

Basic aspects of human dendritic cell biology

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Dendritic cells (DC) play a key role in inducing antigen-specific adaptive immune responses as the most potent antigen-presenting cells (APC). DC develop in two stages during their life time: immature and mature DC. Upon invasion of pathogens, immature DC localized in peripheral tissues such as skin and mucosa take up them and become activated and mature by the stimulation with microbial molecules and proinflammatory cytokines. Thereafter, the mature DC migrate into T cell areas in the draining lymph node. There the DC present antigen peptides on MHC class I and class II molecules, and activate antigen-specific naïve T cells, which then migrate toward the peripheral tissues to function as effector cells. This is how antigen-specific immune responses are initiated by DC.

Importantly, DC are heterogeneous cell population composed of different subsets. An obvious difference exists between “myeloid” DC (mDC) and “plasmacytoid” DC (pDC). These two DC subsets may have different origins, and exhibit distinct reactivity to pathogens by expressing different Toll-like receptors (TLRs) that recognize microbial molecules. mDC, including CD11c⁺ DC in peripheral blood and monocyte-derived DC (MoDC), mainly express TLR1, TLR2, TLR3, TLR4, TLR5, and TLR8, whereas pDC mainly express TLR7 and TLR9. Accordingly, mDC respond to peptidoglycan (TLR2 ligand), poly I:C (TLR3 ligand), and LPS (TLR4 ligand), and secrete TNF- α and IL-6, whereas pDC respond to imiquimod and single-stranded RNA (TLR7 ligand) and CpG DNA (TLR9 ligand), and secrete a vast amount of IFN- α . pDC also secrete IFN- α in response to viruses. This remarkable ability of pDC to produce a large amount of IFN- α suggests that these cells play a key role in antiviral immunity and

also probably in a host defense against various pathogens.

After activated by these pathogens and other stimuli, such as CD40 ligand expressed on activated T cells, mDC and pDC become mature DC. Using monocyte-derived DC, the types of T helper cell responses induced by mDC have been intensively investigated. MoDC stimulated with pathogen-derived molecules (such as LPS) and CD40L produce IL-12p70, and thus induce Th1 responses. In contrast, MoDC stimulated with prostaglandin E₂ and other stimuli lose the ability to produce IL-12, and consequently induce Th2 responses. pDC differentiate into mature DC in response to either IL-3 plus CD40L or viruses. IL-3 and CD40L-stimulated pDC preferentially induce Th2 responses, whereas virus-stimulated pDC induce CD4⁺ T cells to produce IFN- γ and IL-10, which is different from a classical Th1 or Th2 pattern of a cytokine profile. These findings indicate that both mDC and pDC have flexibility to induce different types of T helper cell responses, depending on the stimuli the DC receive. In other words, external environments instruct DC to induce the type of adaptive immune responses that are appropriate to eliminate given pathogens.

How peripheral T cell tolerance is induced is one of the important subjects in immunology. Recent studies have revealed that DC play a central role not only in inducing immunity but also in inducing tolerance. How do DC induce these opposite immunological consequences: immunity versus tolerance? There are two models to explain this; one is that mature DC induce immunity while immature or “semi-mature” DC induce tolerance. The other is that distinct types of DC are able to induce tolerance rather than immunity.

The first model is supported by several findings. For example, T cells stimulated with immature or partially mature DC become anergic and eventually deleted. In another system, CD4⁺ T cells repeatedly stimulated with MoDC differentiate into IL-10-producing regulatory T cells. Furthermore, in vivo targeting of antigens to immature DC using anti-DEC-205 antibody induces antigen-specific tolerance, whereas the addition of anti-CD40 antibody, which induces DC maturation, reverses this tolerogenic effect of immature DC. These data support the model in which the degree of DC maturation determines which immune response occurs: immunity versus tolerance. That is, in the presence of inflammatory stimuli that are induced by “danger signals” such as invasive pathogens, DC become mature and induce immune responses to eliminate the invading pathogens. In steady states where physiological apoptotic death of normal cells occur, DC that engulfed apoptotic self cells remain immature and induce tolerance of autoreactive T cells, thus maintaining peripheral self tolerance.

The second model involves several types of DC that induce T cell anergy or regulatory T cells. DC treated with immunomodulatory cytokines such as IL-10 and IFN- α or with CD8⁺CD28⁻ suppressor T cells express high levels of ILT3 and ILT4 that transmit inhibitory signals into DC. These DC function as tolerogenic DC by inducing alloantigen-specific CD4⁺ T cell anergy. It has been reported that freshly isolated pDC induce antigen-specific CD4⁺ T cell anergy. Interestingly, IL-3- and CD40L-stimulated pDC induce CD8⁺CD28⁻ suppressor T cells that produce IL-10 and inhibit the activation of other T cells in antigen-specific and nonspecific manners. Therefore, DC affected by immunomodulatory factors and pDC untreated or treated with particular stimuli may play an important role in inducing peripheral T cell tolerance.

DC have a remarkable capacity to engulf, process, and present antigens on MHC molecules. Usually, APC present endogenous antigens on MHC class I molecules, whereas they present exogenous antigens on MHC class II molecules. However, in order to induce

cytotoxic T cell responses to viruses that do not infect APC, they need to phagocytose virus-infected cells and present viral antigens on MHC class I molecules. DC, but not other types of APC, have this remarkable ability to “cross-present” exogenous antigens on MHC class I molecules. Similarly, in anti-tumor immune responses, DC need to endocytose tumor cells and present tumor antigens on MHC class I molecules in a stimulatory manner (cross-priming). Immature and/or “tolerogenic” DC may play an important role in inducing peripheral tolerance of CD8⁺ T cells specific to self antigens by cross-presenting them (cross-tolerance). Thus, modulating DC so that they induce either cross-priming or cross-tolerance is important in inducing desirable CD8⁺ T cell responses to viral, tumor, and self antigens. For example, it has been shown that in vivo targeting of exogenous antigens to DC induces CD8⁺ T cell immunity or tolerance depending on whether DC are quiescent or activated. To facilitate cross-presentation of exogenous antigens by DC, it is important to target antigens to some endocytic receptors expressed on DC or to render antigens as particulate forms. It has been reported that antigens incorporated into DC through Fc γ receptors or DEC-205, both of which are representative endocytic receptors expressed on DC, are efficiently presented on MHC class I molecules. This ability of DC to cross-present exogenous antigens will be actively harnessed to enhance anti-viral and anti-tumor immune responses as well as self or allospecific tolerance.

Taken together, DC are endowed with special abilities to incorporate and present antigens on both MHC class I and class II molecules and to induce immunity as well as tolerance depending on their activation state and possibly on the type of DC subsets. Due to these outstanding and versatile abilities, DC will continue to be central in inducing appropriate immune responses to treat a wide array of immune-related disorders including infection, tumor, and allogeneic immune responses.