Chapter

Regulation of the Immune Response in Cysticercosis: Lessons from an Old Acquainted Infection

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Abstract

In the last decades, we have learned some critical lessons about the relationship between the human body and its interaction with many infectious diseases, where regularly, the immune system has a major role in protection. We learned to differentiate between the immune response occurring in either an intracellular or extracellular parasitic infection, between innate and adaptive immune response, between either inflammatory or anti-inflammatory responses, and finally, we learned to recognize very particular mechanisms, such as the inability of the immune system to respond during very particular scenarios, such as the inability of T cells to both proliferate and produce cytokines even after their exposure to mitogens or specific-antigens. Along with our increase in the knowledge in immunology, we figured out that immunoregulation and immunosuppression are processes used by many parasites to reduce the capacity of the immune system to eliminate them, and to persist in the host favoring their transmission and also to complete their life cycles. Immunoregulation involves several mechanisms such as anergy, apoptosis, induction of both suppressive cytokines and membrane-bound molecules, as well as specialized cell populations of the immune system like regulatory T cells, Alternative Activated Macrophages, or Myeloid-derived Suppressor Cells, that together modify the outcome of the immune response. In this chapter we will review the general differences between the different types of immunoregulation, the kind of cellular populations of the immune system used by the helminths *Taenia solium* and *Taenia crassiceps* to induce immunoregulation and immunosuppression and also, the mechanisms used by these parasites such as mimicking molecules of the immune system to replace directly these mechanisms. Understanding and deciphering all these regulatory mechanisms could be useful to develop new tools to control this infection.

Keywords: Cysticercosis, Immunoregulation, Immunosuppression, *Taenia solium*, *Taenia crassiceps*, Regulatory T cells (Treg cells), Alternative Activated Macrophages (AAM), Myeloid-derived Suppressor Cells (MDSC)

1. Introduction

Taeniasis and cysticercosis, both neglected diseases, are two kinds of infections caused by the same parasite, *Taenia solium*. Taeniasis is the intestinal infection caused by the adult form of the tapeworm *T. solium*, while cysticercosis is the tissue

infection caused by the larval stage, cyst or cysticercus of *T. solium* [1]. Whereas taeniasis only affects the human and it is restricted to the small intestine, cysticercosis affect two hosts, the human and the swine, besides this stage of the parasite can allocate at different anatomical sites including the brain, causing neurocysticercosis (NCC). The vast majority of medical findings by natural infection has been made during cysticercosis, given its clinical relevance when the parasite encroaches on the central nervous system including the brain and the eye [2]. In the past, NCC represented a major health problem mainly in developing countries [3], being highly prevalent in the general registration of autopsies [3]. The only way to find samples for the study of NCC, were in patients diagnosed by neuroimaging: magnetic resonance and computed tomography, and also by determination of specific antigens by ELISA and western blot from blood and cerebrospinal fluid samples [4, 5].

Because taeniasis remains asymptomatic, there are no symptoms directly associated with the disease, only general symptoms like abdominal bloating and abdominal pain [1, 5]. For this reason, a model to understand the immunological interactions between the host and the parasite and also, to understand the evolutionary capacity of *Taenia* to survive in the host was necessary. Animal models like hamsters, gerbils and chinchillas, were developed in the past to have a better understanding of the immunology in this field [6], but a limited information about it was published, having a focus in the inflammatory response in the intestinal mucosa of chinchillas receiving an immunosuppressant treatment with methyl-prednisolone [7]. Because of the nature to develop taeniasis and the necessity to have a better understanding of the immune response against *T. solium*, it was necessary to know the immunology and the mechanism of protection used by a "close familiar" to this parasite: *Taenia crassiceps*.

2. General aspects of the immune response during NCC and Taeniasis

T. crassiceps is a tapeworm that generates natural infections in some definitive canine hosts like dogs, red foxes, and wolves in the northern hemisphere of the world. It also has an extensive reproduction rate in the pleural and peritoneal cavities of their intermediate host like wild rodents [8]. For a better understanding of their life cycle, go to the reference [8]. *T. crassiceps* ORF strain was obtained by Dr. Reino Freeman in 1952. This strain has a deficient capacity to develop the scolex, therefore, cannot colonize the intestines of its definitive hosts [9]. Most of the research about the immunology of *T. crassiceps* has been developed with the ORF strain, injecting either 10 or 20 metacestodes of this parasite in the peritoneal cavity of syngenic female BALB/c mice [10, 11].

The immune response against *T. crassiceps* has been investigated in an extensive way. During the acute infection by this helminth a strong Th1 immune response characterized by high levels of IL-2 and IFN-γ is induced and has been associated with host protection, but as the infection becomes chronic, levels of both IL-2 and IFN-γ decrease as well as IL-12 produced by macrophages [12]. These reduced levels of Th1-type cytokines correlate with increased levels of IL-4 at chronic infection stages, suggesting a switch between inflammatory response in the acute infection to an anti-inflammatory response in chronic infection, favoring the adequate microenvironment for both, parasite development and their persistence in the host (**Figure 1**). Susceptibility to *T. crassiceps* infection is STAT6-mediated, characterized by strong IgG1, IgE, IL-4 and IL-13 production [13]. Therefore, unlike the case of the vast majority of helminth parasitic infections, protection during experimental cysticercosis is mediated by Th1-type immune responses, while parasite

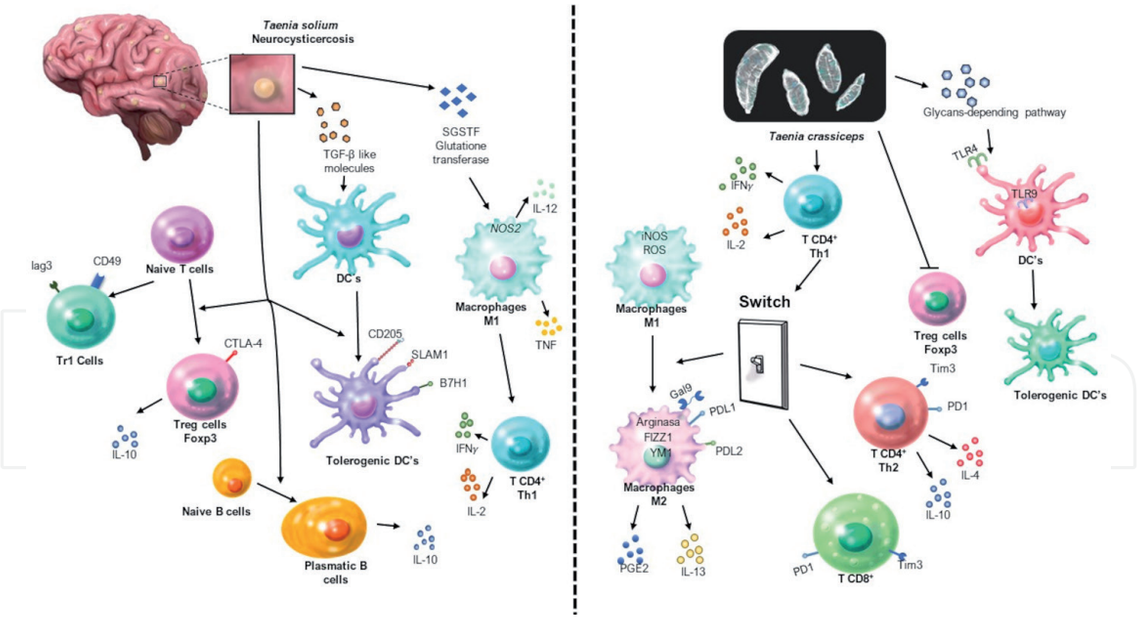

Figure 1.
Hypothetical/integrative model of immune regulation triggered by T. solium *and* T. crassiceps *infection and their released products on different types of cells. Products of both parasites can be recognized by innate cells through several pattern recognition receptors, including TLRs, CD205, among others, and induce tolerogenic DCs or modulate the activation of macrophages by inducing the expression of different inhibitory molecules in its membrane such as PDL1, PDL2, Galectin-9 (Gal-9) as well as soluble inhibitory factors such as PGE2, and IL-13, while favors the expression of genes associated with M2 polarization, such as arginase, FIZZ1 and YM1, leading to the inhibition of T cell proliferation. In contrast, the inflammatory properties of both DCs and macrophages are inhibited by these parasite molecules and the production of TNF-α, IL-12, iNOS and ROS are dramatically reduced. Additionally, TsES and TcES inhibit T cell responses through the induction of T regulatory cells as well as B regulatory cells which both are an important source of IL-10. These infections together with their secreted products can also induce a Th2-biased response and a reduced CD8 response.*

establishment is associated with Th2-type mediated immune responses [14]. One of the most relevant findings observed during experimental cysticercosis, was the reduced proliferative capacity of T lymphocytes obtained from infected mice to either nonspecific or specific antigens during chronic infection, suggesting the strong immunosuppressive capacity of *T. crassiceps* [12, 15].

On the other hand, evidence from subcutaneous, visceral, muscle, lung and cardiac tissue infected with *T. solium* in patients suggest that, out of the nervous central system (NCS), this infection causes no symptoms, reducing the possibility to understand and describe the occurring steps during early immune responses [1, 16]. Once inside of NCS, *T. solium* induces different levels of damage depending on the developing site. If the cysticercus is located in the brain parenchyma, it survives during different periods of time, from months to years, but eventually evolves in resolution [1, 2]. However, if the infection is located outside of the parenchyma's (subarachnoid) brain, it is associated with edema, inflammation and increased mortality rates around 20% in patients without a correct treatment [2, 17]. Besides its location on the NCS, also exists a relationship between the intensity of the symptomatology and the number and size of the larvae causing the infection. In fact, it was recently hypothesized that the gut-brain-axis has a major role in the manifestation of symptoms during NCC, mainly in patients with mental illness, depression and epilepsy [18], highlighting the importance for the microbiota in this field. Also, it was suggested that these interactions for the gut-brain-axis are dependent on galectin-7 (Gal-7) expression in brain endothelial cells during human *T. solium* cysticercosis [19]. Thus, the main actors for the development of cysticercosis are the host immune response, the microenvironment for the parasite development either the gut or NCS, the microbiota, and the host health status.

The immune response described in the *T. solium* rodent model has been helpful and relevant to understand the immunobiology during taeniasis and cysticercosis, being a main feature the suppression of the immune response. Next, we will try to describe both the immunoregulatory mechanisms and the direct effects of molecules secreted by *Taenia* parasites to induce immunoregulation.

3. Immunoregulation during cysticercosis

An inflammatory response during the initial infection process is necessary to induce immunity, to reduce parasite load and finally to have protection in cysticercosis. However, since basic science started to clarify the role of the immune response during cysticercosis, some special discoveries have been observed only in this helminth infection, suggesting a process of transformation from inflammation to an anti-inflammatory response, tipping the balance towards the parasite survival. Is necessary to pay attention in the fact that, during some helminth infections, the Th1 to Th2 switch is caused to keep the balance between immunity in the host with tissue repairing, and for the survival of the parasite o for its expulsion from the host, example of that are *Schistosoma mansoni*, *Nippostrongylus brasiliensis and Heligmosomoides polygyrus* infections [20, 21]. However, this Th1 to Th2 switching in cysticercosis appears to absolutely favor parasite survival. Also, this switch process is an initial step to induce an immunosuppressive process orchestrated by the parasite, or also, as a possibility, the microenvironment caused by the infection has a strong effect culminating in the incapacity to the immune response to react against the infection (**Figure 1**). Some evidence suggests that immunosuppression may be caused by T-cells, myeloid-derived cells or directly by parasite molecules like *Taenia crassiceps* excreted/secreted antigens (TcES) or *Taenia solium* excreted/secreted antigens (TsES). Also, it was suggested that asymptomatic NCC is caused by a strong period of immunosuppression by live *T. solium* parasites, because brain inflammation is not observed during the development of the infection and while the parasite remains alive [22].

3.1 Immunoregulation mediated by T-cells

During some intracellular parasitic infections, like toxoplasmosis, trypanosomiasis and leishmaniasis, an incapacity of T lymphocytes to proliferate in response to antigen-specific or polyclonal mitogens has been described, mainly during acute infection [23–26]. Although the general observation is that the process of immunosuppression starts at the beginning of the chronic *T. crassiceps* infection, it was shown that during acute intraperitoneal (ip) infection in mice, there is a significant decreased percentage of T-CD4$^+$, T-CD8$^+$ cells and B-CD19$^+$ cells at the infection site, starting at 3 days post infection (dpi) and culminating at 16 dpi [27]. These results correlate with increased levels of apoptosis, mainly in eosinophils. Perhaps, *T. crassiceps* begins to develop its suppressive microenvironment since the beginning of the development of the infection, such as reported for protozoan infections. During *T. crassiceps* chronic infection, a reduced proliferative capacity of T cells was described [12], especially in CD8-cytotoxic T cells [28]. Recent observations by our laboratory described that, this reduced capacity to induce cytotoxicity by CD8$^+$ cells is caused by increased expression of Tim-3 and PD1 molecules in an IL4-Rα, STAT-1 and IFN-γ independent-pathway (**Figure 1**, Olguin JE et al., unpublished data). Interestingly, both expression of Tim-3 and PD1 is increased in adaptive regulatory CD4$^+$Foxp3$^-$ T cells but not in natural Treg cells. In fact, during the chronic phase of experimental cysticercosis, we observed reduced percentages of Treg

cells, which is contrasting with some published data. For example, a study reports that cocultured cysticerci of *T. solium* with human monocyte-derived DCs, induces Foxp3 expression in $CD4^+$ naïve T cells *in vitro* and also, increased percentage of suppressive-related molecules (**Figure 1**) [29]. The same research group showed a descriptive study in patients with NCC, observing an increased expression of natural and adaptive Treg cells in blood [30], but the authors did not show, whether these induced and natural Treg cells had the capacity to suppress another population of immune cells, for example either T-CD8 or activated CD4 T cells. Maybe, the differences observed between NCC and experimental cysticercosis in Treg cells are explained by the site where the sample was obtained (NCS and blood in *T. solium*, peritoneum in *T. crassiceps*), and by the nature of the infection. However, it is clear that, whatever scenario is observed, T cell-mediated regulation is a critical mechanism involved during the development of experimental or natural cysticercosis. Also, observations made by our group in *T. crassiceps* infection are different to those done in other helminth infections. A recent study of hookworms like *Ancylostoma duodenale*, *Necator americanus*, *Ascaris lumbricoides* and others, showed by mass cytometry a clear profile of Th2 cells, favoring increased expression of CTLA-4 in Treg cells, and B cells producing IL-10 in infected Europeans and Indonesians patients [31]. Maybe, it is necessary to describe more specific surface markers to define the population of suppressive and/or regulatory T cells. For example, it has been described as a highly suppressive T regulatory Type 1 population (Tr1) during a helminth scenario by the co-expression of CD49 and LAG-3 [32]. Tr1 cells are different from natural regulatory (Treg) cells because they do not express constitutively the Foxp3 transcription factor [33].

As well as in *T. crassiceps* infection, during NCC a period of immunosuppression has been reported. One study extracting polymorphonuclear (PMN) cells from 11 patients diagnosed with NCC, showed a clear immunosuppression in response to TsES antigens from the scolex of *T. solium*, also NCC patients with calcified cysts displayed increased immunosuppression [34]. The same study showed the suppressor capacity of TsES, completely inhibiting the proliferative response to mitogens like phytohaemagglutinin (PHA) and concanavalin A (ConA) [34]. These results are different to those published by a different research group, under the same conditions, where NCC patients without treatment did not show differences in the percentages of $CD3^+$, $CD4^+$ and $CD8^+$ T cell populations. Moreover, blood cells from these NCC patients showed the same proliferative capacity to ConA or crude *T. solium* antigens compared with controls, and finally also PMN cells produced IL-2 [4]. Is not clear what is the correct scenario, maybe another process or data were not considered in the clinical history between these both studies, like age of the patient, sex, or any oncological or immunosuppressive constitutive status. In fact, more recently published data showed that if analyzed groups of patients with NCC are divided by the local site of the infection in either parenchymal (infection is resolved in general) or subarachnoid (increased symptomatology and pathology), the group of patients with subarachnoid infection has an increased immunoregulatory microenvironment characterized by IL-10, TGF-β and expanded Treg cell frequencies *ex-vivo* [35].

3.2 Immune-regulatory myeloid-derived mechanisms

The generation of an immune-regulatory environment could have an effect not exclusively in T cells, but in all immune cells, including all myeloid-derived lineages such as macrophages, dendritic cells (DCs) and PMNs. Thus, myeloid cells are key players in the immune response against cysticercosis. In fact, there is evidence suggesting an increased profile of alternative activated macrophages or

M2 macrophages involved in parasite expulsion and tissue repair during helminth infections, which induce protection to the host [36]. However, in cysticercosis, the scenario appears to be different.

During *T. crassiceps* infection it was suggested that recruited $CD11b^{+}Gr1^{+}$ myeloid-derived suppressor cells (MDSCs) impaired the T cell proliferation by secretion of high amounts of nitric oxide (NO) at early stages of an intraperitoneal infection. This classic inflammatory activation is switched at chronic stages, where $CD11b^{+}Gr1^{+}$ cells express arginase, YM-1 and FIZZ1 genes, associated with an M2 phenotype (**Figure 1**). This immunosuppressive microenvironment favors IL-4 and IL-13 production, expanding the MDSCs population and also, inducing lipid mediators' activation like 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid, associated with the immunosuppression of T cell proliferation [37]. Also, alternative-activated macrophages (AAMs or M2) from chronic *T. crassiceps* infection have the ability to produce high levels of IL-6 and Prostaglandin E2 (see below), reducing the proliferative capacity of $CD4^{+}$ T cells in a STAT-6 dependent-pathway (**Figure 1**) [11], suggesting that AAMs are necessaries to induce the permissive microenvironment for the colonization of *T. crassiceps* infection. In fact, it was demonstrated that an early in vivo depletion of AAMs by using clodronate liposomes, increases the resistance against *T. crassiceps* [38], making stronger the hypothesis that experimental cysticercosis has an AAMs-dependence for a successful infection. Later, it was shown that these AAMs induce anergy on $CD4^{+}$ T cells during *T. crassiceps* infection, and that such an event depends on PDL1 and PDL2 expression in the surface membrane of AAMs [39].

On the other hand, monocyte-derived DCs co-cultured with CD4 naïve cells in presence of *T. solium* cysticerci promotes both, Treg and DCs cells differentiation towards a tolerogenic profile featured by a higher expression of Signaling Lymphocytic Activation Molecule 1 (SLAM1), B7-H1 and CD205 molecules (**Figure 1**). These results suggest that *T. solium* cysticerci has the ability to induce both Treg cells as well as suppressive or tolerogenic DCs [29].

4. Regulatory mechanisms mediated by cytokines, antibodies, and soluble immune factors

4.1 IL-10

IL-10 is produced by innate cells like myeloid and plasmacytoid DCs and macrophages, and is also produced by Breg cells, Th2, Th17 and Treg cells from the adaptive immune response. This capacity to be produced from several immune cell lineages, depends on the signal pathways activated like ERK, and also from transcription factors like STAT3, STAT4, STAT6 and cytokines like TGF-**β** [40]. One of the main features of IL-10 is its capacity to induce immunosuppression, reducing IL-12 and TNF-a levels. By transcriptomic array analyses, we observed that miR-125a-5p, miR-762, and miR-484 microRNAs, are associated with the targeting of inflammatory profiles of macrophages favoring the IL-10 signaling pathway, suggesting that *T. crassiceps* and its products induce post-transcriptional suppression mechanisms of the immune response [41]. Earlier studies performed in experimental cysticercosis caused by chronical *T. crassiceps* infection, indicated a strong Th2 biased immune response featured by high production of IL-4, IL-6 and IL-13 cytokines as well as increased IL-10 levels [12]. These findings were just recently confirmed by an independent group highlighting the importance of IL-10 cytokine [42].

4.2 Transforming growth factor beta (TGF-β)

TGF-β is a cytokine involved in some situations during immune and not immune phenomena. It has a role in the control of cell proliferation and differentiation of some cell types like either Treg or Th17 cells [43, 44]. Also, by itself, it has the capacity to induce a suppressive environment in scenarios where required, like mucosal immune reactions. Dysregulation of TGF-β generates inflammatory disorders such as spontaneous colitis [45]. In the *T. solium* genome were found some genes homologs with the TGF-β receptor family, including some evolved in its down-stream transduction pathway. In fact, it was confirmed by RT-PCR and western blot assays that cysts of *T. solium* express the type I and type II receptor for TGF- β. Also, the addition of TGF- β to the culture media for both *T. crassiceps* and *T. solium* adequate conditions, promotes both the reproduction of *T. crassiceps* and the survival of *T. solium in vitro*. Finally, high levels of TGF-β were found in the cerebrospinal fluid from patients diagnosed with NCC [46]. All these results suggest a strong direct and indirect role for TGF-β in the process of immunosuppression during *T. solium* infection.

4.3 Osteopontin

Osteopontin (OPN) is a Th1 type cytokine upstream of IL-12 that has a role in the granuloma formation in inflamed tissues [47]. It was shown that blood cells co-cultured with TsES or viable cysticerci from *T. solium* led to decreased levels of OPN, IL-12 and IFN-γ. Injection of recombinant OPN into tissues surrounding implanted cysticerci enhances inflammatory responses, which suggests that TsES may have molecules that block OPN activity as a target for immunosuppression [48].

4.4 Antibodies

Humoral immune response has been described for its essential role against helminth infections, being IgE antibody isotype a cornerstone to induce protection [49]. However, during taeniasis and cysticercosis, little information about the role of B cells has been described. It was shown that an antibody called anti-GK-1 (IgG) obtained from the serum of pigs infected with *T. solium*, has an epitope shared by both *T. crassiceps* and *T. solium* [50] and also, has the capacity to inhibit the development of *T. solium* cysticerci into adult stage by recognition of the cyst protein KE7 [51]. This protective role for anti-GK1 antibodies is complement-mediated during *T. solium* infection [50, 52]. However, these results are the only data obtained for humoral immune response during taeniasis and cysticercosis. During experimental cysticercosis and during NCC, is clear that immunosuppression favors the establishment of the parasite, and this GK-1 antibody-mediated mechanism has naturally no success; maybe a molecule of the parasite has the capacity to inhibit this protective function, which in turn induces immunosuppression. Is necessary to clarify this point with specific and deeper experiments.

4.5 Prostaglandin E2

Some lipids from eicosanoid family derivatives from arachidonic acid, like prostaglandin E2 (PGE2), have been described as potent immunosuppressant molecules [53]. It has been described that administration *in vivo* of PGE2 in *T. crassiceps* infected mice favors both parasite growth and cytokine production of IL-10 and IL-6

by splenocytes and reduces the proliferative capacity of splenocytes stimulated with ConA. On the other hand, the administration of indomethacin, an inhibitor of PGE2 synthesis, induced the reduction of both the parasite growth and cytokine production of IL-10 and IL-6, increasing the ConA-proliferative response of splenocytes (**Figure 1**) [54]. These results suggest that *T. crassiceps* can induce the production of PGE2 indirectly from some cellular types, like almost all cells of the host, as a mechanism of immunoregulation [54]. Also, it is possible that some molecules from TcES could be a similar biomolecule like PGE2, mimicking their function and directly inducing immunosuppression, like the TGF-β phenomenon observed during *T. solium* infection.

5. Immunoregulation mediated by Taenia-derived products

5.1 Paramyosin

Paramyosin is an α-helical coiled coil 100 KDa protein that is present in muscle and tegument of the larval stage of *T. solium* [55]. This protein can bind to the protein C1q of the complement, therefore, inhibiting the complement cascade [56]. This was the first evasive mechanism described for this parasite. Vaccine strategies performed to block the activity of this protein resulted in almost 80% of protection [57].

5.2 Glutathione transferase

Glutathione transferase (GST) is an essential enzyme in the metabolism of cestodes, mainly for the detoxification of xenobiotics, it is localized on the cysticerci tegument of *T. solium* [58]. This molecule appears to have a immunomodulatory role given that its use as a putative vaccine was able to reduce parasite load on experimental cysticercosis, mainly by activating macrophages to produce pro-inflammatory cytokines [59]. These data indicate that *T. solium* and *T. crassiceps* may have pro and anti-inflammatory mixed molecules.

5.3 TcES or TsES antigens

Analysis of *T. solium* excreted/secreted antigens (TsES) showed a cysteine protease activity for these molecules, having the capacity to induce apoptosis specifically in $CD4^+$ but no in $CD8^+$ T cells, which is evidence of a direct mode of immunosuppression over a population of the immune response (**Figure 1**). Cocultured cysts of *T. solium* with lymphocytes *in vitro* have not the same effect to induce apoptosis like TsES [60]. Also, it was suggested that natural infection of pigs with *T. solium* cysticerci recruits $CD3^+$ cells to the brain which are killed by apoptosis [61].

Studies in our laboratory demonstrated that TcES products have the capacity to block TLR4 and TLR9 initial signaling pathway in DCs, which has a negative effect over their maturation, their production of pro-inflammatory cytokines and also, to induce alloreactive T cell proliferation, but in an IL-10 independent pathway. All these regulatory effects were carbohydrate-dependent in the TcES, because the chemical alteration of glycans switch this tolerogenic environment to one favoring DCs maturation and secretion of pro-inflammatory cytokines (**Figure 1**) such as IL-12 and TNF-α [62]. Moreover, it was shown that the *in vivo* treatment with TcES, has the capacity to induce the differentiation of monocytes to AAMs expressing PDL1 and PDL2, which in turn down-modulate the activity of experimental autoimmune encephalomyelitis EAE [63]. Furthermore, it was shown that in the murine

model of NCC with the helminth *Mesocestoides corti*, the inhibition of TLR-initiated regulation of inflammatory cytokines exists. This effect is caused by an inhibition of acetylation and phosphorylation of both NF-kB and JNK which causes an accumulation of Ca^{2+} in the endoplasmic reticulum [22]. Probably, this phenomenon is similarly used by *T. solium* during initial establishment of the infection, however, deeper research is necessary in this field (**Figure 1**).

Also, it was shown that the nature of antigens of *T. solium* is essential to induce a proper immune response. Within *T. solium* crude lysate antigen, cyst wall antigen, and cyst fluid antigen, only low molecular weight fractions of cyst fluid are immunodominant, with the capacity to induce the production of inflammatory cytokines, but mainly higher levels of IL-10 and IL-4 by stimulated lymphocytes of patients with NCC [64]. Besides, it was suggested that the time of TcES obtention has a different impact over the kind of immunosuppression observed; TcES obtained early in infection, suppress the proliferative response of splenocytes stimulated with ConA than TcES obtained late in infection. Also, these early obtained TcES suppress the production of IFN-γ and IL-4 efficiently [65].

6. Conclusions

It has been largely known that helminthic infections induce strong Th2-mediated immune responses associated with regulation of inflammatory responses. Here, it has been described the different molecules and pathways altered by *T. solium* and *T. crassiceps* infection. Is noteworthy that some clinical studies point out that this immunomodulation favors both the parasite and host survival when the parasite is allocated in the brain, mainly because the inflammatory response is inhibited, avoiding the damage expected from a strong inflammatory response.

The anti-inflammatory activities and immunoregulatory properties found in both *T. solium* and *T. crassiceps* parasites and their products, can be useful beyond the host–parasite interactions. During some allergic diseases like asthma and rhinitis, the hygiene hypothesis has strengthened the idea of the historical necessity to down-modulate the immune response by mechanisms of natural coevolution, like the infection with helminth parasites [66]. In the same order of ideas, because of all these suppressive capacities of both *T. crassiceps* parasites and their TcES molecules, we hypothesized that it probably has the capacity to modulate chronic diseases associated with inflammation. We observed a clear role of both *T. crassiceps* and their TcES antigens in the modulation of experimental autoimmune encephalomyelitis (EAE) [67, 68], colitis-associated colon cancer (CAC) [69, 70], experimental colitis [71] and type 1 diabetes [72].

Lately, we have observed that the mechanisms used by the parasites that cause infectious diseases, such as taeniasis and cysticercosis, are very similar processes, and we dare to suggest that they are the same, to those occurring during the main oncological (solid) pathologies. The fact that a carcinogenic transformed cell induces an immunosuppressive process through immune-checkpoints such as PD1, CTLA-4 or Tim3, is a mechanism that had already been described in the past, during cysticercosis. So, immunoregulation and immunosuppression are natural selection mechanisms that pathogens take advantage of to be able to survive in a hostile environment and turn it to favor them, to face a variety of processes of continuous and varied attack of the immune response. Therefore, understanding and deciphering the why, how, and when these natural selection processes occur, we will be able to apply the lesson obtained during infectious diseases in processes affecting the current public health, like the main oncological pathologies.

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Conflict of interest

"The authors declare no conflict of interest."

Abbreviations

AAM	Alternatively activated macrophages
ConA	Concanavalin A
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DCs	Dendritic cells
DPI	Days post-infection
EAE	Experimental autoimmune encephalomyelitis
ELISA	Enzyme-linked Immuno Assay
ERK	Extracellular signal regulated kinases
Foxp3	Forkhead box P3 transcription factor
FIZZ1	Found in inflammatory zone 1 gene
Gal-9	Galectin-9
Gal-7	Galectin-7
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-2	Interleukin-2
IL-4	Interleukin-4
IL4Rα	Interleukin4 receptor α
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-13	Interleukin-13
IP	Intraperitoneal
MDSC	Myeloid-derived suppressor cells
NCC	Neurocysticercosis
NCS	Nervous Central System
NO	Nitric oxide
OPN	Osteopontin
PD1	Programmed death 1
PDL1	Programmed Death-ligand 1
PDL2	Programmed Death-ligand 2
PGE2	Prostaglandin E2
PHA	phytohaemagglutinin
PMN	Polymorphonuclear cells
RT-PCR	Real time polymerase chain reaction
SLAMF1	Signaling Lymphocytic Activation Molecule 1
STAT3	Signal transducer and activator of transcription 3
STAT4	Signal transducer and activator of transcription 4
STAT6	Signal transducer and activator of transcription 6
TcES	*Taenia crassiceps* excreted/secreted antigens

TGF-β	Tumor growth factor beta
TNF-α	Tumor Necrosis Factor Alpha
Th1	T helper cells 1
Th2	T helper cells 2
Th17	T helper cells 17
Tim3	T-cell Immunoglobulin domain and Mucin domain 3
TLR4	Toll-like receptor 4
TLR9	Toll-like receptor 4
Treg	Regulatory T cells
Tr1	T regulatory Type 1 population
TsES	*Taenia solium* excreted/secreted antigens

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