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Major Role for CD8+T Cells in the Protection Against *Toxoplasma gondii* Following Dendritic Cell Vaccination

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1. Introduction

Toxoplasma gondii is an obligate intracellular protozoan that infects one-third of the world population. Asymptomatic in immunocompetent hosts, toxoplasmosis has severe consequences in immunosuppressed individuals and can even lead to death.^{1,2} Congenital toxoplasmosis causes development of sequelae later in life, including chorioretinitis, hearing loss or mental retardation.³ *Toxoplasma gondii* is also recognized as being a major cause of abortion in farm animals, such as sheep and goats thus causing substantial reproductive and economic losses.⁴ Additionally, these infected animals are a parasitic reservoir involved in human contamination. Recently it has been reported that *Toxoplasma gondii* has some degree of causal relation to Schizophrenia⁵ because of the positive relationships between the prevalence of *Toxoplasma* antibodies and the development of schizophrenia. A recent article reports that *Toxoplasma* infection in rodents blocks the aversion toward predator odors and develop an attraction suggesting an integrating effect of the parasite.⁶ This study provides an example of the behavioral effects of *Toxoplasma* in models of psychiatric and emotional conditions.

Once human beings or animals have been infected, no drug treatment available at present will eliminate the parasite. Nor is there any vaccine for human use to control the disease.

Primary infection with *T. gondii* results in the setting of both humoral and cell-mediated immune responses and confers long-term protection. This suggests that the development of an efficient vaccine is a realistic goal. Moreover because of the enormous estimated costs and social impact of *T. gondii* infection and the fact that primary infection with this parasite could give the host a protective immunity against re-infection, many studies have investigated possible solutions for an efficient vaccine.^{7,8} However the immune response set following a *T. gondii* infection firstly needs to be clearly defined before a vaccine can be developed.

Host resistance seems to occur *via* synthesis of IFN- γ by NK cells and adaptive T lymphocytes.⁹ Following infection, antigen-presenting cells synthesize TNF- α and IL-12

which induce NK cells to secrete IFN- γ . The combined action of IL-12 and IFN- γ induce a strong differentiation of T helper precursors into Th1 lymphocytes. These CD4⁺ T cells then synthesize large amounts of IFN- γ and IL-2. These two cytokines finally induce CD8⁺ T lymphocytes proliferation and IFN- γ secretion.¹⁰ Thus protection against *T. gondii* infection is mainly attributed to cell-mediated immunity.

Previous studies have shown that both CD4⁺ and CD8⁺ T-cell subtypes are involved in the protection and the relative contribution of these two populations was investigated by adoptive transfer or *in vivo* depletion.¹⁰ The transfer of T cells from infected or immunized mice to naïve mice provided protection against a lethal challenge of *T. gondii*, but this protection was abolished by depletion of CD8⁺ T cells prior to transfer but not by depletion of CD4⁺ T cells^{11,12}. Similarly, transfer of CD8⁺ T cells from chronically infected mice to naïve WT or nude mice was also able to provide protection from *T. gondii* challenge¹¹. However, in response to *T. gondii*, the lack of CD8⁺ T cells could be compensate by a potent NK cell response, though β 2-m-deficient mice remained more susceptible than WT mice.¹³ All these data suggest a prominent role of CD8⁺ cells with a supporting role for CD4⁺ cells during the acute phase as well as during the chronic phase of infection.

CD8⁺ T lymphocytes mediated protection by IFN- γ which has been demonstrated to be crucial by studies using neutralizing antibody to IFN- γ or mice deficient in its production^{14, 15, 16}. Evidence that production of this cytokine and subsequent protection against toxoplasmosis is dependent on CD8⁺ T cells was demonstrated by showing that treatment of infected mice with anti-CD8 antibodies resulted in reduced production of IFN- γ and loss of IFN- γ -mediated protection.^{17, 18} CD8⁺ T cells can also mediate perforin-dependent cytotoxicity against target cells that present the correct peptide in the context of MHC on their cell surface. Several studies have shown that CD8⁺ T cells isolated from immunized or infected mice lysed infected cells or targets pulsed with *Toxoplasma* antigens^{19,20, 21,22}. All these data suggest a prominent role of CD8⁺ cells during the acute phase as well as during the chronic phase of infection.

If IFN- γ is the major cytokine of resistance to *T. gondii*, IL-12 is a crucial initiation cytokine to trigger an efficient cell-mediated immunity. Indeed, IL-12 is a major cytokine secreted in response to *T. gondii* by neutrophils²³, macrophages²⁴, plasmacytoid dendritic cells (pDCs)²⁵, conventional dendritic cells (cDCs)²⁶ and the subset of cDCs expressing CD8 α ²⁷. Recently Mashayekhi et al have demonstrated the critical role of CD8 α ⁺ DCs for activation of innate immunity through IL-12 production during *T. gondii* infection and have shown that CD8 α ⁺ DCs are the only cells whose IL-12 production is required to control acute infection²⁸.

IL-12 is produced in response to Toll-like receptor (TLR) recognition of molecular structures broadly conserved across microbial species²⁹ that triggers the early IFN- γ secretion following *T. gondii* infection. IFN- γ activates various cell-intrinsic antiparasitic defense pathway within infected cells for intracellular elimination of *Toxoplasma*, including the activation of interferon-regulated GTPases (IRGs)^{30,31}, induction of reactive nitrogen intermediates³², tryptophan degradation in human cells³³, and autophagy^{34,35}.

So DCs are the first producers of IL-12 in response to *T. gondii* antigens and several previous studies suggest that DCs play an important role in the setting of the immune response to the intracellular parasite *T. gondii* during the early and chronic phases of infection.

The central role of DCs in controlling immunity makes these cells ideal tools for priming functional immune responses. Many studies have proposed the use of DCs as vaccine vectors. For instance, *T. gondii* extract-pulsed splenic DCs administered *in vivo* induce a strong humoral and cellular immune response and promote protection against a virulent challenge.^{36, 37} It has been also observed that *Toxoplasma* pulsed DCs induced protective immunity against *T. gondii* infection in both syngeneic and allogeneic mouse models. This protection was associated with the induction of humoral and cellular *Toxoplasma*-specific responses³⁸. However, expensive treatments of this type, based on living cells, could be envisaged only for severe diseases, such as cancers, which are specific to the individual due to MHC restriction. For ethical reasons, it is not possible to use live cell lines in an immunisation protocol in humans. New approaches, involving the development of non-live and DNA-free vaccines, must therefore be pursued. Moreover, the use of DCs is limited by the difficulty of obtaining large numbers of cells suitable for vaccination purposes.

If DCs can effectively process *T. gondii* antigens for presentation *in vivo*, their use in a vaccine strategy is not acceptable. It is of interest to study the effector mechanisms induced by *T. gondii*-sensitized dendritic cells as a well-described protective immune response would help the development of new efficient vaccine strategies.

So the relative contribution of two main lymphocytic populations, CD4+ and CD8+, was investigated in a model of chronically infected mice, following dendritic cell vaccination and lymphocyte depletion.

We first determined the role of CD4+ T lymphocytes after an efficient depletion of over 90%. The results revealed a minor role for these cells since CD4-depleted or non depleted mice have similar cytokine secretion profiles in spleen as well as in MLNs. Moreover, depleted mice did not show any significant loss of protection in terms of brain cyst load. These results contrast with those obtained by Casciotti in 2002.¹⁰ They demonstrated that CD4+ T cells are important for early IFN- γ production during *T. gondii* infection and that lack of CD4+ lymphocytes leads to parasite multiplication in the tissues. Moreover CD4 deficient mice exhibited parasite burdens in the brain. Johnson and Sayles also showed the implication of CD4+ cells as they induce CD8+ T cells through the production of IL-2 and maintain CD8+ T cells effector immunity.³⁹ CD4+ T lymphocytes also contributed significantly to protection against chronic infection *via* their role as helper cells for production of isotype-switched antibodies. The contradictory results obtained following infection alone or following vaccination plus infection could result from a particular orientation of the immune response. Indeed, in our protocol dendritic cells could directly prime CD8+ T lymphocytes *via* cross-presentation of *T. gondii* antigens, as previously demonstrated by Gubbels *et al.*⁴⁰

So CD4+ T lymphocytes appeared to be not implicated either in spleen or mesenteric lymph node cytokine secretion or in long-term protection of mice.

We next studied the implication of CD8+ T lymphocytes after an efficient depletion of over 90%. In spleens CD8+ cells seem to be responsible for cytokine synthesis. Indeed, their depletion leads to a significant decrease of both Th1 (IFN- γ and IL-2) and Th2 (IL-10 and IL-4) cytokines. We further confirmed these data by identifying the CD8+ T cells as the IFN- γ -producing cells. These results are in accordance with another vaccination assay where Gazzinelli *et al.* got similar results. They vaccinated BALB/c mice with the mutant *T. gondii* strain TS-4 before depleting them of CD4+ or CD8+ lymphocytes and challenging them with

a lethal dose of tachyzoites. They identified IFN- γ -producing CD8⁺ T cells as the major effectors of immunity *in vivo*.⁴¹ Moreover, in our experiment, CD8⁺ cells depletion induced a loss of protection in mice previously immunized with pulsed dendritic cells, so CD8⁺ cells are crucial for CBA/J mice resistance to *T. gondii* infection. CD8⁺ cells also appear to play a major role in *Trypanosoma cruzi* infection. Mice lacking CD8⁺ T-cell function fail to control a normally non-lethal infection and die early in the acute phase. Moreover, depletion of CD8⁺ T cells in the chronic phase results in increased parasite load.⁴²

In contrast to spleens, MLNs showed increased secretions of cytokines following CD8⁺ depletion suggesting that CD8⁺ T lymphocytes could act as regulatory cells. A recent review summarizes the current knowledge on CD8⁺ Tregs, a newly described CD8⁺ lymphocyte subtype with dedicated suppressor function.⁴³ Although not proven in parasitic infections, their importance in autoimmunity is well-documented and they could be responsible for the moderation of the immune response set in local lymph nodes. It would be of importance to determine which cell population is responsible for the MLN IFN- γ secretion. It has been demonstrated that splenic NK cells could produce this cytokine in response to *T. gondii* in MHC-I deficient mice thus unable to activate CD8⁺ T cells.⁴⁴

So CD8⁺ T lymphocytes appeared as the main effectors, inducing a strong Th1 response in spleen while inhibiting both Th1 and Th2 responses in mesenteric lymph nodes.

This is the first study to point to CD8⁺ lymphocytes as the unique effector population responsible for the protection of mice following efficient DC vaccination and subsequent virulent challenge. This is partly in accordance with a previous description of CD8⁺ T cells as effector lymphocytes while CD4⁺ T cells were crucial for the regulation of the immune response in a very different vaccination assay.¹⁷

We provide further insight into the long-term immunity that protects mice against *T. gondii*, a ubiquitous parasite resulting in severe sequelae in immunocompromised individuals. Future studies will be needed to determine how *T. gondii* antigens are presented to CD8⁺ lymphocytes. A recent study showed encouraging results. Indeed, the authors demonstrated that CD8⁺ DCs were very efficient in processing and cross-presenting exogenous antigen to CD8⁺ T cells. They also highlighted CD24 as an essential co-stimulatory molecule required for CD8⁺ DCs to generate CD8⁺ and CD4⁺ T-cell responses.⁴⁵ The possible roles of various CD4⁺ lymphocyte subtypes and other immune cell populations during the chronic phase of the disease also need to be elucidated, with a view to developing an effective vaccine to be used in animals that serve as a natural reservoir for human contamination.

Finally, the next step to efficiently develop a vaccine strategy will be to identify which parasitic peptides are cross-presented by DCs to CD8⁺ T cells to initiate the specific protective response to *T. gondii*. Blanchard *et al.* recently found that a decapeptide from the dense granule protein GRA6 could effectively induce such protection against *T. gondii*, as assessed by survival of mice.⁴⁶ However, their study was conducted using bone marrow-derived DCs. It could be of interest to target *in vivo* splenic CD8⁺ DCs, known to protect our mice, with such putative protective parasitic peptides.

Fully dissecting the cellular and molecular events leading to this protective response will allow for better design of vaccine strategies to enhance immunity and decrease morbidity and mortality associated with *Toxoplasma* infection.

Thus, transfer of *Toxoplasma* antigens to lymphoid resident DCs is a feature of DC vaccination that can be exploited to improve vaccine outcome.

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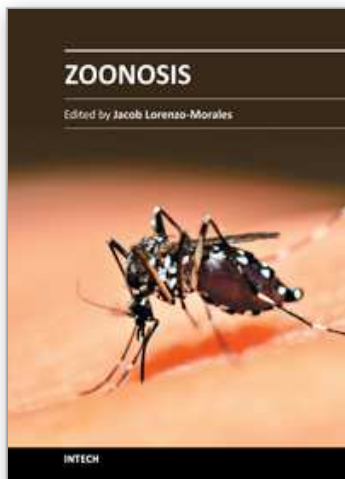
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Zoonosis

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Zoonotic diseases are mainly caused by bacterial, viral or parasitic agents although "unconventional agents" such as prions could also be involved in causing zoonotic diseases. Many of the zoonotic diseases are a public health concern but also affect the production of food of animal origin thus they could cause problems in international trade of animal-origin goods. A major factor contributing to the emergence of new zoonotic pathogens in human populations is increased contact between humans and animals. This book provides an insight on zoonosis and both authors and the editor hope that the work compiled in it would help to raise awareness and interest in this field. It should also help researchers, clinicians and other readers in their research and clinical usage.

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