Parasitic Infections’ Immunomodulatory Effects and Autoimmune Diseases

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ABSTRACT

The hygiene hypothesis has been implicated in the dramatic increase in autoimmune and allergic diseases noticed in recent decades, especially in developed countries. This growth was associated with lesser exposure to diverse immunoregulatory infectious agents. This hypothesis has been proved by many potent epidemiological and experimental studies. The results of these studies along with the analysis of the western world’s microbiome helped us to have a greater idea about microorganisms shared in the hygiene hypothesis, as well as their main mechanisms that have an effect on the immune system. Protozoal infections have been proved to have remarkable immunomodulatory changes in different autoimmune diseases. Helminths and their derivatives were proved to have a protective role. Helminths’ broad immunomodulatory effects have been tested in clinical trials of autoimmune diseases, including inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and type-1 diabetes. In this review, we discussed particular parasitic infections and their immunomodulatory effects on some autoimmune diseases.

INTRODUCTION

This increase in the prevalence of autoimmune and allergic diseases has been attributed to the relatively better hygiene standards that are present in the western world. Those standards included the reduction of exposure to different pathogens, including parasites. Parasites were proved to have multiple anti-inflammatory and immunomodulatory mechanisms for the immune system.

The hygiene hypothesis was the most proposed reason for the disease-dampening effects reported in the different studies analyzing the relationship between parasitic infections and autoimmunity. In this review, we discussed the current studies concerning parasites as potent immunomodulators in autoimmune diseases.

Chronic autoimmune diseases affecting various organs have remarkably increased all over the world in the last few years. During the last decades, epidemiological studies had pointed to a special increase in the incidence of chronic autoimmune-inflammatory CNS diseases such as multiple sclerosis and autoimmune encephalomyelitis ((Trapp and Nave, 2008; Ramagopalan and Sadovnick, 2011).
Hygiene Hypothesis:

The hygiene hypothesis is a term that supported the theory of a potent relationship between infectious disease prevalence with allergic and autoimmune (AI) diseases (Bach, 2002). The prevalence of allergic diseases such as bronchial asthma has increased in the last decades. It reached more than 15% in countries such as the United Kingdom, New Zealand and Australia (Eder et al., 2006). Additionally, atopic dermatitis prevalence has been also elevated in developed countries, as about 2-10% of adults and 15-30% of children were affected (Bieber, 2008). It has been also noted that the prevalence of autoimmune diseases had marked elevation in European countries. It was reported that the prevalence of type 1 diabetes (T1D) among children (0-4 years) was increased in Finland (Harjutsalo et al., 2008).

In addition, a remarkable increase in Crohn’s disease, ulcerative colitis and biliary cirrhosis was noticed in the last years (Rautiainen et al., 2007). In the developed countries, after the industrial progress, great care for hygiene was achieved such as water sanitation, and good food preservation. Moreover, vaccination programs for common childhood diseases were initiated. That resulted in a reduction in the incidence of infectious diseases like hepatitis A virus. Widespread usage of anti-pathogenic medications has also contributed to the elimination of many parasitic diseases like schistosomiasis and filariasis (Zaccone et al., 2006).

Studies had demonstrated the protective effect of exposure to infectious agents in early childhood life against allergic and AI diseases. Riedler et al. (2001) showed that exposure to farming and cowsheds in early life protected against asthma. Regarding exposure to parasitic diseases and their impact on the incidence of allergic diseases, Flohr et al. (2006) documented that schistosomiasis could protect against allergic dermatitis among Vietnamese children. Another study reported the inverse relationship between parasitic infections and the incidence of allergic dermatitis (van den Biggelaar et al., 2004).

It was noted that the incidence of immune-based diseases was about 100% in mice bred in specific pathogen-free (SPF) conditions, while it was very low in mice grown in conventional sanitary conditions, suggesting a strong association with the development of atopic diseases (Bach, 2002). Parasitic infection induction was found to reduce the severity of the disease attacks in multiple sclerosis patients. It was documented that there was an elevation in interleukin (IL) 10 and transforming growth factor (TGF)-β in patients’ blood samples (Correale and Farez, 2007).

*Trichuris suis* ova infection in ulcerative colitis patients resulted in improvement of the symptoms. The same positive effect was also documented in Crohn’s disease patients (Summers et al., 2005a, b). The larval stage of hookworm, *Necator americanus* was injected intradermally to treat Crohn’s disease and produced remarkable effects (Croese et al., 2006). Studies from many countries such as Venezuela (Lynch et al., 1993), Vietnam (Flohr et al., 2006) and Gabon (van den Biggelaar et al., 2004) showed that parasitic diseases elimination had resulted in a higher incidence of atopic diseases such as atopic dermatitis.

In general, infectious agents, especially parasites, might have biological importance for the pharmacological and therapeutic values for treating allergic and AI diseases. Nevertheless, after removing the parts causing the infectious diseases and their pathology, then using the molecules responsible for treating or alleviating the symptoms of the immune-based diseases (Osada and Kanazawa, 2010). Parasitic infections were documented to have therapeutic effects against many autoimmune diseases and will be discussed in this review in detail.
Autoimmune Diseases and Parasitic Infections:

Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is an AI disease characterized by an inflammatory chronic progressive course that affects peripheral joints symmetrically resulting in their damage, irreversible deformities and reduced life expectancy (Mota et al., 2012).

RA affects about 0.2-1 % of the worldwide population. It is more common in females, with its highest incidence among the aged between 30 to 50 years. Its outcome affects both, the patient and society. It affects the life quality of the patients and the productivity of society (De Azevedo et al., 2008). The process begins with the loss of the normal mechanism of self-tolerance to auto-antigens and identifying joint antigens as foreign molecules, which resulted in synovitis and joint destruction. The synovial membrane in this process is the tissue of the target where mononuclear cellular infiltrates occur that lead to synovial hyperplasia, pro-inflammatory cytokines release, and vascular proliferation. Synovial hyperplasia is the nucleus for synovial plannus that causes bone erosion, cartilage, tendons and ligaments destruction resulting in joint damage (Mota et al., 2012).

Innate immune cells, which participate in the inflammatory infiltrate of the synovium, are; mast cells, neutrophils, natural killer cells and the most important cells are macrophages. Macrophages have a dual action in this pathology; they release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-23) as a part of being antigen-presenting cells (APCs), and produce prostanoids and extracellular matrix metalloproteinases (Mota et al., 2012). Concerning disease affecting cytokines, TNF-α has a unique role. It activates macrophages and lymphocytes resulting in exacerbating synovitis. It also stimulates the release of other inflammatory mediators. TNF-α also acts directly on bone resorption by stimulating the receptor activator of nuclear factor kappa-B ligand (RANKL) that activates monocytes into osteoclasts and inhibiting their apoptosis (Schett et al., 2005).

RA is defined as Th17 immune-mediated disease. IL-17 is the main cytokine of this pathway that stimulates the expression of RANKL triggering and exacerbating bone resorption. Anti-apoptotic cytokines like IL-2, IL-4, and IL-15 were elevated in RA which explains the inhibition of T cell apoptosis in this disease (Andersson et al., 2008). Rheumatoid factor was detected in 70-80% of RA patients. B cells also could act as class II APCs with a production of cytokines (Andersson et al., 2008).

In Nigerian villages where there was a higher prevalence of parasitic diseases, the rheumatoid factor seropositivity was detected in many patients. However, interestingly, they had lesser severe clinical and radiological manifestations than parasite-free RA patients (Greenwood et al., 1970). Collagen-induced arthritis (CIA) is characterized by the production of CII-specific antibodies, which is a common feature of RA (Nandakumar, 2010). In addition, rheumatoid factor (RF) was detected in CIA as in RA (Tarkowski et al., 1989). Trentham et al. (1977) injected the rats with CII emulsified in complete Freund’s adjuvant (CFA) that produced polyarthritis with an autoimmune course and an erosive nature. Consequently, other researchers developed CIA in mice and non-human primates (Cathcart et al., 1986).

Schistosoma mansoni infection of male DBA/ 1 mice two weeks prior to injection with type II collagen (IIC) significantly decreased the severity of arthritis. Anti-IIC IgG and IgG2a levels were lower in infected rather than in uninfected mice. Concerning the cytokine-producing potentials in the infected mice, the downregulation of Th1 (IFN-c) and pro-inflammatory cytokines (TNF-α and IL-17A) was observed (Osada et al., 2009). In addition, an upregulation of Th2 (IL-4) and an anti-inflammatory cytokine (IL-10). Schistosoma mansoni infection reduced the
severity of autoimmune arthritis through systemic and local reduction of pro-inflammatory mediators, indicating the potential of parasite-derived materials as therapeutic agents against rheumatoid arthritis (Osada et al., 2009).

Filarial nematodes secrete phosphorylcholine-containing 62-kDa glycoprotein, excretory-secretory-62 (ES-62), which has immunomodulatory activities. This glycoprotein was found to have an anti-inflammatory action in the murine CIA model and human rheumatoid arthritis-derived synovial tissue cultures, as a first step to developing (ES)-62-based drugs. It was documented that ES-62 could inhibit Th1-type responses and reduce antigen-specific IgG2a (a Th1-promoting antibody subclass), with no modulation of IgG1, IgG3 and IgM levels (Harnett et al., 2008).

*Schistosoma mansoni* inhibited CIA through elevated anti-inflammatory cytokines; IL-4, IL-10 and reduced pro-inflammatory cytokines; TNF-α, IL-1β, IL-17A and anti-collagen antibodies (IgG2a) (Osada et al., 2009).

*Schistosoma japonicum* attenuated CIA via a similar mechanism like *Schistosoma mansoni* up-regulated Treg cells (Song et al., 2011).

*Fasciola hepatica* total extract antigen was able to attenuate CIA. It was achieved through activation of tolerogenic dendritic cells (DC) and T-regulatory cells (Treg) that down-regulated TNF-α, anti-collagen antibodies and elevated IL-10, TGF-β (Carranza et al., 2012).

*Hymenolepis diminuta* infection was found to reduce arthritis development in CIA mice through T and B cells dependent mechanisms. The immune-modulatory effect was abolished in T and B cells deficient mice (Shi et al., 2011).

*Acanthocheilonema vitae* ES-62 decreased CIA development in DBA/1 mice through tolerogenic dendritic cells (DC), and B-regulatory cells (Breg) which induced induction of anti-inflammatory cytokine (IL-10), and decreased pro-inflammatory cytokine as TNF-α, IL-6 and IL-17. In addition to reduced anti-collagen antibody production (Pineda et al., 2012).

*Nippostrongylus brasiliensis* infection decreased clinical arthritis incidence and severity in spontaneous arthritis in MRL/lpr mice through enhanced IL-4 production (Salinas-Carmona et al., 2009).

*Trichinella spiralis* alleviated arthritis in CIA model through STAT6 independent mechanism (Osada et al., 2020).

Plasmodium berghei yoelii attenuated adjuvant arthritis in rats (Greenwood et al., 1970).

*Toxoplasma gondii* prevented spontaneous arthritis development in the IL-1R antagonist-deficient mice model through Th1 polarization with consequent Th17 inhibition (Washino et al., 2012). A similar effect was reported with gamma-irradiated *Toxoplasma gondii* in decreasing adjuvant arthritis in mice by declined production of pro-inflammatory cytokines (Hafez et al., 2020).

*Trypanosoma brucei* (*T. brucei*) decreased CIA in mice (De Trez et al., 2015). This effect was attributed to reduced anti-collagen antibody production. *Trypanosoma cruzi* decreased adjuvant arthritis in rats (Mattsson et al., 2000).

*Leishmania* purified proteins from amastigotes reduce arthritis scoring in CIA mice model (O’Daly et al., 2010). A similar effect was reported using *Leishmania major*, *Leishmania* analog of the receptors for activated C kinase (LACK). This effect was attributed to increased IL-4 production while decreased production of pro-inflammatory cytokines; IL-6 and IL-17 (Yang et al., 2018).

**Inflammatory Bowel Disease:**

Clinical trials were conducted using *Trichuris suis* ova and that treatment was effective in relieving Crohn’s disease manifestations in more than 70% of the patients (Summers et al., 2005b).

*Necator americanus* infection improved the clinical condition of patients
with inflammatory bowel disease that increased with time (Croese et al., 2006).

*Schistosoma mansoni* prevented and inhibited trinitrobenzene sulphonate acid (TNBS) induced colitis, through up-regulated IL-4 and IL-10 anti-inflammatory cytokines (Moreels et al., 2004). *Schistosoma japonicum* decreased TNBS-induced colitis through Treg cells and elevated production of IL-4 and IL-5 (Mo et al., 2007).

*Clonorchis sinensis* cystatin (cystain protease inhibitor) inhibited dextran sodium sulfate (DSS) induced colitis. This was attributed to increased IL-10 production while decreased TNF-α production (Jang et al., 2011).

*Trichinella spiralis* attenuated dinitrobenzene sulfonic acid (DNBS)-induced colitis via enhanced secretion of IL-4, and IL-13 while inhibition of IL-1β, myeloperoxidase (MPO) and inducible nitric oxide synthase (iNOS) expression (Motomura et al., 2009).

*Hymenolepis diminuta* inhibited DNBS-induced colitis through the enhanced production of the anti-inflammatory cytokine IL-10 (McKay, 2010).

*Heligmosomoides polygyrus* attenuated colitis via tolerogenic DC that affect T cell response and led to decreased IL-17 production (Blum et al., 2012).

**Celiac Disease:**

*Necator americanus* infection depressed the inflammatory response in the patients through reduced IFN-γ and IL17A production (McSorley et al., 2011).

**Multiple Sclerosis (MS):**

*Trichuris suis* ova was used in MS patients, and this treatment was successful to inhibit new magnetic resonance imaging (MRI) detected lesions. This was attributed to Treg and Breg enhanced activity in helminthic infections, which increased IL-10 and decreased IL-12 production in infected patients. This effect was confirmed when anti-helminthic therapy was used, deteriorated clinical presentation and radiological lesions occur (Correale and Farez, 2007). *Necator americanus, Hymenolepis nana, Ascaris lumbricoides, Enterobius vermicularis, Trichuris trichura* and *Strongyloides stercoralis* infections were tried in clinical studies to compare symptoms between MS parasitic-infected and non-infected patients. The studies showed reduced relapses, disability scores and MRI lesions in infected patients (Correale and Farez, 2007).

**Autoimmune Encephalitis:**

*Schistosoma mansoni* reduced the incidence and the severity of experimental autoimmune encephalitis (EAE) disease. This effect was achieved via the affection of inflammatory cytokines profile; increased IL-4 and IL-10 while decreased TNF-α and IL-12, resulting in reduced CNS inflammatory cell infiltration (La Flamme et al., 2003).

*Schistosoma japonicum* soluble egg antigen diminished EAE pathology via increased IL-4, which decreased CNS inflammation. *Fasciola hepatica* abolished EAE via enhanced tolerogenic DC, M2-macrophages, and IL-10 secreting T-cells activity and decreased IL-17 (Walsh et al., 2009).

*Taenia crassiceps* alleviated EAE by an increased IL-4, IL-10 while decreasing TNF-α, and IL-17 and enhancing M2-macrophages with consequent reduced iNOS expression and CNS inflammation (Reyes et al., 2011).

*Trichinella spiralis* alleviated EAE pathology. This effect was achieved by Treg, tolerogenic DC with increased IL-4, IL-10 and decreased IL-17. A similar effect was reported with *Trichinella pseudospiralis*, which delayed and abolished EAE pathology by an increased IL-4, IL-5, and IL-10 while decreasing TNF-α, IL-1β and IL-17 (Gruden-Movsesijan et al., 2008).

*Trypanosoma cruzi* abolished EAE clinical scoring by decreasing IL-2 while increasing IL-10 and TGF-β (Tadokoro et al., 2004). *Trypanosoma brucei brucei*, alleviated EAE scoring via decreased IFN-γ expression besides reduced anti-myelin
oligodendrocyte glycoprotein (MOG) IgG serum levels (Wållberg and Harris, 2005).

*Plasmodium chabaudi* decreased EAE clinical scoring by affecting IL-17 expression while increased IL-10 and TGF-β (Farias *et al*., 2011).

**Systemic Lupus Erythematosus (SLE):**

*Schistosoma mansoni* infection trials in MRL/lpr mice were effective to turn the glomerulonephritis phenotype from diffuse proliferative to the membranous pattern. It was achieved via increased IL-4, IL-5, IL-10, and TGF-β (Miyake *et al*., 2014).

*Plasmodium chabaudi* infection of female BWF1 lupus mice (SLE model) was successful in the protection of lupus nephritis through reduced nitric oxide (NO) and hydrogen peroxide (H$_2$O$_2$) in both kidney and liver of infected mice (Al-Quraishy *et al*., 2013).

**Type-1 Diabetes:**

*Schistosoma mansoni* infecting non-obese diabetic (NOD) mice with its egg antigens enhanced Treg prevented diabetes in mice (Zaccone *et al*., 2009).

*Dirofilaria immitis* prevented diabetes development in NOD mice through an IgE-dependent mechanism and abrogated class switch from IgM to IgG anti-insulin autoantibodies (Ímaj et al., 2001).

*Litomosoides sigmodontis* prevented diabetes in NOD mice through Th2 polarization and up-regulated FoxP3+ Treg cells (Hübner *et al*., 2009).

*Trichinella spiralis* abolished diabetes occurrence in NOD mice through inhibited pancreatic insulitis and increased IL-4 (Saunders *et al*., 2007).

*Heligmosomoides polygyrus* alleviated and suppressed the severity of diabetes in NOD mice through reduced expression of TNF-α and IL-1β in the pancreas (Osada *et al*., 2013).

**Psoriasis:**

*Schistosoma mansoni* infection in fsn/fsn mice (psoriasis model) protected against psoriatic skin lesions through increased IL-13 and decreased IFN-γ (Atochina and Harn, 2006).

**Graves’ Disease:**

*Schistosoma mansoni* inhibited Grave’s disease development through decreased IgG2a and anti-thyroid stimulating hormone (TSH) receptor antibody levels (Nagayama *et al*., 2004).

**CONCLUSION**

Numerous experimental and clinical studies have documented that infection with the parasites could reduce the severity of some autoimmune disorders. Most of these studies depended on the use of parasitic infections as prophylactic strategies. Particular parasites could be used to treat certain human autoimmune diseases; therefore, these controlled infections could be used as an adjuvant treatment. Nevertheless, the isolation of the effective molecules from the parasites could offer a better prospect in the context of parasitic infections as protective or treatment strategies for autoimmune diseases.

**REFERENCES**

Al-Quraishy, S., Abdel-Maksoud, M. A., El-Amir, A., Abdel-Ghaffar, F. A. and Badr, G. (2013). Malarial infection of female BWF1 lupus mice alters the redox state in kidney and liver tissues and confers protection against lupus nephritis. *Oxidative Medicine and Cellular Longevity, 2013*: 1-10.

Andersson, A. K., Li, C. and Brennan, F. M. (2008). Recent developments in the immunobiology of rheumatoid arthritis. *Arthritis Research and Therapy, 10*(2): 204.

Atochina, O. and Harn, D. (2006). Prevention of psoriasis-like lesions development in fsn/fsn mice by helminth glycans. *Experimental Dermatology, 15*(6): 461-468.

Bach, J. F. (2002). The effect of infections on susceptibility to autoimmune
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and allergic diseases. New England Journal of Medicine, 347(12): 911-920.

Bieber T. (2008). Atopic dermatitis. The New England Journal of Medicine, 358(14): 1483–1494.

Blum, A. M., Hang, L., Setiawan, T., Urban, J. P., Stoyanoff, K. M., Leung, J., et al. (2012). Heligmosomoides polygyrus bakeri induces tolerogenic dendritic cells that block colitis and prevent antigen-specific gut T cell responses. The Journal of Immunology, 189(5): 2512-2520.

Bolland, S., Kole, H. K., Scott, B. and Amo, L. (2018). A single infection with a malaria parasite protects mice from lethal autoimmune glomerulonephritis. The Journal of Immunology, 200(1supplement): 162-163.

Carranza, F., Falcón, C. R., Nuñez, N., Knubel, C., Correa, S. G., Bianco, I., et al. (2012). Helminth antigens enable CpG-activated dendritic cells to inhibit the symptoms of collagen-induced arthritis through Foxp3+ regulatory T cells. PloS One, 7(7): e40356.

Cathcart, E. S., Hayes, K. C., Gonnerman, W. A., Lazzari, A. A. and Franzblau, C. (1986). Experimental arthritis in a nonhuman primate. I. Induction by bovine type II collagen. Laboratory Investigation; a Journal of Technical Methods and Pathology, 54(1): 26-31.

Correale, J. and Farez, M. (2007). Association between parasite infection and immune responses in multiple sclerosis. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 61(2): 97-108.

Croese, J., O’neil, J., Masson, J., Cooke, S., Melrose, W., Pritchard, D., & Speare, R. (2006). A proof of concept study establishing Necator americanus in Crohn’s patients and reservoir donors. Gut, 55(1), 136-137.

De Azevedo, A. B. C., Ferraz, M. B. and Ciconelli, R. M. (2008). Indirect costs of rheumatoid arthritis in Brazil. Value in Health, 11(5): 869-877.

De Trez, C., Katsandegwaza, B., Caljon, G. and Magez, S. (2015). Experimental African trypanosome infection by needle passage or natural tsetse fly challenge thwarts the development of collagen-induced arthritis in DBA/1 prone mice via an impairment of antigen specific B cell autoantibody titers. PLoS One, 10(6): e0130431.

Eder, W., Ege, M. J. and von Mutius, E. (2006). The asthma epidemic. New England Journal of Medicine, 355(21): 2226-2235.

Farias, A. S., Talaisys, R. L., Blanco, Y. C., Lopes, S. C., Longhini, A. L. F., Pradella, F., et al. (2011). Regulatory T cell induction during Plasmodium chabaudi infection modifies the clinical course of experimental autoimmune encephalomyelitis. PLoS One, 6(3): e17849.

Flohr, C., Tuyen, L. N., Lewis, S., Quinnell, R., Minh, T. T., Liem, H. T., et al. (2006). Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: a cross-sectional study. Journal of Allergy and Clinical Immunology, 118(6): 1305-1311.

Greenwood, B. M., Voller, A. and Herrick, E. M. (1970). Suppression of adjuvant arthritis by infection with a strain of the rodent malaria parasite Plasmodium berghei. Annals of the Rheumatic Diseases, 29(3): 321.

Gruden-Movsesijan, A., Ilic, N., Mostarica-Stojkovic, M., Stosic-Grujicic, S.,
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Milic, M. and Sofronic-Milosavljevic, L. (2008). *Trichinella spiralis*: modulation of experimental autoimmune encephalomyelitis in DA rats. *Experimental Parasitology*, 118(4):641-647.

Hafez, E. N., Moawed, F. S., Abdel-Hamid, G. R. and Eldin, E. S. (2020). Immunomodulatory activity of gamma radiation-attenuated *Toxoplasma gondii* in adjuvant arthritic mice. *Journal of Photochemistry and Photobiology B: Biology*, 209: 111920.

Harjutsalo, V., Sjöberg, L. and Tuomilehto, J. (2008). Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. *The Lancet*, 371(9626): 1777-1782.

Harnett, M.M., Kean, D.E., Boitelle, A., et al. (2008). The phosphorycholine moiety of the filarial nematode. Immunomodulator ES-62 is responsible for its anti-inflammatory action in arthritis. *Annals of the Rheumatic Diseases*, 67: 518–523.

Hübner, M. P., Thomas Stocker, J. and Mitre, E. (2009). Inhibition of type 1 diabetes in filaria-infected non-obese diabetic mice is associated with a T helper type 2 shift and induction of FoxP3+ regulatory T cells. *Immunology*, 127(4): 512-522.

Imai, S., Tezuka, H. and Fujita, K. (2001). A factor of inducing IgE from a filarial parasite prevents insulin-dependent diabetes mellitus in nonobese diabetic mice. *Biochemical and Biophysical Research Communications*, 286(5): 1051-1058.

Jang, S. W., Cho, M. K., Park, M. K., Kang, S. A., Na, B. K., Ahn, S. C. and Yu, H. S. (2011). Parasitic helminth cystatin inhibits DSS-induced intestinal inflammation via IL-10+ F4/80+ macrophage recruitment. *The Korean journal of parasitology*, 49(3), 245.

La Flamme, A. C., Ruddenklau, K. and Bäckström, B. T. (2003). Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. *Infection and Immunity*, 71(9): 4996-5004.

Lynch, N. R., Hagel, I., Perez, M., Di Prisco, M. C., Lopez, R. and Alvarez, N. (1993). Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. *Journal of Allergy and Clinical Immunology*, 92(3): 404-411.

Mattsson, L., Larsson, P., Erlandsson-Harris, H., Klareskog, L. and Harris, R. A. (2000). Parasite-mediated down-regulation of collagen-induced arthritis (CIA) in DA rats. *Clinical and Experimental Immunology*, 122(3): 477-483.

McKay, D. M. (2010). The immune response to and immunomodulation by *Hymenolepis diminuta*. *Parasitology*, 137(3): 385-394.

McSorley, H. J., Gaze, S., Davey, J., Jones, D., Anderson, R. P., Clouston, A. and Loukas, A. (2011). Suppression of inflammatory immune responses in celiac disease by experimental hookworm infection. *PloS one*, 6(9), e24092.

Miyake, K., Adachi, K., Watanabe, M., Sasatomi, Y., Oghara, S., Abe, Y., ... & Hamano, S. (2014). Parasites alter the pathological phenotype of lupus nephritis. *Autoimmunity*, 47(8), 538-547.

Mo, H. M., Liu, W. Q., Lei, J. H., Cheng, Y. L. and Li, Y. L. (2007). *Schistosoma japonicum* eggs modulate the activity of CD4+
CD25+ Tregs and prevent development of colitis in mice. Experimental Parasitology, 116 (4): 385-389.

Moreels, T. G., Nieuwendijk, R. J., De Man, J. G., Winter, D., Herman, A. G., Van Marck, E. A., et al. (2004). Concurrent Infection with *Schistosoma mansoni* attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid induced colitis in rats. Gut, 53(1): 99-107.

Mota, L. M. H. D., Cruz, B. A., Brenol, C. V., Pereira, I. A., Rezende-Fronza, L. S., Bertolo, M. B., et al. (2012). Consenso 2012 da Sociedade Brasileira de Reumatologia para o tratamento da artrite reumatoide. Revista Brasileira de Reumatologia, 52(2): 152-174.

Motomura, Y., Wang, H., Deng, Y., El-Sharkawy, R. T., Verdu, E. F., and Khan, W. I. (2009). Helminth antigen-based strategy to ameliorate inflammation in an experimental model of colitis. Clinical & Experimental Immunology, 155(1), 88-95.

Nagayama, Y., Watanabe, K., Niwa, M., McLachlan, S. M. and Rapoport, B. (2004). *Schistosoma mansoni* and α-galactosylceramide: prophylactic effect of Th1 immune suppression in a mouse model of Graves’ hyperthyroidism. The Journal of Immunology, 173(3): 2167-2173.

Nandakumar, K. S. (2010). Pathogenic antibody recognition of cartilage. Cell and Tissue Research, 339(1): 213-220.

O’Daly, J. A., Gleason, J. P., Peña, G. and Colorado, I. (2010). Purified proteins from *Leishmania* amastigotes-induced delayed type hypersensitivity reactions and remission of collagen-induced arthritis in animal models. Archives of Dermatological Research, 302(8): 567-581.

Osada, Y., Shimizu, S., Kumagai, T., Yamada, S. and Kanazawa, T. (2009). *Schistosoma mansoni* infection reduces severity of collagen-induced arthritis via down-regulation of pro-inflammatory mediators. International Journal for Parasitology, 39(4): 457-464.

Osada, Y. and Kanazawa, T. (2010). Parasitic helminths: new weapons against immunological disorders. Journal of Biomedicine and Biotechnology, 2010: e743758.

Osada, Y., Yamada, S., Nabeshima, A., Yamagishi, Y., Ishiwata, K., Nakae, S., et al. (2013). *Heligmosomoides polygyrus* infection reduces severity of type 1 diabetes induced by multiple low-dose streptozotocin in mice via STAT6-and IL-10-independent mechanisms. Experimental Parasitology, 135(2): 388-396.

Osada, Y., Morita, K., Tahara, S., Ishihara, T., Wu, Z., Nagano, I., et al. (2020). Th2 signals are not essential for the anti-arthritic effects of *Trichinella spiralis* in mice. Parasite Immunology, 42(1): e12677.

Pineda, M. A., McGrath, M. A., Smith, P. C., Al-Riyami, L., Rzepecka, J., Gracie, J. A., et al. (2012). The parasitic helminth product ES-62 suppresses pathogenesis in collagen-induced arthritis by targeting the interleukin-17–producing cellular network at multiple sites. Arthritis and Rheumatism, 64(10): 3168-3178.

Ramagopalan SV and Sadovnick AD. (2011). Epidemiology of multiple sclerosis. Neurologic Clinics, 29: 207–217.

Rautiainen, H., Salomaa, V., Niemelä, S., Karvonen, A. L., Nurmi, H.,
Isoniemi, H., et al. (2007). Prevalence and incidence of primary biliary cirrhosis are increasing in Finland. Scandinavian Journal of Gastroenterology, 42(11): 1347-1353.

Reyes, J. L., Espinoza-Jiménez, A. F., González, M. I., Verdin, L. and Terrazas, L. I. (2011). Taenia crassiceps infection abrogates experimental autoimmune encephalomyelitis. Cellular Immunology, 267(2): 77-87.

Riedler, J., Braun-Fahrländer, C., Eder, W., Schreuer, M., Waser, M., Maisch, S., et al. (2001). Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. The Lancet, 358(9288): 1129-1133.

Salinas-Carmona, M. C., De la Cruz-Galicia, G., Pérez-Rivera, I., Solís-Soto, J. M., Segoviano-Ramirez, J. C., Vázquez, A. V., et al. (2009). Spontaneous arthritis in MRL/lpr mice is aggravated by Staphylococcus aureus and ameliorated by Nippostrongylus brasiliensis infections. Autoimmunity, 42(1), 25-32.

Saunders, K. A., Raine, T., Cooke, A. and Lawrence, C. E. (2007). Inhibition of autoimmune type I diabetes by gastrointestinal helminth infection. Infection and Immunity, 75(1): 397-407.

Schett, G., Hayer, S., Zwerina, J., Redlich, K. and Smolen, J. S. (2005). Mechanisms of disease: the link between RANKL and arthritic bone disease. Nature Clinical Practice Rheumatology, 1(1): 47-54.

Shi, M., Wang, A., Prescott, D., Waterhouse, C. C., Zhang, S., McDougall, J. J., et al. (2011). Infection with an intestinal helminth parasite reduces Freund's complete adjuvant-induced monoarthritis in mice. Arthritis and Rheumatism, 63(2): 434-444.

Song, X., Shen, J., Wen, H., Zhong, Z., Luo, Q., Chu, D., et al. (2011). Impact of Schistosoma japonicum infection on collagen-induced arthritis in DBA/1 mice: a murine model of human rheumatoid arthritis. PLoS One, 6(8): e23453.

Summers, R. W., Elliott, D. E., Urban Jr, J. F., Thompson, R. A. and Weinstock, J. V. (2005 a). Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology, 128(4): 825-832.

Summers, R. W., Elliott, D. E., Urban, J. F., Thompson, R. A. and Weinstock, J. V. (2005 b). Trichuris suis therapy in Crohn's disease. Gut, 54(1): 87-90.

Tadokoro, C. E., Vallochi, A. L., Rios, L. S., Martins, G. A., Schlesinger, D., Mosca, T., et al. (2004). Experimental autoimmune encephalomyelitis can be prevented and cured by infection with Trypanosoma cruzi. Journal of Autoimmunity, 23(2): 103-115.

Tarkowski, A., Holmdahl, R. and Klareskog, L. (1989). Rheumatoid factors in mice. Monographs in Allergy, 26: 214–229.

Trapp BD and Nave KA. (2008). Multiple sclerosis: an immune or neurodegenerative disorder? Annual Review of Neuroscience, 31: 247–269.

Trentham, D. E., Townes, A. S. and Kang, A. H. (1977). Autoimmunity to type II collagen an experimental model of arthritis. The Journal of Experimental Medicine, 146(3): 857-868.

Van den Biggelaar, A. H., Rodrigues, L. C., van Ree, R., van der Zee, J. S., Hoeksma-Kruize, Y. C., Souverijn, J. H., et al. (2004). Long-term treatment of intestinal
helminths increases mite skin-test reactivity in Gabonese schoolchildren. *Journal of Infectious Diseases*, 189(5): 892-900.

Wållberg, M., & Harris, R. A. (2005). Co-infection with Trypanosoma brucei brucei prevents experimental autoimmune encephalomyelitis in DBA/1 mice through induction of suppressor APCs. *International immunology*, 17(6), 721-728.

Walsh, K. P., Brady, M. T., Finlay, C. M., Boon, L. and Mills, K. H. (2009). Infection with a helminth parasite attenuates autoimmunity through TGF-β-mediated suppression of Th17 and Th1 responses. *The journal of Immunology*, 183(3): 1577-1586.

Washino, T., Moroda, M., Iwakura, Y. and Aosai, F. (2012). *Toxoplasma gondii* infection inhibits Th17-mediated spontaneous development of arthritis in interleukin-1 receptor antagonist-deficient mice. *Infection and Immunity*, 80(4): 1437-1444.

Yang, F., Fan, X., Huang, H., Dang, Q., Lei, H. and Li, Y. (2018). A single microorganism epitope attenuates the development of murine autoimmune arthritis: regulation of dendritic cells via the mannose receptor. *Frontiers in Immunology*, 9: 1528.

Zaccone, P., Fehervari, Z., Phillips, J. M., Dunne, D. W. and Cooke, A. (2006). Parasitic worms and inflammatory diseases. *Parasite Immunology*, 28(10): 515-523.

Zaccone, P., Burton, O., Miller, N., Jones, F. M., Dunne, D. W., & Cooke, A. (2009). *Schistosoma mansoni* egg antigens induce Treg that participate in diabetes prevention in NOD mice. *European journal of immunology*, 39(4), 1098-1107.

**ARABIC SUMMARY**

التاثيرات المناعية للعدوى الطفيلية وأمراض المناعة الذاتية

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شاركنا فرضية النظافة في الارتفاع الكبير في أمراض المناعة الذاتية وأمراض الحساسية، والتي لوحظت في العقود الأخيرة في الدول الغربية. كان هذا النمو ناتجًا عن التعرض الأقل للعوامل المعدية المختلفة التي تؤثر على المناعة. تم اكتشاف هذه الفرضية من خلال العديد من الدراسات التجريبية والبيئية. ساعدنا نتائج هذه الدراسات في الحصول على فكرة أكبر عن الكائنات الحية الدقيقة المشتركة في فرضية النظافة، بالإضافة إلى آلياتها الرئيسية التي لها تأثير على جهاز المناعة. ثبت أن الدخان الطفيلي ومشتقاتها لها دور وقائي. تم اختبار تأثيرات تدعيم المناعة الواسعة للديدان الطفيلي في التجارب السريرية لأمراض المناعة الذاتية، بما في ذلك مرض التهاب الأمعاء، والتهاب اللمف، والالتهاب المفاصل الروماتويدي، ومرض السكري من النوع الأول. في هذه المقال، نناقش النتائج الطفيلية وتأثيراتها المعدلة للكائنات الحية الدقيقة في فرضية المناعة الذاتية والحساسية. الكلمات المفتاحية: فرضية النظافة، المناعة الذاتية، الحساسية، الدفان الطفيلي، الكائنات الطفيلية الأولية