Possible Correlation between Helminths and Immune System; Immunogenic Antigens of T. Spiralis

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Abstract

Human trichinellosis is one of the most common parasitic zoonosis worldwide caused by nematodes infection of genus *Trichinella.* Human infections occur after consumption of raw or undercooked meat containing encysted larvae. Pigs are a major source of infection in humans. *T. spiralis* adult is one of the smallest nematodes infecting man and is white in color. Humans have established an immunological balance between the TH1/TH17 and TH2 responses, of which the TH1/TH17 response is mostly related to autoimmunity while the TH2 response is related to parasite infections. *T. spiralis* has the unique capacity to make itself "at home" by hiding in the host body in a new type of cell called the “nurse cell”. From this immunologically privileged location, the parasite organizes a long-lasting molecular cross-interaction with the host via excretory–secretory (ES) antigens. They have a variety of effects as they can diminish inflammation caused by muscle cell invasion and regulate immunological responses in a way to be protective for both the host and the parasite. *T. spiralis* is a parasite that causes a long-term infection in the host's skeletal muscles. The parasite could survive until the end of life (in rats) and for several months to years after infection in higher species or humans. Unlike some other internal parasites, it does not damage the host's muscle cells, making it one of the most successful parasitic symbiotes. In human trichinellosis, the innate and adaptive immune responses of the host are activated to resist the invasion of parasites, and undergo the process of elimination. Establishment of *T. spiralis* infection requires modulation of the host's immune response in order to escape their own expulsion, but it must be carefully regulated to avoid threatening host survival.

Keywords: T. spiralis, Helminths, Immune system

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Introduction:

Human trichinellosis is one of the most common parasitic zoonosis worldwide caused by nematodes infection of genus *Trichinella.* Human infections occur after consumption of raw or

undercooked meat containing encysted larvae. Pigs are a major source of infection in humans. It has been documented in 55 (27.8 %) countries throughout the world including the United States, China, Argentina and Russia **(1).**

Dyab *et al.* (2) reported that the prevalence of *T. spiralis* infection in pigs at the Albasatin slaughterhouse in the Cairo Governorate (Egypt) was 1.08 percent. In Upper Egypt, *T. spiralis* infection rate is 5% & 2% in Assiut and Sohage Governorates, respectively **(3).**

The low prevalence rate of trichinellosis in pigs in Egypt may be related to hygienic conditions for raising pigs in private farms. Also, raising Egyptian pigs are mainly indoors away from the infection source. There is no doubt that there is a lack of accuracy in slaughterhouses during the examination of pig trichinoscopy, which is more or less unreliable and needs a trained technician **(2).**

Immune response and immunomodulation

Helminths and immune system

Humans have established an immunological balance between the TH1/TH17 and TH2 responses, of which the TH1/TH17 response is mostly related to autoimmunity while the TH2 response is related to parasite infections **(4).**

Helminthic Infections typically induce Th2-type immunity characterized by the production of high amounts of cytokines IL-4, IL-5, IL-9, IL-10, IL-13 in addition to immunoglobulin E (IgE) and the mobilization of eosinophils, basophils and mast cells. Th2 cell-mediated immunological events can decrease the Th1 response, making the infected person less prone to inflammatory and autoimmune illnesses **(5).**

Different experimental studies on host–parasite relationships showed that some helminths are potent modulators of immune response and could be employed as a therapeutic tool for the prevention and/or reduction of pro-inflammatory events under well-defined conditions **(6).**

However, the mechanisms are still not clearly understood. Also, there are many issues that must be elucidated, such as the effective dosage, potential toxicity and inoculation times **(7).**

Part of the immune system's modulation by parasites is performed by dendritic cells. Dendritic cells do not become traditionally mature when exposed to helminth parasites or their products, yet they are effective inducers of Th2 and regulatory responses **(8).**

Moreover, helminths can interact with the host's adaptive immune response by down-regulating T- and B-cell responses via the stimulation of T-regulatory cells or the anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)-b that can regulate both Th1 and Th2 responses **(9).**

This immunomodulation is hypothesized to be beneficial for both the human host and the parasite; it could protect helminths from being eradicated and, at the same time, protect the host from excessive pro-inflammatory responses that may lead to organ damage **(10).**

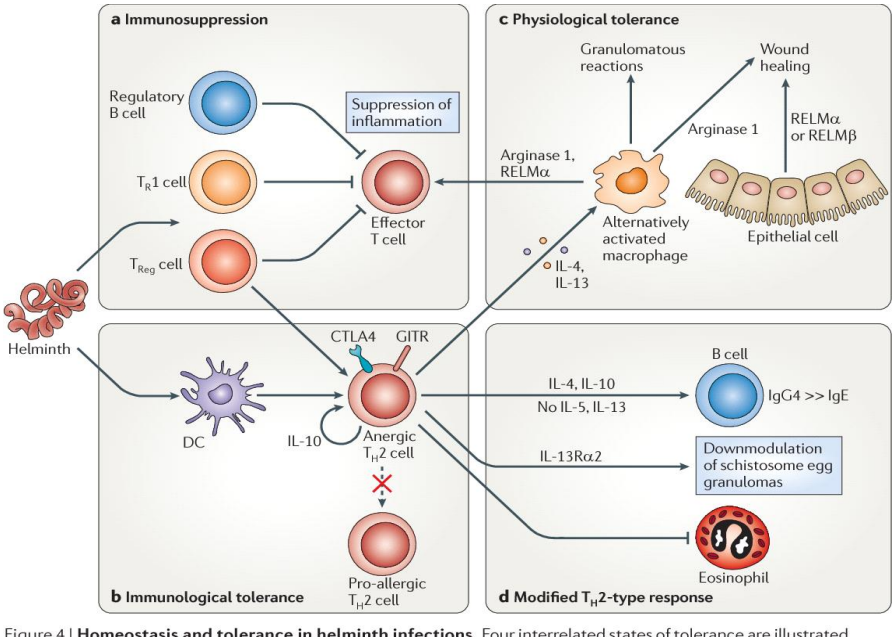

Figure 4 | **Homeostasis and tolerance in helminth infections.** Four interrelated states of tolerance are illustrated

Fig. (1): Homeostasis and tolerance in helminth infections **(5).**

Immunogenic antigens of T. spiralis:

T. spiralis has the unique capacity to make itself "at home" by hiding in the host body in a new type of cell called the “nurse cell”. From this immunologically privileged location, the parasite organizes a long-lasting molecular cross-interaction with the host via excretory–secretory (ES) antigens. They have a variety of effects as they can diminish inflammation caused by muscle cell invasion and regulate immunological responses in a way to be protective for both the host and the parasite **(11).**

Gruden-Movsesijan *et al.* (12) suggested that *T. spiralis* infection is considered a major challenge for the host immune system, since it is induced by the derived antigens that occur in each phase of the parasite life cycle.

These antigens are of concern because they are targets of antibodies that mediate protective immune response against *T. spiralis* and are valuable in the diagnosis of trichinellosis. Those antigens were named *T. spiralis* larvae group (TSL-1) that are released (secreted and/or excreted) by *T. spiralis L1* during the the muscular phase suggesting a functional role in parasitism **(13).**

The study of these molecules is critical to understand the mechanisms of successful parasitism and to develop new therapies and preventive strategies for inflammatory diseases **(7).**

Bai *et al.* (14) stated that antigens of TSL-1 are involved in the interaction with different host cells as enterocytes, muscle cells, as well as immune cells, thus achieving their crucial role in parasitism and induction and modulation of immune response. Researches on ES L1 showed that they consist of 13 different proteins such as proteinase, proteinase inhibitors, glycosidases, phosphatases, heat shock proteins, kinases, endonucleases, enolases, and DNA-binding proteins **(15).**

The 43kDa glycoprotein in ES L1 products is believed to be responsible for the development of nurse cell (NC) after NBL entry into muscle cells; because the gene encoding this glycoprotein is expressed before and after formation of NC but not expressed by adult of *T. spiralis* **(4)**.

T. spiralis—Biology of infection and immune response polarization

T. spiralis is a parasite that causes a long-term infection in the host's skeletal muscles. The parasite could survive until the end of life (in rats) and for several months to years after infection in higher species or humans. Unlike some other internal parasites, it does not damage the host's muscle cells, making it one of the most successful parasitic symbiotes. In human trichinellosis, the innate and adaptive immune responses of the host are activated to resist the invasion of parasites, and undergo the process of elimination **(16)**.

Establishment of *T. spiralis* infection requires modulation of the host's immune response in order to escape their own expulsion, but it must be carefully regulated to avoid threatening host survival **(16)**.

Wang *et al.*, (17) reported that human host invasion by *T.*spiralis larvae elicits a complex immune response, mainly humoral which is characterized by hypergammaglobulinemia, especially IgE and IgG1, as a result of Th2 cell activation. The excess production of these immunoglobulins is partly due to polyclonal activation induced by different parasite antigens and partly to the specific humoral response to the parasite.

Dentritic cells represent a significant link between the innate and adaptive immunity, which plays a major part during immune response to parasites. Dentritic cells act via recognizing pathogen-associated molecular patterns (PAMPs) of ES L1 antigens through distinct pattern recognition receptors (PRRs) that include toll-like receptors (TLRs), C-type lectin receptors (CLRs), node-like receptors, and RIG-I like receptors **(18)**.

Colonna *et al.* (19) observed that upon DCs stimulation with *T. spiralis* ES L1, DCs undergo maturation of phenotypic and functional changes leading to their migration to the lymph nodes and to priming T- cell adaptive immune response via production of different cytokines.

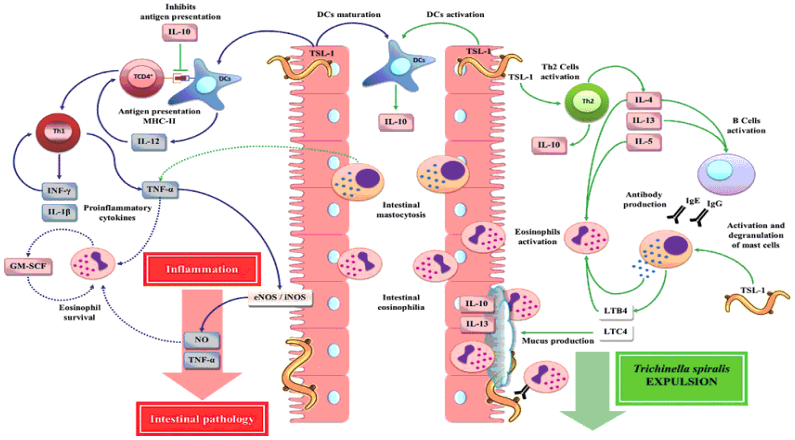

Fig. (2): Immune responses during the intestinal phase of *T. spiralis* infection. **(16).**

Th1 immune response; inflammatory responses:

During the early intestinal phase of *T. spiralis* infection, TSL-1 antigens induce the DCs maturation, leading to the expression of MHC- II and promoting the polarization of the cellular immune response to an early, short Th-1 immune response **(7)**.

This has shown that there is a significant increase of Th1 (pro-inflammatory) cytokines such as interleukin (IL)-12, interferon (INF)-γ, IL-1β and tumor necrosis factor (TNF)-α which together with eosinophilia elicit intestinal inflammatory response, thus leading to the development of intestinal pathology and creating a favorable environment for the survival of *T. spiralis* **(11)**.

Wink *et al.* (20) stated that TNF-α results in expression of iNOS and consequently the production of nitric oxide (NO) which mainly acts as an effector molecule against both intracellular and extracellular parasites.

- **Th2 immune response; *T. spiralis* expulsion:**

The initial exposure to TSL-1 antigens of *T. spiralis* stimulates CD4 + T cells and DCs, resulting in secretion of large numbers of IL-10 which can suppress cell markers, DC-proliferation and antigen presentation and also, leads to inhibition of IL-12 secretion **(7)**.

However, TSL-1 increases the production of both IL-4 and IL-10 derived from Th2 cells with a decrease in IFN-γ levels, polarizing the immune response to a strong cellular immune response of Th2 protective and important for elimination of *T. spiralis* **(8)**.

Wang *et al.* (17) stated that the reduction of IL-10 levels results in a high susceptibility to the primary infection by *T. spiralis*, accompanied with a significant delay in the *T. spiralis* removal and an increase in the parasite burden. Additionally, Mast cells expand rapidly in the intestinal mucosa, mainly within the epithelium, where TSL-1 antigens can directly elicit their degranulation releasing effector mediators such as histamine, serine proteases and TNF-α.

The Th2 immune response is characterized by the production and secretion of other cytokines such as IL-4, IL-5, and IL-13, that stimulate IgE synthesis, stimulating mast cell and eosinophilic hyperplasia, causing immediate hypersensitivity reactions, and promoting expulsion of *T. spiralis* from intestine. In combined effect with Th2 cytokines such as IL-4 and IL-13, these mediators enhance the permeability of epithelial cells, contractility of smooth muscle cells and the mucus production that favor *T. spiralis* expulsion **(21)**.

Immune response of IBD

T lymphocytes are an important class of immunocompetent cells that are classified into CD4+ and CD8+ subsets depending on their function. These subpopulations promote and restrict each other. The dynamic balance of the CD4+/CD8+ ratio determines the state of immune regulation. CD4+ T cells can differentiate into four subtypes of cells with different functions under influence of many cytokines and environmental effects: Thelper (Th)-1, Th2, CD4+CD25+ regulatory T cells (Treg), and Th17 cells **(22)**.

Regulatory T-cells is a subset of T cells with immunomodulatory functions that inhibit the activation and function of other immune cells and participate in the regulation of the body's own immune system. Foxp3 is a core transcription factor that regulates the development and differentiation of Treg cells. Only T-regs that express Foxp3 have immunomodulatory effects. CD4+CD25+ Foxp3 Treg cells can suppress and modulate the excessive immune response. Therefore, this represents an essential homeostatic mechanism by which the host can tolerate the massive burden of innocuous antigens within the gut without responding through profound inflammation **(11).**

CD8+ T cells differentiate into (CD8+CD28-, immunosuppressive T cells, Ts) and (CD8+CD28+, Specific cytotoxic T cells, Tc) under the action of cytokines secreted by CD4+ T cells, Specific killer T cells exert a specific killing effect on infected target cells while Ts cell subpopulations have immunosuppressive effects. Inflammatory bowel disease is accompanied with a Th1 response, marked by elevated levels of proinflammatory mediators as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) as well as low levels of IL-4 and IL-10. However, several studies have suggested that cytokine profile in ulcerative colitis includes both Th1 and Th2 cytokines. The imbalance between Th1 and Th2 cytokines released by the intestinal mucosa determines the intensity and duration of the inflammatory response in experimental colitis **(23).**

Cosmi *et al.* (24) showed that Th17 cells producing interleukin-17 (IL-17) play a crucial role in the induction of colitis. In addition, **Morrison *et al.* (25)** showed that IL-23, released by macrophages and dendritic cells located in the intestinal mucosa, activates signal transducer and activator of transcription-4 (STAT-4) in memory T lymphocytes, stimulating the production of IFN-γ, which contributes to the increase of the inflammation present in colitis.

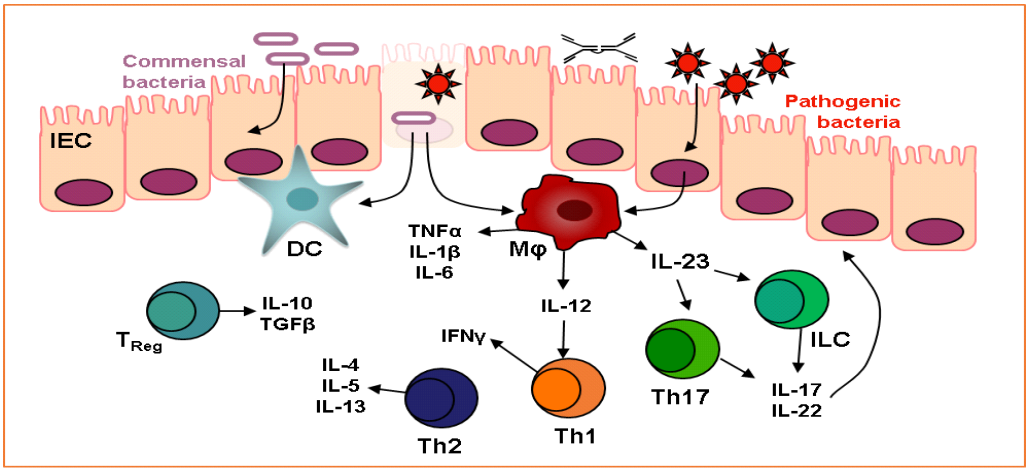

Fig (3): Key cellular populations and mediators in intestinal homeostasis and the pathogenesis of inflammatory bowel disease (DC, dendritic cell; IEC, intestinal epithelial cell; ILC, innate lymphoid cell; Mφ,macrophage; sIgA, secretory IgA; Th, helper T cell; T_{Reg}, regulatory T cell **(26)**

T. spiralis role in modulation of autoimmune and allergic diseases

The prevalence of autoimmune illnesses has risen dramatically during the last century in industrialized countries. However, it is reduced after exposure to infectious pathogens like helminths. The protective effect of infections on immunological diseases has been explained through few methods. Competition and immunoregulation were the most important mechanisms. The first mechanism involved the development of strong immunological response against antigens of the infectious agents that could inhibit immune responses to "weak" antigens like auto-antigens and allergens. Another mechanism includes the role of regulatory T cells and their cytokines including IL-10 and TGF- β that suppress the immune response not only toward an infectious agent but also to bystander antigens **(27)**

Different experimental studies on host–parasite relationships showed that some helminths infections like *T. spiralis, Trichuris muris, Trichuris suis* and *Hymenolepis diminuta* or helminths (eggs, larvae, extracts) can strongly modulate immune response and could be employed as a therapeutic tool for the prevention and/or reduction of some allergic and autoimmune disorders **(6).**

Xu *et al.* (28) used different approach, which implied *T. spiralis* infection after IBD induction by trinitrobenzenesulfonic acid (TNBS). The results were very promising in reduction of mortality rate and the severity of colitis in mice, since they obtained upregulation of Th2 cytokines IL-4 and IL-13 and, downregulation of myeloperoxidase (MPO) activity, IFN-γ expression and reduction in mucosal damage, throughout the course of the disease.In addition, it was showed that the percentages of spleen CD4+CD25+Foxp3+ Treg cells in colitis group were significantly lower than those of the control group while higher in the TsCystatin treatment groups.

Ashour *et al.* (29) found that *T. spiralis* infection that preceded acetic acid induced colitis succeeded in inducing disease amelioration, judged by decreased inflammation rate, improved histopathological changes, and decreased mortality. Proposed mechanisms were the induction of regulatory responses during the chronic phase of *T. spiralis* infection, reflected in elevated proportion of CD4+CD25+Foxp3+ T reg cells that could downregulate Th1/Th17 responses present in ulcerative colitis.

Motomura *et al.* (30) stated that application of *T. spiralis* antigens enhanced the production of Th2 cytokine IL-13 and regulatory cytokine TGF-β, which are responsible for the suppression of Th1- mediated inflammatory response.

Du and coworkers (31) revealed protective effect of recombinant 53 kDa glycoprotein (rTsP53) in treatment of experimental colitis in mice as recombinant p53 caused reduction in IFN-γ and TNF-α (Th1 cytokines) and increased production of Th2 cytokines IL-4 and IL-13 in sera of treated mice.

Saunders *et al.* (32) stated that Helminth-induced Th2 suppression of autoimmune disease was described in case of Diabetes type 1 modulation by *T. spiralis* infection. IL-10 is a key effector cytokine in experimental autoimmune encephalomyelitis (EAE) resolution.

Gruden-Movsesijan *et al.* (12) investigated the impact of *T. spiralis* infection or its products on the progression of EAE. Combined model of *T. spiralis* infection and EAE in Dark Agouti (DA) rats strongly indicated that infection with *T. spiralis* significantly reduced EAE severity in a dose-dependent manner. The infection was accompanied by increased production of IL-4 and IL-10, and the reduction in IFN-γ and IL-17, cytokines crucial for the induction and progression of EAE. Application of ES L1-stimulated DCs into recipient rats prior to the induction of EAE resulted in the reduction of clinical signs and duration of illness. It was attributed that ES L1-stimulated DCs altered the immune response responsible for the development of EAE via decreased production of IFN-γ and IL-17 and increased production of IL-4, IL-10, and TGF-*β*, as well as through activation of CD4+CD25–Foxp3+ regulatory T cells **(7)**.

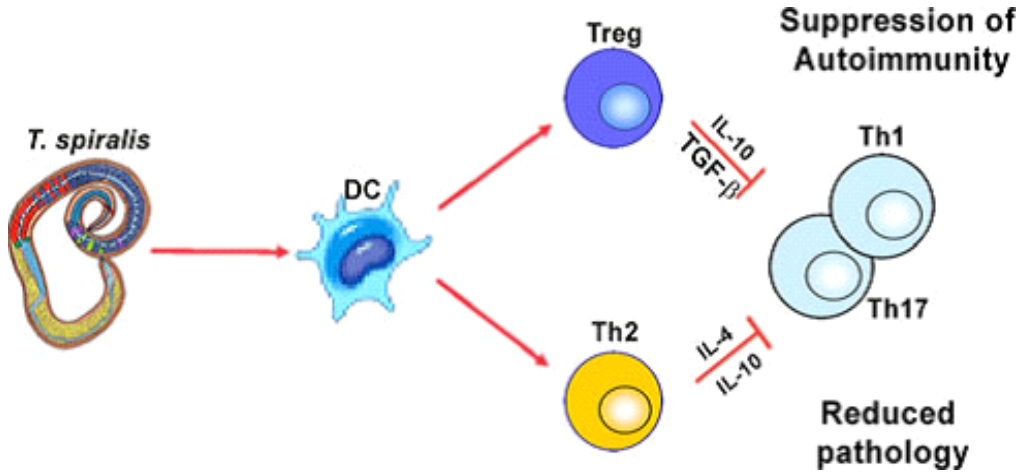

Fig. (4): *T. spiralis*—DC dialog controls the fate of autoimmune disease.
Infection elicits a mixed but predominantly a Th2 polarized immune reaction as well as strong activation of regulatory mechanisms. Activating signals are indicated as arrows and inhibitory interactions are indicated as bars **(8).**

References:

1. **Pozio, E. (2019):** Trichinella and trichinellosis in Europe. *Veterinarski glasnik*, *73*(2), 65-84.
2. **DYAB, A. K., AHMED, M. A., & ABDELAZEEM, A. G. (2019):** PREVALENCE AND HISTOPATHOLOGY OF TRICHINELLA SPIRALIS LARVAE OF SLAUGHTERED PIGS IN CAIRO GOVERNORATE, EGYPT. *Journal of the Egyptian Society of Parasitology*, *49*(2), 439-442.
3. **Sayed, A. S., Hussein, A. A., Arafa, M. I., & Abdo, B. R. N. (2010):** Epidemiological study on trichinellosis in pigs and man in Upper Egypt. *Assiut Veterinary Medical Journal*, 56(125), 280-287.
4. **Wu Z, Wang L, Tang Y, Sun X.** Parasite-Derived Proteins for the Treatment of Allergies and Autoimmune Diseases. Front Microbiol. 2017 Nov 7; 8:2164.
5. **Allen, J. E., & Maizels, R. M. (2011)**. Diversity and dialogue in immunity to helminths. *Nature Reviews Immunology*, *11*(6), 375-388.

6. **Fleming, J. O. (2011):** Helminths and multiple sclerosis: will old friends give us new treatments for MS? *Journal of neuroimmunology*, *233*(1), 3-5.
7. **Sofronic-Milosavljevic, L., Ilic, N., Pinelli, E., & Gruden-Movsesijan, A. (2015):** Secretory products of Trichinella spiralis muscle larvae and immunomodulation: implication for autoimmune diseases, allergies, and malignancies. *Journal of immunology research*, *2015.*
8. **Ilic, N., Gruden-Movsesijan, A., & Sofronic-Milosavljevic, L. (2012):** Trichinella spiralis: shaping the immune response. *Immunologic research*, *52*(1-2), 111-119.
9. **Maizels, R. M. (2020):** Regulation of Immunity and allergy by helminth parasites. *Allergy*, *75*(3), 524-534.
10. **Bruschi, F., Ashour, D. S., & Othman, A. A. (2022):** Trichinella-induced immunomodulation: Another tale of helminth success. *Food and Waterborne Parasitology*, e00164.
11. **Li, J.; Liu, X., Ding, J.; Tang, B.; Bai, X.; Wang, Y. and Wang, X. (2020):** Effect of Trichinella spp. or derived antigens on chemically induced inflammatory bowel disease (IBD) in mouse models: A systematic review and meta-analysis. International Immunopharmacology, 85, 106646.
12. **Gruden-Movsesijan, A., Ilic, N., Colic, M., Majstorovic, I., Vasilev, S., Radovic, I., & Sofronic-Milosavljevic, L. J. (2011).** The impact of Trichinella spiralis excretory–secretory products on dendritic cells. *Comparative immunology, microbiology and infectious diseases*, *34*(5), 429-439.
13. **Yépez-Mulia, L., Hernández-Bello, R., Arizmendi-Puga, N., Fonseca-Liñán, R., & Ortega-Pierres, G. (2007):** Contributions to the study of *Trichinella spiralis* TSL-1 antigens in host immunity. *Parasite immunology*, 29(12), 661-670.
14. **Bai, X., Wu, X., , X., Liu, X., Song, Y., Gao, F., ... & Radu, B. (2012):** Inhibition of mammalian muscle differentiation by excretory secretory products of muscle larvae of Trichinella spiralis in vitro. *Parasitology research*, *110*(6), 2481-2490.
15. **Nagano, I., Wu, Z., & Takahashi, Y. (2009):** Functional genes and proteins of Trichinella spp. *Parasitology research*, *104*(2), 197-207.
16. **Muñoz-Carrillo, J. L., Maldonado-Tapia, C., López-Luna, A., Muñoz-Escobedo, J. J., Flores-De La Torre, J. A., & Moreno-García, A. (2018).** Current aspects in trichinellosis. In *Parasites and Parasitic Diseases* (pp. 175-216). London, UK: IntechOpen.
17. **Wang, N., Bai, X., Ding, J., Lin, J., Zhu, H., Luo, X. and Liu, X. (2020):** Trichinella infectivity and antibody response in experimentally infected pigs. *Veterinary Parasitology*, 109111.
18. **Tang, B., Liu, X., Liu, M., Bai, X., Wang, Y., Ding, J., & Wang, X. (2020):** Effects of TLR agonists on immune responses in Trichinella spiralis infected mice. *Parasitology Research*, 1-6.
19. **Colonna, M., Pulendran, B., & Iwasaki, A. (2006):** Dendritic cells at the host-pathogen interface. *Nature immunology*, *7*(2), 117-120.
20. **Wink, D. A., Hines, H. B., Cheng, R. Y., Switzer, C. H., Flores-Santana, W., Vitek, M. P., ... & Colton, C. A. (2011):** Nitric oxide and redox mechanisms in the immune response. *Journal of leukocyte biology*, *89*(6), 873-891.

21. **McGinty, J. W., Ting, H. A., Billipp, T. E., Nadjsombati, M. S., Khan, D. M., Barrett, N. A. & von Moltke, J. (2020):** Tuft-cell-derived leukotrienes drive rapid anti-helminth immunity in the small intestine but are dispensable for anti-protist immunity. *Immunity.*
22. **Zhu, J., Yamane, H., & Paul, W. E. (2010):** Differentiation of effector CD4 T cell populations (*). *Annual review of immunology*, *28*, 445–489.
23. **Fuss, I. J., Neurath, M., Boirivant, M., Klein, J. S., De La Motte, C., Strong, S. A., ... & Strober, W. (1996).** Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *The Journal of Immunology*, *157*(3), 1261-1270.
24. **Cosmi, L., De Palma, R., Santarlasci, V., Maggi, L., Capone, M., Frosali, F., ... & Berrino, L. (2008).** Human interleukin 17–producing cells originate from a CD161+ CD4+ T cell precursor. *The Journal of experimental medicine*, *205*(8), 1903-191.
25. **Morrison, P. J., Ballantyne, S. J., & Kullberg, M. C. (2011).** Interleukin-23 and T helper 17-type responses in intestinal inflammation: from cytokines to T-cell plasticity. *Immunology*, *133*(4), 397–408.
26. **Maloy, K. J., & Powrie, F. (2011).** Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature*, *474*(7351), 298-306.
27. **Okada H, Kuhn C, Feillet H, Bach JF. (2010):** The "hygiene hypothesis" for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010; 160:1–9.
28. **Xu, J.; Liu, M.; Yu, P.; Wu, L. and Lu, Y. (2019):** Effect of recombinant Trichinella spiralis cysteine proteinase inhibitor on TNBS-induced experimental inflammatory bowel disease in mice. *Int Immunopharmacol.*, 66: 28-40.
29. **Ashour, D. S., Othman, A. A., Shareef, M. M., Gaballah, H. H., & Mayah, W. W. (2013).** Interactions between Trichinella spiralis infection and induced colitis in mice. *Journal of helminthology*, *88*(2), 210.
30. **Motomura, Y., Wang, H., Deng, Y., El-Sharkawy, R. T., Verdu, E. F., & Khan, W. I. (2009).** Helminth antigen-based strategy to ameliorate inflammation in an experimental model of colitis. *Clinical & Experimental Immunology*, *155*(1), 88-95.
31. **Du, L., Tang, H., Ma, Z., Xu, J., Gao, W., Chen, J., ... & Hu, X. (2011):** The protective effect of the recombinant 53-kDa protein of Trichinella spiralis on experimental colitis in mice. *Digestive diseases and sciences*, *56*(10), 2810-2817.
32. **Saunders, K. A., Raine, T., Cooke, A., & Lawrence, C. E. (2007).** Inhibition of autoimmune type 1 diabetes by gastrointestinal helminth infection. *Infection and immunity*, *75*(1), 397-407.