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Review article

TGF-β in Toxoplasmosis: Friend or foe?

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ABSTRACT

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan causing several forms of toxoplasmosis in humans. The main mechanisms that allow the development of the prolonged forms of the disease and its subsequent pathology are yet to be clarified. However, many researchers have hypothesized that immunological and genetic parameters may play crucial roles in the etiology of the disease. Transforming growth factor beta (TGF-β) is a cytokine with a dual role in the regulation of immune responses including those against parasites. However, the relationship between TGF-β and immune responses against *T .gondii* are not fully understood. The important roles played by TGF-β in the development of Th17 and T regulatory lymphocytes, mucosal immunity and regulation of immune responses have been documented and this provides insights into TGF-β function during parasitic infections such as toxoplasmosis. Therefore, the aim of this review is to collate the current information regarding the status and association of TGF-β with *T. gondii* infection.

Contents

1. Introduction

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan which leads to toxoplasmosis in humans and animals [1] and its main route for transmission is through oral ingestion [2]. Infection in immunocompetent individuals is largely asymptomatic

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and the parasite transforms to a latent stage, known as a bradyzoite [3,4]. It has also been demonstrated that under both acquired and genetic immunodeficiency conditions the parasite may become active and attack several tissues resulting in ocular diseases, splenomegaly and encephalitis in adults and abortion and hydrocephalus in fetuses [2]. However, a complete and specific immune response against *T .gondii* can completely clear the parasite from the infected tissues [5]. The mechanisms responsible for the development of toxoplasmosis in some patients and its eradication in others are yet to be fully clarified. However, some investigators have hypothesized that immunological and genetic parameters may play significant roles in the pathogenesis of toxoplasmosis or eradication of the toxoplasma parasites from the infected tissues. The current data suggests that cytokines play a significant role in the development of appropriate immune responses against *T. gondii* as well as the control of its related diseases [1]. Transforming growth factor beta (TGF-β) is a dual function cytokine which plays important roles in the development of Th17 cells, T regulatory (T reg) lymphocytes and mucosal immunity (see next sections) [6,7]. In addition to the activity of TGF-β, previous studies suggest that IL-17A is also an important cytokine which can induce an appropriate immune responses against pathologic microorganisms including parasites but it also plays crucial roles in the development of pathological conditions including autoimmune diseases [8,9]. TGF-β has a fundamental contribution in the development of appropriate mucosal immune responses [10], hence, this cytokine is essential for induction of immune responses against *T. gondii*. However, there is also some evidence suggesting that *T. gondii* is able to suppress immune responses against itself via T reg development [11] and it appears that in this scenario, TGF-β suppresses immune responses via the induction of immune-tolerance against *T. gondii* antigens, through T reg development (see Section 5). Therefore, it appears that TGF-β plays a dual role in toxoplasmosis; hence, the aim of this review was to address the recent information regarding the relationship between TGF-β and pathogenesis of toxoplasmosis.

2. Toxoplasmosis

T. gondii is a coccidian parasite first described in 1908 and is the causative agent of toxoplasmosis and utilizes felids as definitive hosts [12,13]. In human and other warm-blooded animals, *T. gondii* is one of the most common causes of parasitic infections [12]. *T. gondii* infection is distributed worldwide and approximately one-third of humans on the planet, i.e. 25–30%, have been infected with this parasite [14]. The prevalence of toxoplasmosis varies widely between countries, for instance, previous studies reported that in north America, northern Europe, south east Asia and the Sahelian countries of Africa the seroprevalences of toxoplasmosis is low (10–30%), while, in countries of central and southern Europe, moderate prevalence (30–50%) has been found [15]. Furthermore, high prevalence of toxoplasmosis has been reported in Latin America and tropical African countries [15]. Interestingly, it has also been documented that *T. gondii* infections are common in other animals including raccoons, bears, pigs, fox, felids and skunks [14]. *T. gondii* can also induce clinical and subclinical manifestations in wild cervids, marsupials, marine mammals, monkeys and ungulates [14]. Several factors can affect seroprevalence of toxoplasmosis in humans and animals. For example, the survival of oocysts in the environment may be affected by climatic factors, and the infection rates in meat-producing animals play key roles in the prevalence of toxoplasmosis in human populations [16]. For instance, a high prevalence of toxoplasmosis was typically reported in tropical countries with a humid and warm climate [17]. Based on the past investigations, it appears that anthropogenic factors including economic, social, dietary and cultural habits and water quality also influence the prevalence of toxoplasmosis [18]. Interestingly, it has also been shown that toxoplasmosis has a positive relation with age in some countries [18]. It appears that efficiency of the immune system is significantly associated with age, environmental factors and genetics and that these factors play a crucial role in the persistence or clearance of toxoplasmosis.

3. Immune responses

Immune responses against pathogens, including toxoplasmosis, consists of two main arms, innate and adaptive immunities. There are a wide range of cellular and molecular responses against pathogens and some of the immune responses against toxoplasmosis are briefly reviewed in the following subsections.

3.1. Innate immune responses

Innate immunity plays crucial roles in defense against pathogens. Monocyte and macrophages are the most important innate immune populations which induce inflammation via production of several molecules including pro-inflammatory cytokines, nitric oxide (NO) and so on. Thus, the cells are able to kill or suppress *T. gondii* growth [19–21].

Production pro-inflammatory cytokines against *T. gondii* antigens leads to the promotion of effector mechanisms in macrophages [22,23]. *T. gondii* infected macrophages are also the main source of IL-12, which is an important pro-inflammatory cytokine [24]. IL-12 promotes T cells to produce IFN-γ which subsequently increases the activation of macrophages in a positive feedback loop [21].

NK cells are the other innate immune cell that produces IFN-γ in the early steps of infection and can recognize and kill the microorganisms. During the infection they traffic to the site of infection and release IFN-γ and stimulate macrophages. Furthermore, several studies have shown that IL-12 produced by other cells (e.g. dendritic cells, macrophages and neutrophils) stimulates the production of IFN-γ by NK cells [25]. NK cells can also influence adaptive immune responses and that secretion of IFN-γ by NK cells leads to the development of T $CD4^+$ responses [26].

Neutrophils, which are another innate cell population, also play key roles against toxoplasmosis. It has been reported that mice that do not express CXCR2 and CCR1, the main chemokine receptors expressed on the surface of neutrophils, are susceptible to *T. gondii* infection [27], suggesting an important role for neutrophils in the response to the pathogen. They are the first cells that are recruited to the site of infection and can kill microorganisms by generation of reactive oxygen species [28].

3.2. Adaptive immune responses

The role of adaptive immune responses against *T. gondii* have been reported by several studies. Adaptive immunity consists of two main arms, humoral and cellular immunity. Cellular response is more important than humoral immunity against the disease because toxoplasmosis is an intracellular pathogen. T $CD4^+$ or T $CD8^+$ deficient mice are susceptible to *T. gondii* during the chronic stage of the disease [29,30] suggesting the role of these molecules is significant with $CD4^+$ T cells being more important during the chronic phase of infection. Production of IFN-γ and expression of CD40L are two mechanisms which $CD4^+$ T cells use to activate macrophages and other innate immune cells [31]. However, *T. gondii* is an intracellular pathogen and therefore the $CD8^+$ T cells play a more critical role during the infection. Accordingly, the mice that lack $CD8^+$ T cells show increased susceptibility to *T. gondii* [30].