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Dendritic Cells in Transplantation and Immune-Based Therapies

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ABSTRACT

Dendritic cells (DCs) are specialized, bone marrow–derived leukocytes critical to the onset of both innate and adaptive immunity. The divisions of labor among distinct human DC subtypes achieve the most effective balance between steady-state tolerance and the induction of innate and adaptive immunity against pathogens, tumors, and other insults. Maintenance of tolerance in the steady state is an active process involving resting or semimature DCs. Breakdowns in this homeostasis can result in autoimmunity. Perturbation of the steady state should first lead to the onset of innate immunity mediated by rapid responders in the form of plasmacytoid and monocyte-derived DC stimulators and natural killer (NK) and NK T-cell responders. These innate effectors then provide additional inflammatory cytokines, including interferon-γ, which support the activation and maturation of resident and circulating populations of DCs. These are critical to the onset and expansion of adaptive immunity, including Th1, Th2, and cytotoxic T-lymphocyte responses. Rodent models are now revealing important data about distinct DC precursors, homeostasis of tissue-resident DCs, and DC turnover in response to inflammation and pathological conditions like graft-versus-host disease. The use of defined DC subtypes to stimulate both innate and adaptive immunity, either in combination or in a prime-boost vaccine sequence, may prove most useful clinically by harnessing both effector cell compartments.

KEY WORDS

Dendritic cell • Transplantation • Allogeneic • Cell therapy • GVHD • GVL • GVT

DENDRITIC CELLS AT THE CROSSROADS OF INNATE AND ADAPTIVE IMMUNITY

Human Dendritic Cells: Distinct Subsets and Hematopoietic Precursors

From the initial description of dendritic cells (DCs) in human skin [1] to the discovery of DCs in mouse spleen almost a century later [2], progress in the study of DC biology exploded in the 1990s. Investigators developed cytokine-driven methods for expanding and differentiating DCs ex vivo in both mouse and human systems, and further refinements continue to emerge. For the first time, sufficient numbers of DCs have become accessible for large-scale study and applications.

DCs are a central player in all immune responses, both innate and adaptive. DCs are exceptionally potent immunogens under inflammatory conditions, yet are also critical to the induction and maintenance of self-tolerance in the steady state. The heterogeneity of DCs and their activation states afford investigators more opportunities to define and manipulate the immune response using these specialized leukocytes.

Human DCs are all bone marrow–derived leukocytes and compose at least 4 types defined under cytokine-driven conditions in vitro (Figure 1). In addition, trace populations of DCs also circulate in human blood. One type shares phenotypic (lineage negative, $CD11c^{+}$, $CD86^{+}$, $CD123^{+/low}$, and $HLA\text{-}DR^{bright}$) features with cytokine-generated myeloid or conventional DCs in vitro. The other circulating DCs, termed plasmacytoid because of their morphological resemblance to plasma cells [3], are also lineage-negative, $CD86^{+}$, BDCA-2^{+}, and $HLA\text{-}DR^{bright}$, but $CD11c^{neg}$ and $CD123^{bright}$. Freshly isolated plasmacytoid DCs express much lower levels of major histocompatibility complex (MHC) and co-

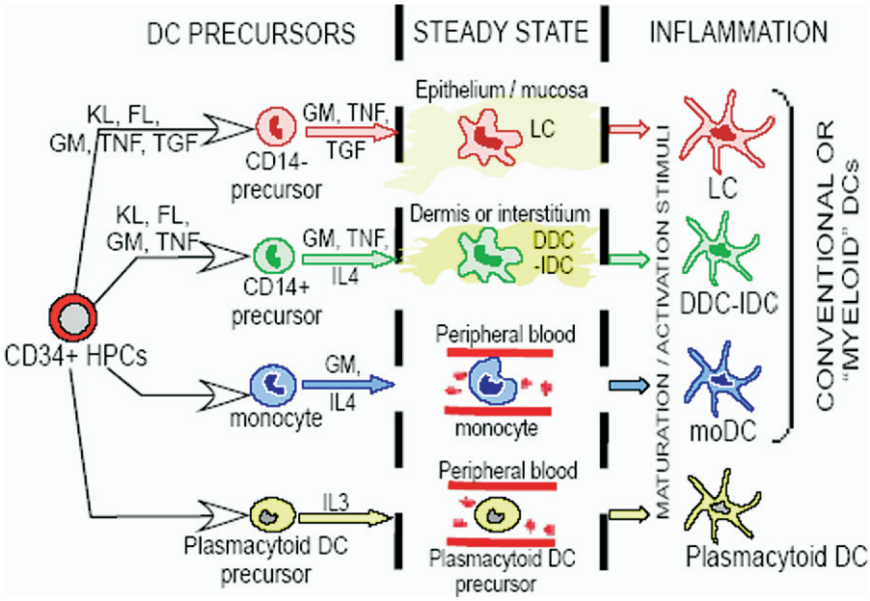

Figure 1. Development of human DC subsets. Precursors in blood and bone marrow (left section) can give rise to 4 types of DCs. Counterparts exist in vivo for each DC type generated with cytokines in vitro, although the moDC has proven more elusive to identify in situ. Trace populations of circulating myeloid or conventional DCs and plasmacytoid DCs also exist in blood. Terminal maturation and activation are complex processes but are necessary for DCs to exert optimal immunogenicity. FL, Flt-3 ligand; GM, granulocyte macrophage colony-stimulating factor; KL, c-*kit*-ligand. (Reprinted from The Journal of Immunology 2005;175:1373-1381 and used with permission, Copyright 2005 The American Association of Immunologists, Inc.)

stimulatory molecules than their conventional DC counterparts [3]. They also capture, process, and load antigens onto MHC molecules less effectively. Thus, these nonactivated plasmacytoid DCs are poor stimulators of T lymphocytes. Interleukin (IL)-3, in combination with CD40L or microbial products, leads to full plasmacytoid DC activation, abundant secretion of type I interferons (IFN), and more potent lymphocyte stimulation [4-6]. CD83 is the cardinal hallmark of both plasmacytoid and conventional or myeloid DC maturation in both mice and humans [7].

A potential point of confusion is that all murine DCs, be they myeloid or plasmacytoid, express CD11c, with the exception that $CD11c^{neg/low}$ Langerhans cells (LCs) up-regulate CD11c only with maturation. Along with low levels of CD11c, murine plasmacytoid DCs also express B220 and Gr1 and up-regulate CD123 only after Flt3-L treatment [8,9].

Monocyte-derived DCs (moDCs) and plasmacytoid DCs have been labeled DC1 and DC2, respectively, because of their propensity to stimulate Th1 versus Th2 type responses, with plasmacytoid DCs implicated as being somehow tolerogenic. This oversimplification, however, neglects stimulation of more varied T-cell responses, including the major physiological role of plasmacytoid DCs as the most abundant source of type I IFNs after activation by viruses [4-6]. It also overlooks the fact that both types of DCs can stimulate the expansion of regulatory or suppressor T cells [10-13], with immature or semimature forms functioning in the steady state to maintain peripheral tolerance and mature forms probably using this mechanism to turn off otherwise unchecked immune responses. Designations like DC1 and DC2 are best avoided in favor of using the more specific terms for various DCs.

DC Maturation and Migration to Secondary Lymphoid Organs

Manipulation of immunity using DCs generated in vitro should exploit the less mature and nonactivated forms to promote tolerance and the activated and mature forms to break tolerance and promote immunity. That said, under physiologic steady-state conditions, DCs are a major component of lymphoid tissues. In this setting, DCs are mostly immature or semimature and efficiently process self-antigens to induce and maintain tolerance [14-16]. All DCs require some form of terminal maturation to become fully immunogenic, however. Thus, DC maturation is a pivotal event in the control of innate and adaptive immunity. Microbial products constitute a physiologic activation stimulus via Toll-like receptors (TLRs) on both plasmacytoid and conventional DCs. CD40L (CD154), either expressed by activated T cells or as a multimeric recombinant protein, can also mature DCs. A combination of inflammatory cytokines that includes IL-1-β, tumor necrosis factor (TNF)-α, IL-6, and prostaglandin E2 [17] is often used to ma-