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TRICHINELLA SPIRALIS AS A POTENTIAL THERAPEUTIC AGENT: FROM A RISKY DISEASE TO A FRIEND

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Abstract

Trichinella spiralis infection is capable of manipulating the human immunological system through modulation of cells and molecules of the host`s immune system. There are different mechanisms of *T. spiralis* for changing the balance of immunological response to be benefit for the parasite and host. Moreover, there is similarity in-between the response of infected muscle cells at early stage of infection and muscle regeneration. As a result, *T. spiralis* may have therapeutic effects in many autoimmune and degenerative diseases.

Key words: *Trichinella spiralis,* Therapeutic agent, Mini-review

Introduction

Trichinella spiralis, that causes trichinosis, is able to infect a wide range of carnivores and omnivores including man (Zhang *et al*, 2018). It spends all development stages; infective muscle larvae, adult and newborn larvae (NBL) within one host (Yang *et al*, 2015). Infection is acquired by intake of infected undercooked or raw meat; larvae are released in stomach and developed into adult within enterocytes of small intestine after molting. Newborn larvae are released and spread to organs and tissues by the circulatory system. Only larvae enter striated muscles develop into mature larvae. *T. spiralis* build their home within the body of host by transforming infected muscle cells into new cells, or nurse cell (Despommier, 1998).

Nurse cell formation: Invasion of the muscle cells by *Trichinella* NBL causes their damage. In response to such damage, muscle cells initiate a regeneration program, begins with the activation of satellite cells (stem cells of skeletal muscles), but invading larvae disrupt this process of regeneration (Wu *et al*, 2005). Therefore, nurse cell formation is complex processes, including infected muscle cell response (de-differentiation, cell cycle re-entry& arrest) and satellite cell responses (activation, proliferation & differentiation) (Wu *et al*, 2013). These processes resulted from conflicting signals produced by muscle cells and larvae as transforming growth factor (TGF-β) signaling pathway& many genes related to cell differentiation, proliferation, cell cycle control, and apoptosis (Milcheva *et al*, 2013).

Dynamic changes in infected muscle cell cytoplasm: During process of nurse cell formation, there are two kinds of cytoplasm; basophilic and eosinophilic cytoplasm. Basophilic cytoplasm is formed by infected muscle cell transformation after NBL invasion while eosinophilic cytoplasm is derived from satellite cells and joined nurse cell (Wranicz *et al*, 1998). These two types of cytoplasm are related to the cellular degeneration and regeneration (Błotna-Filipiak *et al*, 1998).

During the life cycle of *T. spiralis*, each stage produces distinctive antigens and proteins that play a role in the nurse cell formation and inducing specific host immune responses (Bien *et al*, 2013).

Many studies focused on the antigenicity of *T. spiralis* muscle larva (ML), as excretory and secretory (ES) proteins that come mainly from the excretory granules of the stichosome and the cuticles with molecular weight between 40 and 60-kDa and they are

considered the main antigens that induce the immune responses (Wang *et al*, 2013). Besides, there are eight groups of *T. spiralis* larval (TSL-1 to TSL-8) antigens, which play different roles on the immune response and nurse cell formation (Gómez-Morales *et al*, 2008).

In addition, Zocevic *et al*. (2011) found that young adult *T. spiralis* expressed specific antigenic products that correspond to host immune responses. Moreover, other proteins were detected in NBL as glutamic acid-rich protein and others with approximate molecular weights of 64-kDa, 58-kDa, 30-kDa& 28-kDa (Wang, 1997; Nagano *et al*, 2011).

Trichinella spiralis immune response: Interaction between host and *T. spiralis* is complex, resulting in formation of a well-balanced host-parasite relationship (Tian *et al*, 2019). *T. spiralis* induces a T cell dependent response in host with secreted cytokines deeply associated with immune (Th1& Th2), performing vital immuno-regulatory functions (Scalfone *et al*, 2013).

Specific immune cells: During the intestinal phase, intestinal epithelial cells play as immune effector cells in *T. spiralis* expulsion (Yepez-Mulia *et al*, 2009). T helper 2 (Th2) related cytokines, thymic stromal lymphopoietin and IL-25, were produced from these cells, play important roles in the activation of Th2 cell (Koyasu and Moro, 2011). Immune response is mixed Th1/Th2 with initial predominance of the Th1 response (Ilic *et al*, 2012). *T. spiralis* generally triggers a Th 2 protective immune response identified by the characteristic production of Th2 cytokines, including IL-4, IL-5, IL-9, IL-13 & IFN-γ (Ding *et al*, 2017). Besides, other subset of Th cells is of great importance in immunity as Th17. Both Th2 & Th17 cells are activated and proliferated until the initiation of nurse cell formation, but these Th cells are strongly regulated by parasite-induced regulatory T cell (Treg cells) (Kang *et al*, 2012). Trichinosis induced generation of the $CD4^+$ $CD25^+$ $Foxp3^+$ & $CD4^+$ $CD25^-$ $Foxp3^+$ Treg cells in early infection stages, associated with high levels of regulatory cytokines IL-10, TGF-β, & IL-21. These Treg cells suppressed Th17 cell differentiation through interaction between Foxp3 and RAR-related orphan receptor gamma (RORγt) (Elliott and Weinstock, 2012).

Different components of ES secreted by the different stages of *T. spiralis* led to different levels of different types of Tregs and cytokines. For adult survival, it secreted more immunomodulatory products that induced a higher level of Tregs to reduce immune attack to adult parasite in intestine. When larvae migrate to muscle, it was not important to induce the regulatory inhibition as larvae acquire protection by the isolation of capsules in muscle (Sun *et al*, 2019a).

Although trichinosis was considered risky disease to man, but it altered its host's immune response to maintain their life, as they modulate the host immune response in a fashion to enable their long-term survival in the definitive host (Gazzinelli-Guimaraes and Nutman, 2018).

Mechanisms of immunomodulation: 1- At the host-parasite interface, it produces molecules, both on the cuticular surface and/or released in ES products that mediate their ability to survive for long periods of time despite the actions of the host immune system (Vermeire *et al*, 2008). 2- Succinate Coenzyme a ligase beta-like protein (SUCLA-β) is one of the important *T. spiralis* ML ES that belongs to the Succinyl-coenzyme A synthetase gene and plays an important role in a citric acid cycle. This protein may have immunomodulatory effect and its expression level in ML stage was up-regulated by more than 100 times as compared with NBL, showed that Ts-SUCLA-β might be a larval invasion-related protein (Sun *et al*, 2019b). 3- Immunodominant antigens in larvae are distinct from those in adult worms. This antigenic variation, together with the brief period required for larvae to mature to adulthood (36-48 h pi) and develop into fecund adults (four to five d. p.i.), allow intestinal worms to escape the immune response until

they have reproduced (Fabre *et al*, 2009). 4- The resistance of the parasite in muscle tissue is partially dependent on IL- 10 & TGF-β that control the inflammation surrounding the nurse cell through modulating the function of antigen presenting cells, suppression of IFN-γ levels, and preventing inducible nitric oxide synthase (iNOS) production by inflammatory cells (Beiting *et al*, 2007). In addition, IL-10 producing cells specifically reinforce Treg cells to regulate Th2 cytokine production and suppress Th1 & Th17 cells responses during muscle infection (Patel *et al*, 2009). 5- The elaboration of macrophage inhibiting factor (MIF) by *T. spiralis* might alter the host immune response by preventing macrophages accumulation around the cysts of *T. spiralis*-infected cells. Moreover, by inducing further production of endogenous host MIF that creates a local or possibly systemic anti-inflammatory host environment (Vermeire *et al*, 2008). 6- There was cross-reactivity resulted from presence of common epitopes in *Trichinella* antigens and the host autoantigens (Radovic *et al*, 2012). 7- The outer membrane form of paramyosin expressed by *T. spiralis* has a role in the host immunomodulation, presumably by binding to complement C8 & C9, inhibiting the formation of membrane attack complex and protecting the parasite from being damaged by activated complement. This modulation is an effective survival strategy for *T. spiralis* to live within the host (Zhang *et al*, 2011). 8- Multiple co-inhibitory receptors such as lymph-ocyte activation gene 3 (LAG-3), B- & T-lymphocyte attenuator 4 (BTLA-4), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and T cell membrane protein 3 (Tim-3), CD244, and CD160 were expressed in T cells to limit immune-mediated pathology. Helminthes drive sustained expression of T cell inhibitory receptors, which may negatively regulate proliferation and production of the pro-inflammatory cytokines by specific T cells. As these receptors are important in preventing over T cell activation, they may have essential role in preventing parasite-induced immunopathology (Brown *et al*, 2010; Wammes *et al*, 2016). Programmed death -1 (PD-1), one of the inhibitory receptors, may have critical roles in modulating the balance of Th1/Th2 & Treg responses upon infection of *T. spiralis* that lead to its immunomodulatory effect (Cheng *et al*, 2018). As *T. spiralis*-induced expression of Foxp3 is highly dependent on PD-1 expression on immune cells (Francisco *et al*, 2010).

Trichinella spiralis as a part of helminth therapy: Th17 plays an important role in the pathogenesis of various autoimmune inflammatory diseases (Rudner *et al*, 2007). Th9 cells also promoted development of autoimmune and allergic diseases by producing IL-9 that promoted by IL-4 & TGF-β. Production of both IL-9 & IL-17 was associated with blocking of IFN-γ & IL-4 cytokines (Stassen *et al*, 2012). As different pathogen infections induce many inflammatory cascades resulted in the attraction, differentiation and expansion of cells of the innate and adaptive immune system. In addition mechanisms such as bystander activation, super-antigen cross-linking, pathogen-induced necropolis and molecular mimicry might have the active roles in the suppression of the auto-aggressive immune response (Christen, 2019).

As the result of the previous mechanisms, new era of using helminthic therapy in many diseases has been emerged. Oral infection with ova of *Trichuris suis* had been tested in clinical trials for patients with multiple sclerosis, inflammatory bowel disease, allergic rhinitis and food allergy (Jouvin and Kinet, 2012). Also, the products of *Hymenolepis diminuta* (Johnston *et al*, 2010), *Ancylostoma caninum* (Cancado *et al*, 2011), and *Schistosoma mansoni* (Ruyssers *et al*, 2009; Hasby *et al*, 2015) can be used for suppressing the pathology in mouse models of colitis. Nevertheless, the detrimental effects of helminthic infection induced pathology still the major concern. Thus, the use of the helminthic derived antigens may give the bene-

fits of helminthic infection on immune modulation, without hazard of incurring parasitic disease, which got more attention (Maizels, 2016).

Trichinella spiralis and autoimmune disease: Trichinosis could reduce the severity of dinitrobenzenesulphonic acid- induced colitis in mice (Khan *et al,* 2002). Also, Motomura *et al.* (2009) found that rectal submucosal administration of *T. spiralis* crude muscle larvae antigen before induction of colitis can protect against this autoimmune disease. Ashour *et al.* (2014) reported that trichinosis ameliorated the severe inflammation induced by acetic acid, and this amelioration was more pronounced when *T. spiralis* infection preceded induction of colitis. Moreover, trichinosis may decrease the severity of other autoimmune diseases as autoimmune diabetes (Saunders *et al*, 2007). Not only that, but there are other autoimmune diseases like experimental auto-immune encephalomyelitis (Gruden-Movsesijan *et al*, 2008) and adjuvant arthritis (Eissa *et al*, 2016) that can *T. spiralis* or its antigens be used to reduce the severity of these diseases.

Trichinella spiralis and allergy: Extracts from adults (Ts-AE) or muscle larvae (Ts-MLE) were used to treat OVA-induced asthma before OVA sensitization (preventive) or during sensitization (therapeutic) in a mouse model (Sun *et al*. 2019c). This preventive effect of soluble proteins derived from adult *T. spiralis* acted by reducing allergen-specific Th2 responses, including reduced OVA-specific IgE in sera and reduced IL-4 level & eosinophil cells in lungs (Maizels and McSorley, 2016). Besides, *T. spiralis* caused high level of worm-specific IgE competed with allergen-specific IgE binding sites on mast cells or basophils (Lee *et al*, 2008).

The therapeutic effects of *T. spiralis* or its antigens resulted from upregulation of Treg response with increased levels of IL-10 & TGF-β and downregulation of pro-inflammatory cytokines. Some proteins secreted by different *T. spiralis* stages possessed anti-inflammatory activities with role in treatment of allergic and inflammatory diseases.

Trichinella spiralis and regeneration: Skeletal muscle regeneration includes inflammatory cell recruitment to the injured tissue to remove necrotic debris and initiates the repair process, angiogenesis and activation of myogenic progenitor cell or satellite cells. These cells proliferate and differentiate to new muscle cells for repairing or replacing damaged muscle fibers (Sun *et al*, 2009). Extensive studies commented on the similarities between some changes that occur during the response of infected muscle cell at the early stage of *T. spiralis* infection and nurse cell formation with those occurring during muscle cell regeneration, including activation, proliferation and differentiation of satellite cell, and cell cycle re-entry (Wu *et al*, 2008)**.**

During the process of nurse cell formation, invasion of muscles by *Trichinella* NBL causes muscle cell damage that initiates activation of satellite cells undergoing proliferation and re-differentiation (Matsuo *et al*, 2000). Many genes have important roles in muscle myogenesis and regeneration; some of these genes were confirmed to be responding to the process of nurse cell development (Wu *et al*, 2001). Also, many proteins of *Trichinella* ML induced nurse cell formation (Guiliano *et al*, 2009).

Therefore, the influence of local injection of antigens or attenuated larvae of *T. spiralis* was evaluated as a trial to overcome the experimentally induced myopathy in rats by Saad *et al*. (2016) who revealed that intramuscular injection of *T. spiralis* NBL (either treated or irradiated) into drug-induced myopathic muscles showed different responses in amelioration of the myopathic changes. As intramuscular injection of *T. spiralis* NBL antigens is more superior in the improvement and regression of myopathic muscles more than injection of *T. spiralis* NBL (either treated or irradiated). Also, Ko *et al*. (1994) observed that injection of ES proteins of muscle larvae in normal muscles

induced regenerative changes in the muscles through induction of mitosis in satellite cells which are located in the subsarcolemmal region and in the phagocytes located in the interfiber region. Nivin *et al*. (2011) found that using *Trichinella* antigens in form of Britov's vaccine (biopreparation from *Trichinella*) induced cellular immunity stimulated the regenerative processes and accelerated skin wounds healing in mouse model. Some authors studied the possible regenerative effect of different *T. spiralis* antigens components (Fu *et al*, 2005; Nagano *et al*, 2009). One of the important antigen components is 43-kDa glycoprotein mimic myogenic regulatory factors as MyoD and myogenin were critical in muscle differentiation (Vassilatis *et al*, 1992). Two kinds of proteins (Tsmyd-1 &TsJ5), components of ES proteins of *T. spiralis* muscle larvae, were responsible for satellite cells proliferation (Connolly *et al*, 1996; Lindh *et al*, 1998).

Nagano *et al*. (2003) and Nagano *et al*. (2006) found other components of ES proteins of *T. spiralis* muscle larvae as serine proteinase, serine proteinase inhibitor and required cell differentiation 1-like protein (Rcd1) was involved in host muscle cell differentiation. Gounaris *et al*. (2001) reported that *T. spiralis* secretes nucleoside diphosphate kinases that may have a role in the regulation of host cell proliferation and differentiation. Moreover, the immunological basis of the effect of *T. spiralis* on the improvement of myopathy referred to the *T. spiralis* antigens role in induction of a mixed Th1/Th2 cytokine profile with the predominance of Th2 cytokines e.g. IL-4 & IL-9 (Ilic *et al*, 2011). The Th2 cytokines overcame pro-inflammatory Th1 cytokines as IFN-γ, TNF-α, IL-6, IL-8 & IL-1β that were observed in all inflammatory myopathies and statin induced myopathy.

The ES proteins of the *T. spiralis* larvae stimulated Treg cells that produce inhibitory cytokines as IL-10 & TGF-β and decrease IFN-γ production (Ilic *et al*, 2008). These cytokines may counterbalance the muscle destruction caused by the cytotoxic T cells leading to amelioration of the inflammatory myositis.

Conclusion

Trichinella spiralis is a globally distributed food borne infection, with the ability to shape human immune system by immunomodulatory effects and proteins, which alleviate not only the parasite-specific inflammatory responses, but also other autoimmune pathology.

The different mechanisms may assist *T. spiralis* to have therapeutic effects in some autoimmune and degenerative diseases.

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