

## Review

**Viruses, dendritic cells and the lung**

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(Print ISSN 1465-9921; Online ISSN 1465-993X)**Abstract**

The interaction between viruses and dendritic cells (DCs) is varied and complex. DCs are key elements in the development of a host response to pathogens such as viruses, but viruses have developed survival tactics to either evade or diminish the immune system that functions to kill and eliminate these micro-organisms. In the present review we summarize current concepts regarding the function of DCs in the immune system, our understanding of how viruses alter DC function to attenuate both the virus-specific and global immune response, and how we may be able to exploit DC function to prevent or treat viral infections.

**Keywords:** dendritic cell, inflammation, lung, virus**Introduction**

Many viruses utilize the respiratory tract as an entry point into the host. They may target specialized cells of the respiratory tract for initial replication, leading to disease that primarily manifests as illnesses of the lung and upper airways. Alternatively, they may infect mobile elements that are resident in the respiratory tract, or produce viremia that can carry the virus to a secondary target organ. The outcome of these encounters is determined by the early events that occur in the lung at the interface of the innate and adaptive immune responses. The DC has primary responsibility for antigen processing, antigen presentation and T lymphocyte activation, and thus initiates and shapes the adaptive immune response. The ways in which DCs translate messages regarding the lung milieu to T lymphocytes dictate the magnitude, kinetics, and composition of the adaptive immune response, and thereby determine the characteristics of virus-induced disease.

**Dendritic cells as antigen-presenting cells**

DCs are derived from myeloid CD34<sup>+</sup> progenitors in the bone marrow, which can differentiate down one of two precursor pathways (for review see [1]). CD34<sup>+</sup> progenitors may develop into CD14<sup>+</sup>CD11c<sup>+</sup>CD1<sup>-</sup> monocytes, from which immature DCs can be produced in response to granulocyte-macrophage colony-stimulating factor and IL-4, whereas exposure to macrophage colony-stimulating factor leads to macrophage differentiation. The CD34<sup>+</sup> myeloid progenitors can also differentiate into CD14<sup>-</sup>CD11c<sup>+</sup> precursors that yield Langerhans cells in response to granulocyte-macrophage colony-stimulating factor, IL-4, and transforming growth factor- $\beta$ , or macrophages in response to macrophage colony-stimulating factor.

Immature DCs are particularly adept in their ability to capture antigen, and can do so either by macropinocytosis; by endocytosis through C-type lectin receptors, Fc $\gamma$ RI, or

APC = antigen-presenting cell; DC = dendritic cell; HSV = herpes simplex virus; IFN = interferon; IL = interleukin; LCMV = lymphocytic choriomeningitis virus; MHC = major histocompatibility complex; MV = measles virus; TNF = tumor necrosis factor; TRAIL = tumor necrosis factor related apoptosis-inducing ligand.

Fc $\gamma$ RII; or by phagocytosis. The process of antigen capture changes the immature DC both in phenotype and function, transforming the DC into an antigen-presenting cell (APC). The maturation of the DC leads to the migration of the cell from the peripheral tissues into the draining lymphoid organs. CD40 ligand, as well as tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$ , activate DCs, and are important in the conversion of DCs from cells that are primarily involved in antigen capture into APCs.

The transformation into mature DCs is associated with the loss of receptors that are involved in endocytosis and phagocytosis; an increase in the costimulatory molecules CD40, CD58, CD80, and CD86; a change in morphology; and a decreased expression of CD68 and increase in DC-lysosome-associated membrane protein. DCs exit nonlymphoid organs through the afferent lymph, and migrate into the T cell area of lymphoid organs through the coordinated activity of lipopolysaccharide produced by pathogens, the local production of TNF- $\alpha$  and IL-1 $\beta$ , and specific chemokines.

Following antigen uptake and maturation, DCs increase expression of CCR7. The latter is a receptor for the chemokines macrophage inflammatory protein-3 $\beta$  and 6Ckine, which are produced by cells in the lymph node T cell zone, and are responsible for migration of mature DCs into the paracortical area of lymphoid tissue. When DCs encounter T lymphocytes, further DC maturation occurs through CD40 ligand and additional molecules, causing the release of cytokines such as IL-8, fractalkine, and macrophage derived chemokines that can attract lymphocytes. As a result of their maturation process, DCs efficiently express major histocompatibility complex (MHC) molecules, which contain peptide fragments of the processed antigen on their cell surface that can be presented to T lymphocytes in the paracortical area.

When a T lymphocyte has a T cell receptor that is specific for a particular MHC-antigen fragment complex presented by a DC, that T lymphocyte becomes activated when appropriate costimulatory interactions between the DC and T lymphocyte are present (for review see [1]). These costimulatory signals include the interaction of CD80 or CD86 (also known as B7.1 and B7.2, respectively) that is present on the DC with CD28 that is present on the T cell. Without costimulation the T cell receptor-MHC interaction leads to apoptosis rather than activation. DCs present antigen via their MHC class II molecules to CD4<sup>+</sup> T lymphocytes. CD4<sup>+</sup> T lymphocytes are generally divided into two main classes – type 1 and type 2 – that are characterized by the cytokine array produced by the cell. Type 1 cells are important in the immune response to intracellular pathogens such as viruses and mycobacteria, and produce IFN- $\gamma$ , lymphotoxin, and IL-2. Type 2 cells produce a variety of proinflammatory cytokines, such as IL-4, IL-5, IL-9, IL-10 and

IL-13, which are generally important in the development of the humoral immune response. DCs may have an important role in determining the profile of cytokines produced by CD4<sup>+</sup> cells. DCs may have an important role in determining the profile of cytokines produced by CD4<sup>+</sup> cells. In humans, antigen presentation and T-cell activation by the monocyte-derived CD11c<sup>+</sup> DCs secrete IL-12, leading to a Type 1 cytokine profile. In contrast, CD11c<sup>-</sup> DCs induce CD4<sup>+</sup> cells to produce type 2 cytokines [1].

### Dendritic cells in antiviral immunity

Because DCs have the ability to capture and process antigen in tissue in the initial stages of a viral infection, they are particularly suited to prime antiviral immunity. CD8<sup>+</sup> T lymphocytes are also very important in host immunity to viral infections. CD8<sup>+</sup> lymphocytes recognize eight- or nine-amino-acid peptide epitopes presented in the context of MHC class I molecules, leading to lysis of the infected target cell. DCs are particularly effective in antigen presentation, and costimulation and activation of CD8<sup>+</sup> cytotoxic T lymphocytes. For example, DCs infected with polyomavirus, but not infected macrophages, have the capability to prime polyomavirus-specific CD8<sup>+</sup> T lymphocytes *in vivo* [2,3]. DCs infected with other viruses (e.g. influenza [4] and lymphocytic choriomeningitis virus [LCMV] [5]) also induce antigen-specific CD8<sup>+</sup> T lymphocytes.

In a model of influenza A virus infection, mature DCs are superior to immature DCs in stimulating IFN- $\gamma$  production from CD8<sup>+</sup> effector cells [6]. Additionally, only mature DCs, and not immature DCs, have the capability to stimulate expansion and differentiation of cytotoxic T lymphocyte effectors over a one-week period.

Recently, King *et al* [7] found that IL-4 has a profound effect on DC antigen presentation of LCMV and the T lymphocyte response to viral infection. In this mouse model of autoimmune diabetes the LCMV nucleoprotein is expressed in the  $\beta$ -cells of the pancreas, and destruction of the pancreas can be induced by infecting the mice with LCMV, thus causing obliteration of the pancreatic islet by LCMV-specific cytolytic T cells. However, the pancreatic destruction that follows LCMV infection can be inhibited in mice that express IL-4 via the human insulin promoter. IL-4 suppresses this virally induced diabetes by blocking the production of LCMV-nucleoprotein specific cytotoxic T cells. Further analysis revealed that IL-4 increased the number of antigen-specific CD8<sup>+</sup> cells, but inhibited the differentiation of cytotoxic precursors by LCMV-pulsed DCs by increasing B7.2 and decreasing B7.1 expression. Changes in DC antigen presentation and costimulation may also explain recent findings from our laboratory that showed that IL-4 inhibits virus-specific CD8<sup>+</sup> cytolytic activity [8], and shifts the mechanism of lysis from more perforin mediated to more Fas ligand mediated [9].

Effective T cell function is dependent on the maturation of DCs for optimal antigen presentation via the MHC complex. Some viral infections, such as influenza, promote DC maturation after uptake, improving the ability of the host to kill the virus [10–13]. In contrast, poxviruses have developed several different mechanisms to evade immune recognition and elimination. For example, vaccinia inhibits DC maturation within one day after infection, particularly in immature DCs, which have a greater propensity for vaccinia infection, while mature DCs are more likely to function as APCs [14]. Immature DCs that are infected with vaccinia have decreased expression of CD25, CD83, CD86 and human leukocyte antigen DR (markers of mature DCs) as compared with noninfected immature DCs that have also been treated with monocyte-conditioned media, a factor that is known to cause DC maturation [14]. A decrease in CD86 on the DC cell surface could lead to antigenic tolerance, whereas decreased human leukocyte antigen DR expression results in decreased antigen presentation. Vaccinia infection of mature DCs had a lesser effect on DC function [14]. Vaccinia infection of DCs also leads to abortive replication and induction of DC apoptosis – events that further suppress the immune response to vaccinia [14]. In addition, the poxviruses encode receptor homologs of cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\alpha/\beta$  and IFN- $\gamma$ , which are important in the host defense against viral infections [15]. IFN- $\alpha$ , TNF- $\alpha$ , and IL-1 $\beta$  are among the key cytokines that are involved in the induction of DC maturation [13,16–18].

Measles virus (MV) infection has long been recognized as producing a significant systemic immunosuppression that leads to a high mortality rate in undernourished children. MV mediates immunosuppression at the level of the APC by a variety of mechanisms. The binding of MV hemagglutinin to its receptor CD46 results in downregulation of IL-12 [19] and delayed-type hypersensitivity responses [20]. MV has also been shown to inhibit DC maturation, and thus the ability of DCs to present antigen to T lymphocytes. Ordinarily, the CD40 ligand expressed on activated T cells induces terminal differentiation of DCs into mature effector DCs [21,22]. However, the CD40 ligand dependent maturation of DCs is prevented by MV [23]. This has an added effect on the inhibition of IL-12 production [23]. IL-12 is a critical cytokine in the differentiation of CD4<sup>+</sup> type 0 cells to become CD4<sup>+</sup> type 1 cells that produce the antiviral cytokine IFN- $\gamma$  and the potent T cell stimulatory cytokine IL-2 [24]. MV replication also diminishes CD80 and CD86 expression on DCs, leading to less effective antigen presentation to T lymphocytes [23]. In addition to its inhibition of DC maturation, MV also abrogates CD40 ligand dependent CD8<sup>+</sup> T cell proliferation [23].

MV infected DCs can also induce T lymphocyte apoptosis, further impairing the immune response. The mechanism by which MV causes this effect is through MV induction of TNF

related apoptosis-inducing ligand (TRAIL) mRNA and protein expression in human monocyte derived DCs [25]. TRAIL is not believed to be cytotoxic to normal cells, but has been shown to induce apoptosis in several transformed cell lines [26]. Several lines of evidence suggest that TRAIL is involved in lymphocyte apoptosis and participates in the abnormal apoptosis that occurs with infection by immunosuppressive viruses such as HIV type 1, particularly because T lymphocytes from HIV type 1 infected patients are very susceptible to TRAIL induced cell death [26].

DC function is inhibited by other viruses also. Herpes simplex virus (HSV) type 1 interferes with antigen presentation and DC cytokine production [27]. The HSV encoded protein, infected cell peptide 47, has been shown to bind to the transporter associated with antigen processing, and thereby interferes with translocation of processed antigen into the endoplasmic reticulum for association with MHC class I molecules [28,29]. In addition, HSV-1 infection of mature DCs alters their function and phenotype, resulting in impaired T lymphocyte stimulatory capacity. HSV-1 infection specifically leads to degradation of CD83, a cell surface molecule of unknown function that has increased expression during DC maturation [30]. DCs also have the highest frequency of latent HSV-1 as compared with the other professional APCs, B lymphocytes and macrophages [31]. Other viruses, such as dengue virus [32], cytomegalovirus [33] and Venezuelan equine encephalitis virus [34], can also infect DCs and evoke a variety of influences on antigen processing and presentation [35].

Although the primary function of DCs is to initiate an antigen specific immune response, there is evidence that DCs may in some cases provide a safe haven for certain viruses. For instance, DCs can support cytomegalovirus latency and express viral latency associated transcripts [36]. Reactivation of productive cytomegalovirus replication can occur *in vitro* in experimental conditions, which suggests that cell differentiation pathways act as determinants of reactivation [36]. In addition, HIV can be harbored on follicular DCs bound on immune complexes [37]. The virions are resistant to neutralizing antibody in this extracellular setting, and can survive for long periods of time, creating a state of 'clinical' latency.

## Conclusion

DCs are being used in experimental systems as potential therapeutic agents to treat a variety of diseases, and as targets for vaccine antigen delivery. Although it is difficult to know at this time whether such methods will have practical applications, the induction of DCs that contain specific antigenic peptides in the context of MHC molecules to elicit a specific T lymphocyte response is very promising for vaccines and therapeutic strategies. Latouche and Sadelain [38] generated APCs that express epitopes from

the influenza matrix, along with the necessary appropriate costimulatory molecules, that can induce antigen specific cytotoxic T lymphocytes, cytotoxicity and protection.

Recent advances in our understanding of the interaction between viruses and DC function have largely resulted from technological breakthroughs in experimental techniques. Continued work on fundamental aspects of the virus interference with DC function is necessary in order to develop therapeutic strategies to counteract these evasive mechanisms. In addition, defining the interaction of viruses and DCs with the adaptive immune response will lead to new strategies for developing preventive vaccines and improving health.

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