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Review

Dendritic cells and liver fibrosis ☆

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ABSTRACT

Dendritic cells are a relative rare population of specialized antigen presenting cells that are distributed through most lymphoid and non-lymphoid tissues and play a critical role in linking the innate and adaptive arms of the immune system. The liver contains a heterogeneous population of dendritic cells that may contribute to liver inflammation and fibrosis through a number of mechanisms. This review summarizes current knowledge on the development and characterization of liver dendritic cells and their potential impact on liver fibrosis. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

Dendritic cells (DCs) comprise a relative rare and heterogeneous population of specialized hematopoietic cells that play an important role in linking the innate and adaptive arms of the immune system. DCs were first identified as potent antigen presenting cells in mouse spleen and it is now established that they are distributed through most lymphoid and non-lymphoid tissues. Despite the fact that they typically represent only a small proportion within the leukocyte population, they are the primary professional antigen presenting cells and play an important role in monitoring the tissue microenvironment. After capturing antigens, tissue-resident DCs mature and migrate via the afferent lymphatics to the draining lymph nodes where they can present these antigens to T cells. The effectiveness of DCs at presenting antigens and priming T cell responses is one of their defining attributes. Their migratory capacity is also an important feature that distinguishes them from tissue-resident macrophages. DCs are also important producers of multiple cytokines through which they can influence a broad range of other cell types. DCs in the liver are uniquely positioned to monitor the portal circulation, and the ways in which they regulate responses to blood-borne pathogens, hepatic immune tolerance, liver homeostasis and fibrosis continue to be areas of active research. Given their scarcity, heterogeneity and the absence of clear defining surface markers, the investigation of hepatic DCs has thus far been challenging.

2. Subsets of liver dendritic cells

Tissue-resident DCs are present in most tissues; however, there is considerable functional and phenotypic heterogeneity amongst DC populations [1], which also varies based on tissue localization. The functional roles of DCs are often influenced by their specific tissue microenvironments, and certain tissues contain specialized DC populations, such as Langerhans cells in the skin. The DC populations in the liver express similar surface markers to those found in other tissues such as the lung, kidney and pancreas, and much of our understanding of liver DCs is based on studies of analogous DC populations that have been more extensively studied in other lymphoid and non-lymphoid tissues [2,3]. However, the liver seems to play a unique role in the DC traffic: at least in rat, DCs undergo a blood-lymph node translocation via the hepatic sinusoids, which may act as a biological concentrator of circulating DCs into the regional hepatic nodes [4].

DCs are sparsely distributed through the liver, and immunohistochemical studies of patient liver biopsies indicate that they are primarily found in the portal regions and occasionally in the parenchyma [5]. Unlike hematopoietic lineages such as B cells or T cells, a single cell surface marker that can be used to unequivocally identify DCs has yet to

Abbreviations: DC, dendritic cell; MHCII, major histocompatibility class II; IFN, interferon; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; MDP, monocyte DC progenitor; CDP, common DC progenitor; Flt3, FMS-like tyrosine kinase 3; Flk2, fetal liver kinase-2; IRF8, interferon regulatory factor 8; zbtb4/zDC, zinc finger and BTB domain containing 4; ID-2, inhibitor of DNA binding 2; Batf3, basic leucine zipper transcriptional factor ATF-like 3; NK, natural killer; MMP, matrix metalloproteinase; BDL, bile duct ligation; MCP-1, monocyte chemotactic protein 1; TLR, toll-like receptor; DT, diphtheria toxin; TNFα, tumor necrosis factor alpha

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be determined, and distinguishing DCs from other cell types, such as monocytes and macrophages continues to be a challenge in some circumstances. The fact that some of the surface markers that are highly expressed by specific DC subsets in mice are poorly expressed on human DCs and vice versa presents an additional challenge. Nevertheless, considerable progress has been made in recent years in defining sets of cell surface markers that can be used to identify distinct DC subsets.

In multiparametric flow cytometric analyses, DCs in both mice and humans can be identified as $CD45^+$ cells that constitutively express high levels of major histocompatibility complex II (MHCII) while lacking markers for other hematopoietic lineages. This is admittedly a broad definition, and the use of additional markers, such as the high expression of CD11c, can be also useful in identifying DCs. However, effectively excluding other hematopoietic cell types when conducting DC analyses is very important given that many of the surface markers that frequently are used to define DC subsets can also be expressed by other cell types, such as B cells and macrophages. This is particularly true in the setting of inflammation.

Under steady state conditions, liver DCs in both mice and humans can be divided into two major functional classes: classical DCs (cDCs) and plasmacytoid DCs (pDCs). cDCs express high levels of MHCII and function as highly-efficient professional antigen presenting cells. In contrast, pDCs express relatively lower levels of MHCII and have a relatively limited capacity to capture and present tissue antigens and instead function as major producers of type I interferons (IFNs) in response to nucleic acids in the setting of viral infection [6] (Table 1). Reinforcing these functional differences, pDCs share certain molecular and morphological features with B lymphocytes, including typical secretory lymphocyte morphology rather than the eponymous dendritic morphology of cDCs. In naïve C57BL/B6 mice, pDCs comprise the majority of liver DCs and can be identified as a $CD11c^+$ population that expresses CD317 (PDCA1) and Siglec H [7] (Fig. 1A). Human pDCs do not express CD11c but can be identified as HLA-DR^{hi} cells that also express high levels of the type II C-type lectin CD303 (BDCA2) and the IL-3 receptor CD123 [8]. The frequency of these cells in human liver explants and resections is typically much lower than the frequency of pDCs found in the livers of naïve mice (Fig. 1B), and is similar to the frequency observed amongst circulating PBMCs.

The cDC population in the liver can be further divided into two major functionally and phenotypically distinct subsets. In mice, the hepatic $CD11c^{hi}MHCII^{hi}$ cDC population contains a more prevalent $CD103^-CD11b^{hi}$ population and a rarer $CD103^+CD11b^{low}$ population (Fig. 1A), which appear to correspond to the $CD8^-CD11b^{hi}$ and $CD8^+CD205^+$ lymphoid tissue DC subsets, respectively. CD11b expression on the $CD103^-$ DC population tends to be heterogeneous, and the $CD103^-CD11b^{low}$ subset may represent a less mature population. Corresponding counterparts to the $CD11b^{hi}$ and $CD103^+$ DC populations can be identified in human livers by the markers CD1c (BDCA1) and CD141 (BDCA3), respectively (Fig. 1B and C). The $CD1c^+$ population is somewhat heterogeneous for CD14 expression, suggesting that the $CD1c^{low}CD14^{hi}$ DC population may be analogous to the $CD11b^{low}CD103^-$ subset in mice. However, while some studies have defined $CD14^+$ and $CD16^+$ cells in the liver as DCs [3,9], it can be challenging to unequivocally distinguish these cells from monocyte and macrophage populations that may also express high levels of these markers, particularly in the setting of inflammation.

Studies of these DC subsets in other tissues indicate that the $CD11b^+$ subset produces higher levels of most cytokines and chemokines and efficiently processes and presents MHCII-restricted antigens to $CD4^+$ T cells, whereas the $CD103^+$ subset is more efficient at cross-presenting MHCI-restricted antigens to $CD8^+$ T cells [10–12] (Table 1). Studies in humans have similarly shown that $CD141^+$ DCs are more efficient at cross-presenting antigens than $CD1c^+$ DCs [3,13]. However, studies of $CD141^+$ DCs in the skin suggest that this subset may also serve a tolerogenic function by producing high levels of IL-10 and inducing regulatory T cells [14]. This is notable because studies of the total cDC

Table 1
Functional heterogeneity of dendritic cell subsets. While studies have yet to comprehensively elucidate the functional differences of hepatic DC subsets, studies of analogous DC subsets in other tissues suggest distinct functional characteristics. Based on data compiled from [1,10,11,13,14,17–19].

Species	DC type	DC subset	Key functional characteristics
Mouse	pDC • $Lineage^-$ • $CD11c^{int}$ • $MHCII^{int}$ • $PDCA\text{-}1^+$ • Siglec H^+		• MHC Class II presentation ± • MHC Class I cross-presentation ± (but can be induced by TLR stimulation) • Highly responsive to TLR7/9 ligands • Secrete high levels of IFNα during viral infections; negative regulators: Bst2 and Siglec H • Induction of IL-10 secreting Tregs (in vitro) • Induction of oral tolerance (in vivo) and tolerance in vascularized transplants
	cDC • $Lineage^-$ • $PDCA\text{-}1^-$ • $CD11c^{high}$ • $CD11c^{high}$ • $MHCII^{high}$	$CD103^+$ DC (Batf3 dependent DC)	• MHC Class II presentation + • High capacity of MHC Class I cross-presentation to cytotoxic T cells • Express TLR3 and TLR11-12 • Phagocytose apoptotic cells
		$CD103^-$ DC (Batf3 independent DC)	• High capacity for MHC Class II presentation of exogenous antigen • MHC Class I cross-presentation + • Express most TLRs and in addition RIG-1 and MDA5 • Secretes pro-inflammatory cytokines (TNFα and IL-6) after TLR ligation • A subsets with high production of TNFα and iNOS (TIPS DC, monocyte-derived DC)
Human	pDC • $Lineage^-$ • $MHCII^{high}$ • $CD123^+$ • $BDCA\text{-}2^+$		• MHC Class II presentation ± • MHC Class I cross-presentation + • Highly responsive to TLR7/8/9 ligands • Secrete high levels of IFNα during viral infections; negative regulators: BDCA-2 and ILT-7
	cDC • $Lineage^-$ • $CD123^-$ • $BDCA\text{-}2^-$ • $MHCII^{high}$	$CD141^+$ cDC	• MHC Class II presentation + • MHC Class I cross-presentation ++ • Highly responsive to TLR3 ligands • Produce high levels of CXCL10, IL12p70, IFNβ IFNλ after TLR stimulation
		$CD1c^+$ cDC	• MHC Class II presentation + • MHC Class I cross-presentation + • Produce high levels IL-8 at baseline and IL-1β after TLR3 stimulation