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Review

CD40 and the immune response to parasitic infections

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ABSTRACT

The interaction between CD40 and CD154 regulates many aspects of cellular and humoral immunity. The CD40–CD154 pathway is important for resistance against a variety of parasites. Studies done with these pathogens have provided important insight into the various mechanisms by which this pathway enhances host protection, mechanisms by which pathogens subvert CD40 signaling, conditions in which the CD40–CD154 pathway promotes disease and on modulation of this pathway for immunotherapy.
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1. Introduction

CD40 is a member of the TNF receptor superfamily that is expressed on antigen presenting cells (APCs) and various non-hematopoietic cells [1–4]. Its counter receptor CD154 (CD40 ligand) is expressed primarily on activated $CD4^+$ T cells [5,6]. The interaction between CD40 and CD154 controls many aspects of cellular and humoral immunity including T cell-mediated activation of dendritic cells (DC) and monocyte/macrophages, T cell priming, proliferation of B cells, Ig synthesis, isotype switch, and germinal center formation [2,7–12].

The relevance of CD40 in humans was established by the discovery that the congenital immunodeficiency called X-linked hyper IgM syndrome (X-HIM) is caused by the lack of functional CD154 [13]. Although patients with this syndrome exhibit defects in humoral immunity, the most important clinical feature of this immunodeficiency is an increased incidence of infections with opportunistic pathogens that include parasites such as *Cryptosporidium parvum* and *Toxoplasma gondii* [14–17]. Studies using parasites provided important insight into the role of CD40 in regulation of cell-mediated immunity as well as likely explanations for the susceptibility to opportunistic infections observed in patients with X-HIM [17].

2. *Toxoplasma gondii*

T. gondii is an obligate intracellular protozoan of worldwide distribution. The parasite exists in three forms during its life cycle: (1) the tachyzoite, the form of the parasite that infects almost any nucleated cell; (2) the tissue cyst that appears to persist in tissues of the infected host for life; and (3) the oocyst that forms during the sexual cycle that takes place exclusively in the intestine of felines. Infection in humans follows ingestion of poorly coked meat that contains tissue cysts, or ingesting food or water contaminated with oocysts.

Acute infection with *T. gondii* is characterized by dissemination of tachyzoites throughout the body. T cell-mediated immunity and the production of cytokines, notably IFN-γ and IL-12, are critical for control of the infection [18,19]. However, the organism successfully evades eradication. The chronic phase of infection that ensues is characterized by the disappearance of tachyzoites and the formation of tissue cysts (primarily in the central nervous system and skeletal muscle).

T. gondii infection is usually asymptomatic in immunocompetent humans. The development of disorders of cell-mediated immunity results in reactivation of the chronic infection that typically manifests as toxoplasmic encephalitis [20,21]. The other scenario where *T. gondii* infection is of clinical relevance is when the infection is acquired congenitally.

2.1.1. Role of CD40–CD154 signaling in regulation of type 1 cytokine response during T. gondii infection

The fact that patients with X-HIM are susceptible to toxoplasmic encephalitis and disseminated toxoplasmosis [16,17,22,23] plus the demonstration that $CD154^{-/-}$ mice infected with *T. gondii*

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develop encephalitis provide clear evidence of the relevance of the CD40–CD154 pathway in resistance against *T. gondii*. Studies in humans revealed that this pathway regulates IL-12 and IFN-γ production during the interaction between human T cells and *T. gondii*-infected APC [17,24]. Interestingly, *T. gondii* induces profound phenotypic changes in APC that influence type 1 cytokine production. Infection with viable *T. gondii* but not phagocytosis of killed parasites or incubation with *T. gondii* lysate antigens induces activation of purified human monocytes and immature monocyte-derived DC characterized by upregulation of MHC class II, CD40, CD80, and CD86 [17,25–27] (Fig. 1). Human monocyte-derived DC that contain intracellular tachyzoites do not produce IL-12 p70 unless they receive CD40 stimulation from T cells [26] (Fig. 1). Interestingly, IL-12 p70 production is only observed if monocyte-derived DC are infected with viable tachyzoites and not if these cells phagocytose killed parasites or if they are exposed to *T. gondii* lysates [26,28]. Studies using mouse DC revealed that production of IL-12 p70 appears to depend on *T. gondii*-induced IL-12 p40 production and CD40 upregulation, while CD40 stimulation of DC results in balanced production of IL-12 p35 [29]. The studies using human and mouse cells indicate that the response of DC to *T. gondii* together with CD40 stimulation of these cells allow the immune system to induce IL-12 p70 production in situations where such a response would be appropriate [26,29,30].

CD40–CD154 interaction between human T cells and *T. gondii*-infected APC results in IL-12 production that in turn, drives secretion of IFN-γ [17,26] (Fig. 1). However, experiments using neutralizing anti-IL-12 mAb indicated that *T. gondii*-infected APC also induce IFN-γ production independently of IL-12 [26]. This IL-12-indepedent production of IFN-γ may be caused by direct co-stimulation to T cells since it is ablated by simultaneous neutralization of the CD40–CD154 and CD80/CD86–CD28 pathways [26] (Fig. 1). Of relevance, *in vivo* studies in mice demonstrated that pathogen-specific $CD4^+$ T cells of the Th1 phenotype develop in animals deficient in IL-12 [31]. In addition, blockade of both CD154 and CD28 pathways is required for effective inhibition of IFN-γ production in a mouse model of toxoplasmosis [32].

While the role of CD40–CD154 signaling for control of IL-12 production has also been reported in *T. gondii*-infected $CD154^{-/-}$ mice [33], other animal studies revealed the existence of CD40-independent IL-12 secretion in response to *T. gondii* [34]. *T. gondii*

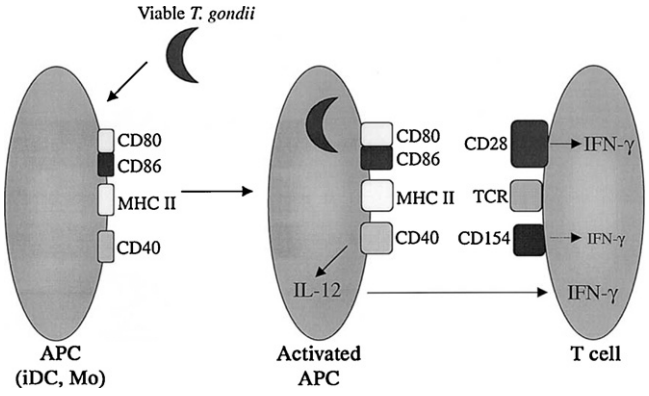

Fig. 1. Role of CD40–CD154 interaction in the induction of a type 1 cytokine response against *Toxoplasma gondii*. Infection of either human immature dendritic cells (iDC) or monocytes (Mo) with viable tachyzoites of *T. gondii* induces upregulation of CD40, CD80, CD86, and major histocompatibility complex (MHC) class II molecules. T cells activated through their T cell receptor acquire expression of CD154. Infected antigen presenting cells produce bioactive IL-12 after CD40–CD154 interaction. In turn, IL-12 induces T cells to secrete IFN-γ. T cells can also produce IFN-γ in response to *T. gondii* in the absence of IL-12. This IL-12-independent secretion of IFN-γ requires CD80/CD86–CD28 and, to a lesser extent, CD40–CD154 interaction (presumably resulting in direct T cell stimulation). TCR, T cell receptor. Reprinted with permission (Ref. [30]).

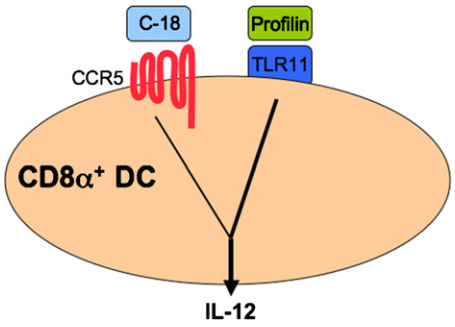

Fig. 2. CD40-indepedent production of IL-12 in response to *T. gondii*. Profilin and cyclophilin-18 (C-18) secreted by *T. gondii* or present in parasite lysates bind to TLR11 and CCR5 respectively expressed on mouse $CD8\alpha^+$ dendritic cells (DC). These two pathways cooperate to induce IL-12 production. TLR11 plays a dominant role in stimulation of IL-12 production. This process occurs independently of CD40 signaling.

lysates induce IL-12 production by mouse $CD8\alpha^+$ DC in a CD40-independentt manner [34]. IL-12 production in response to soluble antigens was explained by *T. gondii* profilin-like protein that binds to TLR11 [35] and in part by *T. gondii* cyclophilin 18, a molecule released by tachyzoites that binds to CCR5 [36,37] (Fig. 2). While this pathway induces IL-12 production in mice, it is not known whether the same can be said for humans. *T. gondii* lysates antigens do not appear to cause IL-12 production by human dendritic cells [28]. Moreover, TLR11 is represented in humans only by a pseudogene [38] that contains a stop codon that would prevent protein expression [39].

Studies in patients with defective CD40–CD154 signaling support the relevance of this pathway in the regulation of type 1 cytokine response in humans. Toxoplasmic encephalitis and disseminated toxoplasmosis have been reported in patients with X-HIM [16,17,22,23]. Peripheral blood mononuclear cells (PBMCs) and T cells from X-HIM patients secrete markedly decreased amounts of IFN-γ in response to *T. gondii* compared to healthy controls [17]. Similarly, PBMC from patients with X-HIM fail to secrete or secrete low amounts of IL-12 after incubation with *T. gondii* [17]. In contrast, IL-12 production in response to Staphylococcus aureus Cowan I strain plus IFN-γ is similar to that in control subjects [17]. Studies using recombinant CD154 trimer further confirmed the relevance of CD154 signaling for regulation of cytokine synthesis. CD154 trimer restores IL-12 secretion in response to *T. gondii* by PBMC from patients with X-HIM, and through this mechanism, it normalizes IFN-γ production in response to the parasite [17]. In addition to regulation of type 1 cytokine production, studies in patients with X-HIM indicate that CD154 appears to be crucial for *in vivo* priming of human T cells against *T. gondii* [17]. Taken together, the studies using *T. gondii* identified defective type 1 cytokine response and impaired T cell priming as likely explanations for susceptibility to opportunistic infections in X-HIM patients.

CD40–CD154 signaling is also relevant to $HIV\text{-}1^+$ patients. Studies using antigenic stimulation by pathogens including *T. gondii* as well as polyclonal T cell stimulation revealed that $CD4^+$ T cells from these individuals exhibit lower levels of CD154 [40–43]. This defect appears to contribute to impaired type 1 cytokine response associated with HIV-1 infection [40,41]. The explanation for diminished CD154 expression in HIV-1 infection likely lies on the fact that the CD40–CD154 interaction induces bi-directional signaling: CD40 not only induces activation of APC but CD40 also regulates CD154 expression. Many studies reported that CD40 decreases CD154 expression [44–46]. Enhanced susceptibility to CD40-mediated regulation likely explains why expression of CD154 during T cell–APC interaction is diminished in $CD4^+$ T cells from $HIV\text{-}1^+$ patients [42]. Studies that used *T. gondii* support a model whereby $CD4^+$ T cells from these patients have an altered set

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