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Review

Myeloid Cells and Hepatic Immune Microenvironment

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Introduction

As a lymphoid organ, the liver continuously undergoes multiple tasks: uptake of blood borne pathogens, metabolite detoxification and barrier towards microbial and other antigens. Among the "soldier" cells, granulocytes, monocytes, macrophages, dendritic cells [DCs] and their immature progenitors represent the most abundant subgroup of leukocytes, collectively called myeloid cells. The prominent role of myeloid cells involved in the hepatic immune environment has greatly expanded in recent years. We believed that liver and bone marrow may have active interaction, and the "liver-bone axis" may be reciprocal.

On the one hand, liver could exert its effect on bone through releasing several cytokines (such as TNF-α, Rankl) and breaking the balance between osteoblasts and osteoclasts, which results in hepatic osteodystrophy. Metabolic bone disease is a quite common complication with chronic liver disease; patients with chronic liver disease have an increased risk of bone fracture, especially those with advanced stages of cholestatic liver diseases [1]. For example, most primary biliary cholangitis [PBC] are present with osteopenia, and 20-44% of PBC are diagnosed with osteoporosis, which is significantly higher than other liver disease [2]. Unconjugated bilirubin and serum from jaundiced patients led to decreased cell viability and defective function of osteoblasts and up-regulated osteoclastogenesis [3].

On the other hand, myeloid cells were actively involved in modulating hepatic immune microenvironment. When circulating through the blood and lymphatic system, they are rapidly recruited to sites of tissue damage and infection, hence playing a pivotal role in the hepatic innate and adaptive immune system [4,5].

Hepatic macrophage holds a crucial position in the pathogenesis of chronic liver injury and heterogeneity has been its most remarkable feature. Macrophage heterogeneity reflects not only in the origin (derived from circulating monocyte precursors or as resident Kupffer cells), their differentiation (roughly classified M1 and M2 polarization), but also their effector functions in this hepatic immune microenvironment. In terms of function, hepatic macrophages initiate and maintain inflammation response and promote liver fibrosis via activating hepatic stellate cells. However, they are also responsible for resolution of inflammation through release of anti-inflammatory cytokines and anti-fibrosis by degradation of extracellular matrix. During the multiple phases of liver injury, the subsets of hepatic macrophages react differently. Zigmond E. et al [6] used overdose of APAP to induce liver injury. As expected, resident Kupffer cells were significantly decreased upon APAP challenge and started recovering by self-renewing at resolution phase. Circulating Ly6Chi monocytes were recruited in a CCR2- and M-CSF-mediated pathway at the necroinflammatory phase and differentiated into ephemeral Ly6Clo macrophage subset at resolution phase.

Same as the components of monocytes found in the human peripheral blood, three major subsets of monocytes in the liver have been reported, the classical CD14++CD16- subset, the non-classical CD14+CD16++ subset, and the intermediate CD14++CD16+ subset [7]. The frequency of hepatic infiltrating monocytes increased in diseased liver tissues [ALD/ NASH and cholestatic liver diseases [PBC/PSC]] compared with healthy controls. In response to transforming growth factor β and interleukin [IL]-10, the classical CD14++CD16- monocytes can undergo intrahepatic differentiation and express CD16 to derive into intermediate CD14++CD16+ monocytes [8]. Regarding to the mouse model, the first evidence for different subsets was provided by Palframan based on the differential expression of a CX3CR1-promoter driven GFP transgene [9]. Subsequent reports have shown that the two subsets identified with this approach had different phenotypic and functional properties, "inflammatory" monocytes that are Ly6Chi CCR2hi CX3CR1low and "alternative" or "patrolling" monocytes that are Ly6ClowCCR2low CX3CR1hi. Dal-Secco et al. report in situ monocyte reprogramming in the liver, from proinflammatory CCR2hi CX3CR1low cells into reparative CCR2low CX3CR1hi cells [10]. Dendritic cells, as the main components of antigen presenting cells, are divided into three subtypes. Hepatic dendritic cells, same as blood dendritic cells, consist of plasmacytoid DCs [CD303+ cells], and two other myeloid CD11c+ subsets [BDCA1 and BDCA3 DCs] [11]. Joshua and colleagues demonstrated that experimental model of biliary obstruction [eg. Bile duct ligation] specifically expanded the myeloid [CD11c+ CD11b+ CD8a-] subtype of liver DCs, while the absolute number of liver CD11c+ B220+ plasmacytoid DCs remained essentially unchanged. Moreover, liver myeloid DCs in BDL have enhanced function at stimulating allogenic T cells to divide [12]. Accumulation of TNFa-producing CX3CR1+ monocyte-derived dendritic cells has been reported to contribute to sustaining inflammation and steatohepatitis progression [13]. According to our team's study [14], immature dendritic cells are key to the pathogenesis of granulomas. And the classical dendritic cell CD11c marker is highly expressed and more sensitive than classical hematoxylin-eosin staining in detecting granulomas associated with PBC and other conditions.

Recently, one population of immature myeloid cells, the myeloid derived suppressor cells [MDSCs] which acts as immune regulatory cell have raised great interest. Myeloid derived suppressor cells represent a phenotypically heterogeneous population of myeloid cells at different stages of maturation/myeloid cell progenitor and precursors of myeloid cells and regulate immune responses by potently suppressing T cell function. Although MDSCs were originally described in tumor-bearing hosts [15], they are also induced under various pathological conditions,

including sepsis [16], autoimmunity and inflammation.

In mice, MDSCs are characterized by the co-expression of the myeloid lineage differentiation antigen Gr1 [Ly6C/G] and CD11b. And in human, MDSCs are usually identified as CD11b+CD33+HLA-DRlo/-. However, MDSCs lack the specific marker so far, which make identification of these cells difficult as those entire surface molecules are shared with other myeloid cell types such as neutrophils, monocytes or myeloid dendritic cells. Therefore, the most convincing feature to identify MDSCs seems to be their suppressive function.

MDSC consist of at least two subpopulations that are termed monocytic MDSC [M-MDSC] and granulocytic MDSC [G-MDSC] in mice. G-MDSCs have a CD11b+Ly6G+Ly6Clow phenotype, whereas M-MDSCs are CD11b+Ly6G-Ly6Chi. In human, CD14 and CD15 are suggested as markers for M-MDSC and G-MDSC respectively, but further investigation is required [17]. G-MDSCs that expressed arginase have been reported increased in disease phases characterized by HBV persistent infection but without immunopathology and potently mediated suppression of T-cell in a partially arginase-dependent manner. G-MDSCs expressed liver-homing chemokine receptors and accumulated in the liver, and their expansion was supported by hepatic stellate cells [18]. In our study with autoimmune liver disease, FXR activation expanded MDSCs in liver, particularly M-MDSCs. FXR activation up regulate expression of PIR-B by binding the PIR-B promoter to enhance the suppressor function of MDSCs. Therefore, MDSCs, especially the monocytic MDSCs, act as a critical negative feedback loop in immune-mediated liver injury [19]. Several studies have shown the compartmental differences of T-cell activation pathways between liver and other organs in autoimmunity [18, 20]. Further studies are required to elucidate the immunosuppression mechanisms of MDSCs involved in immune-mediated and autoimmune liver disease and explore the promising immunotherapy strategy in chronic liver diseases.

As mentioned above, myeloid cells are the most abundant nucleated hematopoietic cells derived from myeloid progenitors cells in the bone marrow of healthy individuals, which differentiate into mature myeloid cells such macrophages, DCs and granulocytes. However, under pathological conditions, this maturation pathway was blocked and the highly immunosuppressive and immature myeloid cells, namely MDSCs, were accumulated within the lesion. Excellent work has been done by Gabrilovich et al to demonstrate the tumor milieu exert effects on the balance of MDSC and its differentiation into tumor-associated macrophage [21]. It will be interesting to explore the mechanism how hepatic inflammatory microenvironment exert its effects on the differentiation and functions of immature myeloid cells.

Besides the immature myeloid cells, innate immune cells of myeloid lineage support tissue homeostasis during steady state. Recent studies have demonstrated that late c-Myb+ Erythro-Myeloid Progenitors seed the fetal liver and give rise to fetal monocytes, which then differentiate into peripheral tissue-resident macrophages able to self-renew into adulthood including liver Kupffer cells [22]. The experimental model of bacterial infection in the liver is of high interest with respect to show the maintenance and functional plasticity of hepatic macrophage cells under challenge. Infected Kupffer cells undergo rapid necroptosis, resulting in the recruitment of circulating monocytes, which differentiate into monocyte-derived macrophages. Initially, monocyte-derived macrophages contribute to antibacterial immunity dependent on a classical IFN-γ -driven inflammatory response. In a second phase, KC necroptosis also initiates a cascade of IL-4-driven events including proliferative expansion and phenotypic changes of monocyte-derived macrophages that promote restoration of tissue integrity after bacterial clearance [23].

It is clearly that myeloid lineage is regulated in liver as a closely integrated system. However, among these different subpopulations, the plasticity and functional changes is complex and governed by common hepatic immune microenvironment. The interaction between liver and bone (including its myeloid lineage cells) provides an opportunity for therapeutic intervention that may concomitantly normalize myeloid cells abnormalities and finally facilitate the hepatic immune homeostasis.

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