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SPECIAL REVIEW SERIES: New ultrastructural discoveries in the pathophysiology of liver diseases

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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.[1] In mice, there are at least three major functional subtypes of DCs in lymph nodes (LNs): myeloid DCs (mDCs; $CD11b^+B220^-CD11c^+$), $CD8\alpha^+$ DCs ($CD8\alpha^+B220^-CD11c^+$), and plasmacytoid DCs (pDCs; $B220^+CD11c^+$), which induce distinct types of effector T lymphocytes.[2,3] 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.[1] 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.[4] 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 a host defense against bloodborne Ags through a liver-specific immune system. Uniquely, Kupffer cells trap bloodborne DCs and translocate them into LNs through the hepatic sinusoids–lymph pathway.[5,6] In this review, we describe the recruitment and function of DC precursors within the inflammation-associated, newly formed compartments ("pathological niches") of the liver, in a *Propionibacterium acnes* (*P. acnes*)-induced granulomatous liver disease model in mice.

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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,[7] endothelial cells,[8] a few pit cells[9] located in the hepatic sinusoid, and stellate (Ito) cells[10] in Disse's space.

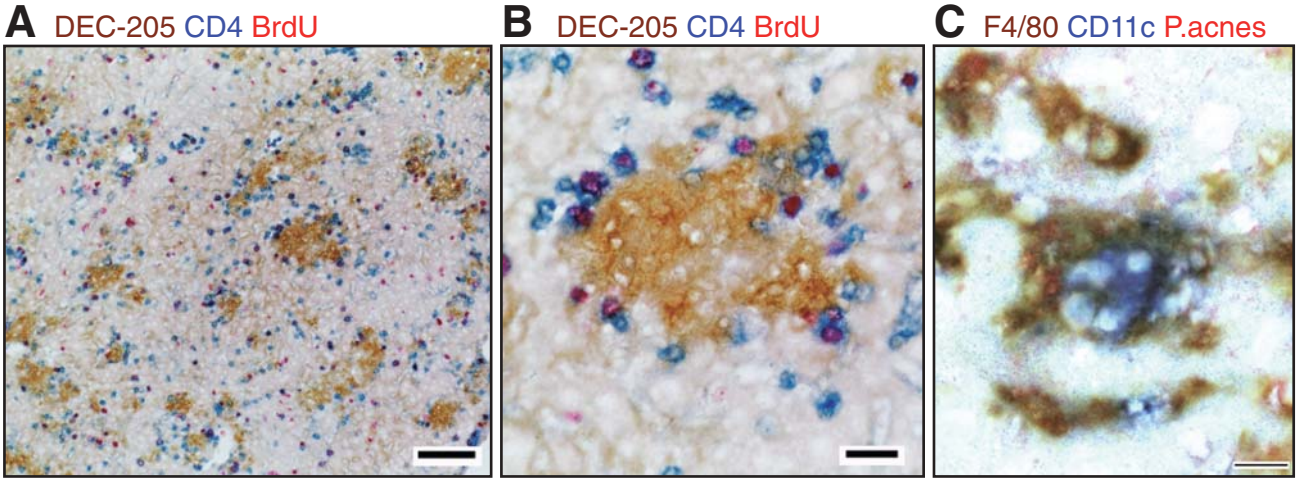

Fig. 1. Sinusoidal granulomas: 6-μm-thick section. **A** Day 7 after *Propionibacterium acnes* injection: DEC-205 (*brown*), bromodeoxyuridine (BrdU) (*red*), and CD4 (*blue*). **B** Clusters between DEC-205$^+$ DCs and BrdU$^+$CD4$^+$ cells. **C** Six hours after *P. acnes* injection. *P. acnes* (*red*)-laden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

These cells and Disse's space together constitute the "sinusoidal functional unit," which is the principal site for capturing bloodborne microorganisms.[11] DCs are shown to be present in the hepatic sinusoid,[6] suggesting their participation in the sinusoidal functional unit. In the steady state, DCs undergo a blood–lymph translocation from the liver to hepatic lymph.[5] This change occurs within the sinusoidal unit because DCs can extravasate through endothelial pores to enter Disse's space.[12] In the pathological state, cell accumulations are formed in Disse's space.[11,13] In *P. acnes*-induced granulomas (Fig. 1A,B), DCs participated in the sinusoidal functional unit at an extremely early stage[14] 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.[9] *P. acnes*-induced portal infiltrates constitute the organization of lymphoid tissue similar to that of peripheral LNs, 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.[14]

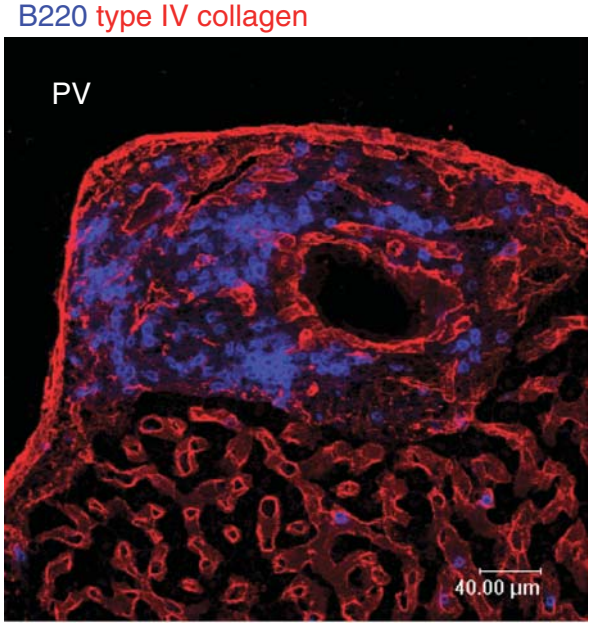

Fig. 2. Portal tract-associated lymphoid tissue (PALT): 10-mm-thick section, 3-D reconstituted image, day 7 after *P. acnes* injection. B220 (*blue*) and type IV collagen (*red*). *PV*, portal vein. *Bar* 40 μm

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

We and others recently identified blood MHCII$^-$CD11c$^+$ cells as circulating DC precursors.[3,14,15] Murine blood MHCII$^-$CD11c$^+$ cells are classified into only two subsets: B220$^-$CD11c$^+$ mDC precursors and B220$^+$CD11c$^+$ pDC precursors. Functionally, mDC precursors showed phagocytotic activity and acquired APC function after culture with granulocyte-macrophage colony-stimulating factor (GM-CSF) plus tumor necrosis factor (TNF)-α.[14,15] In contrast, pDC precursors show poor phagocytotic and APC activities.[15] The numbers of both mDC and pDC precursors in naive mouse blood were extremely low, but increased greatly in response to danger signals.

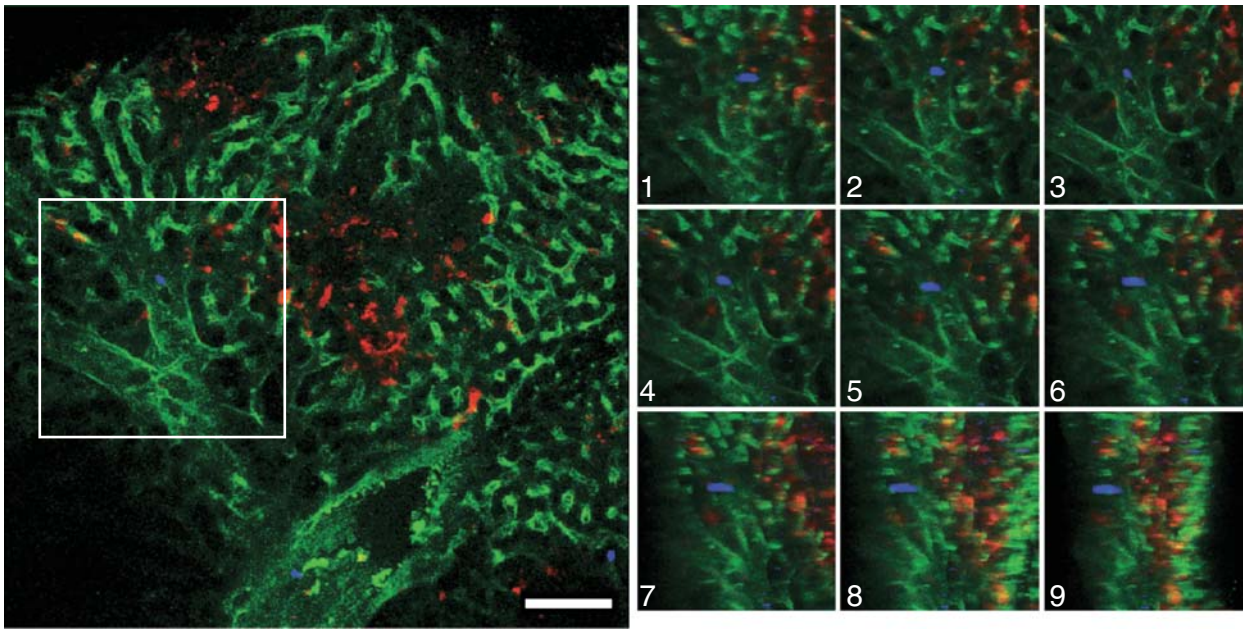

Fig. 3. Recruitment of DC precursors. Whole-mount preparation. An equal number (5×10^6 cells) of CMTMR-labeled myeloid DC (mDC) precursors (*red*) and CMAC-labeled pDC precursors (*blue*) were transferred i.v. into *P. acnes*-primed mice at day 7. Six hours later, fluorescein isothiocyanate (FITC)-labeled *Lycopersicon esculentum* lectin (*green*) was intravenously injected and mice were killed. Animated 3-D reconstitution of serial confocal sections and several rotated images of the *open box* are presented to the *right* in *panels 1–9*. *Bar* 80 μm

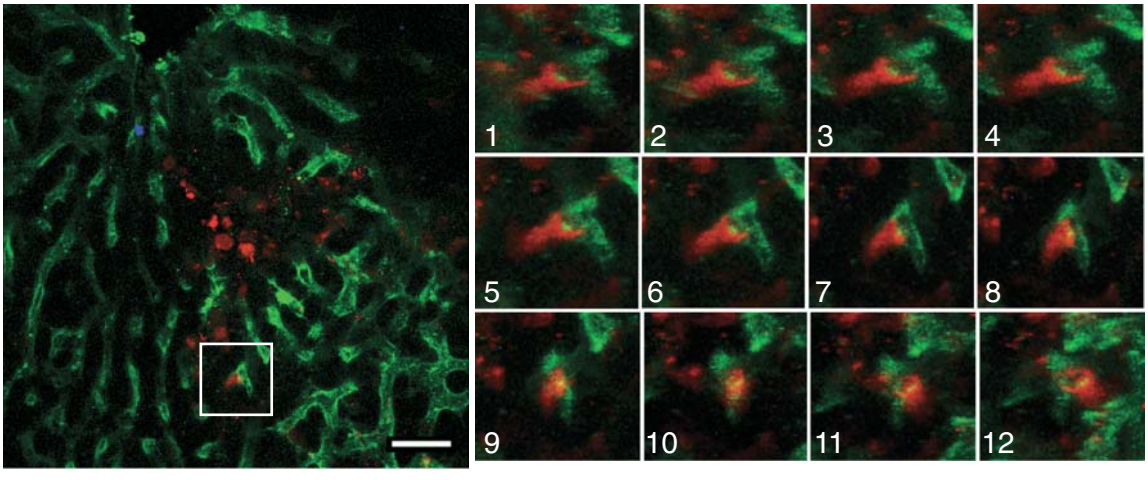

Fig. 4. Extravasation of DCs into granuloma space. Whole-mount preparation, same protocol as Fig. 3. Animated 3-D reconstitution of serial confocal sections and several rotated images of the *open box* are presented to the *right* in *panels 1–12*. *Bar* 40 μm

To test whether these circulating DC precursors actually enter the liver, we simultaneously transferred the same numbers (5×10^6 cells) of fluorescence-labeled mDC and pDC precursors into the granuloma-laden mice. Six hours later, a significant number of mDC precursors were preferentially detected at the sinusoidal granulomas (Fig. 3). Granulomas showed poor vascular networks, but transferred mDC precursors were actually detected at the center of granulomas. Some mDC precursors underwent extravasation from the hepatic sinusoid at the periphery of granulomas (see open box, Fig. 4). Therefore, blood mDC precursors not only extravasated to Disse's spaces but also lodged within granulomas after migrating to the hepatic sinusoid. In addition, some recruited mDCs also migrated into PALT (Fig. 3). The three-dimensional (3-D) view shows that mDCs were detected at tissue spaces outside the portal vein. These mDCs actually interacted with $CD4^+$ T cells in T-cell zones of PALT.[14]

In contrast, transferred pDC precursors were rarely detected at the hepatic sinusoids, including granulomas (see Fig. 3). pDC precursors preferentially migrated into tissue spaces of PALT (see Fig. 3). Because PALT contains

Table 1. DC-mediated granuloma formation

Process	Location	Input (pathway)	Initial phenotype	Interaction	Output (pathway)	Acquired phenotype
Ag-uptake (1 h)	Hepatic sinusoid	DC precursor (circulation–sinusoid)	MHC class II$^-$ DEC-205$^-$ CD11c$^+$ (CCR1/CCR5–MIP-1a)	Kupffer cell Sinusoidal endothelial cell Ito cell	Migrating DC (extravasation to Disse's space) Developing granuloma-forming DC (retention)	MHC class II$^+$ DEC-205$^+$ CD11c$^+$ (CCR7-SLC)
PALT expansion (1 day)	Portal area	Migrating DC (Disse's space or newly formed HEV–tissue space of poratl area)	MHC class II$^+$ DEC-205$^{-/+}$ CD11c$^+$ (CCR7-SLC)	Resident interstitial DC Stromal cell Lymphatic endothelial cell CD4$^+$ T cell B cell	Lymph DC = Ag-transporting DC (afferent lymphatic) PALT-forming DC (retention)	MHC class II$^+$ DEC-205$^+$ CD11c$^+$ (CCR7–SLC/ELC)
Granuloma formation (3 days)	Disse's space	DC precursor (circulation–sinusoid–extravasation)	MHC class II$^-$ DEC-205$^-$ CD11c$^+$ (CCR1/CCR5–MIP-1a)	Kupffer cell Sinusoidal endothelial cell Ito cell Recruited DC CD4$^+$ T cell	Migrating DC (extravasation to Disse's space) Granuloma-forming mature DC (retention)	DEC-205$^+$ CD11c$^+$

Ag, antigen; PALT, portal tract-associated lymphoid tissue; DC, dendritic cells; HEV, high endothelial renule; MHC, major histo compatibility complex

HEV-like structures, pDCs were considered to enter the PALT directly from the circulation through newly formed HEV-like vessels.[14,15] However, the significance of PALT-recruited pDCs remains to be elucidated.

A unique DC system in the liver

I: Kupper cell–DC interaction

There are several steps for mDCs in granuloma formation (Table 1). The first event is an Ag uptake within the sinusoidal functional unit. Kupffer cells may first be activated by ingesting bacteria (see Fig. 1A), and rapidly produce chemokines to recruit immune cells.[16] MIP-1α/CCL3 attracts mDCs as well as CD4$^+$ T cells.[14,17] MCP-1/CCL2 attracts inflammatory monocytes[18] and Mig/CXCL9 attracts CD4$^+$ T cells.[17] Numerous developing granulomas are formed in Disse's space around the bacteria-laden Kupffer cells. Circulating mDC precursors are trapped by Kupffer cells from a very early stage (within 1 h). Recruited mDC precursors themselves produce MIP-1α/CCL3 to induce another wave of mDC precursor migration into the hepatic sinusoid. The intensity of mDC precursor trafficking would determine the efficiency of local antigen surveillance.[4,19] After entering the sinusoidal unit, mDC precursors undergo further maturational processes.

II: PALT expansion

Some DCs are detached from developing granulomas and migrate from Disse's space to the portal area. DCs subsequently move through draining lymphatic pathways to regional hepatic LNs. During this course, DCs will first pass the portal tract because lymphatic capillaries are mostly located in this area (Fig. 5). SLC/CCL21 on the lymphatic capillaries, stromal cells, and vessels may attract mDCs and induce PALT expansion.[14,20]

The biological significance of PALT is not fully established. In the steady state, cellular infiltration in the portal area is rather sparse. In contrast, "portal infiltration" has been described in pathological status. Hence, PALT is an inducible structure similar to bronchus-associated lymphoid tissue (BALT). The liver is also a site for production of antibodies, especially secretary IgA, which are transported into the bile duct. PALT acts as the first-line defense of the lymphatic pathway as well as local immune induction because Ag-responding T-cell proliferation in PALT occurs before the regional LNs. In addition, the loss of PALT by blockade of SLC/CCL21 is accompanied by more advanced hepatocellular damage in the sinusoidal granulomas.[14] These observations indicate the balance between PALT and the sinusoidal granuloma would determine disease outcome.

III: Granuloma formation

The next event is the sinusoidal granuloma formation: an effector response. Part of mDCs remains within the sinusoidal developing granulomas. Kupffer cells surround them in combination with Ito cells, which express α-smooth muscle actin and extend projections into *P. acnes*-induced granuloma.[13] Granuloma-bearing activated Ito cells as well as Kupffer cells produce TGF-β1,[13] which inhibit a migration of mDCs toward SLC/CCL21.[21] Thus, they may force DCs to stay in the sinusoidal unit by downmodulation of the migratory capacity of mDCs. Retained mDCs can proliferate and gradually mature within the central part of a developing granuloma. Accompanied by the maturation of DCs, memory and Ag-responding, proliferating bromo-

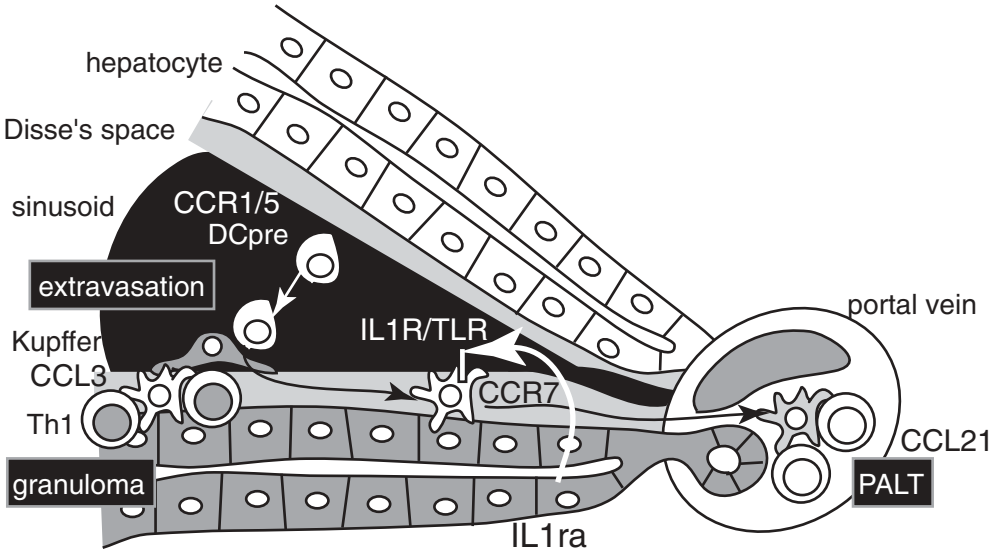

Fig. 5. Sinusoid–portal migration of DCs. Blood DC precursors (CCR1/5$^+$) are attracted by Kupffer cell-derived CCL3 in the sinusoid and extravasate into Disse's space. DCs subsequently migrate to the portal area through the CCR7–CCL21 system and interact with T cells to create PALT. Hepatic cord-derived IL-1ra modulates such migration through IL-1R/TLR signaling on activated DCs. Other DCs reside at Disse's space to develop granulomas

deoxyuridine (BrdU)$^+$CD4$^+$ T cells appear in the granuloma, suggesting that recently activated CD4$^+$ T cells home to the granulomatous areas from regional LNs via efferent lymphatics and systemic circulation (see Fig. 5). Thus, activated mDCs maintain the local inflammation to sequester the microorganism within a cluster of mDCs, macrophages, and interferon (IFN)-γ-producing CD4$^+$ T cells with resultant granuloma formation.

Factors regulating sinusoid–portal migration of mDCs

Given the importance of the balance between granulomas and PALT in determining disease outcome, it is important to know the factors regulating mDC migration from sinusoid to portal area. Usually resident DCs in the portal area have no access to bloodborne particles.[4] The particle-laden rat DCs as well as murine mDC precursors first appeared in the sinusoidal area; both were closely associated with particle- or Ag-laden Kupffer cells. DC-mediated systems for transferring bloodborne Ags from the sinusoidal area to the portal area are considered. Recruited mDCs may phagocytose Ags in the sinusoidal functional unit during interaction with Kupffer cells. After capturing Ags, activated mDCs may extravasate and exit the hepatic lobule because Disse's space is continuous with the tissue space of the portal area.[22] SLC/CCL21 produced in the portal area attracts these mDCs[14] in addition to a passive movement as the result of a negative pressure produced by lymph flow.[4]

We have recently shown that IL-1R/TLR on *P. acnes*-activated mDCs plays important roles in the migration and function of these cells.[23] Hepatocyte-derived IL-1 receptor antagonist (IL-1ra)[24] directly acts on IL-1R/TLR on activated mDCs and modulates their CCR7 expressions. Although appropriate IL-1 optimizes the activation state of mDCs, overactivated IL-1 by IL-1ra gene knockout conversely inhibits mDC maturation and migration within the inflamed liver. Blockade of IL-1ra as well as CCL21 leads to similar outcomes: exacerbation of sinusoidal granulomas with increased serum ALT levels and impaired PALT formation. By controlling IL-1/IL-1R signaling, the hepatic cord may navigate mDC migration through Disse's spaces toward portal areas. In addition, recent investigations have revealed the crosstalk between IL-1R and TLR, the pathogen-associated molecular pattern recognition receptor that regulates DC activation. Thus, the role of IL-1R/TLR signaling on DCs at the site of inflammation needs to be reevaluated.

Modulation of liver disease by DC-derived chemokines

Hepatic granuloma is now considered to be a "pathological niche" for ongoing immune response. Granuloma-forming CD4$^+$ Th1 cell-derived IFN-γ can further activate Kupffer cells to kill or sequester the bacteria. Granuloma-forming DCs maintain ongoing Th1 immune responses by producing appropriate levels of IL-12 and CCL3. DC-derived factors also modulate granulomatous reactions. For example, secondary challenge of *P. acnes*-primed mice with very low dose lipopolysaccharide (LPS) induces TARC/CCL17 and MDC/CCL22 expression by granuloma-residing DCs (Fig. 6). These chemokines recruit Th2-type CD4$^+$ T cells into the liver and rapidly shift local immunity from Th1 toward Th1 plus Th2 responses.[17] Such local Th2 shift causes a severe disease outcome, partly because of the dysregulated function of Kupffer cells and Th1 cells.

In addition, IP-10/CXCL10 produced by mDCs after migrating to hepatic LNs also plays an important role. LN mDC-derived CXCL10 attracts and retains Th1 precursor cells within T-cell zones of the LNs and contributes to the establishment of Ag-specific Th1 cells.[25] Such Th1 cells exit the LNs and recirculate to enter the hepatic granulomas. CXCL10-blocking experiments suggest the role of this chemokine for supplying the appropriate number of granuloma-forming Th1 cells into the liver from the LNs.

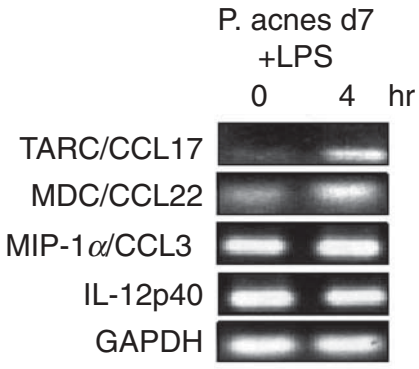

Fig. 6. Chemokine and cytokine expression by liver DCs. Reverse transcriptase-polymerase chain reaction (RT-PCR) for CCL3, CCL17, CCL22, IL-12p40, and internal control, glyceraldehyde phosphate dehydrogenase (GAPDH). Liver CD11c+ DCs are isolated from *P. acnes*-primed mice at day 7 (d7) and *P. acnes*-primed, lipopoly saccharide (LPS)-injected mice at 4 h

Conclusions

Numerous DC precursors rapidly appear in the circulation in response to danger signals, migrate to the site of ongoing immune responses, and create pathological niches such as granulomas and PALT. DC-mediated pathological compartmentalization may be an important process in a host defense. Chemokines regulate DC traveling within these compartments and contribute to the function of DCs. Because functional impairment of DCs has been reported in chronic liver diseases in the human, further studies of DC trafficking will provide better insight to the mechanism of the chronic disease process.

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