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Review

Strategies of *Echinococcus* species responses to immune attacks: Implications for therapeutic tool development

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ABSTRACT

Echinococcus species have been studied as a model to investigate parasite–host interactions. *Echinococcus* spp. can actively communicate dynamically with a host to facilitate infection, growth and proliferation partially via secretion of molecules, especially in terms of harmonization of host immune attacks. This review systematically outlines our current knowledge of how the *Echinococcus* species have evolved to adapt to their host's microenvironment. This understanding of parasite–host interplay has implications in profound appreciation of parasite plasticity and is informative in designing novel and effective tools including vaccines and drugs for the treatment of echinococcosis and other diseases.

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1. Introduction

Echinococcus granulosus and *Echinococcus multilocularis*, which cause cystic echinococcosis (CE) and alveolar echinococcosis (AE) respectively, are great threats to human and animal health. It is estimated that there are nearly two billion humans infected with helminths in the world [1] and around 2–3 million cases of echinococcosis with 0.3–0.5 million being due to AE [2]. *Echinococcus* species have been well studied in an aspect of parasite–host interplay. The infectious course of *Echinococcus* spp. is sophisticated and numerous host- and parasite-derived molecules are involved in it. *Echinococcus* species show differences in development, morphology, maturation, and egg and protoscolex production in different hosts [3–8]. These observations strongly support the idea that the infection and consequent development in a host are an outcome of parasite–host interactions. In agreement with this concept,

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the difference in cytokine production was also observed in the peripheral blood mononuclear cells (PBMCs) from patients with different genetic backgrounds [9].

Echinococcus species and their metabolites can modulate a variety of biological processes in cells or hosts in vitro [10] or in vivo [11]. For example, human basophils co-cultured with *E. multilocularis* vesicle or protoscolex extract were fully stimulated, releasing histamine, interleukin-13 (IL-13) and IL-4. This stimulation depends on IgE and the production kinetics of IL-4 is similar to that elicited by a *Schistosoma mansoni* egg antigen IPSE/alpha-1, which is a secreted glycoprotein and predominantly distributed in the subshell region of eggs [12,13], suggesting a similar mechanism for induction of a Th2 response.

In this review, we outline current knowledge of crosstalk events in echinococcosis and focus on parasite-released molecules involved in defense against host immune attacks, allowing us to understand deeply why parasites have evolved in order to be accommodated to host microenvironments. It is also anticipated to shed light on future studies on the development of anti-echinococcosis drugs and vaccines.

2. Dynamic parasite–host interactions

Host resistance to *Echinococcus* infections is embodied by the induction of delicate immune responses [14]. In mice, immune cells involved in anti-*Echinococcus* infections were dynamically changed in quantity or/and modified in functions at the different infectious stages [15]. Also, dynamic changes in antibody responses were observed in the course of echinococcosis in humans and mice [16]. The determinants involved in resistance to *Echinococcus* infections are not fully understood, but it is clear that the genetic background of hosts has great effects on the outcomes of parasite infection [14,17,18]. Additionally, IL-17 is likely to play a role in protection from the infections [19,20].

During the early infection of an intermediate host, activated oncospheres released from eggs survive various pressures, mainly from Th1 responses, and strive to encyst at preferred parasitic sites. Upon establishment, parasites not only continue to grow and proliferate but also harmonize antibody-mediated and cellular immune attacks (Fig. 1). As far as a host is concerned, the key thing is to keep the balance between parasite clearance and tissue or organ damage by immune responses. The fact that both Th1 and Th2 cytokines and chemokines co-exist in AE patients [10] suggests the presence of a mutual tolerance during the infection, which is essential for parasite proliferation and survival [21]. Therefore the delicate alterations of Th1 and Th2 profiles reflect real-time interactions between parasites and a host.

In the early infection phase, innate immunity may play an important role in controlling parasites' growth. This idea is evidenced by nonspecific antigen-induced protection in rats [14]. Immune effector cells, such as neutrophils and macrophages, are first in line to clear parasite infection but their normal activities can be interfered and even impaired by parasite molecules. An in vitro study demonstrated that a protein secreted by *Echinococcus* spp. was able to block the chemo-attractant activity of neutrophils [22]. It was also shown that normal macrophages were able to promote lymphocyte transformation stimulated by *E. multilocularis* metabolites, whereas the macrophages from the infected mice repressed the transformation and proliferation [23,24]. The functional changes of macrophages may result from the abnormal expression of key molecule(s), such as CD40, on the surface [24]. Eosinophils are involved in clearing infective larvae of parasitic helminths including *Echinococcus* species [14,25], but are rarely seen in mice infected with *E. multilocularis* [26]. The absence may be partially due to a cysteine protease released by parasites because it catalyzes the proteolysis of eotaxin, a pro-inflammatory molecule involved in chemotaxis of eosinophils [26,27].

The chronic stage of *Echinococcus* infection is characterized by a predominant Th2 immune response [5,14,26], partially being a consequence of progressive subversion of production from Th1-associated cytokines to Th2-associated cytokines. The subversion may be

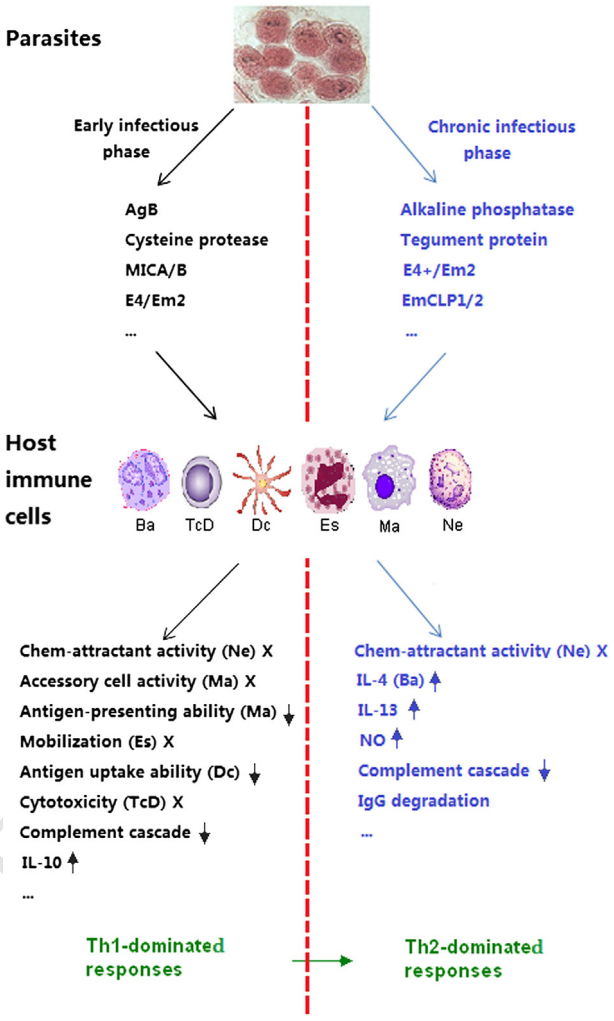

Fig. 1. *Echinococcus* species responses to host immune attacks. In the infection immune cells including neutrophils (Ne), macrophages (Ma), eosinophils (Es), dendritic cells (Dc), $CD8^+$ T cells (TcD) and basophils (Ba) are recruited to combat parasites. Concurrently, *Echinococcus* species dynamically interact with a host and express different active molecules at the different stages, which up- (↑) or down-regulate (↓) or eliminate (X) the functions of effector cells, leading to skewing a Th1-type response in the early phase towards a Th2-predominate response in the chronic phase.

dynamically driven by viable parasites in that specific antibodies against *E. multilocularis* first disappeared upon surgical removal of lesions or in patients treated with drugs [28,29]. Similarly, the occurrence of a Th2 immune response during the early CE infection also depends on viability of parasites [30]. In agreement with the idea, the level of IL-10 that suppresses an inflammatory response was significantly lower in the stimulated PBMCs of cured patients with hepatic lesions than that of patients with progressive AE [31].

3. Potential approaches to defend immune attacks by hosts

3.1. Interference of immune cell proliferation and differentiation

As a cellular surface component, glycosphingolipids are associated with cell proliferation and differentiation. *Echinococcus*-derived glycosphingolipids have been showed to inhibit mitogen-induced PBMC proliferation via down-regulation of IL-2, and the proliferative ability was restored by adding exogenous IL-2 [32].

Antigen B (AgB), one of the immunodominant proteins in the cyst fluid, is a heat-stable lipoprotein comprising of distinct 8 kDa subunits [33]. AgB is involved in host–parasite crosstalks through modulation of immune cell proliferation and differentiation. AgB is expressed in

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