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Review

Lipids, apoptosis, and cross-presentation: links in the chain of host defense against *Mycobacterium tuberculosis*

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Abstract

Eicosanoids regulate whether human and murine macrophages infected with *Mycobacterium tuberculosis* die by apoptosis or necrosis. The death modality is important since apoptosis is associated with diminished pathogen viability and should be viewed as a form of innate immunity. Apoptotic vesicles derived from infected macrophages are also an important source of bacterial antigens that can be acquired by dendritic cells to prime antigen-specific T cells. This review integrates in vitro and in vivo data on how apoptosis of infected macrophages is linked to development of T cell immunity against *M. tuberculosis*.

Keywords: Microbial immunity; Tuberculosis; Infection; Eicosanoids; Cross-presentation; T cell immunity

1. Introduction

Despite the worldwide application of BCG-vaccination and other interventions, *Mycobacterium tuberculosis* (Mtb) remains one of the most successful human pathogens. Eight to ten million new cases of active tuberculosis occur each year due in large part to the large reservoir of asymptomatic people chronically infected with Mtb. A vaccine that prevents pulmonary tuberculosis, the primary contagious form of the disease, could have a major impact on containment of the global epidemic. However, all vaccines that have been developed to date, lead to improved containment of the Mtb, but do not lead to sterilizing immunity. A better understanding of the strategies that Mtb uses to evade host immunity may lead to the development of a more effective vaccine. As an intracellular pathogen that resides primarily in the phagosomal compartment of infected macrophages, Mtb avoids detection by the humoral immune system. Furthermore, despite eliciting a T cell response, Mtb is able to evade many of the anti-bacterial mechanisms mediated by cellular immunity. One idea that several vaccine strategies are trying to exploit is inducing a stronger Mtb-specific $CD8^+$ T cell response. $CD8^+$ T cells play an important immunological role in defending the host against virulent Mtb infection (reviewed in Reference [1]). In support of these objectives, a detailed understanding of how $CD8^+$ T cells are activated during Mtb infection is required. Here we will consider different ideas about how Mtb-specific $CD8^+$ T cells are primed following infection.

2. Priming of $CD8^+$ T cells

$CD8^+$ T cells recognize short peptide antigens that are presented by the class I MHC antigen presentation pathway

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[2]. The class I MHC pathway, which is expressed by nearly every cell type, samples the cytosolic environment (reviewed in Reference [3]). Consequently, $CD8^+$ T cells detect cells with a perturbation of their intracellular environment. As such, it is no surprise that $CD8^+$ T cells play a crucial role in immunity to many different intracellular pathogens. For example, viral proteins synthesized in the cytosol of infected cells are sampled and presented by the class I MHC pathway. Peptides in the cytosol of the cell are transported into endoplasmic reticulum (ER) through the action of the transporter associated with antigen processing (TAP) and tapasin. Once in the ER, peptides are trimmed and form a trimeric complex with the MHC I heavy chain and β2 microglobulin. This peptide-loaded class I MHC complex is transported to the cell surface. Antigen-specific $CD8^+$ T cells are able to identify infected cells by recognizing viral peptide epitopes bound to class I MHC. However, recognition of virally infected cells by $CD8^+$ T cells only leads to $CD8^+$ T cell activation if they have been previously primed. T cell priming refers to the initial activation of naive T cells (see Glossary), which occurs when a T cell recognizes its cognate antigen presented by dendritic cells (DC), an event that usually occurs in the lymph node (LN) (Glossary).

The plasticity of macrophages and DC, their overlapping features and functions, and inability to clearly distinguish between the two cell types, presents problems in studying these two cell types [4–7], both of which are important for immunity to tuberculosis. DC are generally acknowledged to be crucial for the priming of T cells because, in contrast to parenchymal cells, they efficiently pick up antigen in the periphery – at sites of infection or inflammation – and traffic to the LN, where T cell priming occurs. Despite the semantics difficulties, for the discussion that follows we refer to DC as $CD11c^+$ cells that traffic to LN and prime naïve T cells, although we acknowledge this function may not be limited to DC.

In the draining LN, thousands of naïve T cells transiently interact with the DC. If a naïve T cell's TCR recognizes a peptide antigen presented by the DC, a high affinity and longer lasting interaction occurs [8,9]. During such a cognate interaction, the accessory and costimulatory molecules expressed by the DC bind their counter-receptors on the T cell forming an immune synapse. The end result of this interaction is activation of the naïve T cell. An important consequence of priming is that the activation threshold of the T cell is lowered so it is more easily activated during its next encounter with antigen. Once primed, activated $CD8^+$ T cells proliferate, exit the LN and home to sites of inflammation.

Glossary
Definitions.

Priming	T cell priming refers to the initial activation of naïve T cells, which occurs when a T cell recognizes its cognate antigen presented by dendritic cells (DC). This event usually occurs in the lymph node (LN) and requires costimulatory and cytokine signals.
Presentation	Antigen presentation refers to the expression of antigen bound to an antigen-presenting molecule (for example peptides bound to class I or class II MHC molecules) on the cell surface. A T cell that produces a TCR specific for the antigen in the context of the antigen-presenting molecule can recognize the cell. Presentation does not presume whether the T cell has been previously activated (primed) or not.
Cross-priming	Cross-presentation of antigen to naïve T cells resulting in their activation, or priming, is called cross-priming
Cross-presentation	Class I MHC-restricted presentation of exogenous antigens that enter the endocytic compartment (e.g., by phagocytosis) to $CD8^+$ T cells, which ordinarily recognize antigens in the cytosolic compartment.
Detour model	Process by which intracellular bacterial antigens contained in apoptotic blebs and vesicles are taken up by DC and cross-presented to $CD8^+$ T cells.
Exosomes	Small microvesicles (50–100 nm in diameter) that are released from late endosomal compartments of a variety of cell types including macrophages. Exosomes isolated from the culture supernatant of infected macrophages express LAMP1, CD86 and MHC II, and contain bacterial products such as LAM and the 19 kD lipoprotein [52].

3. DC cross-presentation of intracellular cytosolic antigens

How DC acquires intracellular cytosolic antigens is a particularly important question. For pathogens that directly infect DC, the cytosolic production of pathogen-encoded proteins is sufficient. However, a problem arises for pathogens that don't infect DC. For example, certain viruses are tropic for certain cell types, such as epithelial cell, and do not infect DC. If only professional APC such as DC can prime T cells, how is the antigen transferred from an infected epithelial cell to a DC? Cellular mechanisms exist that facilitate the transfer of antigen from infected cells to DC. Uninfected DC can acquire viral antigens when lysis of infected cells releases viral proteins that can be taken up via endocytosis [10]. Alternately, DC can engulf infected cells that are dying. However, uptake of soluble antigen or dying cells results in the transfer of cytosolic antigen into the exogenous antigen-presenting pathway of APC. A second step is required for the transfer of antigen from the endocytic compartment into the cytosolic class I MHC antigen presentation pathway. This later step is referred to cross-presentation [11,12]. Cross-presentation of antigen resulting in the activation, or priming, of naïve T cells is called cross-priming (see glossary) [13–16].

One way that DC can acquire intracellular viral or bacterial antigens is through the uptake of apoptotic vesicles derived from infected macrophages [17]. Albert et al. showed that apoptosis but not necrosis of influenza-infected monocytes conferred upon uninfected DC the ability to prime human CTL in vitro [17]. Similarly, Yrlid et al. found that virulent Salmonella, an intracellular bacterial pathogen, induces apoptosis of infected macrophages in a manner that is dependent upon its type II protein secretion system [9,18]. DC are able to cross-present the bacterial antigens contained in the apoptotic macrophages via the class I MHC pathway. While neither of these studies show that these events occur in vivo, they provide important evidence that microbial antigens contained in apoptotic infected cells can be cross-presented by DC and may be important for priming of $CD8^+$ T cell responses.