Recruitment of dendritic cells to pathological niches in inflamed liver

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Abstract The liver is a specialized organ for host defense and immunity. Recruitment of dendritic cells (DCs) is crucial to host defense in a granulomatous liver disease in mice. In response to danger signals, DC precursors are mobilized de novo into the circulation. Myeloid DC (mDC) precursors are recruited to perisinusoidal spaces and activated to form granulomas. Recruited mDCs subsequently extravasate into Disse’s space and migrate to the portal area to induce portal tract-associated lymphoid tissue (PALT). Some mDCs are remobilized into draining hepatic lymph nodes (LNs) to prime antigen-specific CD4⁺ helper T cells. Kupffer cell-derived CCL3/MIP-1α attracts mDC precursors to the sinusoidal granulomas, whereas PALT composed cell-derived CCL21/SLC attracts activated mDCs to the T-cell zone of PALT. Inflammatory cytokines modulate this sinusoid-portal migration through IL-1R/TLR signaling. Recruited mDCs themselves also produce several chemokines and cytokines that modulate T-cell responses. A unique trafficking of circulating mDC precursors within the inflammation-associated, newly formed compartments (“pathological niches”) is strictly regulated by both homeostatic and inducible chemokines and determines the final efficiency of the immunity in this organ.

Key words Dendritic cell · Chemokine · Granuloma · Kupffer cell · T cell

Introduction

Dendritic cells (DCs) are bone marrow-derived professional antigen-presenting cells (APCs) and constitute a heterogeneous group of cells. In mice, there are at least three major functional subtypes of DCs in lymph nodes (LNs): myeloid DCs (mDCs; CD11b⁺B220⁻CD11c⁺), CD8α⁺ DCs (CD8α⁺B220⁺CD11c⁺), and plasmacytoid DCs (pDCs; B220⁺CD11c⁻), which induce distinct types of effector T lymphocytes. In response to danger signals such as bacterial and viral infection, the DC network rapidly promotes T-cell-mediated immunity to selectively eliminate infected cells. DCs are also heterogeneous in their maturation stages: progenitors in the bone marrow, precursors in the blood, immature DCs in peripheral tissues, antigen-transporting DCs in the afferent lymphatics, and mature antigen-presenting DCs in lymphoid tissues. Because DCs undergo their “effector” function in LNs, the route of LN entry of DCs also has an effect on the establishment of peripheral tolerance and immunity.

The liver is actively screening and capturing antigens (Ags) in the blood by the powerful specialized macrophages known as Kupffer cells, which directly face the bloodstream. Also, a minute amount of microorganisms in the gut may frequently encounter this organ via the portal vein, rendering the liver defense system in an alerted condition. Thus, the liver is considered to play essential roles in the establishment of peripheral tolerance and immunity.

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DCs in two pathological niches: sinusoidal granuloma and portal tract-associated lymphoid tissue

The sinusoidal wall contains several defined cells: Kupffer cells, endothelial cells, a few pit cells located in the hepatic sinusoid, and stellate (Ito) cells in Disse’s space.
These cells and Disse’s space together constitute the “sinusoidal functional unit,” which is the principal site for capturing bloodborne microorganisms. DCs are shown to be present in the hepatic sinusoid, suggesting their participation in the sinusoidal functional unit. In the steady state, DCs undergo a blood–lymph translocation from the liver to hepatic lymph. This change occurs within the sinusoidal unit because DCs can extravasate through endothelial pores to enter Disse’s space. In the pathological state, cell accumulations are formed in Disse’s space. In P. acnes-induced granulomas (Fig. 1A,B), DCs participated in the sinusoidal functional unit at an extremely early stage and some of them seemed to inhabit the developing granulomas in Disse’s space, being surrounded by P. acnes-laden macrophages (Fig. 1C).

On the other hand, the portal area encloses a triad of small bile ducts and branches of the hepatic artery and the portal vein and has been traditionally conceived to be a site of immune response. In fact, inflammatory infiltrates within the portal area are a rather common feature in various liver diseases. P. acnes-induced portal infiltrates constitute the organization of lymphoid tissue similar to that of peripheral LNAs, which contain B-cell follicles (Fig. 2), T-cell areas, and macrophages. Therefore, we term the structure portal tract-associated lymphoid tissue (PALT). The T-cell area of PALT is the initial zone of CD4⁺ T-cell proliferation within the inflamed liver and contains de novo appearing high endothelial cell (HEV)-like structures.

**Increased recruitment of inflammation-associated circulating mDC precursors into sinusoidal granulomas**

We and others recently identified blood MHCII⁺CD11c⁺ cells as circulating DC precursors. Murine blood MHCII⁺CD11c⁺ cells are classified into only two subsets: B220⁺CD11c⁺ mDC precursors and B220⁻CD11c⁺ pDC precursors. Functionally, mDC precursors showed phagocytic activity and acquired APC function after culture with granulocyte-macrophage colony-stimulating factor (GM-CSF) plus tumor necrosis factor (TNF)-α. In contrast, pDC precursors show poor phagocytic and APC activities. The numbers of both mDC and pDC precursors in naive mouse blood were extremely low, but increased greatly in response to danger signals.

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**Fig. 1.** Sinusoidal granulomas: 6-µm-thick section. A Day 7 after Propionibacterium acnes injection: DEC-205 (brown), bromodeoxyuridine (BrdU) (red), and CD4 (blue). B Clusters between DEC-205⁺ DCs and BrdU⁺CD4⁺ cells. C Six hours after P. acnes injection. P. acnes (red)-laden Kupffer cells (F4/80, brown) and CD11c⁺ DCs (blue) in the hepatic sinusoid. Bars A 120 µm; B 40 µm; C 30 µm

**Fig. 2.** Portal tract-associated lymphoid tissue (PALT): 10-µm-thick section, 3-D reconstituted image, day 7 after P. acnes injection. B220 (blue) and type IV collagen (red). PV, portal vein. Bar 40 µm