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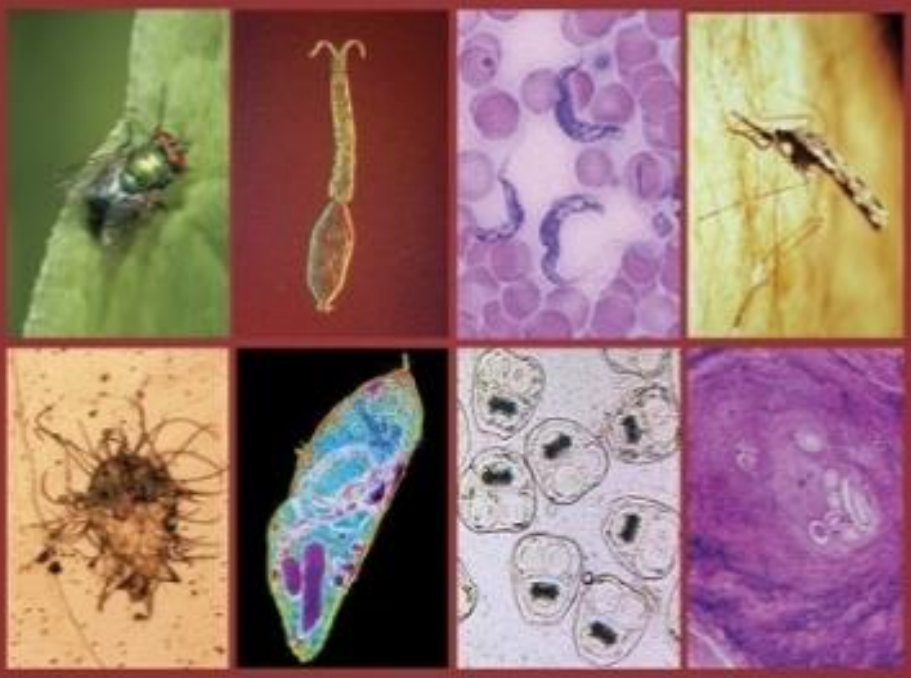

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Parasitic Infections' Immunomodulatory Effects and Autoimmune Diseases

Aliaa M. Elsawey[1*], Nairmen Nabih[1], Gaballah, E.M.[2], Samia E. Etewa[3] and Nora Aboulfotouh[1]

1-Department of Medical Parasitology, Faculty of Medicine, Mansoura University
2-Department of Medical Parasitology, Faculty of Medicine, Damietta University
3-Department of Medical Parasitology, Faculty of Medicine, Zagazig University
E-mail : aliaaelsawey@gmail.com - nairmen_n@yahoo.com - dremangaballah@gmail.com - drsamiaetewa@hotmail.com - dr_nora80@mans.edu.eg

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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-a 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 sulphonic 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, and 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_2O_2) in both kidney and liver of infected mice (Al-Quraishy *et al.*, 2013).

Plasmodium yoelii 17XNL infection of FcγRIIB$^{-/-}$ SLE mice model protected mice from glomerulonephritis by affecting pathogenic leukocytes infiltration into kidney tissues (Bolland *et al.*, 2018).

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 (Imai *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.

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ARABIC SUMMARY

التاثيرات المناعية للعدوي الطفيلية وامراض المناعة الذاتية

علياء محمد الصاوي[1] , نيرمين نبيه[1], ايمان محمد جاب الله[2], سامية السيد عطيوة[3] , نورا ابوالفتوح[1]

1-قسم الطفيليات الطبية, كلية الطب, جامعة المنصورة

2-قسم الطفيليات الطبية, كلية الطب, جامعة دمياط

3-قسم الطفيليات الطبية, كلية الطب, جامعة الزقازيق

شاركت فرضية النظافة في الارتفاع الكبير في أمراض المناعة الذاتية وامراض الحساسية، والتي لوحظت في العقود الأخيرة في الدول الغربية. كان هذا النمو ناتجًا عن التعرض الأقل للعوامل المعدية المختلفة التي تؤثر على المناعة. تم إثبات هذه الفرضية من خلال العديد من الأدلة الوبائية والتجريبية. ساعدتنا نتائج هذه البيانات 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 الديدان الطفيلية ومشتقاتها لها دور وقائي. تم اختبار تأثيرات تعديل المناعة الواسعة للديدان الطفيلية في التجارب السريرية لأمراض المناعة الذاتية، بما في ذلك مرض التهاب الأمعاء، والتصلب المتعدد، والتهاب المفاصل الروماتويدي، ومرض السكري من النوع الأول. في هذه المقال، ناقشنا العدوى الطفيلية وتأثيراتها المعدلة للمناعة لبعض أمراض المناعة الذاتية.

الكلمات المفتاحية: فرضية النظافة، المناعة الذاتية، الحساسية، الديدان الطفيلية، الكائنات الطفيلية الاولية