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# *Trichinella spiralis*: shaping the immune response

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**Abstract** The co-evolution of a wide range of helminth parasites and vertebrates represented a constant pressure on the host's immune system and a selective force for shaping the immune response. Modulation of the immune system by parasites is accomplished partly by dendritic cells. When exposed to helminth parasites or their products, dendritic cells do not become classically mature and are potent inducers of Th2 and regulatory responses. Treating animals with helminths (eggs, larvae, extracts) causes dampening or in some cases prevention of allergic or autoimmune diseases. *Trichinella spiralis* (*T. spiralis*) possess a capacity to retune the immune cell repertoire, acting as a moderator of the host response not only to itself but also to third party antigens**.** In this review, we will focus on the ability of *T. spiralis*-stimulated dendritic cells to polarize the immune response toward Th2 and regulatory mode in vitro and in vivo and also on the capacity of this parasite to modulate autoimmune disease—such as experimental autoimmune encephalomyelitis.

**Keywords** *Trichinella spiralis* · Dendritic cells · Immune response · Autoimmunity

## Helminths and immune system

During evolution, helminth parasites have influenced the vertebrate immune system resulting in distinctive features of the infected host's immune response. Based on the continuous molecular dialog between the pathogen and the host, helminths have developed different evasion and suppression mechanisms enabling establishment of infection with the lowest possible damage to the host.

Infections caused by helminth parasites typically induce Th2-type immunity characterized by the production of high levels of cytokines IL-4, IL-5, IL-9, IL-10, IL-13, IL-21, IL-33 as well as immunoglobulin E (IgE) and the mobilization of eosinophils, basophils and mast cells. CD4+ Th2 cells are major players of this type of immune response, but different non-T cells also contribute to the creation of suitable environment for Th2 cell induction [1]. Immune events orchestrated by Th2 cell type can suppress the Th1 response, which makes the infected individual less susceptible to inflammatory and autoimmune diseases. Experimental models of joint helminth infection and autoimmune disease have been established and provide better insights into the process of immunoregulation [2]. Results obtained from studies of host–parasite relationships indicate that some helminths, as potent modulators of immune response, could be used, under well-defined conditions, as a therapeutic tool for the prevention and/or suppression of pro-inflammatory events [3–5]. The other feature of the response to helminth infection is mobilization of regulatory immune cells and mediators such as regulatory T cells (Tregs), IL-10 and TGF-$\beta$. This regulatory response can dampen both Th1 and Th2 responses, which explains the observation that helminth infection can also control Th2-dominated events such as allergy and atopy [6].

Dendritic cells (DCs) are among the first cells to be encountered by infectious agents and therefore necessary for the development of an adaptive immune response.

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Although the role of DCs in the presentation of Th1 stimuli [bacteria, protozoa and viruses] and the induction of a Th1 type of response is well elucidated, the way DCs elicit a Th2 response is still unclear. Under the influence of Th1 stimuli, DCs become fully matured, with highly up-regulated MHC II and co-stimulatory molecules and elevated production of IL-12 [7]. However, DCs exposed to helminth antigens acquire an activated phenotype that is subtle compared to the one obtained with Th1 stimuli [8]. The observation that helminth antigens applied to DCs culture at the same time as the stimulation with bacterial lipopolysacharide (LPS) impair the development of Th1 response indicates that helminth-stimulated DCs are in fact activated for the induction of the Th2 response [9]. Unlike antigens derived from *Schistosoma mansoni* [10], *Acanthocheilonema vitae* [11] and *Nippostrongylus brasiliensis* [12] that can induce a Th2 type of response via DCs, antigens derived from *Heligmosomoides polygyrus bakeri* [13] under similar conditions promote regulatory response that can suppress both Th2 and Th1 response. When considering data obtained from different helminth model systems, several scenarios are possible: the initiation of a mixed Th1/Th2 response along with the regulatory arm of the response, the predominance of a Th2 response and the subsequent initiation of the regulatory response that suppresses Th1 or the promotion of the regulatory arm of the immune response that is dominant and that suppresses both Th1 and Th2 responses. Mechanisms underlying this phenomenon remain to be full mapped. The focus of this review is to document the way that the helminth *T. spiralis* polarizes the immune response and its ability to control Th1-related autoimmune pathology. The potential of this parasite to modulate function of DCs as key players in the initiation and polarization of adaptive immune response will be discussed. The ability of *Trichinella*-stimulated DCs to shift the immune response toward Th2 and the regulatory mode and to introduce an altered immunological state that would provide a lower susceptibility to a particular autoimmune disease—experimental autoimmune encephalomyelitis (EAE)—will be addressed.

## *T. spiralis*—Biology of infection and immune response polarization

*Trichinella spiralis* is a helminth that establishes a long-lasting infection in skeletal muscles of the host. Depending of the host's longevity, the parasite could successfully persist until the end of life (in rodents) and over several months to years following infection (in higher species or humans). Unlike some other intracellular parasites, *T. spiralis* occupies the host's muscle cells without killing them, which makes it one of the most successful parasitic symbiotes. The infection initially occurs after ingestion of raw or undercooked infected meat. The infective larvae (L1) released after meat digestion undergo a maturation process into adults. The adult reproductive stage positions itself intracellularly in the mucosa of the small intestine. Compared to the muscle phase of infection, the intestinal one is quite brief, and during this phase, adult females release the newborn larvae (NBL). NBL disseminate through the host by the circulation [blood and lymph vessels] until they finally come to their target tissue—skeletal muscles. NBL that invade striated muscle cells develop into infective L1 muscle larvae, a process taking about 20 days.

During the process of the parasite life stage transformation, surface and excretory–secretory products from the parasite are involved in acute inflammatory responses while later on only excretory–secretory products of parasite (ES) keep molecular cross-talking with the host. ES products act in multiple ways—they reduce inflammation provoked by the invasion of muscle cells, modulate the immune response in a way to be protective both for parasite and for the host and at the same time they participate in orchestrating the biological process of host's cell remodeling. The latter will result in the formation of a nurse cell—an immuno-privileged place for *T. spiralis* muscle larvae [14]. Namely, in order to survive in a host environment, *T. spiralis* makes a new architecture in the infected muscles. The parasite constructs a unique place for living and its niche consists of capsule which is composed of a collagenous wall and cellular components. The wall provides some protection to the parasite while the cellular component, named the "nurse cell" due to its function, takes care of its metabolism. Both the wall and nurse cell are of host, not parasite origin.

The process of nurse cell formation is complex and includes infected muscle cell response (de-differentiation with a complete loss of myofibrillar organization, cell cycle re-entry and arrest at G2/M) and satellite cell responses (cells undergo processes of activation, proliferation, re-differentiation and fuse to each other or with the infected muscle cell) [15]. Since the satellite cell is a progenitor cell located within the capsule wall, a new cell can be continuously supplied from the myoblast, even if the present nurse cell dies. This explains why the nurse cell looks intact and active for years in spite of intracellular parasitism. In this way, parasites utilize muscle cell repair mechanisms of the host to establish parasitism [15].

ES products exert a profound effect on the host immune system. After completion of nurse cell formation, ES products remain acting as antigens [provoking long-lasting specific immune response] and/or immunomodulators (influencing a response toward irrelevant antigens). In a number of parasites, as well as *T. spiralis* [16], ES products have been characterized as cistatins, serpins, glycans,

mucins, lectins or cytokine homologs that could influence antigen processing, presentation and subsequent T-cell polarization.

For the establishment of *T. spiralis* infection, modulation of host's immune response is necessary to avoid their own destruction, but it must be carefully balanced in order to omit compromising host survival [17]. Infection with *T. spiralis* is characterized by the induction of a Th1 type of response in the beginning of the intestinal phase. A Th2 type of response, protective and responsible for the parasite expulsion, becomes dominant at the time point when NBL-extensive dissemination takes place [18]. *T. spiralis* rapidly develops to maturity and reproduces before the Th2-mediated expulsion eliminates all adult forms from the gut. Therefore, during the intestinal phase, the immune response is mixed, Th1/Th2, with the initial predominance of the Th1 type of response and the subsequent domination of Th2 [19]. The existence of Treg cells was observed during the muscle phase of infection in the vicinity of invaded tissue [14]. It is likely that chronic stimulation of the immune system by helminth infection can activate regulatory network elements as guardians of homeostasis.

The relative proportion between regulatory and effectors cells can be changed depending on the course of infection [20, 21]. It has been shown that *T. spiralis* possesses a capacity to retune the immune cell repertoire, which further explains why helminths are considered as masters of immunoregulation, acting as a moderator of the host response not only to itself but also to third party antigens.

## Impact of *T. spiralis* antigens on DCs maturation and subsequent T-cell polarization

DCs play an important role in shaping the immune response to parasites [22]. DCs exposed to Th2 antigens derived from helminths such as *S. mansoni*-soluble egg antigen [23] and *N. brasiliensis* excretory–secretory product [12] do not express the conventional sequence of events characteristic for stimulation with Th1 antigens. Although different helminth antigens induce distinct DCs phenotype, the common feature is that DCs acquire an incompletely mature status [24–26].

Since *T. spiralis* completes its life cycle in one host, it is likely that antigens from all three life stages have their own impact on the development and maintaining of the host immune response. Our work has focused on the influence of antigens from different life stages of *T. spiralis* (adult, new born larvae-NBL and muscle larvae-L1) on DC maturation in rat [Dark Agouti rats] and mouse (C57BL/6 mice) model systems. Although maturation profiles were slightly different in both model systems, parasite antigens-stimulated DCs exhibited incomplete maturation [27, 28]. None of the applied parasite antigens showed any effect on the up-regulation of MHC II on rat DCs, but they provoked up-regulation of CD86 and ICAM 1 [27]. Results obtained in mouse DCs showed moderate up-regulation of MHC II, significant up-regulation of CD80 and CD86 and non-significant up-regulation of OX40L and ICAM 1 [28]. In contrast to our results, Leech and Grencis [29] found that *T. spiralis* muscle larvae crude antigens caused complete maturation of mouse DCs, while Langelaar and colleagues [30] observed that *T. spiralis* ES products had no effect on the expression of MHC II and co-stimulatory molecules on mouse DCs. However, our results are consistent with findings of other authors who investigated the impact of various parasitic antigens on DCs phenotype [10, 31–37] and showed that they induced moderately elevated expression of some, but not all DC surface markers.

In spite of the fact that DCs acquire an incompletely mature phenotype under the influence of different parasites including *T. spiralis*, their active status is reflected by the capacity to present antigens to T cells and to produce cytokines. Cytokines produced by DCs are important signals for the initiation and regulation of the immune response to pathogens. IL-12, as a pro-inflammatory cytokine, has an important role in polarization toward a Th1-type response [26]. Besides its role in promoting the regulatory arm of the immune response, the anti-inflammatory cytokine IL-10 may be involved in the polarization of the immune response toward Th2 [38]. IL-10 also has negative feedback regulation—this cytokine produced by DCs can suppress the expression of cell surface markers, proliferation of DCs and antigen presentation [39]. Our unpublished results obtained using IL-10 knock-out mice showed that the lack of IL-10 had no effect on the DC phenotype under the influence of *T. spiralis* antigens compared to wild-type mice, although the functional characteristics of these DCs were quite different. For example, their capacity to present antigens and provoke cytokine production was diminished. Distinct and mutually opposite effects of IL-10 and IL-12p70 on CD4+ T-cell polarization indicate that their production by DCs is reciprocally regulated [40, 41], in other words increased production of IL-10 can inhibit IL-12 secretion. We have shown that pulsing rat DCs with *T. spiralis* antigens induces increased production of the anti-inflammatory cytokine IL-10 and decreased production of the pro-inflammatory cytokine IL-12p70 [27], while the same treatment in mouse DCs induces elevated production of both pro- and anti-inflammatory cytokines [28]. However, a mixed Th1/Th2 type of response rose as a consequence in both cases. The result in mouse DCs is inconsistent with observations that claimed suppression of IL-12p70

synthesis by the elevated IL-10 production [23, 42]. Nevertheless, there are studies on pathogens which induce a Th2 or a mixed Th1/Th2 response that show an increase in the production of both pro- and anti-inflammatory cytokines by DCs [43–45].

The fact that parasites are multi-cellular organisms whose life cycles have specific features may be the explanation for quite different immune responses that they initiate compared to other microbial pathogens and to each other (all depending on genetic susceptibility/or background). The innate immune system not only recognizes parasitic antigens and initiates an adaptive Th2 response, but provides maintenance of Th2 immunity throughout infection [1, 46, 47]. As mentioned earlier, upon encountering parasitic antigens, DCs acquire a semi-matured status but are still capable of inducing T-cell polarization. DCs stimulated with ES-62 antigen from *A. vitae* express an incompletely matured phenotype and induce increased production of IL-4 and decreased production of IFN-$\gamma$ by T cells [11]. On the other hand, pulsing DCs with soluble egg antigen from *S. mansoni*, although inducing an incompletely mature DCs phenotype, results in the elevated production of both IL-4 and IFN-$\gamma$ by T cells [48]. Our experiments showed that, following incubation with DCs primed with *T. spiralis* antigens from different life stages, naïve CD4+ T cells exhibited increased production of IL-4, IL-10 and TGF-$\beta$ and decreased production of IFN-$\gamma$, in rats in vitro (unpublished results). A different profile of cytokine production was obtained in a mouse model. Stimulated DCs induced elevated production of both Th2 (IL-4, IL-9, Il-13 and IL-10) and Th1 (IFN-$\gamma$) cytokines in naïve T cells [28] in vitro. One part of the study was focused on the impact of *T. spiralis* ES L1 antigens on the polarization of immune response via DCs.

ES L1 products are particularly interesting for research as the parasite, during the muscle phase of the infection, achieves communication with the host organism via these products. This means that the host immune system is submitted to the continuous stimulation by ES L1 antigens which, by interacting with immuno-competent cells, modulate the host immune response.

In vitro analyses showed that DCs pulsed with *T. spiralis* ES L1 antigens induce a] a mixed Th1/Th2 cytokine profile after co-cultivation with infection-sensitized T cells [49] similar to the profile found during chronic *T. spiralis* infection [50] and b] a strong shift toward a Th2 type of response after co-cultivation with naïve T cells [49]. In vivo T-cell priming by intraperitoneal application of ES L1-pulsed DCs generated a mixed Th1/Th2 response with the predominance of the Th2 component and the activation of the regulatory arm of the immune response which corresponds to the effect of chronic *T. spiralis* infection [49].

## The role of CD4+CD25+Foxp3+ regulatory T cells in the immune response triggered by *T. spiralis* antigens via DCs

Pathogens and/or tissue damage are the initial signals for DC activation. Consequently DCs induce and regulate effector T-cell responses. However, recent results indicate that DCs are crucial to ensure immunological peace.

The role of DCs is not only to present foreign antigens but also self-antigens in a fashion that promotes tolerance, at least in part through the control of Tregs. Tregs are specialized T cells that exert their immuno-suppressive function through a variety of mechanisms affecting both DCs and effector cells [51].

Helminth parasites activate regulatory pathways of the immune response and consequently control the intensity of both Th1- and Th2-mediated responses [8, 52]. Since Treg cells can actively suppress the immune response, they have a very important role in the maintenance of immune homeostasis [13, 53]. An elevation in the Treg population in an infected host can be explained as a possible evasion mechanism developed by helmiths during the evolution or, on the other hand, it can be the result of a homeostatic mechanism of the immune system that minimizes the pathology and results in prolonged parasite survival.

However, whether and how helminth-derived products act on DCs to induce Tregs has not been determined. One proposed modality by which parasites could modify DCs is that their products prompt DCs to produce anti-inflammatory cytokines, including IL-10 and TGF-$\beta$ while the other is that factors released by helminths mimic immunosuppressive molecules such as TGF-$\beta$, which promote semi-maturation of DCs, thereby creating a permissive microenvironment [51].

Like many other helminths [13], *T. spiralis* provokes an increased number of Foxp3+ Treg cells at the site of muscle inflammation [14]. The role of muscle larvae ES L1 antigen in this process is not clear but it cannot be ruled out. However, although greatly elevated levels of IL-10 and TGF-$\beta$ were produced by T cells co-cultivated with ES L1-pulsed DCs, indicating the potential of ES L1 antigens to induce the regulatory response, the percentage of CD4+CD25+Foxp3+ Treg cells was not increased in the effector cells population obtained in vitro [28, 49]. On the other hand, in vivo priming of the T-cell response by adoptive transfer of ES L1-stimulated DCs into naïve recipients resulted in the significant expansion of this Treg cell population, which corresponds to the immune status observed in live infection [49]. One of the possible explanations for the difference between the results obtained in vitro and in vivo, besides the fact that conditions present in a live organism could not be reproduced in vitro, could be the existence of different Treg subsets, for example, ES

L1-primed DCs in vitro might induce a CD4+CD25+ Treg population that does not express Foxp3 but produces IL-10 and TGF-$\beta$. A similar effect was observed with DCs pulsed with ES antigen from *H. polygyrus* [24]. Data obtained with *T. spiralis* antigens from different life stages showed that DCs stimulated with these antigen preparations can induce neither the expansion of natural Treg cells present in the population of naïve T cells nor de novo expression of Foxp3 in T cells [28].

Unlike these results, Grainger and colleagues [13] showed that ES antigens from *H. polygyrus* and *Teladorsagia circumcincta* have a TGF-$\beta$ mimicking effect and can induce de novo generation of Foxp3+ Treg cells. Since this effect was not observed with ES antigens from *Haemonchus contortus* and *N. brasiliensis*, it can be presumed that the release of TGF-$\beta$ ligands is not a general feature of all helminth parasites. *T. spiralis* has a different life cycle compared to *H. polygyrus*, and differences between life cycles of the parasites indicate distinct benefit from Treg cells for each of them. *H. polygyrus* adults benefit from Treg induction since these worms stay in the intestine of the host for quite a long time and, during chronic infection, a suppressed immune response provides an increase in intestinal egg production and minimizes host pathology. In contrast, during the intestinal phase of the infection, *T. spiralis* benefits more from the strong immune response that controls the magnitude of newborn larvae release and prevents massive muscle invasion and potential host death. The beneficial role of Treg cells for the survival of the parasite during the muscle stage of infection, when newborn larvae are established in the muscle tissue, was indicated by Beiting and co-authors [14] who detected Foxp3+ Treg cells in the infected muscle. Providing homeostasis in the host organism through mobilization of regulatory immune cells, this parasite enables host survival and therefore establishes its own longevity.

Data about the influence of *T. spiralis* antigens on the polarization of immune response indicate that *T. spiralis* can be a potent immunomodulator and that it has a capacity to control Th1-mediated autoimmune diseases.

## *T. spiralis* in modulation of autoimmune disease

The incidence of autoimmune diseases has increased significantly over the past century in industrialized countries. According to the "hygiene hypothesis," which postulates that exposure to the infectious agents decreases the subsequent risk of autoimmune or atopic diseases, the reason for the elevated level of these diseases is at least partly attributable to immuno-dysregulation resulting from lack of exposure to microorganisms that have evolved an essential role in the establishment of the immune system [54, 55].

Few mechanisms have been proposed for the explanation of the protective effect of the infections on immune disorders. The main two are competition and immunoregulation [56]. The first mechanism considered the development of strong immune response against antigens of the infectious agents that could inhibit responses to "weak" antigens such as auto-antigens and allergens [54]. Another mechanism refers to the role of regulatory T cells, capable of suppressing the immune response not only toward an infectious agent but also to bystander antigens [56]. The suppressive effect of IL-10 and TGF-$\beta$ produced by regulatory T cells after stimulation with infectious agent can be extended to immune responses engaged in autoimmune and allergic diseases.

Helminth parasites, as inducers of predominantly Th2 and regulatory responses, have been shown to influence the outcome of autoimmune and allergic diseases [57–61]. During infection, helminths demonstrate a range of immuno-modulatory effects which provide the down-modulation of the response to bystander antigens and the prevention of an excessive inflammatory response [62]. A number of experiments carried out on animal models of human autoimmune diseases revealed that helminth infections or application of helminth products can prevent the onset or ameliorate autoimmune diseases. Different life stages and/or antigens of *S. mansoni* can significantly inhibit or delay the development of autoimmune Type 1 diabetes [T1D] [57, 63], EAE [64, 65] and experimental colitis [66]. *Hymenolepis diminuta*, also a Th2 polarizing agent, can tame the symptoms of experimental colitis [67]. ES-62 antigen derived from *A. vitae* was shown to be a potent modulator of collagen-induced arthritis [68]. Summers and colleagues [69, 70] observed that the induction of Th2 immune response by intestinal helminth *Trichuris suis* can down-modulate inflammatory bowel disease [IBD], especially Crohn's disease, as a chronic Th1 intestinal inflammatory process. Colonization with *H. polygyrus* can suppress the established experimental colitis in mice and transfer of mesenteric lymph node T cells from animals harboring this parasite into colitic recipients can also inhibit colitis [71]. As mentioned earlier, our investigation focused on the parasitic nematode *T. spiralis* and its impact on the host immune system and immune response to bystander antigens. Other authors have shown that *T. spiralis* infection reduces the severity of colitis [Th1-mediated disease] in mice [72]. Besides the direct effect of the infection, this disease can be modulated by rectal submucosal administration of *T. spiralis* crude muscle larvae antigen [73]. *T. spiralis* infection also alters the immune response responsible for the progression of autoimmune diabetes [74]. Although the impact of *T. spiralis* on the

modulation of host's immune system is recognized, mechanisms involved in the control of the response to unrelated antigens are still not completely defined.

Investigations conducted in our laboratory are focused on the influence of *T. spiralis* on the modulation of EAE—the experimental model of multiple sclerosis [MS] as the chronic inflammatory, demyelinating and neurodegenerative disorder of CNS. The obtained results showed that established *T. spiralis* infection successfully ameliorates EAE in DA rats in a dose-dependent manner [75]. Infection with *T. spiralis* L1 muscle larvae reduced the severity of EAE as judged by lower maximal clinical score, cumulative index, duration of illness and the number of spinal cord mononuclear cell infiltrates in infected animals compared to the uninfected EAE-induced group. The events that take place at the T-cell level under the influence of *T. spiralis* are presented in Fig. 1. The infection was accompanied by increased production of IL-4 and IL-10, which influenced the reduction in IFN-$\gamma$ and IL-17 characteristic for EAE immune response. The decreased production of these cytokines coincided with alleviation of the disease [50]. Since IFN-$\gamma$ and IL-17 are considered as crucial cytokines for the initiation and progression of EAE, it is possible that the amelioration of EAE in our model in rats could be the consequence of the decreased capacity of their lymph node cells to produce these two cytokines upon specific antigen stimulation [50]. The enhanced production of IL-4 correlating with the helminth-induced Th2 suppression of autoimmune disease which was observed in our model system of joint *T. spiralis* infection and EAE was already described in case of T1D modulation by *T. spiralis* infection [74] and in the model where *S. mansoni* influenced the course of EAE [65]. As for the role of IL-10 in the modulation of EAE, Bettelli and co-authors [76] have shown that it is a key effector regulatory cytokine in this disease. It has also been suggested that IL-10 is responsible for the modulation of autoimmune disease observed during infection with *S. mansoni* [57] and *H. polygurus* [77].

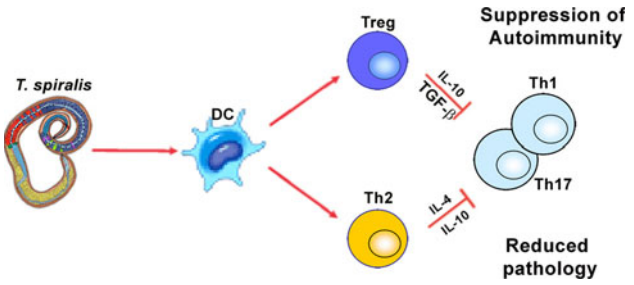


**Fig. 1** *T. spiralis*—DC dialog controls autoimmune disease fate. Infection generates a mixed but predominantly a Th2 polarized immune response with strong activation of regulatory mechanisms. Activating signals are indicated as *arrows* and inhibitory interactions are indicated as *bars*

IL-10 can be a product of Th2 cells but it is also considered a key mediator of regulatory T cells, among others, CD4+ CD25+Foxp3+ T cells, as very important regulators of the immune response [78]. These cells have a role in the beneficial outcome of EAE [79]. Our study showed that transfer of T-cell-enriched population of cells, isolated from *T. spiralis*-infected animals, into uninfected ones before EAE induction, provided a protective effect on the recipients [49]. Transferred cells produced high levels of IL-10 and contained an increased proportion of CD4+ CD25+Foxp3+ T cells, which could affect the course of the disease. These observations support the opinion that regulatory cells participate in modulation of EAE. Our findings that a mixed but predominantly Th2 type of immune response as well as the engagement of regulatory arm of immune response, both induced by chronic *T. spiralis* infection, are involved in the suppression of EAE, contribute to the understanding of pathways that can be used for manipulation of the immune response and provide an insight into a promising new tool for treatment of autoimmune diseases.

## Future perspectives

The results of our studies so far have shown that chronic infection with *T. spiralis* potently alters the course of EAE and that DCs stimulated with metabolic products of *T. spiralis* muscle larvae [ES L1] have a strong potential to provoke the modulation of immune response equivalent to the one observed during chronic infection. Further studies will be focused on the role of ES L1 antigens in conditioning the host immune system and consequently modulation of EAE. To date, we cannot tell which component[s] of this complex mixture of soluble molecules is/are responsible for eliciting the hereby described polarization of immune response that benefits the host. There are only a few DC-activating ligands of helminth origin that have been identified so far [80]. Defining particular molecules in the composition of ES L1 antigens and pattern recognition receptors [such as toll-like receptors and C-type lectins] on the DC surface that are involved in their recognition and binding would provide valuable information on mechanisms involved in mounting and modulating the immune response by this particular helminth. Our previous studies have shown that the mannose receptor, a C-type lectin receptor expressed on the surface of antigen-presenting cells, recognizes and binds components of ES L1 antigens [81]. Of great importance would be the application of these results in the development of new therapeutic approaches for treatment of different autoimmune and allergic diseases.

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