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The role of dendritic cells in *Mycobacterium tuberculosis* infection

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The immune response against *Mycobacterium tuberculosis* is multifactorial, involving a network of innate and adaptive immune responses. Characterization of the immune response, a clear understanding of the dynamics and interplay of different arms of the immune response are critical to allow the development of better tools for combating tuberculosis. Dendritic cells (DCs) are one of the key cells in bridging innate and adaptive immune response through their significant role in capturing, processing and presenting antigens. The outcome of interaction of *M. tuberculosis* with DCs is not fully understood and the available reports are contradictory were some findings reported that DCs strengthen the cellular immune response against mycobacterium infection whereas others reported *M. tuberculosis* impairs the function of DCs were infected DCs are poor stimulators of *M. tuberculosis* Ag-specific CD4 T cells. Other studies showed that the outcome depends on *M. tuberculosis* strain type and type of receptor on DCs during recognition. In this review I shall highlight the recent findings in the outcome of interaction of *Mycobacterium tuberculosis* with DCs.

Introduction

Tuberculosis (TB) is one of the most devastating diseases of mankind and remains a major health threat in Africa with a much higher incidence in the Sub-Saharan part of the continent. *M. tuberculosis* is the predominant cause of TB in human and it was first identified as the causative agent of TB by Robert Koch in 1882. It is an extraordinary effective human pathogen infecting one-third of the world's population resulting 8.8 million cases and 1.45 million deaths annually.[1] The inhalation of small size respiratory droplet nuclei (1–2 μm or less) through the respiratory tract is the most common route of entry of the tubercle bacillus. The respiratory droplet nuclei are small enough in size to pass into the lower respiratory tract escaping the anatomical barriers of nasopharynx and upper respiratory tract.[2] Once inhaled droplets pass the lower respiratory tract and are deposited in the alveolar spaces and phagocytic cells, mainly macrophages, take up the bacteria, which assist in the induction of a rapid inflammatory response and accumulation of cells. Although alveolar macrophages are the first cells to engulf, dendritic cells and monocyte-derived macrophages also take part in the phagocytic process.[3,4]

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Endocytosis of *M. tuberculosis* involves multiple receptors such as complement receptor (CR), Fc receptor (FcR), surfactant protein A (Sp-A) and its receptors, scavenger receptor class A, Toll-like receptor (TLR) CD14, mannose receptors and the DC-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN).[5] Some receptors allow silent entry (CR), and others induce defense mechanisms (FcR).[6,7] The subsequent intracellular fate of mycobacteria is considered as predetermined by the mode of entry into macrophages;[8] however, experiments have shown that intracellular trafficking of *M. tuberculosis* did not significantly alter by blocking individual receptors.[5]

Once organisms have made their way into the lung, they have four potential fates.[9,10]

(1) Killing and elimination of the bacilli with the initial host immune response, and these individuals do not develop TB due to this exposure event. No clinical or immunological evidence of this interaction is apparent.

(2) Immediately after infection the bacilli can grow and multiply, causing clinical disease (primary TB).

(3) Development of "latent infection" where the bacilli persist in a sub-clinical (quiescent) form. The bacteria may become dormant or may persist at low numbers, and are prevented from unchecked replication by the immune system and never cause disease at all. This phase is manifested only as positive tuberculin skin test (latent TB) or positive interferon gamma release assay.

(4) Reactivation of the dormant bacilli or escape from the quiescent phase with resultant disease (reactivation TB).

Immunology of Tuberculosis

The protective response to *M. tuberculosis* is complex and multifaceted involving many components of the immune system. Macrophages and DCs are key cells in the immune response to *M. tuberculosis* by presenting antigens to T cells in the context of both MHC class I and II. T cells in turn activate macrophages to kill the bacteria by secreting IFN-γ and TNF.[11] Furthermore, macrophages and DCs play an important role in recruitment of cells at the site of infection by secreting the proinflammatory cytokines IL-1 and IL-6.[12]

Activated macrophages kill engulfed pathogenic bacteria via different mechanisms, including phagosome-lysosome fusion, generation of reactive nitrogen intermediates, particularly nitric oxide and generation of reactive oxygen intermediates. The maturation of phagosomes is a dynamic process where the phagosomes, which contain engulfed microbes fuse with lysosomes and then modified by transient fusion with endocytic organelles.[13,14] The phagolysosome fusion represents a major antimicrobial mechanism where engulfed microbes are degraded by intralysosomal acidic hydrolases.[11]

DCs are superior antigen presenting cells (APCs) and they help in maximizing the recognition of antigens by T cells in the draining lymph nodes.[15-17] However, the outcome of interaction of *M. tuberculosis* with DCs is not fully understood and the available reports are contradictory.

M. tuberculosis is a classic example of a pathogen that resides intracellularly within macrophages and for which the protective response relies on cell-mediated immunity. Studies demonstrated that acquired immunity to *M. tuberculosis* requires contributions by multiple T cell subsets: $CD4^+$ T cells, $CD8^+$ αβ and γδ T cells and CD1 restricted T cells.[18]

CD4 T cells play a dominant role in the protective response against *M. tuberculosis*.[19] The mycobacteria reside within macrophage vacuoles; therefore, mycobacterial antigens are loaded on MHC class II and presented to CD4 T cells through endocytic antigen presentation pathway. Upon activation, CD4 T cells secret IFN-γ, IL-2 and TNF, which in turn activates macrophages.[11] CD4 depleted or disrupted mice and adoptive transferred showed that CD4 cells are important cells for controlling infections.[20-24] In humans, the necessity for $CD4^+$ T cells to help control of infection is shown by the rapid acceleration of TB in HIV positive patients who have loss of CD4 T cells.[25] Moreover, CD4 cells are also important to enhancing APC function through interaction of CD40-CD40L between CD4 T cells and APC and this in turn can facilitate APC medicated induction of other T cells such as CD8 T cells.[26]

Other roles played by CD4 T cells include induction of apoptosis through perforin and granulysin, FAS-L or TNF-α lytic pathways,[27] help for B cells and CD8 T cells, and production of other cytokines.[28] Studies in CD4 depleted or deficient mice have also showed that CD4 cells have other roles in addition to IFN-γ production in controlling mycobacterial infections.[29]

The MHC class I-restricted CD8 T cells contribute to protective immunity against TB;[30,31] however, mechanisms underlying CD8 T cell stimulation are not fully understood. The stimulation of CD8 T cells require mycobacterial peptide presentation by MHC I products, which generally occurs in the cytosol not readily accessed by *M. tuberculosis*. Two pathways have been proposed: first, *M. tuberculosis* can enter into the cytosol of infected DCs, and this leads to direct loading of MHC I molecules.[32] Second, apoptosis of macrophages infected with *M. tuberculosis* results in mycobacterial antigens carrying vesicles, which are taken up by DCs in the vicinity and leads for cross priming.[33] CD8 T cells that are specific for mycobacterial antigens can produce IFN-γ and secrete perforin and granulysin, which lyse host cells and attack *M. tuberculosis* directly.[34]

CD1 restricted T cells, γδ T cells and CD8 T cells restricted by non-classical HLA CD1 molecules participate in the response against *M. tuberculosis* in humans.[35-37] CD1 molecules present glycolipid antigens, which are found in the cell wall of mycobacterium to T cells, which in turn secretes IFN-γ and express cytolytic activity.[38,39]

Studies in mouse showed that γδ T cells partially protect against high doses of *M. tuberculosis* infection and they are important in regulating granuloma formation.[40,41] In humans, these cells comprise about 5% of the whole T cell population in peripheral blood.[37] The γδ cells have a mycobacteriocidal activity via granule and stimulation of these cells with phospholigands induces IFN-γ production.[42] Therefore, these cells are believed to be part of the first line of defense against TB.

Cytokines are key molecules which play role in disease protection, progression or development of pathophysiology. Different animal and human studies have firmly established that cytokines have a major role in determining the outcome of infection with *M. tuberculosis.* Studies in mice and human showed that IFN-γ is a critical cytokine involved in the control of *M. tuberculosis* infections. Mice with a genetic deficiency for IFN-γ are very susceptible to infection with virulent *M. tuberculosis* with a shorter mean survival time and a less NOS2 production, indicating that macrophage activation was defective, contributing to the susceptibility of IFN-γ gene knockout (KO) mice.[43] The importance of this cytokine has also been confirmed in humans who have a mutation in their IFN-γ receptor and this was associated with a heightened susceptibility to mycobacterial infections.[44]

TNF also play a central role in the initiation and maintenance of controlling *M. tuberculosis* by activating macrophages and facilitating granuloma formation.[45-47] TNF-α in synergy with IFN-γ activate macrophages to produce RNI and mice deficient in TNF-α or the 55-kDa TNF receptor succumbed to infection.[45,48] TNF-α or its receptor is also an important molecule, which affects cell migration to, localization and the granulomatous response following *M. tuberculosis* infection.[49] In addition, reactivation of latent disease in rheumatoid arthritis patients after neutralization of TNF with specific monoclonal antibodies signifies the importance of this cytokine.[50]

The other important cytokine to control *M. tuberculosis* infection as in the case of most intracellular infections is IL-12. The susceptibility of IL-12p40 gene deficient mice to *M. tuberculosis* and the therapeutic role of IL-12 strongly support an important role for this cytokine in the protective immune response against *M. tuberculosis*.[51,52] In chronically *M. tuberculosis* infected mice administration of IL-12 DNA has been reported to reduce the bacterial load.[53] Mutations in the IL-12p40 receptor *IL-12RB1* gene are also strongly associated with susceptibility to TB.[54]

Chemokines (chemotactic cytokines) are largely responsible for cell trafficking to the site of infection; however, their role in *M. tuberculosis* infection have been investigated to a limited extent. *M. tuberculosis* induced elevated levels of a variety of chemokines, including IL-8 (CXCL-8), monocyte chemoattractant protein 1 (MCP-1) (CCL-2), MCP-3 (CCL-7), MCP-5

(CCL-12), regulated on activation normal T cell expressed and secreted (RANTES/CCL-5), MIP1-α (CCL-3), MIP1-β (CCL-4), MIP-2 (CXCL-2) and IP-10 (CXCL-10)[55,56] and their receptor like CCR5 and CXCR4.[57]

Dendritic Cells Origin and Function

Dendritic cells originally identified by Steinman and his colleagues (1972) comprise a family of antigen presenting cells that are central to the initiation of immune responses in their capacity to orchestrate signals derived from the different parts of the immune system.[58] DCs are the most potent antigen presenting cells than any other antigen presenting cell. DCs can take up an array of different antigens, including viruses, bacteria, parasites, extracellular fluid and apoptotic bodies released by dying cells, process and present antigens to T cells in the form of peptides bound to both MHC class I and class II molecules.[59] They originate from stem cell precursors in the bone marrow and circulate as precursors in blood before entering tissue where they become resident immature DCs. DCs do not express a single surface molecule and combination of markers is used to define the different dendritic cell subsets.[60]

Useful information about the antigenic composition in the periphery is provided to the secondary lymphoid tissues by DCs. At the immature stage of development, DCs express high intracellular MHC II, Endocytosis, phagocytosis, high CCR1, CCR5 and CCR6; low CCR7, CD40, CD54, CD80, CD83, CD86 and CD58 and are specialized in antigen capture residing at the peripheral sites.[61] In peripheral tissues DCs capture and process antigens via different pathways: (1) Macropinocytosis where fluid from the extracellular milieu is taken up into pinocytic vesicles and antigen is concentrated by expelling excess water,[62] (2) endocytosis via lecitin receptors such as mannose receptor, DEC-205, Langerin or DC specific ICAM 3 grabbing non-integrin (DC-SIGN),[63,64] (3) Fc receptors (FcγRI, FcγRII and FcγRIII) and complement receptors (CR3) can mediate efficient internalization of immune complexes or bacteria,[65] (4) phagocytosis of apoptotic and necrotic cell fragments, viruses, bacteria including mycobacteria and/or intracellular parasites[66] and (5) Toll-like receptors (TLRs) in pathogen recognition including LPS, peptidoglycan, lipotheicoic acid and lipoprotein.[67]

After antigen uptake, DCs migrate to the draining secondary lymphoid organ and during this migration, DCs undergo a maturation process with downregulation of the capacity to capture antigen and upregulation of antigen processing and presentation. Matured DCs are characterized by high surface MHC II, low endocytosis, low phagocytosis, low CCR1, CCR5, CCR6, high CCR7 and high CD40, CD54, CD80, CD83, CD86 and CD58.[68]

Dendritic Cells and Their Role in *M. tuberculosis* Immune Response

Dendritic cells are the most potent professional antigen presenting cells for priming naïve T cells, an important source of IL-12 and are highly efficient cells in inducing antimicrobial and antitumor immune responses.[69] However, the outcome of interaction of mycobacteria with DCs is not fully understood and the available reports are contradictory.

A number of studies indicated that DCs strengthen the cellular immune response against mycobacterium infection.[3,70-73,] At the onset of inflammatory response against *M. tuberculosis*, DCs are highly represented at sites of *M. tuberculosis* infection.[74-76] Immature DCs present in the lung mucosa are specialized for antigen uptake and processing. After interacting with pathogens, they mature and migrate in lymphoid organs where they prime T cells through cell surface expression of MHC and costimulatory molecules and secretion of immunoregulatory cytokines such as IL-12.[61]

In the contrary, others reported that *M. tuberculosis* inhibits DCs maturation and masks the presence of the pathogen and impairs its ability in stimulating antigen specific T cells. Others reported the fate of DCs maturation depends on the type of receptors during recognition where interactions of *M. tuberculosis* with TLR results in DC activation characterized by high IL-12 secretion during early infections whereas interactions with DC-SIGN prevent DC activation by blocking TNFκB activation that results in high secretion of IL-10.[77]

We and others showed that infection of monocyte derived dendritic cells (MDDCs) with *M. tuberculosis* leads to upregulation of MHC I and MHC II, CD40, CD54, CD58 and CD80,[3,78] a phenotype consistent with activation of DCs and increased production of proinflammatory cytokines such as IL-12, TNF-α, IL-1 and IL-6 that lead to maturation, and possibly migration and antigen processing and presentation. DCs help for T cell activation and generating effective cell mediated immunity through successfully presenting antigen to T cells at local lymph nodes and also infected DCs disseminate mycobacteria.[17,71,79] Another study indicated that *M. tuberculosis* infected MDDC showed a strong increase in CD83 expression as well as in co-stimulatory molecules CD40, CD80 and CD86 and adhesion molecules, CD58 and CD54.

Conversely, *M. tuberculosis* infected monocyte derived macrophages (MDM) showed enhanced expression of co-stimulatory and adhesion molecules CD40 and CD54 and a slight down-regulation of MHC class II DQ expression. No changes in CD80, CD86, CD64 and MHC class II DR were observed. Contrary to MDM, MDDC showed a significant upregulation of class II DR and DQ molecules, suggesting that *M. tuberculosis* infected DCs are likely to function as efficient APCs compared with *M. tuberculosis* infected macrophages, in addition, *M. tuberculosis* infected DCs stimulate production of IFN-γ by T cells unlike MDM.[12] A cross talk between DCs and *M. tuberculosis* infected polymorphonuclear neutrophils through DC-SIGN and Mac-1 induces maturation of DCs which can initiate T-cell responses directed against *M. tuberculosis*. Activation of T cells and production of IFN-γ can amplify the early inflammatory response, leading to macrophage activation and removal of bacteria.[80]

In mice, depletion of DCs impaired their ability to mount effective CD4 T cell response which in turn resulted in a significant loss of control over bacterial replication, resulting in huge bacterial loads in the lungs and spleen.[81] There are also

studies which reported genetic deficiency of DCs or mutation of genes associated with DCs lead for BCG-osis and spontaneous *Mycobacterium kansasii* infection.[82] Other studies also showed that *M. tuberculosis* infected DCs produce high level of chemokines such as CCL3, CCL4, CXCL8, CXCL9 and chemokine receptors such as CCR7, which are important in the migration of NK and T cells.[83]

On the other hand, there are studies which reported that a very low or no upregulation of surface molecules and production of anti-inflammatory cytokines by *M. tuberculosis* infected DCs. *M. tuberculosis* impairs DCs maturation, reduce secretion of IL-12 by DCs and inhibit their ability to stimulate T cell proliferation.[84-86] *M. tuberculosis* infects DCs with high frequency and impairs their function in vivo. In this study they showed that DCs transport *M. tuberculosis* from the lungs to the local draining lymph node during the early stages of infection and these cells are poor stimulators of *M. tuberculosis* Ag-specific CD4 T cells despite expressing surface MHC class II and costimulatory molecules.[87] It has been shown that *M. tuberculosis* infected DCs had low capacity to present mycobacterial antigens and stimulates *M. tuberculosis* specific $CD4^+$ T cells in vivo.[88,89] Furthermore, *M. tuberculosis* infection induced production of several cytokines like IL-10 which can decrease DCs trafficking to draining lymph nodes.[90]

A recent study showed a delayed accumulation of lung DCs in comparison with mice inoculated with PPD and this delayed DCs accumulation in the lungs could be an evasion/pathogenic mechanism of *M. tuberculosis* to avoid early generation of protective responses, by delaying the early expansion of truly effector T cells[91] and other recent study reported that *M. tuberculosis* directs T helper 2 cell differentiation by inducing interleukin-1β production in DCs[92] and also promotes regulatory T-Cell expansion via induction of programmed death-1 ligand 1 (PD-L1 and CD274) on DCs.[93]

Other study reported that the activation and cell trafficking ability of *M. tuberculosis* infected DCs dependent upon the type of *M. tuberculosis* strain and suppressing the migration of MoDC and modulating its cell trafficking ability may be a mechanism used by *M. tuberculosis* to paralyze the early immune response of the host.[94] Mycobacterial H37Rv cell wall, mannose-capped lipoarabinomannan (ManLAM) and phosphatidylinositol mannosides (PIMs), had divergent effects on functional polarization of human DCs with regard to their maturation and pro-inflammatory cytokine responses. Highly purified H37Rv ManLAM induces a vigorous pro-inflammatory response while PIM is strongly anti-inflammatory.[95]

Conclusion

The ability of DCs in the lung to migrate to the regional lymph nodes is a critical step in the immune response against *M. tuberculosis* infection. However, the available information in the outcome of interaction of DCs with *M. tuberculosis* is contradictory. Some findings reported that DCs strengthen the cellular immune response against mycobacterium infection whereas others reported *M. tuberculosis* impairs the function of DCs, and some findings reported that the outcome depends on the *M. tuberculosis* strain type and type of receptor on DCs during recognition.

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