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Editors

HIV Interactions with Dendritic Cells

Infection and Immunity

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Preface

We are excited to introduce this book as an addition to a new series, *Topics in HIV and AIDS Research*. We expect that this volume and other important topics of the book series efficiently promote basic and clinical research of HIV and AIDS in a timely fashion. In this book, we aim to provide the latest research summaries and critical analyses of a broad scope in HIV interactions with dendritic cells (DCs).

As a group of professional potent antigen-presenting cells, DCs bridge the innate and adaptive immune responses. Studying the mechanisms of HIV-1 interactions with DCs is critical to understand HIV pathogenesis and develop more effective interventions against HIV infection and AIDS. DCs perform a pivotal role in the induction and regulation of immune responses. However, HIV impairs DC function and exploits these cells to spread viral infection to target $CD4^+$ lymphocytes. Studies of simian immunodeficiency virus in the macaque model demonstrated that DCs are important for initiating viral infection and spread in vivo. Interactions between HIV and DCs are of vital importance because these cells are among the first to encounter the virus at the mucosal surface. HIV-1 can hijack DCs to facilitate initial stages of viral infection and promote further dissemination throughout the host. Moreover, HIV interactions with DCs alter innate and adaptive immune responses and may thus facilitate viral persistence. In contrast, DCs have been targeted for developing more effective AIDS vaccine by enhancing antigen presentation and immune responses.

Given the recent research progress and the advance in the techniques in studying HIV interactions with host cells and factors, there is a critical need for a reference book on HIV interactions with DCs. This book targets a broad readership to facilitate HIV/AIDS research and provides a practical tool for HIV researchers to continuously address novel questions. The chapter contributors of this book attempted to summarize the literature in the field and provide critical analysis and future directions. The authors are internationally recognized scientists who have contributed significantly to the study of HIV and DC interactions and display complementary expertise in cellular, molecular, virological, immunological, preclinical and clinical research.

We would like to highlight some features of the book: (a) The book systematically addresses HIV interactions with DCs with emphasis on HIV infection and

immunity; (b) State-of-the-art progress in studying HIV interactions with DCs using virological and immunological approaches; (c) A combination of basic and clinical aspects in studying HIV interactions with DCs; and (d) Providing future directions for the specific research topic in each chapter.

This book covers the following important and interesting topics: (1) Immunobiology of DCs and the influence of HIV infection; (2) Antiviral immune responses by human Langerhans cells and DCs in HIV-1 infection; (3) Plasmacytoid DCs in HIV infection; (4) Cellular and viral mechanisms of HIV transmission by DCs; (5) Role of glycosphingolipid in DC-mediated HIV-1 *trans*-infection; (6) Simian immunodeficiency virus interactions with macaque DCs; (7) Interactions between HIV-1 and innate immunity in DCs; (8) HIV impairment of immune responses in DCs; (9) HIV-derived vectors for gene therapy targeting DCs; and (10) Targeting DCs for improved HIV-1 vaccines.

The primary audience for this book includes HIV-1 and AIDS basic and clinical researchers, PhD or MD graduate students, and postdoctoral researchers in virology, immunology, infectious diseases, and pathology fields. This book is suitable for use in university classrooms or seminars. The possible courses in which the book could be used include the following: advanced virology, retrovirology, viral immunology, viral pathogenesis, advanced topic in HIV and AIDS research, and progress in microbiology and immunology.

We hope that the readers will appreciate this book as much as we enjoyed preparing it. We thank all the authors for their timely contributions.

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Chapter 1
Immunobiology of Dendritic Cells and the Influence of HIV Infection

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Abstract Recent progress in phenotyping of human dendritic cells (DCs) has allowed a closer alignment of the classification and functions of murine and human dendritic cell subsets. Marked differences in the functions of these human DC subsets and their response to HIV infection have become apparent, relevant to HIV pathogenesis and vaccine and microbicide development. Systems biology approaches to studying HIV uptake and infection of dendritic cells has revealed how markedly HIV subverts their functions, especially in relation to the trafficking pathways and viral transfer to T cells. Furthermore the interactions between DCs and other innate immune cells, NK cells, NKT cells and gamma delta T cells are now known to influence DC and T cell function and are also disturbed by HIV infection in vitro and in vivo. Such cellular interactions are potential targets for vaccine adjuvants and immunotherapy.

1.1 Introduction

Dendritic cells (DC) are a family of professional antigen presenting cells (APC) that form an important link between the innate and adaptive immune systems. They are found as specific subsets in tissue and blood and are of either myeloid or plasmacytoid

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origin. Sessile myeloid DCs located in the peripheral tissues, and to some extent in blood, act as sentinels to detect and bind foreign antigens. In this state they are "immature" and rapidly endocytose and then process them by cathepsins in the endolysosomal pathway or, if infected within the cytoplasm, via proteosomal degradation. This leads to a process of DC maturation and then usually migration to the submucosa or draining lymph nodes to present foreign antigen bound via MHCI or MHCII to activate CD8 or CD4 lymphocytes respectively, thereby eliciting a cellular and aiding a humoral immune response. Plasmacytoid DCs (pDCs) are found mainly in the blood and lymph nodes and function primarily to provide antiviral defence by secretion of very large quantities of interferon (IFN)-α after migration to areas of foreign antigen exposure or inflammation. In this setting they can also present antigen to and activate T-cells. Certain subsets of DCs are also able to "cross-present" exogenous antigens taken up by endocytosis which then enter the MHCI (rather than MHCII) processing pathway to allow peptide presentation to CD8 lymphocytes. DCs also interact with other immune cells, including natural killer (NK), NKT, gamma delta T cells and B lymphocytes. They may interact with two of these cell types simultaneously, e.g. $CD4^+$ T and B lymphocytes to stimulate antibody production.

1.2 Dendritic Cell Classification, Origins and Development

1.2.1 Myeloid Dendritic Cell Classification (Table 1.1)

The accessibility of a variety of murine lymphoid tissues has allowed more rapid progress in defining murine rather than human DC subsets.

Table 1.1 Comparison of classification of murine and human dendritic cells

	Mice	Human
Blood	$CD8^+$ DC	$BDCA3^+$ $CD141^+$ DC
	$CD8^-$ DC	? $CD11c^+$ $CD1c^+$ DCs
	?	$CD16^+$ $MDC8^+$ DCs
	Monocyte derived DC (at inflammatory sites)	Monocyte derived DC (at inflammatory sites)
	Plasmacytoid DC	Plasmacytoid DC
Skin/mucosa	Langerhans cell	Langerhans cell
	$CD103^-$ Dermal DC	CD14 or $CD1a^+$ Dermal DCs?
	$CD103^+$ langerin + dDC	?BDCA3/$CD141^+$ DC

?: human or murine equivalent is unknown

1.2.1.1 Murine Myeloid Dendritic Cell Subsets

CD4 and CD8 (as an αα rather than αβ dimer), the CLRs DEC205 and langerin, the α chain of Mac1, and CD11b are used to distinguish murine DC subsets.

In lymphoid tissue there are five subsets of myeloid DCs found in normal mice: $CD4^-/CD8^+$, $CD4^+/CD8^-$, $CD4^-/CD8^-$ DCs are all found in the spleen and lymph nodes. Additionally, $CD4^-/CD8^-/CD11b^+/DEC205^+$ DCs and mature $langerin^+/CD11b^+/DEC205^+$ Langerhans cells (LC) (which have migrated from epithelia) are found in the lymph nodes only. $CD8^+$ DCs are concentrated in the T cell areas and the $CD8^-$ DCs in the marginal zones of lymph nodes; however, $CD8^-$ DCs migrate into the T cell zones after microbial stimulation.

In skin and mucosa the DC subsets differ between stratified squamous and columnar/cuboidal mucosa. Only LCs are found in the epidermis of stratified squamous epithelium and there are two subsets of dermal DCs, which can be differentiated according to CD103 expression. The $CD103^-$ dermal DC subset is similar to lamina propria DCs beneath columnar/cuboidal epithelium. In inflamed mouse skin these resident populations are augmented by infiltrating monocytes which differentiate in situ into monocyte-derived DCs (Eidsmo et al. 2009; Shortman 2012; Shortman and Liu 2002; Villadangos and Schnorrer 2007; Villadangos and Shortman 2010).

1.2.1.2 Human Myeloid Dendritic Cell Subsets

Human myeloid DCs can be divided into functional subsets based on anatomical distribution and the expression of cell surface markers.

In blood "classical" DCs express CD11c and CD1c (BDCA1) and a CD141 BDCA3 expressing subset equivalent to mouse $CD8^+$ DCs has also been defined (Ziegler-Heitbrock et al. 2010). DC like blood cells that express CD16 and M-DC8 (MacDonald et al. 2002; Schakel et al. 2006) have been recently classified within the monocyte population (Ziegler-Heitbrock et al. 2010), although it is clear that they share many properties with DCs rather than monocytes (Cros et al. 2010). The $CD141^+/BDCA3^+/CLEC9A^+$ subset and the murine equivalent of the $CD8\alpha^+$ DC found in lymph nodes are both capable of cross-presentation of pathogen antigens (Poulin et al. 2010).

In skin and stratified squamous anogenital mucosa there are at least three DC subsets—the well-characterized epidermal LCs expressing CD1a and langerin, and two found within the dermis that express either CD1a or CD14 (BDCA3/CD141 DCs have also been found in dermis recently). LCs characteristically express Birbeck granules, composed of langerin in endosome-like compartments, and often appear tennis racket shaped by electron microscopy. Both dermal subsets express the mannose receptor but only the CD14 expressing population expresses DC-SIGN (Turville et al. 2002). It is likely that in time, these DC subsets will be further divided based on the discovery of new novel expression markers (Ju et al. 2010).