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Role of CD8$^+$T cells in the host response to *Chlamydia*

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Abstract

Chlamydia infections constitute a major public health problem. Although multiple arms of the immune system participate in the control of *Chlamydia* in infected hosts, T lymphocytes are essential. This review focuses on the roles that CD8$^+$T cells may play in immunoprotection and immunopathology following recognition of *Chlamydia*-infected cells.

Keywords: *Chlamydia*; CD8$^+$T cells

1. Introduction

Members of the *Chlamydiaceae* family are obligate intracellular Gram-negative bacteria that include the human pathogens *Chlamydia trachomatis* (*Ct*) and *Chlamydia pneumoniae* (*Cpn*). While *Ct* is responsible for ocular and sexually transmitted diseases that can result in blindness and infertility, *Cpn* is a common cause of upper respiratory infections and pneumonia and has been associated with several chronic inflammatory conditions such as atherosclerosis and chronic obstructive pulmonary disease (COPD) [1–3]. When diagnosed early, *Chlamydia* infections can be treated with antibiotics. However, the high costs required to identify and treat individuals with mild or no symptoms limits the feasibility of this control strategy. Moreover, hosts can remain chronically infected despite chemotherapy, and some antibiotics may induce chlamydial persistence [4]. Thus, development of safe and effective vaccines represents a cost-effective approach that would have a greater impact on the high prevalence of *Chlamydia* infections and the prevention of severe long-term sequelae.

Like all chlamydiae, *Ct* and *Cpn* have a unique biphasic developmental cycle alternating between an infectious metabolically inert elementary body (EB) and a replicating metabolically active reticulate body (RB). After entry into susceptible cells such as epithelial cells, macrophages, endothelial and smooth muscle cells, the EB remains within a non-acidified vacuole known as an inclusion, where it differentiates into a RB, which replicates by binary fission. The generated progeny differentiate back into EBs that are then released upon host cell lysis to infect other cells. Under certain conditions, however, *Chlamydia* enters a persistent non-replicating stage but remains capable of resuming a productive cycle when the adverse conditions are no longer present. During *Chlamydia* infections, the immune system of the infected host encounters antigens expressed at various stages of the chlamydial developmental cycle and during persistence.

Although our knowledge of bacterial antigens and defense mechanisms that lead to protective immunity against *Chlamydia* has increased substantially in recent years, developing vaccines or immunotherapies against *Ct* and *Cpn* will require an improved and comprehensive understanding of all the elements of the immune system that act in concert to control chlamydial growth and facilitate pathogen clearance without causing immunopathology. Because type 1 T cells play a central role in anti-*Chlamydia* immunity, immune-based control strategies against *Ct* and *Cpn* will need to stimulate this group of lymphocytes. However, to develop T cell-stimulating *Chlamydia* vaccines it will be important to dissect

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the antigen-specific T cell responses that correlate with protective effector mechanisms from those that associate with the promotion of chlamydial persistence and tissue damage.

Numerous studies have shown that type 1 cytokine-secreting $CD4^+$T (Th1) cells inhibit *Chlamydia* replication mostly via the secretion of IFNγ and by stimulating the protective function of other immune and inflammatory cells [5]. However, given the obligate intracellular nature of *Chlamydia*, there is an increased interest to determine the contribution of $CD8^+$T cells in controlling replication of these pathogens. This review describes the evidence supporting a role for $CD8^+$T cells in the response to *Chlamydia* infection and the consequences of $CD8^+$T cell-mediated recognition of *Chlamydia*-infected cells as it relates to immunoprotection and immunopathology.

2. Evidence of a role for $CD8^+$T cells in the immune control of *Chlamydia*

An intact T cell compartment is required for resistance against *Chlamydia* infection. T cell-depletion and -adoptive transfer experiments have, respectively, ablated and reconstituted protection in naïve mice challenged with *Chlamydia* [6,7]. Moreover, in *Chlamydia*-infected experimental animals, both $CD4^+$ and $CD8^+$T cell subsets are detected at the site of infection [8–11]. Using mice made deficient of $CD4^+$ or $CD8^+$T cells by antibody treatment or as a result of mutations in the CD4, CD8, major histocompatibility complex (MHC) class II, or β_2-microglobulin genes, the relative contribution that each of these two T cell subsets play in protective immunity against *Chlamydia* has been investigated. Although both $CD4^+$ and $CD8^+$T cells contribute to protection, differences exist depending on the model of chlamydial infection studied. For instance, depletion of $CD8^+$ but not $CD4^+$T cells in immune mice abrogates protection upon challenge with *C. psittaci* [12]. Similarly, in the absence of $CD8^+$T cells, increased bacterial burdens and disease severity are observed during both a primary and secondary infection with *Cpn* [13,14]. By contrast, in *C. trachomatis*-infected and reinfected mice, depletion of $CD4^+$T cells abrogates protection more significantly compared to the depletion of $CD8^+$T cells [15,16]. Nevertheless, protective $CD8^+$T cells are elicited following *Ct* infection [15,17]. It should be noted that $CD4^+$T cells are often needed for the induction and preservation of a functional $CD8^+$T cell response and in their absence, both $CD4^+$ and $CD8^+$T cell effector functions are impaired. Thus, the minor role that some studies have reported for $CD8^+$T cells in the immune control of *Chlamydia* may be underestimated.

Most information on the immune response to *Chlamydia* has been obtained from work with mice. In general, mouse models have proven to be excellent systems to study the immune mechanisms that are thought to control *Chlamydia* in humans. However, the successful design of a vaccine for *Chlamydia* will require validation of mouse data in humans and an increased understanding of the correlates of protective immunity in infected humans. Thus far, however, relatively few studies have evaluated human T cell immune responses to *Chlamydia*. Yet, like in mice, both T cell subsets are detected at the site of infection, and available data strongly suggest that T cells play an important role in protective immunity [18–20, unpublished]. However, the contribution of $CD4^+$ and $CD8^+$T cells to the human anti-*Chlamydia* immure response remains unknown.

3. Pathogen-specific $CD8^+$T cells are elicited during *Chlamydia* infection

An increasing body of evidence indicates that *Chlamydia* infection primes a pathogen-specific $CD8^+$T cell response in mice and humans. In pioneering studies using *Ct* murine infection models, it was shown that splenic $CD8^+$T cells could specifically lyse *Chlamydia*-infected fibroblasts, and that *Ct*-specific type 1 cytokine-producing $CD8^+$ cytotoxic T (Tc1) cells were partially protective when adoptively transferred into infected mice [17,21,22]. Nearly 5 years later, human leukocyte antigen (HLA) class I-restricted *Ct*-specific cytolytic $CD8^+$T cells were detected in the peripheral blood mononuclear cells (PBMC) from individuals with history of previous *Ct* infections of the genital tract [23].

More recently, the lungs of *Cpn*-infected mice were shown to include pathogen-specific $CD8^+$T cells with an ex vivo capacity to produce IFNγ and exert cytolytic effector function upon recognition of *Cpn*-infected macrophages [24,25]. *Cpn*-reactive $CD8^+$T cells have also been detected in PBMC from *Cpn*-exposed individuals, in sputum from patients with COPD that are infected with this pathogen, and in *Cpn*-positive plaque from atherosclerotic persons [26,27] unpublished.

Most studies supporting the priming of $CD8^+$T cells during *Chlamydia* infection have searched for T cells that are restricted by classical MHC class Ia molecules. However, a *Chlamydia*-specific non-classical MHC class Ib-restricted $CD8^+$T cell response is also stimulated in *Ct*- and *Cpn*-infected hosts. Studies with *Cpn*-infected mice showed that primed pathogen-specific $CD8^+$T cells include a subpopulation of Tc1 effectors that exerts non-classical MHC class Ib-(H2–M3)-restricted lysis of *Cpn*-infected macrophages and that upon adoptive transfer into naïve mice, reduce lung *Cpn* loads following infectious challenge [25]. Using PBMC-derived $CD8^+$T cells from *Ct*- or *Cpn*-exposed humans, the majority of *Chlamydia*-reactive $CD8^+$T cells recognize infected cells in a non-classically restricted manner [28, unpublished].

4. Access of *Chlamydia* antigens to the MHC class I processing and presentation pathway

$CD8^+$T cells keep a constant vigil for signs of infection by surveying a vast array of peptides presented in complex with MHC class I molecules on the surface of all nucleated cells. These MHC class I-bound peptides are generated through a process known as antigen processing. In the classical pathway of MHC class I antigen processing, proteins located in the cytosol are ubiquinated and then cleaved by the proteasome. The resulting peptide fragments are then translocated into the lumen of the endoplasmic reticulum (ER) via the transporters associated with antigen processing (TAP) where