disorders, a meta-analysis of atopic dermatitis (AD) has shown inverse relationships with exposure to endotoxins, early day care, and contact with animals (Flohr et al., 2005). The risk of the early onset of allergic rhinitis (AR) was inversely correlated with viral infections during childhood, in addition to cumulative exposure to siblings before the age of 2 years (Matheson et al., 2009). Not only

overt infections but also non-invasive exposure to pathogen-derived products, such as endotoxins (Gereda et al., 2000), are considered responsible for prevention of atopy (von Mutius, 2007). In the case of autoimmune diseases, the risk of T1D is reduced in children living with siblings, sharing a bedroom and of households that often move (Cardwell et al., 2008b). A population-based study in Canada demonstrated correlations between IBD and high socioeconomic status and low rates of enteric infections (Green et al., 2006). The report also revealed a positive correlation between IBD and MS.

3. Evidence that does not match the hygiene hypothesis

In great contrast to T1D and MS, rheumatoid arthritis (RA) has been declining in prevalence in recent decades (Gabriel &Michaud, 2009). Moreover, its geographical distribution is very different from that of T1D or MS. That is, RA is generally evenly distributed in the world and does not have a "North-south gradient". (Shapira et al., 2010b). The geographical distribution of systemic sclerosis (SSc) seems to be contrast to those of T1D and MS. Within Europe, SSc is less frequent in the north than south (Shapira et al., 2010b). In the case of ankylosing spondylitis (AS), a genetic factor (HLA-B27) rather than environmental factors seems to explain the prevalence of the disease (Shapira et al., 2010b). Therefore, the geographical distribution and/or chronological transition of some autoimmune diseases cannot be explained by the hygiene hypothesis.

For atopic disorders, the sibling effect itself has been confirmed (Benn et al, 2004; Matheson et al., 2009; Cullinan et al., 2003). However, some authors suggest that infections in early life do not explain the observed sibling effect (Benn et al., 2004; Cullinan et al., 2003). In a report on the preventive effects of endotoxins against AD (Flohr et al., 2005), apparent infections in early life were shown to increase the risk of AD. In a meta-analysis of relationships between exposure to furry pets and asthma and allergic rhinitis, there were different effects in different species of animals. That is, exposure to dogs increases the risk but exposure to cats decreases it (Takkouche et al., 2008). Moreover, in a meta-analysis of interrelationships between vaccinations with bacterial products (BCG and pertussis vaccine) and the incidence of asthma, no statistical association was found (Balicer et al., 2007). For T1D, there was no association between routinely recorded infections in early life and subsequent risk of the disease (Cardwell et al., 2008a). In addition, T1D had inverse relationships with asthma (Cardwell et al., 2003). These finding do not match the hypothesis that infections and exposure to pathogens protect against both atopy and autoimmunity. A systematic review of mycobacterial infections and atopy (Obihara et al., 2007) found that the negative correlations between them were mainly based on cross-sectional studies. The authors, therefore, claimed that population-based prospective studies would be needed.

Regarding etiology of MS, two hypotheses have been proposed (Milo & Kahana, 2010). The "prevalence hypothesis" postulates that MS is caused by a pathogen common in high-incidence areas. In contrast, according to the more accepted "poliomyelitis-hygiene hypothesis", certain infections in early childhood protect against MS whereas infections with the same infectious agents later in life (e.g. adolescence) cause the disease, as in the cases of poliomyelitis. This concept is different from that of the "original" hygiene hypothesis, in that people living in hygienic conditions (= non-infected people) are protected from the disease. Epstein-Barr virus (EBV) is one of the infectious agents suspected to be causative of MS. Individuals infected with EBV in early childhood have a lower risk of MS than those infected in adolescence and as a consequence, suffer from

infectious mononucleosis (IM). Additionally, non-infected people are known to have the lowest risk of MS (Ascheiro & Munger, 2010), suggesting the plausibility of the poliomyelitis-hygiene hypothesis. In addition to the causal relationship betwen EBV and MS, a number of infectious agents (HCV, rotavirus, Coxsackie virus, HHV-6, *Helicobacter pylori*, *Trypanosoma cruzi* etc.) were reported to have an association with autoimmunity (Kivity et al., 2009; Getts & Miller 2010).

Collectively, numerous reports seem to contradict the hygiene hypothesis. In the 99th Dahlem Conference on Infection, Dr. Matricardi tried to reconcile the conflicting evidence (Matricardi, 2010). For instance, infections with orofecal pathogens like hepatitis A virus (HAV) were shown to be inversely correlated with atopy whereas infections of airborne viruses (measles virus, mumps virus, rubella virus etc.) were not (Matricardi et al., 1997; Matricardi et al., 2000). He proposes gastrointestinal infections that stimulate immunological changes in gut-associated lymphoid tissue (GALT) to be important for protective effects against atopic diseases (Matricardi, 2010, Matricardi et al., 2000). Likewise, to explain why some microorganisms protect against immunological disorders and others do not, a refined version of the hygiene hypothesis, the "old friends hypothesis" has been proposed (Rook, 2009). According to this hypothesis, immunological disorders develop if "old friends" (=microorganisms present in humans for a long time on the evolutionary time scale) are expelled from the body. Parasitic helminths and saprophytic bacteria are representative "old friends". To avoid having to fight the host's immune systems long term, they become relatively harmless and continuously activate regulatory dendritic cells (DCs) and regulatory T cells (Treg) at background levels. Consequently, the presence of "old friends" renders hosts resistant to immune dysregulation. This hypothesis seems very attractive, especially to explain immunoregulatory mechanisms by parasitic helminths.

4. Influence of helminth infections on human autoimmune disorders

There have been a few papers on the interrelationships between helminth infections and autoimmune diseases in humans. Correale and colleagues have reported the influence of helminth infections on MS. In a prospective, double-cohort study, they found that MS patients infected with helminths (*Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercolaris* or *Enterobius vermicularis*) showed fewer exacerbations, reduced disability scores, and lower MRI activity compared with uninfected MS patients (Correale & Farez, 2007). Furthermore, the infected MS patients showed an increase in myelin basic protein (MBP)-specific IL-10 and TGF-β - producing cells and a decrease in IL-12 and IFN-γ - producing cells. B cells from helminth-infected MS patients tend to produce high levels of IL-10, brain-derived neurotropic factor (BDNF), and nerve growth factor (NGF) (Correale et al., 2008). More importantly, some MS patients who received anti-parasite treatment, due to an exacerbation of helminth-derived symptoms, showed an increase in MS activity (Correale & Farez, 2011). The authors also showed that both B cells and DCs from intestinal helminth-infected MS patients had increased expression of TLR2 and some of immunological changes observed in helminth Ag-exposed cells were TLR2-dependent (Correale & Farez, 2009). Collectively, these results suggest that parasitic helminths have anti-MS activity in humans. Fleming & Cook (2006) summarized the relationship between prevalence of *T. trichiura* and MS at the country / regional level. According to the data, MS is prevalent only in *T. trichiura*-free countries. Regarding other autoimmune diseases, in a case-control study in Okinawa (Japan), *S. stercolaris* was less frequent in the autoimmune liver disease group than

control group, suggesting that the parasite might protect against autoimmune liver diseases (Aoyama et al., 2007). Most recently, Mutapi et al. (2011) reported epidemiological study in Zimbabwe on the interrelationships between *Schistosoma haematobium* infection and auto-reactive antibody levels. They found an inverse relationship between infection intensity and anti-nuclear antibody (ANA) levels in schistosome- endemic areas. According to the study, anti-helminthic treatment significantly increased ANA levels.

5. Influence of helminth infections on human atopic disorders

Compared to studies on human helminth infections and autoimmunity, reports on the interrelationships between helminth infections and atopic disorders are much more common. However, as there is considerable variation in results among the reports, systematic reviews and meta-analyses are important. According to reviews of cross-sectional studies on the relationships between current parasitic infections and athma and atopy (Leonardi-Bee et al., 2006; Flohr et al., 2009; Feary et al., 2011), both intestinal helminths (Hookworms, *Ascaris*, *Trichuris*, *Strongyloides*, *Enterobius*) and schistosomes significantly lowered reactivity in the skin prick test. In contrast, only hookworm infections lowered the risk of asthma significantly; odds ratio (OR) = 0.50 (Leonardi-Bee et al., 2006). It is worth noting that *Ascaris* infections heightened the risk of asthma (OR = 1.34). Other geohelminths had no significant effects on the risk of asthma.

The evidence obtained in cross-sectional studies is indirect. Direct evidence of ameliorating effects of helminths can be obtained by intervention studies. According to the review literature above (Flohr et al., 2009), in some intervention studies, allergic skin sensitization increased after de-worming treatment. This finding was reproducibly observed in independent studies in Venezuela (Lynch et al., 1993), Gabon (van den Biggelaar et al., 2004) and Vietnam (Flohr et al., 2010). However, in a study in Ecuador (Cooper et al., 2006), there was no increase in the prevalence of atopy or clinical allergies after de-worming treatment. Furthermore, in the study in Vietnam (Flohr et al., 2010), the clinical symptoms of allergy did not worsen in the treated group despite the increased sensitization. Remarkably, a study in Venezuela (Lynch et al., 1997) showed a clinical *improvement* in asthma after regular anti-helminthic treatment. Taken together with cross-sectional studies of allergies in helminth-infected individuals, the overall results could be summarized as follows: 1) In general, parasitic helminths suppress skin sensitization. 2) However, parasitic helminths do not always suppress clinical allergies and can sometimes worsen allergic symptoms. Regarding the timing of helminth infections, a study in Brazil is especially noteworthy (Rodrigues et al., 2008). In the study, heavy infections with *T. trichiura* in early childhood were shown to reduce reactivity to allergens in later childhood. Even if the child was not infected at the time of the skin test, this protective effect was observed. Cooper et al. (2009) summarized studies on helminth infections and clinical allergies in a review, in which he stated that different helminths have different effects on allergies depending on the timing of exposure. According to the review, *Trichuris* and hookworms are protective, whereas *Ascaris* and *Toxocara* may be risk factors in certain situations. Further studies, especially de-worming intervention studies or therapeutic clinical trials using helminths, may be necessary to establish a general view of the anti-allergic effects of helminths.

6. T cell subsets and autoimmunity

Until several years ago, major autoimmune diseases such as MS, T1D, RA and CD and animal models thereof had been classified as Th1-dependent diseases. Recently, however,

the finding of a critical role for IL-23 in the pathogenesis of some experimental forms of autoimmune diseases (Cua et al., 2003; Murphy et al., 2003) and subsequent discovery of a pathogenic T cell subset producing IL-17 (Th17) (Langrish et al., 2005; Park et al., 2005) has led us to revisit the "Th1/Th2 paradigm". The simplified "Th1/Th2 paradigm" still explains many immunological phenomena, but there is accumulating evidence of the importance of Th17 in the pathogenesis of autoimmunity. By using IL-17-deficient mice, essential roles of IL-17 in the pathogenesis of autoimmune disease have been demonstrated directly (Nakae et al., 2003a, 2003b; Komiyama et al., 2003). Development of the Th17 lineage is antagonized by both Th1-related cytokines (IL-12 and IFN-γ) and a Th2 cytokine (IL-4) (Park et al., 2005; Nakae et al., 2007). Conversely, IL-23 and IL-17 negatively regulate Th1 differentiation (Nakae et al., 2007). Therefore, the balance of these Th subsets is much more complex than previously believed. Complicating the situation further is the recent finding that Th17 is not a stable subset and can be changed to the Th1 phenotype; i.e. plasticity of Th17 (Kurschus et al., 2010; Dong, 2011). The fate of Th17 cells depends on their surrounding environment (Dong, 2011; Lee et al., 2009) and Th17's pathogenic nature depends on the conversion to Th1 cells, in the case of experimental T1D (Martin-Orozco et al., 2009; Bending et al., 2009). The relative importance of each Th subset to the pathogenesis may differ with the disease model, however in most cases, the pathogenicity of Th1 and Th17 is still under debate. There is a report that a transcription factor, T-bet, is essential for the encephalitogenicity of T cells rather than cytokine production (Yang et al., 2009). In contrast, T-bet seems to be a negative regulator in experimental autoimmune myocariditis (Rangachari et al., 2006). Given the unstable nature of the Th17 subset and disease heterogeneity of individual patients, antagonism of both the Th1 and Th17 subsets would be a better choice for the successful suppression of autoimmune diseases. From this viewpoint, parasitic helminths may have ideal immunomodulatory activities for treatment of autoimmunity.

7. Effect of helminths on experimental autoimmunity

7.1 Experimental autoimmune encephalomyelitis (EAE)

EAE in rodents has been widely used as an animal model of MS. In EAE, both Th1 and Th17 have been reported to be encephalitogenic and their relative importance depends on the mouse strain and MOG epitope used for immunization (El-behi et al., 2010). In addition, Th1 and Th17 have different encephalitogenic roles as demonstrated by pathological observations; e.g., distinct cellular infiltrates (macrophage predominant or neutrophil predominant) and distinct sites of inflammation (mainly in the spinal cord or mainly in the brain) (El-behi et al., 2010; Domingues et al., 2010). These observations reinforce the necessity for an antagonistic effect against both Th1 and Th17 for ideal immunomodulatory medicines.

Studies of therapeutic effects of helminths on EAE are summarized in Table 1. Anti-encephalitogenic effects have been observed in all three groups of parasitic helminths; i.e. nematodes (*Heligmosomoides polygyrus* (Wilson et al., 2010), *Trichinella spiralis* (Gruden-Movsesijan et al., 2008), *Trichinella pseudospiralis* (Wu et al., 2010)), trematodes (*Schistosoma japonicum* (Zheng et al., 2008), *Schistosoma mansoni* (Sewell et al., 2003; La Flamme et al., 2003), *Fasciola hepatica* (Walsh et al., 2009)) and cestodes (*Taenia crassiceps*) (Reyes et al., 2011). Among them, there are some distinct results in the effects of schistosomes. According to Sewell et al. (2003), the intra-peritoneal injection of schistosome eggs protected mice from EAE, whereas La Flamme et al. (2003), reported that a similar injection did not have

protective effect. In general, a down-regulation of both Th17 and Th1 cytokine expression has been demonstrated (Walsh et al., 2009; Wu et al., 2010; Reyes et al., 2011) except in papers published before the emergence of the Th17 concept (Sewell et al., 2003; La Flamme et al., 2003). Regarding cellular involvement in the suppression, B cells highly expressing CD23 were shown to be responsible for EAE suppression (Wilson et al., 2010) in adoptive transfer experiments. In that study, B cells from IL-10-deficient mice as well as from wild-type mice conferred protection against EAE. The involvement of AAMΦ is also plausible, because AAMΦ markers are increased in the brain in *T. crassiceps*-infected EAE mice (Reyes et al., 2011). In addition, abrogation of schistosome-induced anti- encephalitogenic effects in STAT6-deficient mice (Sewell et al., 2003) might support the importance of AAM Φ.

Helminth	Treatment	Proposed mechanism	Refs
Heligmosomoides polygyrus	Adoptive transfer of infected mouse cells	B cells, Independent of IL-10	Wilson et al., 2010
Trichinella spiralis	Infection		Gruden-Movsesijan et al., 2008
Trichinella pseudospiralis	Infection	IL-17↓, IL-6↓, IL-1β↓, IFN-γ↓, TNF-α↓	Wu et al., 2010
Schistosoma japonicum	Egg Ag i.p.	IFN-γ↓, IL-4↑	Zheng et al., 2008
Schistosoma mansoni	Egg i.p.	IFN-γ↓, IL-4↑, TGF-β↑, IL-10↑, Dependent on STAT6	Sewell et al., 2003
	Infection	IL-12/23 p40↓, IFN-γ↓, TNF-α↓, IL-4↑	La Flamme et al., 2003
Fasciola hepatica	Infection	IFN-γ↓, IL-17↓, Dependent on TGF-β, Independent of IL-10	Walsh et al., 2009
Taenia crassiceps	Infection	IL-17↓, TNF-α↓, IL-4↑, IL-10↑ AAMΦ markers↑	Reyes et al., 2011

↓ : down-regulation, ↑ : up-regulation

Table 1. Suppressive effect of parasitic helminths on EAE.

7.2 Experimental T1D

Non-obese diabetic (NOD) mice have been used widely as an animal model of T1D. Spontaneous destruction of pancreatic β-cells and subsequent hyperglycemia are observed in NOD mice. The pathogenesis of T1D in this mouse has been studied extensively, however, there is still considerable controversy over the relative contribution of Th1 (or IFN-γ) and Th17 (or IL-17). Anti-IFN-γ treatment rendered NOD mice resistant to cyclophosphamide (CY)-accelerated diabetes (Debray-Sachs et al., 1991). In contrast, in IFN-γ deficient NOD mice, neither insulitis nor diabetes was prevented although the onset was delayed (Hultgren et al., 1996; Gysemans et al., 2008). These findings suggest that IFN-γ is involved in, but not essential to, the pathogenesis. IFN-γ is not itself detrimental to β-cells, but induces apoptosis when acting with IL-1β or TNF-α (Gysemans et al., 2008). Regarding this pro-apoptotic effect, dual roles of IFN-γ in NOD mice have been indicated; i.e. IFN-γ induces β-cell destruction via STAT-1 but protects β-cells via IRF-1 (Gysemans et al., 2008). On the other hand, pathological roles of IL-17 have been also suggested in mice (Miljkovic et al., 2005: Emamaullee et al., 2009) and humans (Honkanen et al., 2010). Anti-IL-17 antibody prevented diabetes in NOD mice when administered around the time of onset (Emamaullee et al., 2009). At present, it is reasonable to conclude that both Th1 and Th17 play some role in diabetogenesis in NOD mice.

Along with NOD mice, inducible T1D models have been used for diabetes research. One of them is streptozotocin (STZ)-induced diabetes. STZ is a glucosamine- nitrosourea compound specifically toxic to pancreatic islet β-cells (Yamamoto et al., 1981). Multiple low-dose administrations of STZ cause immune mechanism-mediated β-cell destruction and diabetes in mice (Kantwerk-Funke et al., 1991). In this T1D model, pathogenic roles of both IL-12/IFN-γ axis (Herold et al., 1996; Müller et al., 2002; Gysemans et al., 2005; Cetkovic-Cvrlje & Uckun, 2005) and IL-23/IL-17 axis (Miljkovic et al., 2005, Mensah-Brown et al., 2006) have been suggested, as in NOD mice.

T1D model	Helminth	Treatment	Proposed mechanism	Refs
Spontaneous T1D in NOD mice	*Litomosoides sigmodontis*	Infection, Worm Ag	IL-4↑, IL-5↑, Treg	Hübner et al., 2009
	Heligmosomoides polygyrus	Infection	Independent of IL-10 and Treg	Liu et al., 2009
	Trichinella spiralis	Infection	IL-4↑, IL-10↑	Saunders et al., 2007
	Schistosoma mansoni	Infection / Egg i.p.	Anti-insulin IgG↓	Cooke et al., 1999
		Eggs, Egg Ag, Worm Ag i.p.	NKT cells↑	Zaccone et al., 2003
		Egg Ag i.p.	Treg	Zaccone et al., 2009
Streptozotocin-induced diabetes in mice (Multiple low dose model)	*Schistosoma mansoni*	Infection		EL-Wakil et al., 2002
	Taenia crassiceps	Infection	AAMΦ	Espinoza-Jiménez et al., 2010

↓ : down-regulation, ↑ : up-regulation

Table 2. Suppressive effects of parasitic helminths on experimental T1D.

Studies of the therapeutic effects of helminths on experimental T1D models are summarized in Table 2. As in the case of EAE, all three groups of helminths (nematodes, trematodes and cestodes) have preventive effects against experimental T1D models. As Treg cells play an important regulatory role against diabetogenesis (Brode et al., 2006; Ott et al., 2005), some authors suggest that they are also responsible for the anti-diabetogenic effects of helminths (Hübner et al., 2009; Zaccone et al., 2009). However, other reports do not support the importance of Treg cells (Liu et al., 2009; Espinoza-Jiménez et al., 2010). This inconsistency probably suggests the presence of distinct suppressive mechanisms in each parasite species. In our recent study, intestinal helminth infection protected mice from diabetes induced by multiple low-doses of STZ in a STAT6-independent manner (unpublished observation). This finding suggests that immune polarization from Th1 to Th2 induced by helminths cannot explain the anti-diabetogenic effect. Further studies using gene-targeted mice are needed to elucidate the anti-diabetogenic mechanisms of helminths.

7.3 Experimental autoimmune arthritis

There are various models of autoimmune arthritis in rodents. Collagen-induced arthritis (CIA) is one of the most widely used classical models of RA (Stuart et al., 1982). In this model, anti-collagen antibodies are responsible for the destruction of cartilage (Terato et al., 1992). Regarding cytokines, TNF-α, IL-1β and IL-6 are crucial to the inflammatory bone destruction in autoimmune arthritis (Ferraccioli et al., 2010; Möller & Villiger, 2006). However, the most important factor in the bone destruction is receptor activator of NFκB ligand (RANKL). This cytokine is induced to express on osteoblasts and synovial fibroblasts

by IL-17 and acts on osteoclast precursors to stimulate their differentiation into multinucleated osteoclasts (Okamoto & Takayanagi, 2010). An essential role for IL-17 in the pathogenesis of CIA has been demonstrated directly by using IL-17-deficient mice (Nakae et al., 2003a). IL-17 is an essential pathological factor also in other models of arthritis; e.g. IL-1 receptor antagonist-deficient mice (Nakae et al., 2003b), Ag-induced arthritis (AIA) (Irmler et al., 2007) and glucose 6-phosphate isomerase (GPI)– induced arthritis (Iwanami et al., 2008). Thus, these models could be considered Th17-dependent. In contrast, IFN-γ is now considered an ameliorating factor in CIA (Kelchtermans et al., 2009; Chu et al., 2007) and in AIA (Irmler et al., 2007). However, in proteoglycan-induced arthritis, IFN-γ (not IL-17) is responsible for the pathogenesis (Doodes et al., 2008). Taken together, models of autoimmune arthritis are mainly dependent on Th17 but exceptions do exist. In human RA, the pathological importance of TNF-α, IL-1 β, IL-6 and IL-17 has been demonstrated directly by the striking efficacy of biological drugs targeting those cytokines (Nixon et al., 2007; Jones & Ding, 2010; Genovese et al., 2010). In addition, an anti-RANKL monoclonal antibody has been approved for osteoporosis and is now under clinical development for RA (Pageau, 2009).

As described in section 3, the global distribution and trends of RA do not match the hygiene hypothesis (Gabriel & Michaud, 2009; Shapira et al., 2010b). In addition, to our knowledge, there is no report of anti-RA effects of parasitic helminths in humans. Nonetheless, several investigators (including us) have found anti-arthritic effects of helminths or helminth-derived products in rodents. Those studies are summarized in Table 3. We ourselves have reported suppressive effects of a blood fluke, *S. mansoni,* on mouse CIA (Osada et al., 2009). In that study, the *S. mansoni* infection reduced the severity of CIA as evaluated using scores of arthritis and numbers of arthritic paws. Histopathological observation revealed the prevention of bone destruction in the infected mice. According to an analysis of splenic cytokine production pattern, production of IL-17A, TNF-α and IFN-γ were down-regulated and that of IL-4 and IL-10 was up-regulated. The real-time PCR analysis of inflamed paws showed the striking augmentation of the gene expression of bone-absorptive pro-inflammatory mediators (IL-1β, IL-6 and RANKL) observed in non-infected arthritic mice to be abrogated in infected mice. *S. mansoni* is a gonochoristic worm and forms a pair in the portal vein. Egg deposition in the infected host organs is the major stimulus of Th2-polarization (Grzych et al., 1991) and other immunomodulatory events such as Treg induction (Taylor et al., 2006). In our experiments, the severity of CIA correlated inversely with the numbers of worm pairs, theoretically proportional to the number of eggs produced (Osada et al., 2009). In addition, in a time-course experiment, the splenic cytokine modulation (including down-modulation of IL-17 and TNF-α) was observed from 6 to 8 week post-infection, which corresponds to the beginning of egg deposition (unpublished observation). However, repeated intra-peritoneal injections of soluble egg antigen (SEA) did not protect mice from CIA and viable eggs lost their ability to suppress IL-17 production by freeze-thawing and subsequent crushing treatment (Osada et al., 2010). Therefore, a viable infection, which supplies viable eggs continuously, may be essential for the schistosome-induced anti-arthritic effects. By plotting the relationship between infection intensity and severity levels, we have found that a single pair of worms was enough to abrogate the augmentation of pro-inflammatory mediators and approximately 4 pairs were enough to suppress the onset of arthritis (Osada et al., 2009).

Arthritis model	Helminth	Treatment	Proposed mechanism	Refs
Collagen-induced arthritis (CIA) in mice	*Ascaris suum*	Worm Ag i.p.		Rocha et al., 2008
	Acanthocheilonema viteae	ES-62 i.p.	IFN-γ↓, TNF-α↓, IL-6↓, Anti-collagen IgG↓	McInnes et al., 2003
	Schistosoma mansoni	Infection	IL-17↓, TNF-α↓, IL-6↓, RANKL ↓, Anti-collagen IgG↓	Osada et al., 2009
	Schistosoma japonicum	Infection	IL-4↑, Anti-collagen IgG↓	He et al., 2010
Zymosan-induced arthritis (ZYA) in mice/rats	*Ascaris suum*	Worm Ag i.p./p.o.	NO↓, IL-1β↓	Rocha et al., 2008
Adjuvant-induced arthritis (AIA) in rats	*Schistosoma japonicum*	rSj16 i.p.	TNF-α↓, IL-1β↓,NO↓, IL-10↑	Sun et al., 2010
Spontaneous arthritis in MRL/lpr mice	*Nippostrongylus brasiliensis*	Infection		Salinas-Carmona et al., 2009
	Heligmosomoides polygyrus	Infection		
FCA-induced monoarthritis in rats	*Hymenolepis diminuta*	Infection	IL-10 from CD4+ cells	Shi et al., 2011

↓ : down-regulation, ↑ : up-regulation

Table 3. Suppressive effects of parasitic helminths on experimental arthritis.

In addition to the down-regulation of pro-inflammatory cytokines, pathogenic anti-collagen IgG levels were lowered in the infected mice. Since our publication, other investigators also have demonstrated therapeutic effects of schistosomes on arthritis models. He et al. (2010) showed that *S.japonicum* suppressed CIA. However, infection at 2 weeks before CIA induction resulted in an exacerbation of the disease, whereas infection at 7 weeks before induction prevented the disease. This is in contrast to our study in which infection at 2 weeks before induction reduced the severity of CIA. The reason of this discrepancy is not clear, but as speculated by He et al., the difference in parasite species (*S.mansoni* and *S.japonicum*) might have affected the outcome. Sun et al. (2010) demonstrated that a recombinant protein of *S. japonicum* (rSj16) ameliorated adjuvant-induced arthritis in rats. The authors observed a suppression of IL-12 production and augmentation of IL-10 production in rSj16-treated bone marrow-derived dendritic cells (BMDCs). A filarial nematode-derived phosphorylcholine- containing glycoprotein, ES-62, was proven to suppress ongoing CIA (McInnes et al., 2003). In vitro, ES-62 suppressed LPS-induced production of TNF-α and IL-6 from RA synovial cells. Moreover, ES-62 also inhibited TNF-α production in human T cells and macrophages. Regarding the involvement of regulatory cytokines and cells, Shi et al. (2011) reported that IL-10 from CD4+ cells of infected mice was important for anti-arthritic effects of the rat tapeworm *Hymenolepis diminuta*. They also found that the absence of IL-4Rα chain signaling in mice cancelled the anti-arthritic effects of the worm. These findings seem to suggest the importance of Th2-polarization by the parasite, however, we recently found that the Th2-polarizing intestinal parasite *H. polygyrus* did not protect mice from CIA but rather, exacerbated the disease (unpublished observation). The anti-arthritic mechanisms of helminths seem complicated, probably because of the heterogeneity of both experimental models and parasites.

7.4 Experimental colitis as a model of IBD

Human IBD includes heterogeneous inflammatory diseases of the intestines. For instance, in terms of T cell subset, CD had been considered a "Th1 disease", but at present, the importance of the Th17 subset in the pathogenesis of CD is emphasized (Sarra et al., 2010).

Increases in both IL-17 and IL-12 mRNA in CD and UC patients has been reported (Nielsen et al., 2003). The most striking evidence of the involvement of IL-23/Th17 axis is the finding of Th17-related genes (including IL-23R gene) as susceptibility genes for CD (Brand, 2009). In contrast, Th2-related cytokines are dominant in UC (Sarra et al., 2010). Likewise, models of colitis are also composed of diseases with a distinct pathogenesis (Strober et al., 2002). Experimental colitis induced by the intra-rectal injection of hapten, such as TNBS or DNBS, resembles human CD and its development seems independent of IFN-γR (Camoglio et al., 2000) and dependent on IL-17R signaling (Zhang et al., 2006). Colitis can be also induced by causing dysfunction in epithelial cell barrier. Supply of drinking water containing dextran sulfate sodium (DSS) induces this type of colitis. In this model, T and B cells are dispensable (Dieleman et al., 1994) and macrophages seem to play both a pathological role (Bauer et al., 2010) and a regulatory role (Qualls et al., 2006; Smith et al., 2007). Considering predominant expression of Th2-related cytokines in the chronic phase, DSS-induced colitis resembles UC (Alex et al., 2009). Interestingly, neutralization of IL-17 aggravates the model (Ogawa et al., 2004), suggesting that IL-17 plays a protective role against DSS-induced colitis. By contrast, another study demonstrated that the colitis was alleviated in IL-17A deficient mice (Ito et al., 2008). The reason for this discrepancy is not clear, but might be due to different mouse strains used in their experiments as indicated by Ito et al.

Using these models of colitis, a number of studies on helminth effects have been conducted (Table 4). Generally, helminths seem to ameliorate TNBS/DNBS- induced colitis. It is worth noting that even worms that usually cause intestinal pathology by laying a large number of eggs in the mesenteric vein (i.e. *Schistosoma* spp.) have anti-colitic effects (Moreels et al., 2004; Ruyssers et al., 2009; Elliott et al., 2003; Mo et al., 2007; Zhao et al., 2009; Bodammer et al., 2011; Smith et al., 2007). A down-regulation of Th1/Th17-related cytokines and up-regulation of anti-inflammatory cytokines are observed in most studies. However, only a few papers have provided direct evidence of the involvement of certain cells or cytokines. For instance, anti-colitic effects of *S.mansoni* (Elliott et al., 2003) and *H.diminuta* (Hunter et al., 2005) were demonstrated to be STAT6-dependent. The latter authors also a showed the anti-colitic effect of the worms to be dependent on IL-10 and the presence of macrophages (Hunter et al., 2010). In contrast to the regularly observed helminths' ameliorating effects on Th1/Th17 dominant (TNBS/DNBS- induced) models, macrophage-mediated or Th2-dominant (DSS-induced or oxazolone- induced) colitis was not alleviated or rather worsened by some helminth infections (Table 4). This exacerbation seems due to the robust Th2-polarization by the helminths; e.g. *H. diminuta* infection worsened oxazolone-induced colitis via IL-5 induction and consequently caused eosinophila (Wang et al., 2010), demonstrated by a loss of exacerbation in eotaxin-deficient mice or anti-IL-5 antibody-treated mice. The finding that anti-colitic effects of schistosome male worms were lost in DSS-induced colitis when mice were infected with worms of mixed sex (Smith et al., 2007) may support the speculation, because the Th2-polarizing ability of schsitosome eggs (produced in mixed sex infection) is more potent than that of adult worms (Grzych et al., 1991). Weinstock's group has been studying anti-colitic mechanisms of the intestinal helminth *H.polygyrus* by using colitis in IL-10-deficient or TGF-βRII dominant negative (DN) mice (Elliott et al., 2004, 2008; Ince et al., 2009). According to the studies, the helminth's anti-colitic effect depends not on IL-10 but on TGF-β signaling. This finding does not mean that host-derived TGF-β is necessary, because it has been recently shown that *H. polygyrus*-derived "TGF-β-like molecules" mobilize host TGF-β signaling and induce subsequent Treg cell development (McSorley et al., 2010; Grainger et al., 2010).

Colitis model	Helminth	Treatment	Effect	Proposed mechanism	Refs
TNBS/DNBS-induced colitis	*Ancylostoma caninum*	Worm Ag i.p.	A		Ruyssers et al., 2009
	Heligmosomoides polygyrus	Infection	A	Mast cell-mediated, Neural control of secretory function	Sutton et al., 2008
	Trichinella spiralis	Worm Ag i.r.	A	IL-1β↓, iNOS↓, IL-13↑, TGF-β↑	Motomura et al., 2009
	Schistosoma mansoni	Infection	A	IL-2↑, IL-4↑	Moreels et al., 2004
		Egg i.p.	A	IFN-γ↓, IL-4↑, STAT6 dependent	Elliott et al., 2003
		Worm Ag i.p.	A	IFN-γ↓, IL-17↓, TGF-β↑, IL-10↑	Ruyssers et al., 2009
	Schistosoma japonicum	Egg i.p.	A	IFN-γ↓, IL-4↑, IL-10↑, Treg↑	Mo et al., 2007
		Egg i.p.	A	IFN-γ↓, IL-10↑、TLR4↓	Zhao et al., 2009
	Hymenolepis diminuta	Infection	A	TNF-α↓, IL-10↑, IL-4↑, AAMΦ-dependent, IL-10/STAT6 dependent	Hunter et al., 2005; Hunter et al., 2010; Johnston et al., 2010
DSS-induced colitis	*Ancylostoma ceylanicum*	Worm Ag / ES Ag i.p.	A	IFN-γ↓, IL-17↓, TNF-α↓	Cançado et al., 2011
	Acanthocheilonema viteae	Cystatin i.p.	A	IL-10 producing MΦ	Schnoeller et al., 2008
	Toxascaris leonina	Galectin homologue i.p.	A	TGF-β↑, IL-10↑	Kim et al., 2010
	Schistosoma mansoni	Infection (male only)	A	MΦ dependent, Treg/IL-10/IL-4/IL-13/TGF-β independent	Smith et al., 2007
		Infection (mixed)	N		
		Egg Ag i.p.	N		
		Infection (mixed)	A	TNF-α↓	Bodammer et al., 2011
		Egg Ag i.p.	N		
	Hymenolepis diminuta	Infection	E		Reardon et al., 2001
Oxazolone colitis	*Hymenolepis diminuta*	Infection	E	IL-5↑, Eosinophils↑	Wang et al., 2010
Piroxicam-induced colitis in IL-10 deficient mice	*Heligmosomoides polygylus*	Infection	A	IL-17↓, IL-10 independent	Elliott et al., 2004; Elliott et al., 2008
Colitis in TGF-βRII DN mice	*Heligmosomoides polygylus*	Infection	N	TGF-β signal dependent	Ince et al., 2009
Rag/IL-10-/- Tcell transfer	*Heligmosomoides polygylus*	Infection	A	Modulation of DC function	Hang et al., 2010

↓ : down-regulation, ↑ : up-regulation A: Amelioration, E: Exacerbation, N: No effect

Table 4. Effects of parasitic helminths on experimental colitis.

8. Clinical trials of parasitic helminths against immunological disorders

The administration of non-pathogenic or hypo-virulent parasitic worms could be considered for the treatment of immunological disorders. Several clinical trials using parasitic worms have been and are currently being conducted. Significant therapeutic effects have been confirmed in some of these studies. Weinstock's group conducted trials with *Trichuris suis* (porcine whipworm) ova (TSO) against CD (Summers et al., 2005a) and UC (Summers et al., 2005b), and demonstrated significant efficacy. TSO is also being tested for MS and promising results have been obtained in a phase I trial (Fleming et al., 2011). Regarding allergic disorders, Bager et al. (2010) found no therapeutic effect of TSO on allergic rhinitis. However, Summers et al. (2010) critically commented on the report that it was premature to conclude that TSO is ineffective on allergic rhinitis because the TSO treatment was too late and not sufficient. *Necator americanus* (Hookworm) is also under clinical trials for asthma (Feary et al., 2010) and CD (Croese et al., 2006). The advantage of this worm is its long life in the host (at least 6 years) and no need for repeated inoculation (Elliott and Weinstock, 2009). The parasite was well-tolerated without severe adverse effects on asthmatic patients, but a safe dosage of the parasites (10 infective larvae) did not show significant therapeutic efficacy (Feary et al., 2010).

9. Concluding remarks

There are two ways of developing parasite-based biomedicines for clinical use. One approach is the direct applications of non-pathogenic/hypo-virulent viable helminths to patients, as introduced in section 8. In addition to TSO and hookworms, other hypo-virulent helminths could be considered for human application. However, before clinical trials, sufficient accumulation of epidemiological and experimental evidence of their therapeutic efficacy is required. Hypo-virulent intestinal nematodes (e.g. *Trichostrongylus* spp.), intestinal trematodes (e.g. *Metagonimus* sp.) and intestinal tapeworms (e.g. *Hymenolepis diminuta*) may become candidates for such studies in the future. It is also essential that the parasites can be maintained in domestic or experimental animals. This is because parasites that infect only humans cannot be maintained and expanded efficiently for clinical use. Another way of developing parasite-based biomedicines comes from the identification of effector molecules of parasites. Considerable numbers of immunomodulatory molecules have been identified from helminths (Harnett W & Harnett MM, 2010). The majority have shown therapeutic effects on experimental autoimmunity or allergy. Some investigators reported that viable parasites were superior to administration of the antigens of parasites (Hunter et al., 2010; Bodammer et al., 2011; Osada et al., 2010) in therapeutic efficacy. In addition, there is still considerable controversy over the roles of regulatory cells (e.g. Treg, Breg or AAMΦ) and regulatory cytokines (e.g. IL-4, IL-10, TGF-β) in helminth-induced immunomodulation. Therefore, further investigation is needed to elucidate the immunomodulatory mechanisms of viable parasite infections, and new findings obtained there should help to establish an optimal screening system for anti-autoimmune/anti-allergic substances from parasitic helminths.

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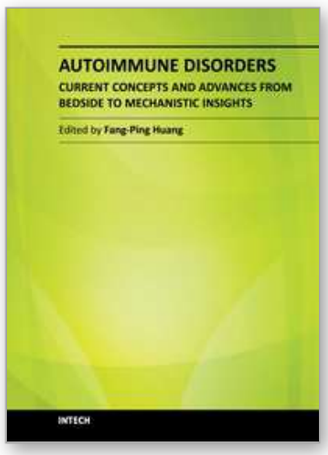

Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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