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**Dear Editor**  15 August, 2017

I am pleased to resubmit revised manuscript entitled as „ **Liver cystic echinococcosis in human host and immune and autoimmune follow-up: A review**“ to reconsideration for publication in the World Journal of Hepatology (MN. 34072).

We revised this manuscript according to the requests of all reviewers and editors of BPG. We believe that this manuscript is appropriate for publication by WJH because this journal seeks articles related to the economics of health and medical care. Our manuscript creates a paradigm for future studies of a number of key aspects of the host-parasite interactions that is important for better understanding of immunology of parasite in infections. Our objective is consideration of the current data useful for characterization of host protective immune mechanisms, which could be useful for development of a new more effective vaccines and other synthetic agents for protection and treatment against parasitic infections. Issues related to this topics regarding purification and action of many immune modulatory molecules, their site effects and action to parasites remain as challenges.

This manuscript has not published and is not under consideration for publication elsewhere. We have no conflicts of interest to declare. We also improved and polished English.

**Please enclosed revision in the manuscript in red color and highlighted:**

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**Liver cystic echinococcosis and human host immune and autoimmune follow-up: A review**

**Grubor N *et al*.** Liver cystic echinococcosis and immunity

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**Abstract**

Cystic echinococcosis (CE) is an infectiuos disease caused by the larvae of parasite *Echinococcus granulosus* (*E. granulosus*). To successfully establish an infection, *E. granulosus* release molecules that modulate host immune functions, favoring a strong anti-inflammatory response and perpetuating parasite survival in the host. The literature was reviewed using MEDLINE, and an open access search for immunology of hydatidosis was performed. Accumulating data from animal experiments and human studies provided us with exciting insights into the mechanisms involved that affect all parts of immunity. Here, we review some of the existing developments and discuss how these observations assisted with a better understanding of the immunology of *E. granulosus* infection in man. The aim of this study is to define more clearly the events that challenges immune and autoimmune responses to protect *E. granulossus* from elimination and to minimize severe pathology in the host. Understanding the immune mechanisms of *E. granulosus* infection in an intermediate human host will provide, we believe, a more useful treatment with immunomodulating molecules and possibly better protection from parasitic infections. Moreover, future studies for understanding the mechanisms of *E. granulosus* immune regulation will reveal novel compounds that may alter and improve their potential inflammatory responses. In contrast, according to the ’hygiene hypothesis’, clinical applications that decrease the incidence of infection in developed countries and have done so more recently in developing countries are at the origin of the increasing incidence of both allergic and autoimmune diseases. Thus, an understanding of the immune mechanisms of *E. granulosus* infection is extremely important.

**Key words:**Echinococcus granulosus; Immunity; Autoimmunity; Lymphocytes; Cytokines; Dendritic cells

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**Core tip**: The most common location of a hydatid echinococcal cyst is in the liver. The survival of Echinococcus within host tissues, despite the development of specific antibodies, is possible due to specific immunomodulation induced by parasites. Successful survival of parasites indicates that they have developed multi-level mechanisms of evasion against host protective mechanisms to provide their propagation. Complement modulation, a metabolic adaptation to the host microenvironment, plentiful thermostable immunogenic antigen B in the cystic fluid, and induction of CD4+CD8+Foxp3+ T cells allows the persistence of the parasites. Parasites influence dendritic cell (DC) maturation and impair activation by toll-like receptor. It seems that DC-parasite interaction is pivotal in triggering and regulating parasite induced immunity.

Grubor N, Jovanova-Nesic K, Shoenfeld Y. Liver cystic echinococcosis and human host immune and autoimmune follow-up: A review. *World J Hepatol* 2017; In press

**INTRODUCTION**

Cystic hydatidosis is a global parasitic zoonosis caused by the larvae of the dog tapeworm *Echinococcus granulosus*[1]. Humans become contaminated by ingestion of parasite eggs after close contact with infected dogs. After ingestion of parasite, the oncosphere (also named exacanth larvae) is released from the keratinized embryophore in the stomach and intestine of the intermediate host (herbivores or humans), where it penetrates the small intestine wall *via* hook movements. Its life cycle develops in dogs and other canids that harbor the adult tapeworm. The larval metacestode form develops in different organs of the intermediate host[2**]**. The most common location of the hydatid cysts is in the liver (70%) or lungs (20%), but occasionally they may find their way to other organs (kidney 2%, spleen 2% and brain less than 2%)[3]. The eggs develop into larvae when they cross the intestinal wall of the intermediate host, and the oncosphere is then carried out *via* portal vein flow into the liver and other organs where the oncosphere then undergoes a metamorphosis towards the metacestodes. The metacestodes implant into the organ and grow into cysts[4**]**. This formation consists of an inner, cellular ‘germinal layer’ (GL) and an outer, glycan-rich and acellular ‘laminated layer’ (LL) (Figure 1)[[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Brehm1)**[]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Brehm1)**. Organs may also be reached through the lymphatic system **[**6]. Echinococcal cysts is surrounded by pericyst (adventia) from the periparasitic host tissue, which surround the larval endocyst (Figure 1A, B). The endocyst is composed of a cuticular or laminal acellular outer layer and an inner layer, the germinal proligerous layer, which gives rise in a fertile cyst to root capsules and protoscoleces[7]. Some cysts may also harbor daughter cysts of variable sizes (arrows in Figure 1C). Cysts also contain developing protoscoleces (PSCs), which constitute an infectious agent. Protoscolex may develop into adult tapeworm if ingested by a suitable definitive host. Some vesicles adhere to the walls by means of a peduncle or remain free within the hydatid fluid. A large number of these vesicles (endogenous daughter vesicles) and free protoscoleces float in the hydatid fluid, together forming the co-called “hydatid sand“. Offspring vesicles in the hydatid fluid have the same constitution and the same mission of the vesicle mother. The hydatic liquid is clean and clear, containing secretions from both the parasite and host and all the elements from the “inner wall“of the cyst. It has an identical composition to that of the host’s serum (Na, K, Cl, and CO2), a density between 1.008 and 1.015, and alkaline pH[8]. Therefore, in this way, protoscoleces may evolve into either a new cyst or an adult parasite. As the cyst later becomes a successful xenograft in the host, it progressively enlarges until symptoms or complications appear[9,10]. In humans, its clinical manifestations range from asymptomatic infection to severe, potentially fatal disease. The parasite die due to dysfuntion of germinal membrane (detached, aging or micrortaumatisms) but the scolex may transform into vesicle trying to preserve the species [11].

The survival of *Echinococcus* within the host tissues, despite the development of specific antibodies (Abs), is possibly the result of specific immunomodulation induced by the parasite[12]. This phenomenon has been the subject of study by many researchers during the last two decades. They aimed to investigate the host responses to the parasite. The aim of the present study was to review these modifications of the immune and autoimmune responses induced by *E. granulosus*. For better understanding of host-parasite interactions in this review human clinical study used complementary to animal studies. However, although some of the immune responses involved in infection have been addressed, protective mechanisms are largely unknown.

**IMMUNE RESPONSE TO *E. GRANULOSUS* INFECTION OF THE HOST**

***Effects on Innate Immunity***

Almost exclusively within the intermediate host's liver, the cyst-like metacestode vesicles grow infiltratively, like a malignant tumor, into the surrounding host tissue. The host immune system reacts to these formations. But there is no data of granulosis-induced immune suppression in echinococcosis on the molecular and cellular level, particularly in the early stages of the infection. On the other hand, there is no doubt that the defensive immune reaction is missing and parasite survive. Successful survival of parasites indicates that parasites have developed some mechanisms of evasion from host protective mechanisms to preserve their propagation[13**]**. A significant number of studies on both humans and mice have indicated that at the beginning, T helper 1 (Th1) dominates immune responses after parasite infection (Figure 2) characterized by the release of interferon-γ (IFN-γ) and after priming by dendritic cells (DCs) with IL-12[11,14]. Both are effective in the elimination of the parasite at an early stage. However, it has become clear that the parasite, probably by its excretory/secretory products, actively influences the host immune response, leading it to the Th2 response and parasite survival**.** Namely, the Th2 cytokine profile of IL-4, IL-5, immunosuppressive IL-10 and transforming growth factor beta (TGF-β) are generally associated with susceptibility to the parasite and progressive disease[15]. On the other hand, the polymorphonuclear (PMN) leukocyte, basophil-mast cell and monocyte participation showed intense local inflammatory reaction to protoscoleces (PSCs)[16**]**. Significant increases in the chemiluminescence response, superoxide (O2) production and phagocyte index have been detected in patients with dead cysts compared with healthy subjects, whereas a marked reduction in all the above markers was observed in patients with live cysts[17**]**. Thus, the PMN leukocytes of infected patients are in an activated state both functionally and metabolically[18]. Regarding basophils, the human basophil degranulation test was found to be positive in 33% of patients with hydatid disease (HD)[19**]**. Furthermore, evidence of increased histamine release from hydatid patient basophils following a challenge with anti-human IgE has also been obtained[20**]**. It can be concluded that both the generation of histamine releasing factor (HiRF) and production of IgE, which can bind cytokines, may be involved in this stage of infection[21**]**. This histamine releasing factor was found to activate basophils through surface-bound IgE, cytokine production and Th2 cell activation[16,21-23].

Additionally, it is well known that the surface of many parasitic helminths, including *E. granulosus*, is able to activate the alternative pathway of the complement system[24,25]. Although the complement can lyse protoscoleces of *E. granulosus*, some products from this parasite are able to consume the complement, which is an ability that has been proposed as the basis of an invasion mechanism by the parasite[25**]**. However, the levels of component 3 of complement (C3) and chemolitic complement in challenged mice yielded no evidence of complement consumption[25**]**. Moreover, C3 levels were significantly increased in patients with hydatid disease compared to controls[16,26**]**. Thus, it is possible that local consumption at the site of infection may exist, leading to systemic consumption in the more active cysts. Finally, the existence of several mechanisms of complement modulation was found when comparing complement activation *in vitro* by different *E. granulosus* extracts[27]. These findings further enhanced the possibility of their significant role in the susceptibility of infection and/or maintenance of the disease.

To survive in the host tissues, the parasite must be able to adapt metabolically to the host microenvironment, and antigen (AgB) could be involved in this process. Additionally, many antigen B (AgB) molecules in the hydatid cyst fluid possibly guarantee parasite survival. The termostabile AgB (166 kDa) that resists boiling for 15 min without losing antigenicity with gene family comprising at least 10 unique genes in five subclasses which are differentialy expressed[28] in its lifecycle, except EgAgB3 expressed predominantly in all cell stages[29]. These findings are fundamental for determining the expression levels and biological function of AgB. AgB proteins are highly immunogenic, and acts directly to innate and adaptive immunity. Some are involved in lipid detoxification, transport and metabolism with their fatty acid binding properties**[**30,31]. Thus, AgB could be involved in the process of parasite survival in the host microenvironment. It is well known that its 12 kDa subunit is a serine protease inhibitor with strong chemoattractant activity and with the ability to inhibit human neutrophil chemotaxis[32,33**]**, allowing the released protoscoleces to develop into secondary cysts[10**]**. AgB co-incubated withEchinococcus primary cells, representing theinvading oncosphere or metacestode vesicles. In these conditions, a significant proportion of DCs underwent apoptosis, and the surviving failed to mature[34**]**. In contrast, those exposed to protoscoleces up-regulated maturation markers and did not undergo apoptosis**.** After pre-incubation with primary cells and metacestode vesicles, DCs showed a strongly impaired ability to be activated by the Tall-like receptor ligand LPSs, which was not observed in those pre-treated with protoscolex excretory/secretory (E/S)-products[35**]**. The induction of CD4+CD25+Foxp3+ T cells to metacestode E/S-products suggests that these cells fulfill an important role for parasite persistence during chronic echinococcosis. The immunomodulatory products of parasites are therefore of high interest for understanding by infections induced immunopathology and allergy treatment.

**EVASION MECHANISMS OF *E. GRANULOSUS* IN THE HOST**

***Characterization of Molecules Involved in Evasion***

In intermediate hosts, protoscoleces develop exclusively in fertile cysts. This formation also consists all of three membranes (inner cellular, outher glicin rich and laminated acellular) [36]. In infection with E. granulosus cystic form can induce IgG that cross the tegument and plasma membranes between laminar and germinal layers of the cyst. There IgG recognize specific cystic antigens, and antigen-antibody complex may inhibit proliferative process of protoscoleces, but why it is not happening? Due to germinal lyer of the cyst is a barrier for immunocompetent cells of the host [36]. Except this the parasite evolving other immune evasion strategies [37]. *E. granulosus* can use two main mechanisms to undermine the host immune response: (1) passive escape, in which the parasite, during the development of a hydatid cyst, avoids the damaging effects of an immune host response; and (2) immunomodulation, in which the parasite is involved in the host immune response to trigger the impact[38,39].

***Circulating Antibodies as Immunological Markers in Cystic Echinococcosis (CE)***

Although patients with hydatidosis contain amount circulating IgG, IgM, IgA and IgE antibodies (Abs) to *E. granulosus*, no one of them is associated with host protection[40**]**. IgG4 in echinococcosis is not able to complement fixation neither is cytophilic, also weekly binding to Fc fragment of immunoglobulins, then is not functional. All of these will support the parasite evasion of host immune response [41]. At the same time, parasite-specific IgG4 antibodies can inhibit IgE mediated degranulation of effector cells, reducing allergic pathology in the host and prolonging parasite survival[42**]**. In agreement with this study are findings thatalbendazole-treated patients who exhibited a good therapeutic and clinical response to treatment had significantly lower levels of serum IgG4 antibodies than poor responders or non-responders. Additionally, data obtained from mass screening in various countries showed a reverse trend of IgG1 antibody levels[40,42**]**. Additionally, patients without allergic manifestations had IgG4 antibodies specific for EA21, whereas patients with allergic manifestations showed IgE specific to EA21. Authors have suggested that cystic echinococcosis IgG4 apparently acts to block pathogenic processes, minimizing severe pathology in the host[42**]** and providing parasite survival (Figure 2).

***Immunomodulating Molecules: Role of Antigen B and Other New Antigens***

In patients with cystic echinococcosis (CE) with Th2 polarized microenvironment, besidesAgB, EgTeg and EgEF-1 β/δ, several other parasite molecules can elicit Th2phenotype. The proteomic approach emphasizes the presence of a large number of antigenic proteins associated with parasites. Antigen B (AgB) modulates DC maturation and suppresses IL-12p70, but not IL-6 release[43]**.** As allergic targets in cystic echinococcosis (CE) in acute cutaneous allergic manifestation, at a molecular level, three conserved constitutive proteins have been identified: EgEF-1 β/δ, EA21 and Eg2ASP70[44**-**47**]**. At least two of these proteins appear to have immunomodulatory properties. EgEF-1 β/δ influences immunomodulation and is released after the death or degeneration of protoscoleces[45**]**.Furthermore, the induction of CD4+CD25+Foxp3+ T cells in metacestode excretion/secretion products suggests that these cells play important role in parasite survival during chronic echinococcosis[35,48**]**. The immunomodulatory products of parasitic helminths are therefore of high interest for understanding immunopathology during infections and for the allergy treatment. Future immunological studies should investigate the role and possible immunomodulatory effects of these proteins. However, the development of the disease highlights the difficulty in understanding the host-parasite relationship[49,50**]**. More investigations is necessary for integration of these studies with previous results to recognize well the extreme complexity of the host-parasite interactions, extremely important for the development or improvement of CE diagnosis, treatment, and control strategies.

***Immunomodulation by cytokine production***

Plasticity of both the nature and magnitude of immune host responses depend on infective agents that permit the immune system to tailor its defense strategy. Th1 and Th2 cells are not pre-committed cells with defined phenotype, their phenotype is result of a multistep differentiation process, thus a precursor population acquires secretion of different cytokines profiles[47**]**. The most important in this process is how *E. granulosus* antigens (Ags) encountering the immune system in humans can influence this differentiation decision. Increased level of IgG4 and IgE antibodies and induced eosinophilia suggesting that the immune response establishes in *E. granulosus* infection is Th2-dominated and that *E. granulosus* antigens modulate polarized T-cells (Figure 2). Data obtained from *E. granulosus* experimental infections supported the hypothesis that early IL-10, secreted by B cells in response to mitogens, may favor parasitic survival and the establishment of a polarized type-2 cytokine response[50**]**. There are many evidence of molecular studies that IL-4/IL-10 impairs the Th1 protective response allowing the parasite survival in human host [51**]**. In addition,patients responsive to albendazole inperipheral blood monocyte cells **(**PBMCs) showed high amounts of IFN-γ (Th1-derived), whereas PBMCs from patients who did not respond produced IL-4 and IL-10 (Th2 derived)[14**]**. These findings are in concordance with a molecular studies that detected IL-12p40 mRNA in 86% of successfully albendazole-treated patients at the end of chemotherapy who expressed a high level of IFN- γ and TNF-α DNA[15,52**]**. Finally, patient with an inactive cyst expressing Th1 phenotype, while patients with with active and transitional cysts showed mixed Th1/Th2 and Th0 phenotype[53]. No parasite antigen driven IL-5 and scarce IL-4 and IL-10 in seronegative patients were detected[54**]**. Seronegativity occurs due to the host or parasite factors or both preclude the possibility of Th2 cell activation and this is limiting or preventing the production of IL-5, crucial for immunoglogulin expression. It has been shown recently that the bone marrow-derived dendritic cells (DCs) present in the most non-lymphoid tissues, exhibit a potent capability to capture or process antigens[55**]**. Also inflammatory mediators or microbial agents promote the migration of DCs into secondary lymphoid organs. By maturation, DCs lose their antigen (Ag) capturing ability and gain an increased capacity to prime T-cells [56]. Thus, DC-parasite interactions are pivotal in triggering and regulating parasite-induced immunity. *E. granulosus* hydatid fluid modulates DC differentiation and cytokine secretion as well**[**57**]**. Finally, these cellular findings established that *E. granulosus* also modulates DC maturation, priming them to polarize lymphocytes into Th2 cells[58,59**]**.

**ADAPTIVE IMMUNITY**

***Role of dendritic cells in parasite evasion***

Dendritic cells(DC) are antigen presenting cells recognized as a link between the innate and adaptive immune systems. They are included in induction of Th1, Th2 or Th17-dominated immune responses[60]. Upon pathogen recognition, DCs as antigen presenting cells take up the antigens and undergo maturation in the presence of up regulated MHC/HLAmice/man) complex and co-stimulatory molecules such as CD86 and CD80[34,[60](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Everts1)]. After migration to the T cell area of lymph nodes, DCs interact with naïve T cells to promote adaptive immune responses towards the Th1, Th2, and Th17 [61,62]. However, they are also targets of parasites to establish immune evasion by induction of regulatory T cells (T-reg). Mejri *et al,* 2011demonstrated that peritoneal DCs from chronically infected mice, representing the late stage of alveolar echinococcosis[63]. Furthermore, DCs from intraperitoneally infected mice specifically modulated CD4+ and CD8+ T cell responses, suggesting their immunosuppressive T regulatory function in echinococcosis[[63]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Mejri1)[.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Mejri1) Moreover, during infection of the intermediate host, migration of parasitic larvae from the intestinal entry site to the liver and late metastasis to other organs (lung or brain) strongly suggest that these larvae encounter DCs*in vivo*[64]*.* However, despite the general importance of DCs in cellular host-parasite interaction, the identification and characterization of immunomodulatory molecules that are released by *Echinococcus* larvae and have an influence on DC function, is limited. Compared to nematode and trematode infections, immunomodulatory functions of DCs in cestode, and that belonging and echinococcus granulosus, have drawn significantly less attention, although this is clearly an emerging field. In two reports, Reyes *et al*[[66](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Reyes1)] and Terrazas et al[67] investigated the effects of excretory/secretory (E/S)-products of Taenia crassiceps cysticerci on the activation of murine DCs, representing the metacestode larval stage of by Taenia infection. DC of succeptible mouse strain when preincubated with parasite E/S product, authors observed impaired DC maturation in response to Toll-like receptor (TLR) dependent stimuli, particularly when DCs of infected susceptible mouse strains. [[66,67](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Reyes1)]. However, whether these interactions are of major relevance in vivo remains unclear**,** since intact parasite tissue usually prevents direct contact between hydatid cystic fluid and host immune effector cells, and the spectrum of metacestode excretory/secretory-products does not necessarily overlap with the spectrum of proteins present in hydatid cystic fluid. Although it is generally assumed that AgB might leak out of intact metacestode vesicles or be released early during an infection from damaged metacestode material[[68]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Siracusano1), the authors could not detect AgB in the E/S-products of in vitro cultivated echinococcal metacestode vesicles, despite the fact that this component was well expressed in HCF[[**69**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Bernthaler1)]. Dendritic cells pulsed with unfractionated helminthic proteins generate antiparasitic cytotoxic T lymphocyte [70]. Thus, crude metacestode antigen preparations containing vesicle fluid, somatic parasite proteins and contaminating host components, tested concerning their effects on DCs, failed to induce maturation as did a purified mucin-type glycoprotein (Em2) that is usually expressing at the surface of LL-containing metacestode vesicles[71,72]. However, it is well established that apoptosis, extrinsically triggered by infectious agents such as viruses, parasites, or bacteria, usually results in a bystander effect of induced immunosuppression[[73]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Kushwah1)[.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Kushwah1)

***Bystander effects of parasite-induced immunosuppression***

In parasitic helminths, the induction of DC apoptosis has already been reported in nematodes in which it strongly limits their capacity to produce pro-inflammatory IL-12 and prevents T cell activation and proliferation[[74](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Semnani1)]. Different from others investigator accept the possibility that the diminished function of dendritic cells in metacestode infection is by induction of apoptosisof immature cells rather that due to direct inhibition of DC maturation. Through parasite E/ products of the metacestodes. It could establish a strong immunosuppressive environment around parasite lesions. At the beginning of the infection. TBF-β signaling are envolved very early in this process because in animal evolusion they are expressed very early in all invertebrate. Therefore, it is conceivable that the strongly diminished ability of DCs that were pre-incubated with E/S-products of primary cells and the metacestode to LPS, as observed in their study, was indirectly mediated by the induction of apoptosis in a subset of immature DCs, rather than by direct inhibition of DC maturation through parasite E/S-products. Since the uptake of apoptotic DCs induces immature DCs to secrete TGF-β, which induces differentiation of naïve T cells into Foxp3+ T-reg[[73](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Kushwah1)], excretory/secretory (E/S)-products of the metacestode, and particularly of primary cells, it could thus establish a strongly immunosuppressive environment around parasite lesions already at the beginning of an infection. Because TGF-β-signaling mechanisms have already evolved very early in animal evolution, TGF-β-like cytokines are expressed by a wide variety of free-living but also parasitic invertebrates[75,76**]**.

In sharp contrast to co-incubation with primary cells and metacestode vesicles, DCs exposed to E/S-products of protoscoleces were clearly activated, as assessed by the up-regulation of surface activation markers (MHCII and CD86), secreted elevated levels of IL-6 (but no IL-10), and strongly impaired the ability of DCs to produce IL-12 in response to Tall-like receptor (TLR) stimuli lipopolysaccharides (LPSs) [74]. This phenotype resembles that of DCs that have been incubated in the presence of *E. granulosus* hydatid cyst fluid (HCF) and isolated AgB[55,59]. However, in contrast to these investigations, DCs incubated with protoscolex compounds as presented in their study did not release elevated levels of IL-10, as reported by Rigano *et al*[[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Rigan1)], or IL-12, as reported by Kanan and Chain[59]. It seems that AgB is only weakly expressed by protoscoleces [79, 30]. In general, however, the phenotype of DCs upon co-incubation with E/S-products of protoscoleces is largely comparable to that of DCs incubated with certain *Trypanosoma* antigens, which have been closely associated with the induction of Th2-dominated immune responses[[78](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/" \l "pntd.0001516-Pletinckx1)]. In any case, the marked differences between the responses of DCs to E/S-products of early versus late developmental stages of *E. multilocularis* clearly demonstrates that an induction of tolerance in DCs is not a general characteristic of *Echinococcus* material but rather that the E/S repertoire of primary cells and metacestodes has specifically evolved to fulfill these purposes[80]. Care should therefore be taken in the interpretation of results that have been obtained concerning the immune response during echinococcosis (intermediate host infection) using co-incubation-systems of *Echinococcus* protoscoleces with host cells[81-87] or by employing the mouse model of peritoneal, protoscolex-induced secondary alveolar echinococcosis for short-term infections[88]. The oncosphere that undergoas metamorphosis phases toward metacestode are able to induce poorly responsive IL-10 secreting DCs in vitro [88]. These findings suggests that similar mechanisms might also further investigation by methods of primary cells could resolve the molecular nature of echinococcus products that are responsible for these effects. This effect is somewhat reduced at the chronic stage (metacestode), leading to poorly responsive, immature DCs, but a Foxp3+-T-reg-inducing environment is no longer present in the protoscolex stage. Although findings have concentrated on *in vitro* interactions between parasite larvae and DCs, thus excluding the possible influence of other immune effectors or epithelial cells, the clear induction of poorly responsive, apoptotic and IL-10 secreting DCs in response to primary cells suggests that a similar mechanism might also be operative in the tissue surrounding the early metamorphosing oncosphere. If so, this process might be important for early establishment of the parasite during a phase of relatively high vulnerability to the host immune system. Whereas in the chronic phase, after production of the laminar layer (LL), a slightly altered profile of excreted/secreted products that mainly induces T-reg could support long-term persistence and infiltrative growth of the metacestode, as previously suggested[89]. The molecular nature of *Echinococcus* E/S-products that are responsible for these effects is currently being investigated using the available genome sequence information[5,77**]**, which are recently established methods for genetic manipulation of primary cells[[90](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/#pntd.0001516-Spiliotis4)].

**CYSTIC ECHINOCOCCOSIS AND AUTOIMMUNITY**

Host autoimmunity to *E. granulosus* is initiated by a combination of genetic predisposition and environmental triggers. Genetic susceptibility, environmental stimuli and defective regulation of immune reactions are responsible for follow-up autoimmune reactions to these parasites. A combination of autoimmunity environmental triggers and genetic predisposition can lead to immune imbalance and could influence the appearance of autoimmune diseases (Figure 3). Cystic echinococcosis and others parasitic diseases at their source will require an understanding of how the abnormal immune reactions arise, how they are sustained, and the intrinsic mechanisms used to suppress these responses in patients with cystic echinococcosis and healthy controls. A final goal of this study is to exploit this existing knowledge from research in this area for better understanding the pathogenesis of autoimmune diseases induced by *E*. granulosus host infection important for development of strategies for reestablishing the normal balance between efector and regulatory immune responses. The underlying mechanism of autoimmunity is defective elimination and/control of self-reactive lymphocytes. Clinical results have demonstrated that patients with cystic echinococcosis show increases in the peripheral Treg number, related cytokines IL-17 and IL-23, and transcription factors Foxp3 and TGFβ-1 levels compared to control healthy subjects[91**]**. The Th17/Treg balance controls inflammation and may play an important role in the pathogenesis of immune evasion [91**]** To assess whether this balance was broken, Rosenblum *et al*[92**]** detected Th17/Treg functions at different levels including cell frequencies, related cytokine secretions and key transcription factors in cystic echinococcosis (CE) (Figure 3). The results indicated that a Th17/Treg functional imbalance exists in patients with chronic cystic echinococcosis, suggesting a potential role for a Th17/Treg imbalance in the pathogenesis of immune evasion in echinococcosis. Regarding to genes associated with autoimmune diseases, the strongest associations are with particular HLA alleles[93**]**. Moreover, it is still not definitively known how different HLA alleles contribute to any autoimmune disease. It is unlikely that a disease-associated allele is especially efficient at displaying the autoantigens targeted by self-reactive T cells due to most HLA alleles are capable of presenting self-antigens also in healthy subjects. Yet, most healthy individuals have autoreactive T cells that escape thymic deletion[94,95**].**

***Genetic Susceptibility to Host Autoimmunity***

Using knowledge of the genes involved to elucidate the pathogenesis of autoimmune diseases is much more discouraging for other polymorphisms with chanse lower than those for HLA alleles. Besides that cytokine and cytokine receptor genetic polymorphisms have been linked to many different autoimmune diseases. The best example of this is *IL23R*. IL-23, as they are cytokine that augments the pro-inflammatory capacity of Th17 cells[91,92**]**. Genetic polymorphisms in *IL23R* have been discovered in ankylosing spondylitis, Behcet’s disease, Crohn’s disease, psoriasis, and ulcerative colitis[96**]**. Inflammatory Th17 cells have also been associated with tissue damage in all of these diseases, and targeting these pathways with monoclonal antibodies specific for either p40 (a subunit of IL-23) or IL-17A has shown efficacy in almost all of these disorders[43,97**]**. Thus, genetic polymorphisms in *IL23R* have in some cases been correlated with responses to targeted anti-cytokine therapies. But the development of many human autoimmune diseases is result of reaction of multiple genes involved. Predisposition to develop most human autoimmune diseases it thought a result of gene polymorphism of these genes. There are few examples in which genetic alterations in a single gene result in fulminant autoimme diseases. The two best examples of monogenetic autoimmune diseases are autoimmune polyendocrine syndrome (APS) and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. These diseases directly result from mutations in *AIRE* and *FOXP3* gene[98,99**]**, leading to dysfunction in central (APS) and peripheral (IPEX) tolerance. Another example is autoimmune lymphoproliferative syndrome, a rare lymphoproliferative disorder caused by mutations in Fas or the Fas ligand or in caspases downstream of Fas signaling. These mutations result in a defective Fas-mediated apoptotosis and chronic lymphoproliferative causing lymphadenopathy, splenomegaly, and autoimmune cytopenias[100**]**. Discovery of the single genes responsible for these disorders has greatly contributed to our understanding of the cellular and molecular pathways that are dysfunctional in many autoimmune diseases.

***Environmental Triggers for Host Autoimmunity***

Environmental triggers are factors originating outside of the body, such as parasites, bacteria, viruses, toxins and medications. Infections have long been suspected to trigger autoimmune reactions[101,102**]**. Multiple theories have been proposed to explain this association. and excessive innate/pattern recognition receptor activation. Epitope sreading and antigenic complementary are few between many theories proposed, as well as a pattern recognition receptor activation. Evidence of *Epstein bar virus* (EBV) infection in postmortem brain tissue has been associated with MS but not with other inflammatory disorders[103**]**. Systemic infections have been reported to trigger relapses in patients with relapsing-remitting multiple sclerosis through enhancement of myelin-specific T cell responses[101**]**. Another example of the association of infections with autoimmunity is that of periodontal infections and rheumatoid arthritis[104]. In contrast, infections are also postulated to protect against some autoimmune diseases. In this way infections of germ-free mice with *Bacteroides fragilis* has been reported to protect against experimental autoimmune encephalomyelitis (EAE), by induction of Treg cells[105**]**. In that way, a higher incidence of MS and type 1 diabetes is suppose to correlate with a decreased number of infections in developed countries[106**]**.

***Defective Regulation as the Cause of Autoimmunity***

The peripheral tolerance to tissue antigens could be induced by the low-level of natural cell death through the tolerance o dendritic cell populations f107]. Toerance of dendritic cells can influence low level of natural cell death in the tissue antigens, respectively [107]. If tolerance is the main abnormality in autoimmune processes, which kind of tolerance is processed in induction of autoimmune diseases? In SLE maturation of naïve B cells can produce antoantibodies even before encounter with antigens, suggesting that defects in early B cell tolerance checkpoints may contribute to disease development[108**]**.. defects in the deletion of immature B cells in the bone marrow, in receptor editing, and in the control of mature B cells in peripheral tissues have all been proposed[108**]**. Findings indicate that defects in the deletion of immature B cells in the bone marrow, in receptor editing, and in the control of mature B cells in peripheral tissues have all been proposed[108**]**.

Regarding T cell-dependent autoimmunity and inflammatory autimmune dideases, imbalance between effector and regulatory T cells play a fundamental role in initiation of human autoimmune diseases [109].

It also appears likely that decreases in the number of functional Tregs or resistance of effector T cells to regulation plays a role in the initiation of human autoimmune disease. However, the data from patients with different autoimmune diseases tend to be variable and often inconsistent, often due to the limitedassesibility of human tissue. Eventually, when adequate numbers of these cells are obtained, their function (or lack thereof) is usually assessed by *in vitro* assays that may not accurately recapitulate their functional capacity *in vivo*. Longitudinal studies of effector and Treg cells that are specific for target self-antigens in human disease remain a considerable technical challenge. The self-perpetuating nature of autoimmune diseases may help to explain why these conditions reach the propagation phase. The self-antigens that drive autoimmune reaction obviously cannot be eliminated. This problem is compounded by the emergence of new antigenic epitopes as a result of tissue damage and alterations in self-proteins, the phenomenon known as epitope spreading. Epitope spreading sets up a vicious cycle in which newly created antigenic epitopes activate more lymphocytes of different specificities and recruit these cells into the reaction, leading to more tissue damage and the emergence of even more novel epitopes targeted by autoreactive lymphocytes. Severe autoimmune reaction creates an inflammatory environment in which multiple immune cells interact to produce cytokines and other mediators that amplify the reaction, creating a catastrophic inflammatory loop. Plasmacytoid dendritic cells IFN-I that is produced during inflammatory reactions, is a biomarker for the progression of SLE and may be involved in the propagation of this disease[110**]**. The prolonged survival of *E. granulosus* metacestodes within the human host indicates that some mechanisms are operating to permit evasion of the host immune response. Several authors have described autoimmune phenomena in patients with cystic echinococcosis. Autoimmune hemolytic anemia due to IgM cold agglutinin with anti-I specificity was found to be induced in patients with cystic echinococcosis. Moreover, the cleavage fragment of C3 has been detected on the erythrocyte membrane of a number of cystic echinococcosis patients, suggesting that parasitic antigens may evoke antibodies that cross with human erythrocytes[111**]**. Furthermore, anti-neutrophil cytoplasmic, anti-myeloperoxidase and anti-lactoferrin antibodies have also been revealed in the sera of cystic echinococcosis patients[112**]**. However, no significant correlations have been observed between cystic echinococcosis and anti-nuclear antibodies, tissue specific autoantibodies and rheumatoid factors. In contrast, Aslan and coworkers[113**]** have measured significant levels of antinuclear antibodies, anti-mitochondrial and anti-smooth muscle antibodies in patients with cystic echinococcosis in comparison to age- and sex-matched healthy individuals. Antiphospholipid antibodies, anti-cardiolipin antibodies and anti-dsDNA have been shown to be associated with several infectious diseases and some autoimmune diseases such as systemic lupus erythematosus and anti-phospholipid syndrome. Such elevated levels of these antibodies could be explained by the antigenic mimicry between the parasite antigens and host proteins[114**]**. Since cardiolipin and phospholipids are abundant in most cells of multicellular organisms, the former is an important component of the inner mitochondrial membrane, where it constitutes approximately 20% of the total lipid composition[115**]**, while phospholipids are a class of lipids and a major component of all cell membranes as they can form a lipid bilayer[116**]**. Moreover, autoantibodies class I and class II MHC gene products have also been demonstrated in cystic echinococcosis patients, which may contribute to impairment of the host immune responses. Chronic and multiple infections with viruses, such as Epstein-Barr virus and cytomegalovirus and bacteria, such as *H. pylori*, may also play a role in the evolvement of autoimmune diseases in susceptible individuals[117**].**

Finaly, parasites are masters of immune regulation and they are surviving well in the human host and the host attempting to eradicate them [119]. From a translational perspective, knowledge of immune events as a response to infection with a helminth parasite could be used to reduce the intensity of unwanted inflammatory reactions. In addition, poorly characterized cestode extracts can regulate murine and human immunocyte function, yet the impact of these in the context of autoimmune or allergic diseases is poorly understood. Helminth parasites are masters of immune regulation, a likely prerequisite for long-term survival by circumventing their host’s attempt to eradicate them[119]. From a translational perspective, knowledge of immune events as a response.

CONCLUSION

*E. granuslosus* is very complex multicellular parasite. As many pathogens is higly immunogenic for human host. Thus, the host immunity play a most important role in host-parasite relationship in human ehinococcosis. The secretory and excretory products from parasite influences immune and immune competent cells in human host and stimulate humoral and proinflammatory cell-mediated immune responses, releasing of significant antibody production, and activate T cells and other antigen-presenting cells in human host. Thus, the understanding of the immune mechanisms is of fundamental importance for revealing of a basic protective processes in human with hydatidosis. No doubth that protective antibodies are also extremely important for development of a new more efective vaccines against *E. granulosus* and other parasites. Knowledge of immune events as a response to infection with a helminth parasite could be used to reduce the intensity of unwanted reactions such as a variety of auto-inflammatory diseases and allergy. Substantial data have accumulated showing that inflammatory reactions that promote a variety of auto-inflammatory disease are dampened as a consequence of infection with helminth parasites *via* either the mobilization of anti-worm spectrum of immne reactions or direct effects of bioactive immunomodulatory molecules released from the parasite. Also the cestode extracts are poorly characterized and their impact on autoimmune and allergic diseases are poorly examinated due to the mechanisms of reaction are not understood. Yet issues related to this topics regarding purification of immunomodulatory molecules, their site effects and action to parasites remains as challenges that need to be addresed.

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**Footnotes**

**Nonstandard abbreviations used:** FOXP3, forkhead box protein P3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

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**P-Reviewer:** Giorgio A, Kamiyama T, Singh S **S-Editor:** Kong JX **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Serbia

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Thank you for yours effort and useful instructions about revision of this manuscript.

With best regards.

Sincerely,

Prof. Katica Jovanova-Nesic, PhD

**Extensive re-revison made in the revised manuscript MN: 34072**

**Queries of Editor about the manuscripr MN-34072:**

**Query:**

**Ad 1**. Please revise the manuscript according to the ithentidate check report.

**Answer:** Extensive re-revison was made in the rerevised manuscript MN: 34072 according to attached check report.

We have doneextensive correctionof our manuscript entitled as **„Liver cystic echinococcosis in human host and immune and autoimmune follow-up: A review**“ Manuscript with highlihted correction in rad color is attached in the resubmited manuscript.

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**Ad 2.** Detailed address of institution:

**Answer:** Immunology Research Center, Vojvode Stepe 458, 11221, Belgrade, Serbia

**Query:**

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**Answer:** It is checked through the text.

**Query:**

**Ad 4.** Please provide source to access the reference like this and all following:

## **Answer:** 8 **Menezes da Silva A**. **Human Echinococcosis: A Neglected Disease**

In: Gastroenterology Research and Practice; Senturk H Ed; Hindawi Publishing Corporation: Cairo, 2010; Vol. 2010, pp. 1-9. Gastroenterology Research and Practice Volume 2010 (2010), Article ID 583297, 9 pages <http://dx.doi.org/10.1155/2010/583297> GoogleScholar

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**Responses to reviewers**

**Comments Reviewer’s code: 02462322**

This is an excellent review article discussing the immunology of Echinococcus Granulosus which mostly effects the liver, but can also infect lungs and other organs in the body such as the spleen, brain, heart, and kidneys.

The article is well written except for very few spelling errors like Orgns instead Organs.

The only question is appropriatness of this article for a Hepatplogy journal. This article is not clinically relevant and not a topic of interest for most Hepatologists. This article suits more for an Immunology or Infectious disease journal.

**Answer:** Thank you for yours wonderful comment about the essence of this review in which the immune mechanisms included in the human host liver infected with *Echinococcus Granulosus* is the main topic.

Dear reviewer 02462322 we have done extensive revision of this manuscript, and we hope that you could be satisfied with this corrections. They are highlighted in revised manuscript enclosed with all document that we re-submited to the Journal of Hepatology.

Yes, we agree that *E. garnulosus* may infect and other organs such as: lung, kidneys, heart, spleen and the brain, but in more than 70% liver is infected with this parasite. Less than 20% lung, about 2% kidneys, and less than 0.2% of the brain are preferentialy secondary infected. Why mainly the liver? First of all because of liver is a blood reservoir and can provide them easy to interfere hosts metabolic activity and to debilitate the host organism, as well as its immune system. The talent of parasites for invasion and then evasion follow-up of the immune responses is the most important characteristic for their long-term survival in the host. On the other side, other parasite such as  *Echinococcus Multilocularis* is the main parasite that inviding the lung of the human host. Whether the Th2 immune responses that is characteristics of the chronic stage of of alveolar echinococcosis (AE) provided (or supported) by direct contact between protoscoleces and dendritic cells (DC) within intermediate host lung is well examined, remain highly questionable? Since the larval stage is only produced very late in the infection and different from liver, the lung cannot stay a long time with echinococcal infection, for direct contact between protoscoleces and host DC wich is necessary, this immune reaction is examined extensively in the liver cystic echinococcosis. Moreover, for the explanation of the immune mechanisms of parasitic infections, which is extremely dificult, more confirmed scientific data of immune responses obtained in other infected organ such as the lung, kidneys, spleen and the brain need to be done.

Thank you for careful check. We improved and polished English.

Bearing in mind that this manuscript is divoted to the liver cystic echinococcosis, we are convinced that the World J of Hepatology is the right place for this publication and will be grateful if this artical could be published in this journal.

Regarding to clinically relevance and interest of Hepatologists for immune mechanisms, patients for sure will be very satisfied with the decision of Hepatologists and all other spcialists to be more interested on the immune mechanisms of parasitic infections. Then they can recognize simtoms of E. granulosus infection in patients more before ultrasound and scann immaging. These infections are increasing daily, especially in not developed and developing countries, and that except surgical approaches, no other relevant vaccines or medication still existing.

**Comments Reviewer’s code: 00537002**

The authors well reviewed that the understanding of the immune mechanisms to E. granulosus infection is extreme important. This information is useful for clinical management. This paper is unique, interesting and well reviewed. It is suitable for publication in Experimental and Therapeutic Medicine.

**Answer:** Thank you very much for your wonderfull comments. We supose that this article is suitable for more than one journal, but it will be great to be accepted for publication in Worl Journal of Hepatology.

**Comments Reviewer’s code: 03473431**

The review is complete, well written and I congratulate the authors. The paper is suitable for publication without changes.

**Answer:** We appreciate your kindness and wonderful comment. Thank you very much for yours effort to read this paper.