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SHAPING NAIVE AND MEMORY CD8+ T CELL RESPONSES IN PATHOGEN INFECTIONS THROUGH ANTIGEN PRESENTATION

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1. INTRODUCTION

The phenotypic and functional studies carried out during recent years have highlighted the enormous heterogeneity among dendritic cells. These specialized cells possess a variety of features that make them highly efficient agents for the detection of pathogens and induction of immune responses. Unraveling how the phenotypic, molecular, and functional signatures of dendritic cells regulate the decision-making process during an immune response has been the focus of intense research in recent years. The advances in our understanding have implications for the development of vaccine strategies that are targeted to individual subpopulations of dendritic cells.

2. DENDRITIC CELLS OF SPLEEN AND LYMPH NODES

Dendritic cells (DC) are professional antigen-presenting cells (APC) that have an extraordinary capacity to stimulate naive T cells and initiate primary

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immune responses to pathogens. They are continuously generated in the bone marrow and are widely distributed as immature DC to both lymphoid and non-lymphoid tissues[1].

Gaining an understanding of the origins and development of DC has proven difficult. This is attributable to their rarity in lymphoid tissues (<1%). Both common lymphoid and common myeloid progenitors appear to have the capacity to differentiate into the different subsets of conventional DC suggesting that the DC lineage has incredible developmental flexibility[2,3]. While some reports have described the conversion of one DC type to another[4–6], other studies have failed to find strong evidence to support such a developmental relationship. Most of our information on DC behavior and their classification are derived from studies examining DC phenotype and function in their steady-state environment[7]. However, it is likely that these details may need to be modified as we better understand the enormous plasticity of DC in effectively shaping an immune response to pathogens.

The existence of multiple DC subsets with distinct microenvironmental niches points toward unique functional specialization of different DC. In the spleen and lymph nodes (LN) up to seven subsets of DC that express intermediate to high levels of the integrin CD11c have been described[8–13]. One of these subsets corresponds to the IFNα-producing plasmacytoid DC (pDC)[11,12]. The three conventional DC populations found in the spleen can be distinguished using the surface markers CD4, CD8α, CD11b, and CD205 (Table 1). One subset expresses CD8α together with CD205, but lacks expression of CD11b (CD8 DC). Another subset expresses CD4 and CD11b, but not CD205 (CD4 DC), while a third subset expresses only CD11b. This latter subset is referred to as the double-negative (DN) DC. A fourth subset of DC found in lymph node (LN) but not in spleen expresses both CD205 and CD11b. This subset is the equivalent of the "interstitial" DC found in many peripheral tissues. In the skin they are referred to as dermal DC, while an equivalent DC subset dominant in the LN draining the lung (interstitial-like), but also found in the hepatic and renal LN and Peyer's patch, expresses CD205 but not CD8α or CD11b[8,14]. In addition to dermal DC are those DC resident only in the epidermis of the skin, the Langerhans cells.

Langerhans cells that have migrated to the draining LN express CD11b, CD205, and low or negligible amounts of CD8α. The current paradigm suggests that interstitial, interstitial-like DC, and Langerhans cells ("tissue-derived DC") carry antigens from peripheral tissues to the draining LN, where they present them to other lymphoid cells. This contrasts with the three conventional DC subsets found in spleen and LN that do not appear to traffic from peripheral tissues prior to entering the secondary lymphoid tissues. Rather, they appear to be best defined as "resident DC," which have originated from the bone marrow precursors that seed secondary lymphoid tissues via the blood[7].

Table 1. Conventional DC Subsets in Mouse Lymphoid Tissues

DC subsets					Tissue distribution**			
	Surface marker*							
Subset designation	CD8	CD4	CD205	CD11b	Spleen	Mes-enteric LN	Skin-draining LN	Visceral LN
CD8 DC	+++	–	++	–	++	+	+	+
CD4 DC	–	+++	–	+++	++++	+/–	+/–	+/–
DN DC	–	–	–	+	++	+++	++	++
Dermal/ interstitial DC	–	–	+	+	+/–	++	++	+
Langerhans cells	+	–	+++	+	–	+/–	+	–
Interstitial-like DC***	–		++	–	–	+	+	+++

* The relative level of expression of each surface marker on DC subsets.

** The relative frequency of DC subsets is expressed by the number of '+' symbols: 50–70% (++++), 30–50% (+++), 20–30% (++), 10–20% (+), and <5% (+/–).

3. ROLE OF DENDRITIC CELLS IN PATHOGEN RESPONSES

3.1. Priming Naive T Cells

Classically, priming of naive $CD8^+$ T cells requires professional APC that can efficiently present endogenous or pathogen-derived antigens on major histocompatibility (MHC) class I molecules in combination with the necessary costimulatory molecules to facilitate full activation of T cells. However, whether each of these elements is strictly required to be provided by a professional APC to enable T cell priming has remained contentious. Pathogens usually provide an abundant source of antigen together with pathogen-derived components (for example, cell wall lipids) that are themselves highly inflammatory. Together, such signals may to be sufficient for many cells of the body that express MHC class I molecules to activate T cells, thereby sidestepping the absolute requirement for professional APC.

Early studies by Staerz and collegues[15] showed that, following influenza infection, mice failed to develop virus-specific $CD8^+$ T cells when phagocytic cells were depleted in vivo, but that priming was restored when macrophages were administered. This provided the first direct evidence that phagocytic cells play an important role in priming $CD8^+$ T cell responses to viral infection. Sometime later Rock and colleagues[16,17] exploited the sensitivity of most bone marrow-

derived cells to irradiation to demonstrate that bone marrow-derived cells are essential for virus-specific $CD8^+$ T cell priming. In these studies irradiated C57BL/6 recipient mice were transplanted with bone marrow from $Tap1^{o/o}$ mice. This type of bone marrow lacks the transporter required for presentation of immunogenic peptides to $CD8^+$ T cells. Analogous approaches have utilized bone marrow cells that carry mutant MHC class I molecules that are unable to present immunogenic peptide from the antigen under examination. In these systems, only parenchymal cells (non-bone marrow-derived cells) would be able to present antigens to $CD8^+$ T cells. Such an approach has been used to examine the response to vaccinia virus, lymphocytic choriomeningitis virus, and influenza virus[17,18]. Collectively these studies have elegantly demonstrated that virus-specific naive $CD8^+$ T cell responses require antigen to be presented on MHC class I molecules by bone marrow-derived cells.

While the above experiments have established that bone marrow-derived cells are generally required to elicit pathogen-specific responses, it has proven far more difficult to elucidate (i) whether presentation of virus-derived antigens is strictly limited to bone marrow-derived professional APC, and (ii) if so, what is the exact identity of these APC. The approach to the first problem was pioneered by Debrick et al.[15], and more recently refined by Jung et al.[19], who designed an elegant transgenic mouse model to eliminate $CD11c^+$ cells. The latter group developed transgenic mice that express the diphtheria toxin receptor fused to the green fluorescent protein (DTR-GFP) driven by the CD11c promotor. Mouse cells do not naturally express the diphtheria toxin receptor and thus $CD11c^+$ cells become susceptible to the cytotoxic effects of diphtheria toxin, allowing inducible ablation of DC in vivo. Strikingly, mice that were depleted of DC failed to develop T cell responses following either malaria, *Listeria monocytogenes,* or viral infections, confirming the crucial importance of DC in initiating naive $CD8^+$ T cell responses to pathogens[19,20].

The second problem described above, that of defining the specific identity of DC actually presenting the pathogen-derived antigens, has been facilitated by several laboratories, including our own, developing very careful methods for direct ex vivo DC purification and analysis. These approaches have been used to mainly examine pathogen systems and will be described in greater detail below.

3.2. Identifying the Main Movers and Shakers in Infection

DC show amazing phenotypic diversity, resulting in the many different subsets described above. Such diversity raises the notion that, like T cells and B cells, DC subsets represent specialized populations of immune cells that respond to different types of antigens or pathogens. This tantalizing concept has fueled an extensive search for DC subtypes that might differentially regulate the induction of T cell immunity or, alternately, T cell tolerance, in vivo[8,21–27].

Two experimental approaches have been used to examine which DC subsets are essential for the $CD8^+$ T cell response to a number of pathogens. Importantly, these experiments hinge on developing highly sensitive in-vitro assays that allow the monitoring of antigen presentation by the very low number of DC thought to carry pathogen-derived antigens. Both approaches involve inoculating mice with a pathogen and at various time points after infection the draining LN or spleen are dissociated and the DC subsets isolated. These highly purified populations are then co-cultured with T cell hybridoma lines or naive transgenic T cells. In the first experimental system, purified DC are co-cultured with a T cell hybridoma line specific for an MHC class I-restricted peptide derived from the pathogen. Conventionally, the response elicited has been analyzed by measuring interleukin-2 production. However, this approach has rarely proven sufficiently sensitive in pathogen systems to accurately analyze antigen presentation. This further supports the notion that only very small numbers of DC actually carry the viral antigen of interest. More recently, the difficulty in detecting MHC class I presentation directly ex vivo from pathogen-infected animals has been circumvented by using T cell hybridomas that express the *lacZ* gene. This feature enables individual cells that have been stimulated by antigen-bearing cells to become blue on exposure to β-galactosidase[8,21,28]. The advantage of T cell hybridomas is that they are independent of costimulatory requirements and therefore provide a highly sensitive readout for analyzing antigen presentation ex vivo. Interestingly, however, not every cell type that is able to stimulate a *lacZ*-expressing hybridoma can activate naive T cells. To explore which cells have the capacity to fully signal a naive T cell, 5,6-carboxy-fluorescein succinyl ester (CFSE)-labeled naive T cell receptor transgenic cell proliferation has been used. This technique has been central to understanding which cells are essential for the T cell-APC interaction that leads to immunity. Nevertheless, differences in the sensitivity of the respective TCR transgenic cells together with a lack of TCR transgenic T cells for both $CD4^+$ and $CD8^+$ T cell epitopes, which would permit MHC class II antigen presentation to be monitored simultaneously, has left significant gaps in our understanding of how the pathogen response is molded.

3.3. Dendritic Cell Subsets in Pathogen Infections

DC are crucial in mounting an effective cytotoxic T cell response to both lymphocytic choriomeningitis virus (LCMV) and the bacterium *Listeria monocytogenes*[19,29,30]. This most likely involves a complex interplay of different DC populations, encompassing not only conventional DC but also plasmacytoid DC and novel subsets such as Tip DC[29,31,32]. In the case of LCMV, the influx of IFNα-producing pDC limits viral replication[33]. In *Listeria monocytogenes* infection, Tip DC ($CD11c^+CD11b^+$ DC), so named for their production of tumor necrosis factor-α (TNFα) and inducible nitric oxide synthase (iNOS), provide cytokine-directed innate control of infection[31]. Although both pDC and Tip DC can pre-

sent pathogen-derived antigens, presentation is very inefficient when compared to conventional DC and was not required for generation of antigen-specific adaptive immunity[31].

It is likely that the route of foreign antigen invasion into the body is a major factor determining which DC and other APC are involved in the transport of antigen to the LN and, in some instances, the subsequent transferral of antigen within the lymphoid organs to secondary DC. Access to secondary lymphoid tissues typically occurs either via the blood (for example, malaria, yellow fever, and lyme disease) or by transport from peripheral sites such as the lung, gut, or skin. Classically, tissue-derived DC have been implicated as central for initiating immunity. However, more recent rigorous examination of this concept has illustrated that the migratory tissue-derived DC are not always able to prime naive T cells. For example, our group has recently demonstrated that Langerhans cells in mice were unable to prime naive $CD8^+$ T cells following cutaneous infection with herpes simplex 1 (HSV-1)[26].

Further analysis of the differential roles of DC subsets in priming naive virus-specific $CD8^+$ T cells has been undertaken in our laboratory during recent years[8,24–26,34]. In particular, one subset of DC, the CD8α DC, appears to play an integral role in presenting virus-specific antigens to naive T cells during infection. We have shown that virus administered via the blood results in MHC class I antigen presentation solely by this conventional CD8α DC subset. Moreover, this was also the case for other viruses, including HSV-1, influenza virus, vaccinia virus, LCMV, and *L. monocytogenes*[25], suggesting that CD8α DC represent a common pathway for handling and presenting pathogen-derived antigens. These studies, however, did not examine the role of DC subsets in $CD4^+$ T cell presentation following infection. In contrast to the central role played by CD8α DC, $CD11b^-$ (interstitial) DC seem to be largely responsible for priming naive $CD4^+$ T cells. For example, Filippi et al.[35] showed that following *Leishmania major* infection $CD11b^-$DC presented the MHC class II-restricted LACK antigen to $CD4^+$ T cells. Similarly, analysis of MHC class II presentation to $CD4^+$ T cells during herpes simplex 2 (HSV-2) infection revealed $CD11b^-$DC as the main APC in draining LN[36]. Interestingly, Langerhans cells did not prime $CD4^+$ T cells following either *L. major* or HSV-2 infection. In our own studies of antigen presentation to $CD8^+$ T cells following HSV-1 infection, neither Langerhans cells nor dermal DC could activate naive T cells despite the abundance of antigen associated with both these DC at the infection site.

Our study examining $CD8^+$ T cell immunity to viral lung infection revealed evidence for the interplay between the migratory tissue-derived DC ($CD11b^-$ $CD8\alpha^-$) and LN resident blood-derived CD8α DC in priming naive $CD8^+$ T cells[8]. To track DC migration from the lung, CFSE was administered intranasally following virus infection. This dye labeled peripheral lung DC and allowed us to establish that MHC class I antigen presentation was accomplished by the tissue-derived migratory $CD11b^-CD8^-$DC subset. In addition, the LN resident

blood-derived CD8α DC efficiently presented viral antigens; however, given that they were not labeled by CFSE, it is most likely that they acquired antigen from the immigrant tissue-derived DC.

Table 2. Dendritic Cell Populations Associated with Pathogen Infections

Infection	DC subset	Naïve T cell activated	Origin/ function	Reference
HSV-1 (cutaneous, subcutaneous)	$CD8\alpha^+$	$CD8^+$	blood-derived Ag presentation	24–26
HSV-2 (vaginal)	$CD11b^+$	$CD4^+$	tissue-derived Ag presentation	36
Influenza A, HSV-1 (intranasal)	$CD8\alpha^+$	$CD8^+$	blood-derived Ag presentation	8 and unpub. (GTB)
	$CD11b^+$	$CD8^+$	tissue-derived Ag presentation	
LCMV, vaccinia virus (intravenous, intraperitoneal)	$CD8\alpha^+$	$CD8^+$	blood-derived Ag presentation	25,37
Reovirus	$CD8\alpha^+$	$CD4^+$	blood-derived Ag presentation	14
	$CD11b^{low}$	$CD4^+$	tissue-derived Ag presentation	
Listeria monocytogenes	$CD8\alpha^+$	$CD8^+$	blood-derived Ag presentation	37
	TipDC	…	iNOS antigen presentation	
Leishmania major	$CD11b^+$ (dermal DC) $CD8\alpha^+$	$CD4^+$	tissue-derived Ag presentation	39

*Presentation to $CD4^+$ T cells has not been examined. **Presentation to $CD8^+$ T cells has not been examined. ***T cell subset has not been determined.

In a model of reovirus infection of the gut, Fleeton et al.[14] similarly identified two populations of DC involved in generating $CD4^+$ T cell responses to the virus. These were the CD8α DC and $CD11b^{low}$ DC subsets. This latter subset appears to be analogous to the $CD11b^-$ DC found in the lung and visceral LN both in phenotype and function, and they were found to be important for transporting apoptotic material from the gut epithelium to the mesenteric LN for

transfer to resident CD8α DC. These two studies underline the importance of the migratory tissue-derived DC in transporting viral antigens to the draining LN for transfer to LN-resident DC as a generalized mechanism for amplifying the $CD8^+$ T cell immune response.

3.4. Amplification of Memory CD8+ T Cells in Secondary Infections

A number of studies have identified the ability of various APC — such as DC, macrophages, or even epithelial cells — to differentially present viral antigens. Such work has led to the proposal of an elegant model in which during a primary immune response DC are the essential drivers of T cell priming. In contrast, during a recall response, non-DC, particularly those that are tissue resident, would be ideally positioned to rapidly amplify memory T cells ("tissue mediated")[40]. This would presumably provide the most efficient mechanism for removing infection at the site of entry. From a teleological perspective, such a schema could explain how tissue-mediated antigen presentation influences and facilitates the memory T cell response in vivo. However, it would be extremely important to first determine whether the memory T cells, like naive T cells, in fact depend only on DC to drive their development and differentiation. The current concept that memory T cells could be activated by parenchymal cells is supported by findings showing that memory T cells have a lower threshold for activation and have less stringent costimulation requirements than naive T cells[41–43]. This would argue that memory T cells are more promiscuous than naive T cells in responding to antigen presented by non-DC. To formally address this issue, our group[27] and Zammit et al.[20] established complementary systems in which it was examined whether a bone marrow-derived cell, or specifically a DC, was required to activate and amplify memory $CD8^+$ T cells in pathogen infections. Remarkably, both studies showed that memory $CD8^+$ T cells were largely dependent on DC to maximize the recall response to infection. Furthermore, this amplification of memory T cells was reliant on the migratory DC transporting antigen to the draining LN. However, some amplification of effector cells was detected in the lung bronchoalveolar lavage following influenza infection, supporting that non-DC may represent a *bone fide* cell type capable of stimulating memory T cells allowing a tissue-mediated frontline defense against pathogen invasion[20,27]. Interestingly, though, a similar outcome was not apparent when infection was transmitted via a cutaneous route with HSV-1[27]. These studies provide an important new conceptual viewpoint of memory T cells, showing that the interaction with DC is a major mechanism driving both naive T cell activation and memory T cell reactivation.

4. CONCLUSIONS

The heterogeneity and complexity of the DC network have been probed through many meticulous studies over recent years. From this body of work has emerged a picture showing a complex and dynamic interplay between DC subsets and other immune cells. Although much remains to be unraveled about the precise details about the DC subsets and molecular mechanisms regulating DC interactions with T cells, two important observations have emerged that challenge our previous views of the behavior of these cells. The first salient conclusion of the studies presented here is that the induction of T cell immunity to peripheral pathogens requires the tissue-resident migratory DC to transport antigen captured in the periphery to the draining lymph node, where transfer of antigen to other DC can occur. This transfer appears essential to initiating and amplifying T cell immunity, as unexpectedly not all migratory DC (for example, Langerhans cells) are themselves able to stimulate robust T cell responses. Second, memory T cells share with naive T cells a significant dependence on DC to initiate the recall response to pathogens in vivo. This surprising finding raises important questions about how memory T cells are regulated in vivo and how we can harness their features to best recall them in secondary immune responses. Understanding the complex interactions between DC subsets and other immune cells has important implications for the development of targeted vaccine strategies that target specific DC populations in vivo.

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