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Trichinella-induced immunomodulation: Another tale of helminth success

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ABSTRACT

Trichinella spiralis is a unique parasite in that both the adults and larvae survive in two different intracellular niches in the same host. The immune response, albeit intense, is highly modulated to ensure the survival of both the host and the parasite. It is skewed to T helper 2 and regulatory arms. Diverse cells from both the innate and adaptive compartments of immunity, including dendritic cells, T regulatory cells, and alternatively activated macrophages are thought to mediate such immunomodulation. The parasite has also an outstanding ability to evade the immune system by several elaborate processes. The molecules derived from the parasites including *Trichinella*, particularly the components of the excretory–secretory products, are being continually identified and explored for the potential of ameliorating the immunopathology in animal models of diverse inflammatory and autoimmune human diseases. Herein we discuss the various aspects of *Trichinella*-induced immunomodulation with a special reference to the practical implications of the immune system manipulation in alleviating or possibly curing human diseases.

1. Introduction

Worms provoke nothing in the spirits of ordinary people but disgust. Nevertheless, modern science revealed that worms are accomplished endoparasites; they manipulate, since the very first moments of parasitism, the immune system of the host to ensure their survival as well as the host's. It seems that helminths have succeeded throughout the human history to keep the immune system *busy* – a situation that preserved the human host from allergies and autoimmune diseases: the plights of our modern era. Nowadays scientists strive to decipher the underlying molecular mechanisms of helminth-induced immunomodulation in the hope of exploiting these insights to alleviate or cure human diseases in the domain of general medicine such as allergies and autoimmune disorders; in oncology; and in transplantation medicine. We therefore have the right to wonder: do helminths become a blessing in disguise?

The parasitic nematode *Trichinella* is characterized by an extremely wide host range and geographical distribution (Pozio, 2021). At present, ten different species have been described: *T. spiralis*, *T. nativa*. *T. nelsoni*, *T. britovi*, *T. murrelli*, *T. patagoniensis*, and the recently described species *T. chanchalensis* (Sharma et al., 2020) are all included in the clade of encapsulating species, while *T. pseudospiralis*,

Abbreviations: AW, adult worm; NBL, newborn larva; ML, muscle larva; IIL, intestinal infective larva; ES, excretory–secretory; ES L1, ES product of *T. spiralis* muscle larva; Ts-AES, ES from adult *T. spiralis*; Th, T helper; IFN- γ, interferon-γ; TNF- α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; IL, interleukin; NOS, nitric oxide synthase; Treg, regulatory T cell; Breg, regulatory B cell; AAM, alternatively activated macrophage; CAM, classically activated macrophage; Tol-DC, tolerogenic dendritic cell; TLR, toll-like receptor.

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T. papuae and *T. zimbabwensis* belong to the clade of non-encapsulated species (Pozio, 2021). Trichinellosis, the disease caused by this parasite, is under control in countries in Europe and U.S.A., but it is emerging in both the industrialized and middle-income countries, such as China, Argentina and some eastern European ones (Pozio, 2021).

During infection with *Trichinella*, the immune system is stimulated by different molecules of the parasite, localized either on the cuticle of the worms or present in the excretory–secretory (ES) products (Grencis and Campbell, 2021). Interaction of helminth-derived molecules with the host immune system can drive a shift from an inflammatory towards an anti-inflammatory type of immune response.

Today it is known that *Trichinella*-derived molecules, as is the case with molecules derived from some other helminths, can modify antigen presenting cells such as dendritic cells (DCs) and downregulate adaptive immune responses, through the induction of a regulatory network that include regulatory T cells (Tregs), alternatively activated macrophages (AAMs) and regulatory B cells (Bregs) (Grencis and Campbell, 2021). This immunosuppressive network, induced by the parasite, together with cytokines produced by diverse hematopoietic and non-hematopoietic cells, appears to be essential for parasite survival and its effect can be evaluated for possible use in the treatment of inflammatory disorders such as in experimental models of allergies and autoimmune diseases (Rzepecka and Harnett, 2022).

2. *Trichinella*'s encounter with the host immune system

Experimental research on animal models of intestinal nematode infections including *T. spiralis* infection highlighted the early events during invasion of the intestine by the nematode parasites. Once the infective larvae reach the intestine, they are detected by intestinal epithelial cells, particularly a group of specialized chemosensory cells called tuft cells. These cells are activated by helminth-derived products and/or by signals from adjacent tissue damage and they then begin to secrete cytokines like IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). These alarmins in turn activate type 2 innate lymphoid cells (ILC2s) to release a variety of type 2 response cytokines such as IL-5 and IL-13. Characteristically, high ILC2-derived IL-13 levels act on epithelial progenitor(s) to promote lineage specification towards tuft and goblet cells, thereby creating a positive feedback circuit through expansion of IL-25-expressing tuft cells. Shortly, the antigen presenting cells, mainly the dendritic cells, appear in the scene to initiate adaptive immune responses against the invading nematode parasites, that are indispensable for eliminating infection and mediating tissue healing (Grencis et al., 2014; Gazzinelli-Guimaraes and Nutman, 2018; Sorobetea et al., 2018).

Besides many proteolytic enzymes, the multicellular helminth parasites, as soon as they interact with epithelial tuft cells and antigen presenting cells, release immunoregulatory products that induce predominantly Th2-biased immune responses. This kind of immune polarization involves the production of specific antibody subclasses, such as IgE, IgG1, and IgG4, as well as cytokines such as IL-4, IL-5, IL-9, IL-10, IL-13, IL-21, and IL-33, which results in the expansion and mobilization of several immune cell populations such as helper T cells, eosinophils, basophils, mast cells, macrophages, and fibroblasts. The synergy between these different cell types and antibodies induces hypersensitivity reactions, which are characterized by vascular leakage, cellular infiltration, smooth muscle hypercontractility, angiogenesis, mucus secretion by goblet cells, and collagen deposition, which collectively are important strategies of defense against invasive helminthic infections (Maizels et al., 2004; Ilic et al., 2012; Faz-López et al., 2016; Sorobetea et al., 2018).

Other than driving the immune response towards type 2 immunity, helminth infections are well known to induce the regulatory arm of immunity, implicating cells and mediators, such as regulatory T and B cells, AAMs, IL-10, and transforming growth factor-β (TGF-β). Notably, the immune downregulation does not only concern relevant helminth antigens, but also extends to third-party antigens (Ilic et al., 2012; Maizels and Mcsorley, 2016).

T. spiralis is unique among helminths as both the adults and larvae live in two different niches in the same host, namely the small

Table 1
Key effector players during *Trichinella* infection

Effector	Function(s)
Intestinal phase	
CD4+ Th2 cells	Secretion of cytokines to trigger all adaptive Th2 immune responses
ILC2	Release of several type 2 cytokines
Mast cells/Basophils	Release of mediators that mediate intestinal inflammation
Goblet cells	Secretion of mucus that help trap the parasites
Eosinophils	Role controversial; release of toxic products and cytokines; ADCC
Macrophages	Release of mediators; smooth muscle contraction
IL-4	IgE production and transport; goblet cell stimulation; eosinophil activation
IL-5	Recruitment and activation of eosinophils
IL-13	Goblet cell proliferation and differentiation; stimulation of smooth muscle contraction; migration and activation of DCs
IgE	ADCC
Muscular phase	
CD4+ Th2 cells	Release of type 2 cytokines
Inflammatory cells	Present around nurse cells but fail to eliminate the larvae
Antibodies (IgG1, IgE)	Increased in serum; do not affect muscle larvae

Data compiled from several sources (Bruschi and Dupouy-Camet, 2014; Grencis et al., 2014; Fabre et al., 2009; Sorobetea et al., 2018). ADCC: antibody-dependent cellular cytotoxicity; ILC: innate lymphoid cells; DCs: dendritic cells.

intestine and the skeletal muscles. In between the two, the migrating juveniles may gain access to any body tissue or space, and, failing to develop further, they cause acute injury and inflammation (Bruschi and Dupouy-Camet, 2014). *T. spiralis* is therefore best regarded as both intestinal and tissue parasite. Most of our insights on the immune response are derived from studies on rodents which are natural hosts. The assessment of immunity in a large natural host like the pig confirms these insights (Wang et al., 2020a), and human data seem to coincide (Bruschi and Dupouy-Camet, 2014). During the intestinal phase, the initial reaction is moderate Th1 response to be switched rapidly to robust Th2 response. Th2 immunity is also operant at the level of the skeletal muscles. The regulatory arm of immunity is also activated to prevent damage to both the parasite and the host. However, the latter eventually gets rid of the adult worms, but the muscle larvae persist in their unique intracellular niche (Ilic et al., 2012). Table 1 summarizes the main effector players during *Trichinella* infection.

3. How does *Trichinella* elude the host immune system?

Despite the availability of these peculiar biological niches, the chance for *Trichinella* larvae to thrive successfully in a host depends largely on their ability to escape from the host immune response. Different evasion mechanisms of the host's immune response have been described during the time and they can be distinguished in two categories: i) antigen-dependent (including anatomic seclusion, antigen stage-specificity, shedding and renewal, and molecular mimicry); ii) direct effects on the host immune response (Bruschi, 2004; Bruschi and Chiumiento, 2012).

3.1. Antigen-dependent mechanisms

Anatomic seclusion and stage-specificity are the most relevant mechanisms among those antigen-dependent. Although encysted in the muscle fibres, muscle larvae (L1) interplay with the host, releasing antigens and continuously stimulating the host immune response. In the case of infections with encapsulated species, they are secluded, thereby protected from either antibodies or effector cells, such as macrophages and eosinophils, using a defensive strategy. This is not valid for *T. pseudospiralis*, and possibly other non-encapsulating species, which, with an offensive strategy, would interfere with the neuro-endocrine-immune system (Stewart, 1995).

Stage-specificity of the antigens is demonstrated by the observation that early antibodies are specific for adult worms but do not recognize newborn larva (NBL) antigens; these can be bound by antibodies specific for their surface antigens only starting from the fourth week of infection. At that time the parasite is already inside the nurse cell (NC), protected from the immune system response. Furthermore, during the first hours of life, NBL undergoes changes in surface proteins (Jungery et al., 1983), and in sensibility to effector cells in either mice (Gansmüller et al., 1987) or humans (Venturiello et al., 1993).

3.2. Mechanisms affecting the host immune response

Modification of the host immune responsiveness by the parasite operates at a central level (when the regulatory pathways of immune response are mainly involved) and at a peripheral level (in this case effector systems are modulated) (Bruschi, 2002).

3.2.1. Central mechanisms of immune modulation

Trichinella can modulate the host response at a central level by several mechanisms: induction of immune suppression, polyclonal lymphocyte activation, induction of blood and tissue eosinophilia, and downregulation of signal transducer and activator of transcription (STAT) 4-IL-12.

Immune suppression During trichinellosis, immune suppression was observed in skin allograft rejection experiments, and a depressed response to several non-parasitic antigens such as goat red cell, Japanese encephalitis B virus, and cholera toxin, was also observed in experimentally infected mice (Bruschi, 2002; Bruschi and Chiumiento, 2012). This depression is particularly evident during NBL production; this led the authors to suggest the ability of this stage to release lymphocytotoxic factors, not yet identified (reviewed in Bruschi, 2002).

Components of *T. spiralis*-derived products can suppress the response to thymus-dependent, but not that to thymus-independent parasite antigens (Leiro et al., 1988). In particular, the suppression of host thymus-dependent response was showed against *Trichinella* antigen FCp1, a molecule containing phosphorylcholine (PC) (Leiro et al., 1988). This immunomodulation acts during the primary and secondary responses to *Trichinella* infection, and it is directed exclusively against own antigens and not versus other parasite-derived PC-bearing antigens.

Polyclonal lymphocyte activation It increases the IgG and IgM levels in both infected experimental animals and humans (Bruschi, 2002). However, the main characteristic of trichinellosis is represented by increased total IgE levels which can be considered an evasion mechanism of immune response (Watanabe et al., 2005).

Eosinophilia The increase in blood and tissue eosinophils is a hallmark of helminth infections and consequently of infection with *Trichinella* spp. The role of these cells in protecting the host or the parasite is greatly debated (Bruschi et al., 2008). If in a primary infection the eosinophils protect the parasite from macrophage activation and the subsequent NO production; in a secondary infection, when antibodies are present, it is clear that they act protecting the host (Huang and Appleton, 2016).

Downregulation of STAT4/IL-12 Kobpornchai et al. (2020) identified cystatin, TsCstN, as a protein derived from the L1 stage of *T. spiralis*. Using the recombinant TsCstN (rTsCstN), it was shown that this protein is internalized in macrophages and is able to alter downstream T-cell priming. Control of macrophage responses and their downstream interactions with T cells are often coordinated by transcription factor STAT4. The effects of recombinant rTsCstN, derived from *T. spiralis* ML, relied upon negative regulation of IL-12 and STAT4 phosphorylation. This would lead to a specific suppression of IFN-γ production, but not of IL-17A. In this way the parasite could evade the Th1-based immune response, facilitating the establishment of the muscle stage (Kobpornchai et al., 2021).

Induction and/or expansion of dendritic cells and various regulatory cell populations are other crucial centrally acting immune evasion mechanisms employed by helminths including *Trichinella* that will be discussed in the next section in detail.

3.2.2. Peripheral mechanisms of immune modulation

Other mechanisms of escape of immune response are represented by increase in immune complex production, induction of blocking antibody, and inhibition of complement assembly (reviewed in Bruschi, 2002; Näreaho et al., 2009). More recently, paramyosin derived from *T. spiralis*, as well as its recombinant form, were shown capable to bind C1q, thus inhibiting the classical complement activation. As a consequence, there is no formation of the complement membrane attack complex (MAC) and the parasite evades the host complement attack (Sun et al., 2015).

Other escape mechanisms which can be utilized by *Trichinella* are those which allow the parasite to block effector functions by producing orthologue (L-dopachrome-methyl-ester-tautomerase) of macrophage migration inhibitory factor – an ability common to other nematodes such as *Trichuris muris* and *Brugia pahangi* (Pennock et al., 1998), or by modifying the host leukocyte function (Bruschi et al., 2000).

3.2.2.1. Downregulation of NOSII. Particular attention has been paid to modulation by *Trichinella* of nitric oxide synthase (NOS) II expression and production. A specific gut inflammatory reaction results in inhibition of NOS II expression; in fact, local jejunal inflammation induced by *T. spiralis* systemically inhibits the transcription of NOS II gene, protein expression, and enzyme activity. Furthermore, the inhibition induced by infection reduces also the expression of this enzyme even when stimulated by endotoxin and it is specific for this NOS isoform (Bian et al., 2001).

It has also been shown that the IL-4Rα-STAT6-dependent pathway is involved in the induced inhibition of host NOS II by the parasite, but this phenomenon occurred also in athymic nude mice, suggesting independence on T cells. The parasite would produce a not yet identified substance able to inhibit expression in cultured RAW264.7 cells (a macrophage cell line) of NOS II but not that of cyclooxygenase 2, another protein induced by pro-inflammatory cytokines. Despite the fact that endogenous IL-4 and IL-13 are the only known IL-4Rα ligands, these cytokines are not required for activating the pathway (Bian et al., 2005).

4. How does *Trichinella* tame the host immune system?

4.1. Dendritic cells

The active interaction of *Trichinella* and DCs is well described, and in general, it seems to follow the usual trend of helminths to modulate the immune response via stimulation of DCs. Research has indicated that DCs acquire a partially mature and tolerogenic phenotype upon stimulation by *Trichinella* antigens (Ilic et al., 2012). It was shown for the first time by Ilic et al. (2008) that antigens isolated from all the three stages of *T. spiralis* life cycle induce incomplete maturation of bone marrow-derived dendritic cells (BMDCs), isolated from dark Agouti (DA) rats and consequent polarization of the immune response towards regulatory and Th2 types. Moreover, the *T. spiralis* antigen-stimulated rat DCs exhibited incomplete maturation with failure of upregulation of MHC II and increased expression of CD86 and ICAM 1(Ilic et al., 2012).

It has been demonstrated in in vitro experiments that DCs pulsed with ES product of *T. spiralis* muscle larvae (ES L1) induce strong Th2 response after concurrent cultivation with naïve T cells, and mixed Th1/Th2 cytokine pattern following co-culture with *Trichinella*-sensitized T cells (Gruden-Movsesijan et al., 2011), akin to the cytokine profile detected in established *T. spiralis* infection (Gruden-Movsesijan et al., 2010). Likewise, T-cell priming by intraperitoneal administration of ES L1-pulsed DCs produced mixed Th1/Th2 with predominance of the Th2 and regulatory arms of the immune response (Gruden-Movsesijan et al., 2011).

Recently, Zhang et al. (2018) have proved that *T. spiralis* heat shock protein (Ts-Hsp) 70 induces immune responses against *Trichinella* infection through activating DCs via toll-like receptors (TLR) 2 and TLR4 either in vivo or in vitro. Another molecule, recombinant *T. spiralis* glutathione-S-transferase (rTs-GST), has been found to modify the maturation and function of DCs (Jin et al., 2019). Likewise, Ilic et al. (2018) demonstrated that under the effect of ES L1, DCs, derived from human mononuclear cells, exhibited impaired maturation but retained their ability to induce differentiation of T cells i.e., acquired tolerogenic phenotype. The latter was characterized by little expression of HLA-DR, CD 86, and CD 83 as well as moderate expression of CD40, in addition to an unaltered generation of IL-12 and increased production of the regulatory cytokines TGF-β and IL-10, compared to controls. The ability of the ES L1 to produce tolerogenic DCs (Tol-DCs) has been found to occur via stimulation of TLR2 and 4.

4.2. Foxp3-expressing T regulatory cells, IL-10, and TGF-β

It is now well established that Tregs are an indispensable element of the immune system for maintenance of T-cell homeostasis. These cells have been characterized by constitutive expression of surface CD4 and CD25 (IL-2 receptor α chain) and by the expression of Foxp3 (Sakaguchi, 2005). Foxp3, whose gene encodes a forkhead-winged helix transcription factor scurfin, is not only a molecular marker of these cells, but also essential for the development and maintenance of their regulatory function (Hori et al., 2003; Fontenot et al., 2003). Treg cells are typically anergic and do not produce IL-2 (Shevach, 2002); instead, upon activation, they suppress the proliferation and cytokine production of conventional CD4+ T cells, as well as that of CD8+ T cells and polarized Th1 and Th2 cells

(Piccirillo and Shevach, 2004; Chatila, 2005). Typically, these cells are significantly recruited and activated during chronic infections, particularly parasitic diseases (Belkaid et al., 2006). The CD4+ CD25+ Treg subset, which naturally arises in the thymus, can also be peripherally induced by immunogens including helminth antigens (Zhang et al., 2001), and has been found crucial for the limitation of parasite-induced immunopathology (Belkaid et al., 2006).

Tregs exert their suppressive actions by several means that may be differentially employed according to the microenvironment and the attendant immunopathology (Piccirillo and Shevach, 2004). In in vitro assays, Tregs seem to rely on cell–cell contact, as Tregs express granzyme A and exhibit perforin-dependent cytotoxicity against target cells, denoting the likelihood of direct killing. On the other hand, by using in vivo models, the immunosuppression is found to be either IL-10 dependent, TGF-β dependent or both (Piccirillo and Shevach, 2004; Fehérvari and Sakaguchi, 2004).

IL-10 is a downregulatory cytokine that is not a cell type-specific, but largely expressed by many immune cells. It targets elements of both innate and adaptive immunity and exerts immunosuppressive functions to mitigate tissue damage caused by excessive immuno-inflammatory responses, particularly during the resolution phase of infection and inflammation, and to ensure homeostasis to gut microbiota (Ouyang and O'Garra, 2019). Increased production of IL-10 is a consistent feature of the immune response of the host during helminthic infections and one important mechanism of helminth-induced immunoregulation (Ilic et al., 2012). Paradoxically, IL-10 has been found crucial in both the immune defense against *Trichinella*, and the immunoregulation during the course of trichinellosis in the small intestines and skeletal muscles (Beiting et al., 2007; Fabre et al., 2009; Bruschi and Dupouy-Camet, 2014).

TGF-β is a pleiotropic cytokine secreted by many immune and non-immune cells. It is involved in many biological and physiological processes. Regarding the immune system, TGF-β is a potent immunosuppressive cytokine through actions on both cell differentiation and cell proliferation. For example, TGF-β has the ability to inhibit proliferation of T lymphocytes and thymocytes. Its role on the immune cells depends largely on the surrounding cytokine milieu and the context of the immune response (Morikawa et al., 2016). TGF-β seems to play an important role in the regulation of several immuno-inflammatory responses during helminthic infection (Maizels et al., 2004). Typically, during *Trichinella* infection, TGF-β is upregulated in both the skeletal muscles and small intestines, and therefore, is supposed to play a role in immune system modulation, possibly in concert with IL-10 (Beiting et al., 2007; Ilic et al., 2012).

The interrelationship between Tregs and pathogens ranges from one of reciprocal benefit (détente cordiale), to instances where the regulatory response appears to chiefly privilege the pathogen at the expense of the host (detente contraire) (Rouse and Suvas, 2004). Moreover, several lines of evidence indicate that Tregs have the beneficent role of limiting the severity of bystander tissue injury in cases where the immune response to pathogens is excessive or prolonged (Rouse and Suvas, 2004). Typically, helminth parasites are able to modulate the host adaptive immune response by downregulating T- and B-cell responses via the recruitment and activation of Tregs or the regulatory cytokines IL-10 and TGF-β that can suppress both Th1 and Th2 responses (Maizels and Yazdanbakhsh, 2003). Such immunomodulation is assumed to be beneficial for both the human host and the parasite; it protects helminth parasites from being eliminated and, meanwhile, protects the host from robust pro-inflammatory responses that may cause organ or tissue damage (Harnett and Harnett, 2006; Maizels and McSorley, 2016). Expansion of Tregs is a universal feature of helminth infections such as schistosomiasis (Singh et al., 2005), toxocariasis (Othman et al., 2011), strongyloidiasis (Malpica et al., 2019), and filariasis (Mukherjee et al., 2019). Accumulating evidence has indicated that expansion of Tregs during helminth infections requires the involvement of DCs (Ilic et al., 2012).

T. spiralis is no exception: CD4+ Foxp3+ T cells are recruited in the intestine (Cho et al., 2012; Ashour et al., 2014) and skeletal muscles (Beiting et al., 2007) in the vicinity of adults and larvae of *T. spiralis*, respectively. Researchers assume that in natural infections, the presence of Tregs is as advantageous in the muscle phase as in the intestinal phase. It is suggested that the limitation of the immuno-inflammatory responses in the muscle ensure survival of both the infective larvae of *Trichinella* and the host – a situation that guarantees the propagation of the parasite. On the other hand, it seems more beneficial to keep a certain level of immunity against adult worms in the intestine in order to avoid prolonged and enhanced survival of adults with the possibility of overwhelming the host by many migrating offspring larvae (Ilic et al., 2012).

In an elegant study using gene-targeted knockout mice, adoptive transfer of specific T cell populations, and in vivo antibody treatments, Beiting et al. (2007) have demonstrated that there is a cooperative interplay between effector T cells on one hand, and Tregs, IL-10, and TGF-β on the other hand, that permit survival of muscle larvae of *T. spiralis* while protecting the host from excessive inflammatory responses. Moreover, Gruden-Movsesijan et al. (2010) revealed that chronic *T. spiralis* infection in DA rats caused a significant increase in the proportion of CD4+ CD25+ Foxp3+ cells accompanied with high level of IL-10 production when compared with uninfected rats.

In another interesting recent study, Sun et al. (2019a) demonstrated that Foxp3+ Tregs were significantly increased in the spleens of *T. spiralis* infected mice. Also, they found that parenteral administration of *T. spiralis* ES induced robust Treg responses in the spleens of mice, characterized by increase of CD4+CD25+Foxp3+ and CD4+CD25–Foxp3+ Tregs associated with elevated levels of IL-10 and TGF-β. Moreover, *T. spiralis* adult worm ES products (Ts-AES) and muscle larvae ES products (MES) were both able to prime BMDCs in vitro to induce their maturation and to produce anti-inflammatory cytokines IL-10 and TGF-β. Characteristically, *T. spiralis* AES- and MES-pulsed DCs were able not only to present antigens to sensitized CD4+ T cell to induce their proliferation but also to stimulate naïve CD4+ T cells to differentiate to Tregs secreting IL-10 and TGF-β. The passive delivery of *T. spiralis* AES- and MES-pulsed BMDCs to naive mice allowed these animals to produce more Tregs.

Research has indicated that *Trichinella* antigens are able to expand Treg populations in the host through engagement of multiple pattern recognition receptors (PRRs) expressed on Tol-DCs namely: TLR2, TLR4 and DC-SIGN (Ilic et al., 2018; Zhang et al., 2018; Cvetkovic et al., 2020). DC-SIGN signaling by *T. spiralis* antigens is required for tolerogenic signatures of human DCs (Cvetkovic et al., 2020). That's why these distinctly activated and modified DCs are described asTol-DCs. Ilic et al. (2018) showed that ES L1-treated DCs triggered the expansion of IL-10 and TGF-β-secreting CD4+CD25+Foxp3+ T cells in indolamine 2,3 dioxygenase (IDO)-1-dependent way and enhanced the suppressive activity of the primed T cells. This process was mediated by TLR2 and TLR4. Interestingly, Jin et al. (2020a) have identified another set of pattern recognition receptors (PRRs), namely nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that may be involved in the induction of Tol-DCs upon interaction with *Trichinella* antigens. Specifically, the receptor subtype NLRP3 (NLR family, pyrin domain containing 3) was found to play a role in the induction of Th2 and Treg polarization in response to *T. spiralis* muscle larvae ES products given the fact that NLRP3$^{-/-}$ mice treated with larval ES are less able to trigger Th2 and Treg responses than control mice. Further, mice lacking NLRP3 displayed significantly increased larval burdens in the muscle compared to wild type mice.

Little is known about the mechanisms of recruitment and migration of Tregs to the *Trichinella*-infected tissues of the host, namely the small intestine and skeletal muscles. Chemokines are directly involved in the homing of lymphocytes including Tregs to different body tissues. Ahn et al. (2016) investigated the state of chemokines in the intestine and muscles of *T. spiralis* infected mice. Foxp3+T cell counts were found to peak in the intestinal tissues at the end of the second week post-infection to diminish afterwards. Chemokine receptors were moderately elevated in the intestine. In contrast, the muscles showed more pronounced Foxp3+ T cell recruitment with marked increase in the expression chemokine genes, namely Gzmb, OX40, and CTLA-4. Moreover, upregulated gene expression of chemokine receptors in muscles, CXCR3, CCR4, CCR5, CCR9, and CCR10 was observed.

4.3. Alternatively activated macrophages

Among the attempts of *T. spiralis* to control the inflammatory processes and subsequent tissue damage, it inhibits the classically activated macrophages (CAMs) and instead induces the AAMs or M2 macrophages. In contrast to CAMs, AAMs fail to generate NO from L-arginine but instead the cross-regulatory enzyme arginase (Gordon, 2003; Maizels et al., 2004). AAMs can be identified by their expression of several molecular markers: the enzyme arginase-1 (Arg-1), members of the chitinase family (YM-1, YM-2, and AMCase), resistin-type molecules (Fizz family members), TGF-β, and mannose receptor (MMR/CD206) (Faz-López et al., 2016). Furthermore, diverse types of transcription factors, such as STAT6, Kruppel-like factor (KLF) 4, and interferon regulator factor (IRF) 4, are associated with AAMs (Date et al., 2014).

AAMs are active in at least three functional categories. Firstly, in sharp contrast with CAMs which are efficient in immune protection but produce pro-inflammatory products that can induce collateral tissue damage, AAMs produce anti-inflammatory molecules such as IL-10 and TGF-β and exert selective immunosuppressive functions, thus protecting tissues against detrimental immune responses. Secondly, they are implicated in tissue repair and healing as they stimulate the fibrinogenic activity and promote angiogenesis and tissue repair. Finally, there is strong evidence of their role as effector cells, mediating some immune responses against parasites (Noël et al., 2004; Maizels et al., 2004; Faz-López et al., 2016).

Helminths exhibit the outstanding ability to induce AAMs as a strategy of modulation of the immune system of the host. AAMs seem to interfere with some aspects of potent effector Th2 immune responses and dampen the excessive inflammation that may ensue during the infection. Nearly all tissue resident and migratory helminth parasites show such ability of AAM induction (Faz-López et al., 2016; Maizels and McSorley, 2016).

In common with other helminths, *T. spiralis* is a potent inducer of polarization of macrophages towards AAM pathway very early in the course of infection. AAMs have been induced by *Trichinella* antigens in both in vivo and in vitro models. Many studies of animal models of autoimmune disorders especially inflammatory bowel diseases confirmed AAM induction in the intestine by *Trichinella* antigens. More details will be given in the next sections of this review. For instance, Ding et al. (2016) reported that during the early intestinal phase of *T. spiralis* infection, the peritoneal macrophages were significantly increased and confirmed their alternatively activated phenotype. Regarding the muscle phase, macrophages are increased in the muscle around the NC and even inside them. However, no data are available whether these cells are AAM or not (Fabre et al., 2009).

As an example of in vitro analyses, Jin et al. (2020b) investigated the immunomodulatory effect of *T. spiralis* muscle larvae thioredoxin peroxidase-2 (TsTPX2) in the regulation of Th2 response. They found that rTsTPX2 could directly drive peritoneal macrophages to the AAM phenotype. Moreover, they demonstrated that rTsTPX2 as well as the adoptive transfer of rTsTPX2-activated macrophages (MrTsTPX2) could induce Th1-suppression with reduced levels of Th1 cytokines (interferon (IFN)-γ, IL-12, and tumor necrosis factor (TNF)-α) and elevated levels of Th2 cytokines (IL-4 and IL-10). Another in vitro study reported that recombinant *T. spiralis* P53 (rTsP53) transformed bone marrow derived macrophages into AAMs (Chen et al., 2015).

4.4. Regulatory B cells

Bregs, also called IL-10-secreting B cells, have long been described. They induce regulatory immune responses through B-cell receptors, CD40 and possibly TLR signaling. Moreover, these cells are found to effect a regulatory function through the secretion of TGF-β and even through activation or recruitment of Tregs (Fillatreau et al., 2002; Ashour, 2013). Bregs have been described in several helminth infection models. For example, in a murine model of schistosomiasis, B cell-mediated FcR-dependent signaling has been implicated in the downregulation of the Th2 response as mice deficient in B lymphocytes or the Fc receptor exhibited marked exacerbation of granulomatous inflammation (Jankovic et al., 1998). Likewise, Ndlovu et al. (2018) have found that within the B cell compartment, IL-4Rα-expressing B cells in particular down-modulate the detrimental egg-induced tissue granulomatous inflammation to enhance host survival during schistosomiasis in mice.

Xie et al. (2021) have provided the first evidence of expansion of Bregs during *T. spiralis* infection in mice. Elevated levels of IL-10 were detected in the spleen and mesenteric lymph nodes of *T. spiralis*-infected animals. Moreover, the rates of IL-10-producing CD19+CD1d^{high}CD5+ Bregs and CD19+ cells were upregulated during the infection. They also have showed that the induced B cell phenotype resembles that of transitional type 2 marginal zone precursor B cells (T-MZP) subsequent to *T. spiralis* infection.

4.5. Other mechanisms

Research has indicated that during the course of helminth infection, the regulatory molecules glucocorticoid-induced TNF receptor family-related protein (GITR) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are upregulated. The increase in the co-inhibitory molecule CTLA-4 is much more pronounced than that of the co-stimulatory molecule GITR with the net result of T cell hyporesponsiveness in helminth infections (Maizels et al., 2004).

Furze et al. (2006a) investigated the dynamics of the regulatory molecules CTLA-4 and GITR during murine infection with *T. spiralis*. Expression of GITR and CTLA-4 was rapidly upregulated on cells of the spleen and mesenteric lymph nodes, with nearly 80% of CD4+ T cells expressing GITR by the 7th day post-infection, synchronizing with the release and migration of newborn juveniles. As the infection proceeded to the chronic muscular phase, expression of GITR was normalized, whereas that of CTLA-4 persisted as late as the 60th day. Furthermore, treatment with anti-CTLA-4 antibody led to increased IgE levels, elevated production of IL-4 and IL-10, as well as reduction of counts of larvae recovered from skeletal muscle.

IL-13 is an essential cytokine in the immune response against helminth parasites including *T. spiralis*. It is also responsible for many elements of immunopathology during the evolution of helminthic infections (Maizels et al., 2004; Sorobetea et al., 2018). Interestingly, McDermott et al. (2005) demonstrated that the soluble IL-13 decoy receptor IL-13Rα2, which regulates IL-13 responses, was induced upon *T. spiralis* infection. The degree to which this decoy receptor contributes to the protection against Th2-mediated immunopathology is to be determined by further research.

One of the established functions of natural killer (NK) cells is regulation of the immune response, almost through secretion of regulatory cytokines. NK cells have been found to increase during *T. spiralis* infection (Bany et al., 1992). Although McDermott et al. (2005) described the presence of IL-13-producing intra-epithelial NK cells during *T. spiralis* infection; the possibility of the presence of regulatory subsets of NK cells among the recruited NK cells cannot be excluded.

5. *Trichinella*-derived molecules: a panacea for modern human diseases?

T. spiralis can be maintained in the laboratory, thus, guaranteeing the availability of its antigens (Intapan et al., 2006). Different *Trichinella* antigens have been described long ago. Identification and specification of molecular components of *Trichinella* antigens aimed to apply them in serodiagnosis (e.g. *T. spiralis* cystatin (TsCstN) (Liu et al., 2021a), actin-5c and cysteine protease (Yang et al., 2015) and vaccination studies (e.g. *T. spiralis* paramyosin (Ts-Pmy) (Wang et al., 2017) and *T. spiralis* (*Ts*-Hsp70) (Fang et al., 2014)).

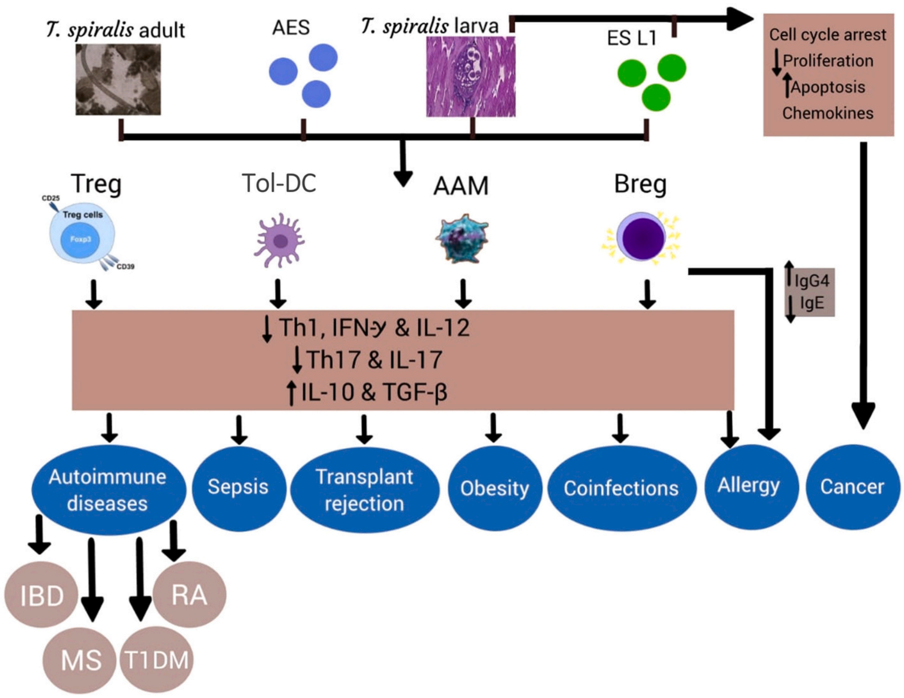

Fig. 1. *Trichinella*-induced immunomodulation of various human disorders.
ES L1: ES product of *T. spiralis* muscle larvae; AES: ES from adult *T. spiralis*; Treg: regulatory T cell; Breg: regulatory B cell; AAM: alternatively activated macrophage; Tol-DC: tolerogenic dendritic cell; IBD: inflammatory bowel disease; RA: rheumatoid arthritis; MS: multiple sclerosis; T1DM: Type 1 diabetes mellitus.

Furthermore, the ability of *T. spiralis* to manipulate the host immune response is beneficial for both the host and the parasite. It can protect the host from excessive inflammatory response and tissue damage and at the same time protect the parasites from being eliminated (Radovic et al., 2015). There is much evidence that the immunomodulatory effects of *T. spiralis* had promising results in protecting and/or ameliorating autoimmune and allergic diseases in animal models (Smallwood et al., 2017). However, since treatment with live helminths carries certain risks, studies have focused on identifying parasite-derived molecules with immunomodulatory capacity as a potential therapeutic option for different immunopathological diseases (Rzepecka and Harnett, 2022).

Some of the efforts to use *T. spiralis*-derived molecules in experimental models mimicking human diseases are highlighted below and summarized in Fig. 1.

5.1. Autoimmune diseases

5.1.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory condition of the gastrointestinal tract that manifests as ulcerative colitis or Crohn's disease (Blumberg and Strober, 2001). Crohn's disease is accompanied by a Th1 response with marked elevation of inflammatory mediators; IFN-γ and TNF-α, and low levels of IL-4 and IL-10. Ulcerative colitis is characterized by Th2/Th17 immune response imbalance (Fuss et al., 2004; Strober and Fuss, 2011).

Different animal models of chemically induced colitis have been described. 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis is a well-established model of intestinal inflammation that elicits a Th1-polarized colonic immune response and exhibits important histological features of human Crohn's disease (Camoglio et al., 2000). While the dextran sulfate sodium (DSS)-induced colitis model is also widely used because of its simplicity and many similarities with human ulcerative colitis (Cao et al., 2018).

Khan et al. (2002) investigated for the first time the impact of *T. spiralis* infection on alleviating colitis in mice, induced by dinitrobenzenesulfonic acid (DNBS) (Crohn's disease model), 21 days after *Trichinella* infection. Later, studies have identified some *Trichinella*-derived molecules capable of ameliorating Crohn's disease in animal models. Du et al. (2011) revealed the immunomodulatory properties of recombinant 53 kDa glycoprotein of *T. spiralis* (rTsP53) in the treatment of TNBS-induced colitis in mice. It provoked reduction of IFN-γ and TNF-α (Th1 cytokines) and increased production of IL-4 and IL-13 (Th2 cytokines) in sera of treated mice. Moreover, IL-10, TGF-β and the markers of AAM (Arg-1 and FIZZ1) were upregulated in the mucosa.

Trichinella adult serine protease-like protein (Ts-ADSp-7) was identified as an effective component of *T. spiralis* serine protease (Wu et al., 2009). Pang et al. (2020) showed that recombinant Ts-ADSp-7 (rTs-ADSp-7) could significantly alleviate TNBS-induced colitis in mice by increasing the percentage of Tregs. It significantly reduced IFN-γ, TNF-α and IL-17 expression, while the levels of IL-4, IL-5, IL-10 and TGF-β were significantly higher in the group treated with rTs-ADSp-7.

Serine protease inhibitors (serpins) are a superfamily of proteins (Ts-serpins) localized in *T. spiralis* stichosomes of muscle larvae and adult worms. They inhibit serine protease activity and help the parasite to invade the defensive barriers, and to escape the host's immune attack (Molehin et al., 2012). Moreover, Ts-serpins play an important role in ES product-mediated immunoregulatory effects during *T. spiralis* infection. The role of Ts-serpins and recombinant Ts-serpins–treated bone marrow-derived macrophages (BMDMs) was investigated in TNBS-induced colitis. They induced the upregulation of anti-inflammatory cytokines and inhibited the level of pro-inflammatory cytokines in mesenteric lymph nodes (MLNs) and peritoneal cells by directly activating AAM as well as the secretion of IL-10 (Xu et al., 2020).

Similarly, the effect of *T. spiralis* infection on acetic acid-induced colitis (ulcerative colitis model) was investigated by Ashour et al. (2014). They have found that *T. spiralis* infection that preceded the induction of colitis succeeded in inducing regulatory immune responses and elevated proportion of $CD4^{+}CD25^{+}Foxp3^{+}$ Treg cells resulting in decreased intestinal inflammation. Interestingly, the adoptive transfer of either peritoneal macrophages from *T. spiralis*-infected mice two weeks post-infection or BMDMs treated with *T. spiralis* ES proteins inhibited the inflammation in DSS-induced colitis. *T. spiralis* induced AAM polarization with increased production of anti-inflammatory cytokines such as TGF-β and IL-10 and reduction in the pro-inflammatory cytokine level (Kang et al., 2019).

ES from adult *T. spiralis* (Ts-AES), injected intraperitoneally daily for 7 consecutive days, significantly ameliorated the manifestations of DSS-induced colitis and reduced the severity of intestinal inflammation through upregulation of Treg cells and its regulatory cytokines; IL-10 and TGF-β and downregulation of pro-inflammatory cytokines (IFN-γ, IL-6 and IL-17) in the spleens, MLNs and colon of treated mice (Yang et al., 2014). Similar findings were reported regarding the therapeutic effect of recombinant Ts-Pmy protein (rTsPmy) emphasizing the role of Treg cells in amelioration of DSS-induced colitis (Hao et al., 2021). While Wang et al. (2020b) suggested that enhanced AAM polarization is the involved mechanism in attenuation of the DSS-induced colitis severity with Ts-AES. Moreover, they investigated the impact of Ts-AES on macrophage polarization in vitro. They found that Ts-AES significantly induced M2 polarization with higher expression of CD206 and Arg-1 on the surface of macrophages. Meanwhile, the expression of NOS II and TNF-α was inhibited.

Most recently, extracellular vesicles (EVs) have become the focus of interest in many studies highlighting their role in delivery of bioactive molecules, such as functional proteins, carbohydrates, lipids, mRNA and noncoding RNAs, from helminths to different host cells that modulate the host-parasite interactions via series of intracellular signaling events (Coakley et al., 2015). Kosanović et al. (2019) showed, for the first time, that EVs carry immunomodulatory proteins and have the capacity to induce regulatory responses independently in the same way as the *T. spiralis* ES L1 products from which they were isolated. Yang et al. (2020) showed that *T. spiralis*-EVs are potent immune modulators with the ability to attenuate mucosal intestinal inflammation with improvement of the clinical signs of TNBS-induced colitis in mice. Ts-EVs induced Th2/Treg cell differentiation and dramatically reduced the expression of pro-inflammatory cytokines; IFN-γ (Th1) and IL-17A (Th17), whereas the anti-inflammatory cytokines such as IL-10 and TGF-β were increased significantly in the intestinal tissue. Similar findings were reported by Gao et al. (2021) in DSS-induced colitis. Besides, they observed that Ts-EVs increased the infiltration of AAM into the colon with increased expression of CD206 (AAM marker) in the MLNs of mice treated with Ts-EVs.

5.1.2. *Experimental autoimmune encephalomyelitis (EAE)*

Multiple sclerosis (MS) is an autoimmune chronic inflammatory and demyelinating disease. It is characterized by focal lymphocytic infiltration that leads to damage of myelin and axons associated with extensive neurodegeneration and progressive disability (Kamińska et al., 2017). MS immunopathology is mediated by myelin-reactive Th1 and Th17, with increased production of IFN-γ and IL-17 (Moser et al., 2020).

Experimental autoimmune encephalomyelitis (EAE) has been widely used as an animal model for the human disease MS. In EAE, Th1 and Th17 cells migrate into the CNS and promote the inflammatory process (Fletcher et al., 2010).

T. spiralis infection meliorates EAE induced in DA rats in a dose-dependent manner with an optimal dose of 500 *T. spiralis* L1 (Gruden-Movsesijan et al., 2008). Further studies showed that *T. spiralis* ES L1 induced switch of the immune response to Th2 regulatory type with increased production of $CD4^+CD25^+Foxp3^+$ Treg cells and downregulation of the Th1/Th17 response resulting in significant reduction in EAE severity and reduced duration of illness in treated animals (Radovic et al., 2015). Bruschi et al. (2021) suggested that *T. spiralis* ES L1 induced amelioration of EAE could be related to lower expression of matrix metalloproteinase (MMP)-9 in the spinal cord of ES L1-treated rats with reduced number of infiltrating cells and increased production of anti-inflammatory cytokines IL-4 and IL-10.

Moreover, Gruden-Movsesijan et al. (2010) showed that transfer of T cells isolated from *T. spiralis*-infected animals, before EAE induction, provided a protective effect on the recipients. Transferred cells contained an increased proportion of $CD4^+CD25^+Foxp3^+$ Treg cells and produced high levels of IL-10, which could affect the course of the disease. Antigens of *T. spiralis* muscle larvae (Aranzamendi et al., 2012) or its components e.g., Ts-Pmy (Guo et al., 2016) are potential candidates for the induction of stable Tol-DCs with an increased capacity to suppress the inflammatory immune response through expansion of highly potent IL-10- and TGF-β-producing Tregs. DCs stimulated with *T. spiralis* ES L1 induced Tol-DCs that ameliorated EAE successfully in animal models (Sofronic-Milosavljevic et al., 2013).

In a recent interesting study, Gruden-Movsesijan et al. (2020) observed that imunoglobulins from the sera of MS patients recognized some ES L1 components, namely 45, 49 and 58 kDa proteins. This study highlighted the possible role of these molecules in immunomodulation of the immune response and amelioration of EAE. However, there is a chance of molecular mimicry with self-antigens and thus promoting tolerance with regulatory T cell expansion (Pontes-de-Carvalho et al. (2013).

5.1.3. *Rheumatoid arthritis*

Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated disease characterized by chronic inflammation and synovial hyperplasia leading to destruction of cartilage and bone with permanent disability (Bevaart et al., 2010). There is a strong evidence that abnormally activated Th1 and Th17 cells and impaired $CD4^+CD25^+Foxp3^+$ Treg cells contribute to the pathogenesis of RA (Cope et al., 2007).

Animal models of RA with similarities to human disease include: rat adjuvant arthritis (AA), collagen-induced arthritis (CIA), and antigen-induced arthritis in several species. A rat model of AA has been widely used in pre-clinical studies. This model offered a reliable onset and progression of robust, easily measurable poly-articular inflammation with a RA-like changes (Bendele, 2001).

Cheng et al. (2018) demonstrated that *T. spiralis* infection significantly attenuated the pathology of CIA in mice mostly through reduction of Th1/Th17 pro-inflammatory responses and inducing Th2/Treg polarization via programmed death 1 (PD-1) pathway. The intradermal injection of autoclaved *T. spiralis* antigen (ATSA) in a rat model of AA can ameliorate the clinical manifestations with a significant increase in Treg cells, and elevated levels of IL-17, IFN-γ, and IL-10. The authors suggested that the unexpected high levels of IFN-γ attained with ATSA treatment may contribute to their anti-arthritic effect in this model of AA in which *Mycobacteria* are the main antigenic component (Eissa et al., 2016).

Chen et al. (2020) identified a 14-amino acid peptide derived from Ts-Pmy which was further modified with a membrane-targeting signal to increase its retention time in the joint cavity and enhance its ability to inhibit complement activation. Intra-articular injection of the modified peptide markedly ameliorated knee swelling. It decreased the synovial hyperplasia and inflammatory cell infiltration and reduced membrane attack complex (MAC) deposition in the synovial connective tissue in mice with antigen-induced arthritis.

5.1.4. *Type 1 diabetes mellitus*

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by cytotoxic Th1 mediated self-destruction of insulin-secreting islet beta cells in the pancreas (van Belle et al., 2011).

Animal models for type 1 diabetes range from animals with spontaneously developing autoimmune diabetes such as the non-obese diabetic (NOD) mouse and the Biobreeding (BB) rat or chemically induced diabetes using streptozotocin or alloxan (King, 2012).

$CD4^+CD25^+Foxp3^+$ Treg cells have recently been considered as powerful mediators to re-balance of Th1/Th2 in autoimmune diabetes (Liu et al., 2016). Moreover, Saunders et al. (2007) showed that *T. spiralis* infection delays the onset and prevents the progression of T1DM. However, the underlying mechanisms were not so clear. IL-4 was induced in the presence of *T. spiralis* infection, but there was no reduction in the production of IFN-γ. The authors suggested that the activation of Th2 response may not be the only reason for the observed improvement of the disease. However, some studies reported that IFN-γ has a protective rather than a disease promoting effect (Krakowski and Owens, 1996). No further studies regarding the role of *Trichinella*-derived molecules in T1DM have been conducted. Therefore, the effect of *Trichinella* infection and of parasite-derived molecules in T1DM has to be investigated thoroughly.

Similar improvement was observed in type 2 diabetes. *Trichinella* infection of obesity mice model improved insulin resistance and glucose tolerance. Moreover, decreased expression levels of CAMs markers including CD11c, NOS II and IL-6 were observed, while AAMs markers including CD206, Arg-1 and IL-10 were increased in adipose tissue and peritoneal lavage cells of residential macrophages isolated from the infected group, compared to uninfected control animals (Okada et al., 2013).

5.2. Allergy

Allergy is a hypersensitivity immune response initiated by exposure to allergens. Allergic disorders include asthma, allergic rhinoconjunctivitis, skin allergies, food and drug allergies and anaphylaxis (Johansson et al., 2004).

The most frequently used animal model for allergy is the ovalbumin (OVA) one in which mice are injected with OVA and an adjuvant. With subsequent exposure to aerosolized or intranasal OVA, experimental allergic airway inflammation (EAAI) is produced (Chapman et al., 2014).

Park et al. (2011) showed that the *T. spiralis* regulatory mechanisms could ameliorate EAAI and suppress the inflammatory cellular infiltration in the lungs. They observed recruitment of Treg into draining lymph nodes with significant increase in IL-10 and TGF-β levels. However, Aranzamendi et al. (2013) demonstrated that the chronic phase of *Trichinella* infection resulted in more protection against EAAI and it produced higher numbers of splenic $CD4^{+}CD25^{+}Foxp3^{+}$ Treg cells.

More interestingly, the adoptive transfer of Treg cells in the spleen from chronically infected mice induced partial protection against EAAI via IL-10 (Aranzamendi et al., 2013). Similarly, the adoptive transfer of either of peritoneal macrophages from *T. spiralis*-infected mice two weeks post-infection or BMDMs treated with *T. spiralis* ES proteins inhibited airway inflammation in OVA model. *Trichinella* induced AAM polarization with increased production of anti-inflammatory cytokines such as TGF-β and IL-10 (Kang et al., 2019).

Yuan et al. (2019) investigated the protective effect of Ts-AES, injected intraperitoneally once every other day for seven times, on OVA-induced allergic rhinitis in mice. They observed decreased serum IFN-γ, increased serum IL-10 and TGF-β levels and remarkably improved pathological damages of the nasal mucosa in the treated group. Similar findings were reported by Sun et al. (2019b) in OVA-induced asthma. They demonstrated that mice treated with Ts-AES, prior to (preventive) and with (therapeutic) OVA sensitization, showed significant reduction of inflammatory cells infiltration around the airway and blood vessels and reduction of allergen-specific Th2 responses, including reduced OVA-specific IgE in sera and reduced IL-4 level and eosinophil cells in lungs. They reported that more improvement in lung tissue pathology was observed in the preventive model than in the therapeutic model which was associated with a higher reduction in OVA-specific IgE level, with a concomitant increased IL-10 levels.

The immunomodulatory effect of *T. spiralis* thioredoxin peroxidase-2 (TsTPX2), a protein derived from *T. spiralis* muscle larvae ES products was investigated by Jin et al. (2020b). They stated that TsTPX2 could suppress Th1 immune responses and promoting Th2 cytokines, IL-4 and IL-10 via polarization of macrophages into the AAM phenotype. They suggested that TsTPX2 provides a novel

Table 2
T. spiralis molecules with potential regulatory functions

Trichinella molecule	Localization in the parasite	Function(s)	Regulatory mechanism(s)
TGF-β ligand homologue from *T. spiralis* (He et al., 2020).	Widely distributed in most metazoans (Herpin et al., 2004).	Participation in many biological processes such as development and immunoregulation (Herpin et al., 2004).	TGF-*β* is a key molecule in the repair of the airway epithelium in allergic diseases and in fibrosis and infectious diseases (Tran, 2012).
T. spiralis cystatin (TsCstN)	Identified in β-stichocytes of the stichosome and in the ES-L1 of *T. spiralis* (Tang et al., 2015).	Protease inhibition and immunomodulation (Ochieng and Chaudhuri, 2010).	Downregulation of pro-inflammatory cytokines, NOS II and CAMs markers and induction of regulatory phenotype of BMDMs (Bisht et al., 2019; Kobpornchai et al., 2020).
T. spiralis cathepsin B-like protein (rTsCPB)	ES antigens of *T. spiralis* AW and ML (Zhan et al., 2013).	Host cell invasion, tissue migration, immune modulation/suppression, and parasite survival in the host (Hu et al., 2021).	Induction of AAMs macrophages ameliorating intestinal injury in intestinal ischemia/reperfusion model (Liu et al., 2015a).
T. spiralis glutathione-S-transferase (TsGST)	Somatic proteins of *T. spiralis* different stages (NBL, AW, ML and upregulated in IIL) (Li et al., 2015).	Detoxification enzyme essential for development and survival of the parasite and infective larval invasion (Liu et al., 2017).	Decrease of the LPS-induced elevated level of pro-inflammatory cytokines of dendritic cells and enhancement of the level of regulatory cytokines IL-10 and TGF- β (Jin et al., 2019).
T. spiralis calreticulin (*Ts*-CRT)	Somatic antigen of all the stages of *T. spiralis* (NBL, ML and AW) (Zhao et al., 2017).	Immune evasion and survival in host by inhibition of C1q-initiated complement classical activation pathway (Ferreira et al., 2004).	Immunomodulatory protein to neutralize C1q-induced complement activation (Shao et al., 2020) and increase IL-10 production (Mendlovic et al., 2015).
T. spiralis 7C2C5Ag Three glycoproteins (45, 49 and 53-kDa proteins)	ES antigen of *T. spiralis* ML (Cvetkovic et al., 2016). 53-kDa glycoprotein could be also expressed in AW (Nagano et al., 2009).	Involved in many biological activities and evasion of host immunity (Nagano et al., 2009).	Activation of tolerogenic DC phenotype and polarization of T cells towards Th2 and induction of anti-inflammatory responses (increase IL-10 production) (Cvetkovic et al., 2016).

AW = adult worm; IIL = intestinal infective larva; ML = muscle larva.

therapeutic method to various inflammatory disorders like allergies.

ES L1 products of muscle larva contain a complex mixture of 43 glycoproteins, identified as 13 proteins and their isoforms (Robinson and Connolly, 2005) and more than 280 protein components in Ts-AES were identified (Yang et al., 2017). The immunomodulatory effects of many of these components are still awaiting to be investigated. Some other *T. spiralis* molecules that are suggested to have potential regulatory functions against autoimmune and allergic diseases are presented in Table 2.

5.3. Sepsis

Sepsis is a systemic inflammatory response syndrome induced by infection. Bacterial lipopolysaccharides (LPS) can trigger sepsis and lead to over production of inflammatory mediators such as TNF-α, IL-1β and IL-6, leading to multiorgan failure and even death (Du et al., 2014).

A polymicrobial sepsis animal model is performed by cecal ligation and puncture (CLP). The pathology associated with this model is similar to that observed during clinical peritonitis (Rittirsch et al., 2009).

Du et al. (2014) demonstrated that treatment with Ts-ES from muscle larvae reduced mortality and protected organ function in mice with CLP-induced polymicrobial sepsis. Administration of Ts-ES to septic mice significantly reduced the serum levels of several inflammatory cytokines; TNF-α, IL-1β, and IL-6 and elevated regulatory factors; IL-10 and TGF-β. Moreover, Ts-ES downregulated MyD88 and NF-κB activity in macrophages obtained from the peritoneal lavage of septic patients.

The therapeutic effect of Ts-AES on CLP induced septic acute lung injury (ALI) in mice was studied by Li et al. (2021). They found that treatment with Ts-AES significantly improved the survival rate of septic mice. Ts-AES alleviated sepsis-induced ALI via induction of Treg cells with the increased levels of IL-10 and TGF-β in serum and lung tissues as well as splenocytes of mice treated with Ts-AES possibly through inhibiting HMGB1 (a cytokine mediator of inflammation), TLR2 and MyD88 pathway. Recombinant *T. spiralis* 53-kDa ES protein exhibited anti-inflammatory properties and rescued mice from LPS-induced damage of endotoxemia (Chen et al., 2016) and ALI (Wei et al., 2021). rTsP53 was found to be a strong immunomodulatory agent that down-regulated pro-inflammatory mediators (TNF-α, IL-1β, and IL-6) and simulated IgG1 isotype. Moreover, it induced the polarization of AAM and the anti-inflammatory cytokine IL-10 (Wei et al., 2021).

5.4. Malignancy

Tumor biotherapy is a new modality of cancer treatment. It utilizes immunological and/or molecular biological agents aiming to boost the immune system to suppress or eliminate tumors (Torre et al., 2015).

Many animal models are used in experimental studies of tumors, with an organ-specific property, including transplanted tumor models, chemically induced malignancies, environmentally induced cancer or genetically engineered cancer models. They can mimic the clinical cancer progress from the early stage on (Liu et al., 2015b).

Although the impact of *T. spiralis* infection or its derived antigens, on tumors in vivo or malignant cell lines in vitro, has been investigated by a limited number of studies, they showed a significant and promising influence on the rate of tumor progression or even inhibit tumor growth and dissemination (Wang et al., 2009b; Zhang et al., 2009).

During *T. spiralis* NC, formation, de-differentiation and cell cycle arrest of infected muscle cells occur (Wu et al., 2008a). These changes are associated with upregulation of the expression of some apoptosis-related genes such as p53, SMAD2 and SMAD3 that act as tumor suppressor genes as well as the apoptosis factors such as Bcl-2 associated protein X (BAX), TNF-α, caspase 3, caspase 8 and caspase 9 (Boonmars et al., 2005; Wu et al., 2008a; Samanta and Datta, 2012). It was suggested that *T. spiralis* NC formation apoptotic pathway is a possible mechanism that can suppress cell proliferation or induce apoptosis of the tumor cells (Wu et al., 2008a; Wang et al., 2009b).

Elhasawy et al. (2021) showed that *T. spiralis* infection in hepatocellular carcinoma (HCC) animal model produced a certain level of decreased progression of the tumor with increased rate of apoptosis as shown by the decreased expression of Bcl-2 at 30- and 40-days post-infection and subsequently had a positive impact on the survival of rats. Other studies involving the anti-tumor effect of *Trichinella* infection in different tumor models are reviewed by Liao et al. (2018).

Luo et al. (2017) suggested that *T. spiralis* ES proteins can induce apoptosis in small-cell lung cancer cells. They detected the low expression of anti-apoptosis genes Bcl-2 and Livin (another anti-apoptosis protein) and increased expression of pro-apoptosis genes Cyt-C, Apaf-1, caspase-9 and caspase-3 in cancer cells co-cultured with *T. spiralis* ES proteins. Similar findings were reported by Vasilev et al. (2015) in vivo. They showed that *T. spiralis* ES L1 antigen inhibited the survival of B16 melanoma cells in a dose-dependent manner. They revealed that *T. spiralis* ES L1 antigen triggers apoptosis through caspase-8 and caspase-3 with significantly higher numbers of apoptotic cells among melanoma cells.

Wang et al. (2009b) suggested that *T. spiralis* apoptosis-related genes are responsible for cancer cell apoptosis. They showed that *T. spiralis* crude extract from a mixture of AW and NBL inhibited the growth of five tumor cell lines; murine forestomach carcinoma (MFC), murine ascitic hepatoma (H22), murine sarcoma (S180), human chronic myeloid leukemia (K562), human hepatoma (H7402) cell lines in vitro and significantly enhanced the regression of MFC, H22 and S180 in vivo in animals grafted with these cell lines.

Gong et al. (2011) investigated the anti-tumor effect of tropomyosin, a component of *T. spiralis* myofibrils, compared to *T. spiralis* crude antigens and ES L1 antigens. They found that these treatments inhibited the development of myeloma SP2/0 similarly. Recombinant *T. spiralis* protein A200711 (L-aminoadipate-semialdehyde dehydrogenase- phosphopantetheinyl transferase) has a pro-apoptotic effect on human hepatoma H7402 cells and it was proposed as a therapeutic agent in HCC treatment (Wang et al., 2013). Muscle larvae ES products were studied for identification of *T. spiralis* proteins with anti-tumor activity and the following proteins were detected; histone H2A, cleavage and polyadenylation specificity factor unit 2, armadillo segment polarity protein and eukaryotic initiation factor 4A and serine proteinase inhibitor Kazal-type 4) (Luo et al., 2016). An apoptotic effect of ES was also shown in vitro on either HeLa or the histiocytic lymphoma U937 cell lines (Piaggi et al., 2021).

However, the anti-tumor effect of *Trichinella* may not be dependent only on its apoptotic effect. Some studies reported the role of immune response triggered by *T. spiralis* including activation of macrophages, NK cells, and cytotoxic T lymphocytes, and the secretion of some chemokines and cytokines such as TNF-α (Liao et al., 2018). Kang et al. (2013) showed that *T. spiralis* infection reduced tumor growth and lung metastasis of B16-F10 melanoma cells through decreasing the production of some chemokines, such as CXCL9, CXCL10, IL-4, CXCL1 and CXCL13. Pulmonary NK cells from *T. spiralis* infected mice were able to upregulate the cytotoxic activity against the semi-syngeneic tumor cells with increasing effect with time post-infection (Liao et al., 2018). Some *T. spiralis* proteins that are suggested to have anti-tumor effects are summarized in Table 3.

5.5. *Allograft rejection after transplantation*

Successful allograft transplantation is challenged by acute and chronic cell mediated allograft rejection. This process is mediated through the release of pro-inflammatory Th1 cytokines (Ingulli, 2010). It has been shown that the prolonged allograft survival regulated by helminth infection was consistently associated with a significant decrease in the levels of pro-inflammatory cytokines (IFN-γ and IL-17) and a parallel increase in Th2/Treg cytokines (IL-4 and IL-10) (Deng et al., 2016).

Chimyshkyan et al. (1976) reported that skin allograft necrosis occurred much later in *T. spiralis* infected mice (26.2 days) as compared to non-infected mice (12.5 days). Moreover, the splenic cells of *T. spiralis* infected mice did not induce or slightly induced graft-versus-host reaction. Moreover, increasing the infective dose of *T. spiralis* (Alkarmi et al., 1995) and the duration of infection before transplantation (Svet-Moldavsky et al., 1969) resulted in improvement in allograft survival.

Several studies reported the positive impact of *T. spiralis* and *T. pseudospiralis* on graft survival (reviewed in Kiss et al., 2020). All of them showed that allograft survival was significantly improved in *Trichinella*-treated groups, with marked decrease in graft necrosis. Supporting these observations, Dutta et al. (2010) and Deng et al. (2016) suggested that the prolonged survival of a transplanted graft is associated with decreased $CD8^+$ T cells, suppressed Th1/Th17 responses, and increased Treg cells within the graft tissue in experimental group infected with *T. spiralis* or its derived products.

5.6. *Coinfections*

Some earlier studies investigated *Trichinella* coinfection with other pathogens. Mice infected with *T. spiralis* are protected from early death on coinfection with *Trypanosoma equiperdum* (Wagner and Nembhard, 1976). They postulated that the immune response to *Trichinella* inhibited the multiplication of *T. equiperdum*. Similarly, *T. spiralis* induced resistance to intraperitoneal challenge with

Table 3
T. spiralis proteins with potential anti-tumor effects

Protein	Localization	Function(s)	Anti-tumor mechanism(s)
Caveolin-1 (cav-1)	On the surface of *Trichinella* oocytes and embryos and decreased during NBL development (Hernandez-Bello et al., 2008).	Oocyte maturation and embryogenesis during development, with a gender-specific expression (Hernandez-Bello et al., 2008).	Tumor suppression by inducing cell cycle arrest and apoptosis (Goetz et al., 2008).
Heat shock proteins 70 (TS- HSP70)	Somatic and ES antigen of *T. spiralis* ML and AW (Wang et al., 2009a).	Involvement in several biological processes such as invasion of host tissue, larval migration or molting, immune modulation and metabolic processes (Somboonpatarakun et al., 2018).	Acting as potent immunoadjuvants that can provoke more powerful anti-tumor effects (Wang et al., 2012).
Retinoblastoma binding protein 4 (Rbbp4) from *T. spiralis*	Expressed in myeloma cells in the presence of *T. spiralis* infection (Deng et al., 2013).		Retinoblastoma protein is a potent regulator of cellular proliferation, control chromatin cohesion, chromatin structure and tumor proliferation and differentiation. It is involved in inhibiting breast cancer MCF 7 cell growth (Witkiewicz and Knudsen, 2014).
Natural killer cell triggering receptor (NKTR) protein from *T. spiralis*	Expressed in myeloma cells in the presence of *T. spiralis* infection (Deng et al., 2013).		Induction of cytotoxic NK cells in the tumor microenvironment with anti-tumor activity in a B-cell lymphoma model (Miyazaki et al., 2021).
T. spiralis tropomyosin	Cytoskeletal protein (Gong et al., 2011).	A component of *T. spiralis* myofibrils that play a role in Ca^{++} dependent regulation of muscle contraction (Gong et al., 2011).	Anti-tumor activity in the myeloma cell line SP2/0 (Deng et al., 2013) and transitional cell carcinoma of the urinary bladder (Pawlak et al., 2004).
c-Ski	An oncoprotein expressed in *Trichinella* infected muscle cells (Wu et al., 2008b).	A co-repressor protein that turns off the transcription, and results in cell cycle arrest and transformation of *Trichinella* infected muscle cells (Wu et al., 2008b).	Production of tumor growth inhibiting cytokines such as TGF-β (Tong et al., 2009).

Listeria monocytogenes at 7 or 21 days after *T. spiralis* infection with longer survival time than *Listeria* mono-infected mice (Cypess et al., 1974). *T. spiralis* infection has also attenuated influenza-associated pathology in mice (Furze et al., 2006b).

A recent study revealed that *T. spiralis* alleviates pulmonary inflammation triggered by respiratory syncytial virus (RSV) infection. Pre-existing *T. spiralis* infection produced specific antibodies cross-reacting with RSV. In addition, enhanced production of RSV-specific IgM, IgG, and IgA antibodies were observed in Ts-RSV coinfected mice. Moreover, *T. spiralis* downregulated pro-inflammatory cytokines e.g., nuclear factor-κB (NF-κB) and the inflammatory cellular infiltration in the lung as well as increased the antioxidant enzyme expression e.g.,NAD(*P*)H:quinone oxidoreductase (NQO1) which decreased the RSV oxidative stress in coinfected mice with subsequent improvement of lung inflammation (Chu et al., 2020). Vice versa, Chu et al. (2019) indicated that immune responses induced by RSV infection contribute to resistance against subsequent *T. spiralis* infection.

On the contrary, *Trichinella* infection increased the host susceptibility to Japanese encephalitis virus infection (Lubiniecki et al., 1974). Similarly, it had been shown that coinfection of *T. spiralis* and *Toxoplasma gondii* resulted in higher number of *Toxoplasma* cysts in the brains of mice infected with *Trichinella* and challenged later with *Toxoplasma* than in mice infected with *Toxoplasma* alone (Yusuf et al., 1980).

Furthermore, many studies highlighted the coevolutionary dynamic crosstalk between intestinal commensal bacteria and helminths and its impact on the intestinal homeostasis in the host (Gause and Maizels, 2016). Liu et al. (2021b) observed that the mouse intestinal flora; *Bacteroides*, *Lactobacillus*, *Escherichia* and *Akkermansia* were more abundant in *T. spiralis* infected mice compared with the uninfected mice. In the meantime, some probiotic strains have been evaluated to modulate *Trichinella* infection (Jiang et al., 2016). Moreover, the increased level of probiotics in *T. spiralis* infected mice can be correlated with *T. spiralis*-induced immunomodulatory functions and its therapeutic effect on inflammatory colitis (Liu et al., 2021b). Recently, Chen et al. (2021) deciphered the time-related gut microbial composition during *T. spiralis* infection. They suggested that gut microbial biomarkers may serve as an indicator for early *T. spiralis* infection.

Contradictory findings were reported regarding coinfection of *Trichinella* and *Plasmodium*. Prior *Trichinella zimbabwensis* coinfection with *Plasmodium berghei* elicited a higher percentage of *P. berghei* parasitaemia as compared with the *P. berghei* mono-infected group with significant increase of TNF-α, IL-10, and CXCL10 levels (Murambiwa et al., 2020). However, the elevated anti-inflammatory IL-10 may play a major role in antagonizing the pro-inflammatory cytokines that can reduce the malaria specific pathologies such as cerebral malaria, lactic acidosis and acute renal failure (Hartgers and Yazdanbakhsh, 2006). In contrast, Mei et al. (2020) reported that *T. spiralis* and *P. berghei* coinfected mice showed lower *P. berghei* parasitaemia and more severe hepatosplenomegaly and increased liver pathology compared with *P. berghei* mono-infected mice. It is worth noting that CAM markers were increased in the liver, spleen, or peritoneal macrophages of coinfected mice with increased expression of IL-1β, IL-6, and NOS II response, which may contribute to the liver damage of coinfected mice. At the same time, they reported increased Gal-3 expression, a feature of AAMs activation, but its exact role is not yet identified.

5.7. Obesity

The effect of *T. spiralis* infection on diet-induced obesity in lean mice feeding a high-fat diet (HFD) was investigated. *T. spiralis* infection affects CAM/AAM polarization in gonadal fat, shifting it towards the anti-inflammatory M2 phenotype that may contribute to the altered lipid metabolism. *T. spiralis* infection attenuated the hepatic histopathological changes caused by HFD such as hepatocellular vacuolation and increased frequency of lipid droplets. Moreover, the adipocyte size, the gonadal white adipose tissue, was decreased significantly by *T. spiralis* infection as compared to non-infected mice on HFD (Kang et al., 2021). Interestingly, they reported that the elimination of *T. spiralis* (by anthelminthics 21 days post infection) retained the anti-obesity effects. It is suggested that *T. spiralis* infection could reduce the risk of fatty liver diseases and hepatic steatosis.

5.8. Future perspectives

Unfortunately, none of the experimentally identified *Trichinella* molecules have proceeded to clinical trials, most probably due to safety issues. Therefore, studies aiming to provide safe, specific target, as well as increased efficacy of *Trichinella*-derived molecules are required.

It is well known that the delivery of immunomodulatory molecules via nanoparticles (NPs) provides better targeting effects on antigen presenting cells and potentiates accumulation and longer persistence in the tissues (Prasad et al., 2015). Both gold NPs (GNPs) and graphene quantum dots (GQD) were described as excellent delivery systems, which could be easily utilized to potentiate the immunomodulatory effects of specific *T. spiralis* components. The surface of cellulose nanofibers (CNF) and poly (d,l-lactic-*co*-glycolic acid) (PLGA) nanofibers are suitable for delivering *T. spiralis* products due to the large surface available for modification, slower biodistribution and prolonged exposure in local tissues compared to spherical NPs (Ilic et al., 2021).

An interesting experiment showed that NPs loaded with a heat shock protein, could prevent T1DM when delivered orally to NOD mice (Chen et al., 2018). Based on this finding, *T. spiralis* ES L1 heat shock proteins and other immunomodulatory molecules such as proteinases, proteinase inhibitors and proteases could be delivered via NPs for treatment of autoimmune diseases.

As mentioned above, *T. spiralis*-EVs have important properties that make them suitable for therapeutic approaches of autoimmune diseases. However, the biggest challenge in their use is the limited availability of sufficient quantities for clinical trials with constant characteristics (García-Manrique et al., 2018). This could be overcome by designing artificial EVs or integration of *T. spiralis*-EVs with NPs. Better outcome is expected especially because tolerogenic NPs and conjugated antigens to NP-based therapies are developed as specific immunotherapies to treat autoimmune disease (McCarthy et al., 2017).

6. Concluding remarks

Trichinella is an exemplary helminth parasite that establishes itself successfully within the host and propagates efficiently in nature. It implements a panoply of elaborate strategies to elude the immune system of the host at different levels of innate and adaptive immune responses. The parasite also excels in manipulating the immune system of the host, implicating a complex interactive network of regulatory cells and anti-inflammatory mediators. This process is multifaceted, preserving both the parasite and the host, and, unintentionally, it does not only influence the immune reactivity to relevant targets, but also to a variety of bystanders such as autoantigens, allergens, and microbiome determinants. Therefore, it can protect the host from an array of hyperimmune disorders, metabolic dysfunction, and malignancy.

Digging deep into how the helminth parasites including *Trichinella* modulate the immune system provides us with many insights about different compartments, elements, and interactions within the immune system that hopefully could be translated into future therapeutics. Unsurprisingly, *Trichinella*-derived molecules, in particular ES products, are currently the focus of intensive research aiming at discovering agents for retuning the immune system in various disorders of immune dysregulation. Since *Trichinella* infection or molecules interfere with many aspects of the immune system, a word of caution is in order here: possible adverse effects of *Trichinella*-based therapies have to be anticipated and thoroughly evaluated to ensure safety for humans.

Declaration of Competing Interest

On behalf of other Authors Dalia Ashour and Ahmad Othman I declare that we have no conflict of interests.

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