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Immunobiology 211 (2006) 3–9
Immunobiology
www.elsevier.de/imbio

REVIEW

Complexity and function of cytokine responses in experimental infection by *Echinococcus granulosus*

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Received 8 April 2005; accepted 2 September 2005

Abstract

Cytokines are important in the regulation of the immune system and are secreted by a variety of cells in response to self and non-self stimuli. Communication within cells, in the same or distant anatomical sites, occurs via cytokines which determine the quality and intensity of inflammatory and adaptive immune responses. Infection by helminths is characterized by a dominant secretion of type-2 cytokines; IL-4, IL-5, IL-10 (among others), which down-regulates the induction and functions of type-1 cytokines. The molecular mechanisms involved in the polarization of type-2 responses and their biological significance in helminthic infections are unknown, and probably depends on each host–parasite system. Understanding these issues may contribute to immune therapy against parasitic infections.

Here we summarize our data obtained in *Echinococcus granulosus* experimental infection regarding type-2 cytokine induction and its putative role in the host–parasite interaction. Results suggest that induction of cytokine responses at different stages of infection is complex and depends on several parameters. In addition, they support the hypothesis that early IL-10, secreted by B cells in response to non-proteic antigens, may favour parasite survival and the establishment of a polarized type-2 cytokine response.

Keywords: Cytokine responses; *Echinococcus granulosus*; Glycoconjugates; Hydatid disease; IL-10

Contents

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doi:10.1016/j.imbio.2005.09.001

Introduction

Hydatid disease caused by the larval stage of the tapeworm *Echinococcus granulosus* is endemic in many parts of the world (Rausch, 1995). Secondary infection in humans constitutes an important medical problem: it occurs by dissemination of protoscoleces after the accidental rupture of cysts, and is due to the ability of protoscoleces to develop into new cysts (Thompson, 1995) evading the host immune response.

Experimental hydatidosis by inoculation of protoscoleces in mice is the current model to study the interactions between the host immune system and the parasite.

In this model, the host reacts to the protoscoleces producing innate local and adaptive systemic responses, which have been characterized by many authors (Heath, 1970; Araj et al., 1977; Cox et al., 1989; Jansen et al., 1992; Lui et al., 1992; Ferragut and Nieto, 1996; Severi et al., 1997).

The first signs of immune reaction can be observed with the naked eye in the peritoneal cavity or liver, as small accumulation of cells and protoscoleces, as early as 5–7 or 15 days after infection, respectively (Riley et al., 1984, 1985; Jenkins et al., 1986).

In our hands, and depending on the time point after infection, live or dead protoscoleces as well as early cysts are present in these reactions. Interestingly, we have observed that live protoscoleces, contrary to dead ones, detach easily within a short time from host cells in vitro. Kinetic analyses carried out in our group indicate that experimental infection by *E. granulosus* should be divided into: early infection (until day 20) and late infection (from day 21), depending on the predominant parasite stage, protoscolex or cyst. In both phases, the host produces humoral and cellular immune responses, but neither of them are able to eliminate the infection (Araj et al., 1977; Lui et al., 1992; Hernández and Nieto, 1994; Ferragut and Nieto, 1996). This suggests that each parasite stage utilizes evasion mechanisms to survive in an immunological hostile environment. The nature of those mechanisms and whether they are shared by protoscoleces or cysts remains unknown.

Given the biological complexity of this infection, we believe that a systematic analysis of the host–parasite interaction at the cellular and molecular level is needed to elucidate those mechanisms.

Type-2 cytokine responses: a hallmark of helminthic infections

A feature of infections by helminths is that they polarize the cytokine response toward a type-2 pattern, i.e. secretion of IL-4, IL-5, IL-10. The role of this response in the host–parasite interaction remains unknown in many infections and does not correlate with resistance in all cases (Finkelman et al., 1991; Reiner, 1994; Maizels and Yazdanbakhsh, 2003).

Although T helper cells contribute to polarization of cytokine responses (Mosmann et al., 1986; Scott et al.,1989), other non-Th populations can also secrete some type-1 or type-2 cytokines. This means that parasite-induced type-2 responses should not be correlated only with T-CD4+ cell stimulation, unless formally demonstrated.

The interest in understanding the role of type-2 responses in parasitic infections lies in the possibility of modulating these responses through the regulatory functions of cytokines. Thus, a non-protective type-2 response might be turned into a protective type-0 or type-1 response by immune intervention. However, progress in these approaches has been hampered by the lack of fundamental knowledge necessary for the rational design of immune therapy.

In this regard, we are interested in defining for the experimental infection with *E. granulosus*:

(1) the nature of parasite molecules able to stimulate type-2 cytokines;
(2) the cellular population (s) and receptor (s) interacting with those antigens;
(3) the importance of parasite load and anatomical localization, and
(4) the biological significance of type-2 responses.

Cytokine response against *E. granulosus*: the importance of parasite stage and load

Our hypothesis is that *E. granulosus* induces an early type-2 cytokine response which favours the establishment of infection. Once the protoscoleces survive and some of them differentiate into cysts, other mechanisms may operate to protect the cysts from the immune response and allow their growth.

Firstly, we analysed the cytokine response by cells from infected mice at different stages of infection. Results indicate that early infection by *E. granulosus* induces a type-2 cytokine response, which is consistent with one of the main features of helminthic infections. Splenocytes from infected mice secrete IL-10, IL-4 and IL-5 but not IFN-γ in response to specific stimulation in vitro. This response was detected from week 1 to 3 after infection in mice infected with 2000 protoscoleces (Dematteis et al., 1999). At later time points, week 4 or chronic infection (week 37), the cytokine profile changes towards a type-0 profile with significant levels