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Review

The role of Kupffer cells in hepatic diseases

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ABSTRACT

Kupffer cells (KCs) constitute 80–90% of the tissue macrophages present in the body. Essential to innate and adaptive immunity, KCs are responsible for the swift containment and clearance of exogenous particulates and immunoreactive materials which are perceived as foreign and harmful to the body. Similar to other macrophages, KCs also sense endogenous molecular signals that may result from perturbed homeostasis of the host. KCs have been implicated in host defense and the pathogenesis of various hepatic diseases, including endotoxin tolerance, liver transplantation, nonalcoholic fatty liver disease, and alcoholic liver disease. In this review, we summarized some novel findings associated with the role of KCs in hepatic diseases, such as the origin and mechanisms KCs polarization, molecular basis for caspase-1 activation called "non-canonical inflammasome pathway" involving the cleavage of Gsdmd by caspase-11, the important role of microRNA in liver transplantation, and so on. A better understanding of KCs biological characteristics and immunologic function in liver homeostasis and pathology may pave the way to investigate new diagnostic and therapeutic approaches for hepatic diseases.

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Abbreviations: APCs, antigen-presenting cells; DAMPs, danger-associated molecular patterns; DCs, Donor-derived dendritic cells; ET, endotoxin tolerance; FFA, free fatty acids; Gsdmd, gasdermin D; HDAC11, Histone deacetylase 11; HFD, high fat diet; HMGB1, high mobility group box-1 protein; IFN, interferon; IRAKs, interleukin-1 receptor-associated kinases; IRF3, interferon regulatory factor 3; IRI, Ischemia-reperfusion injury; KCs, Kupffer cells; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; MCDD, methionine- and choline-deficient diet; NAFLD, nonalcoholic fatty liver disease; NASH, steatohepatitis; NLRs, NOD-like receptors; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; ROS, reactive oxygen species; RNS, reactive nitrogen species; SCOS1, suppressor of cytokine signaling 1; SECs, inusoidal endothelial cells; SH2, Src homology 2; SHIP1, Src homology 2 (SH2) domain-containing inositol-5-phosphatase 1; TAK1, TGF-beta-activated kinase 1; TLRs, Toll-like receptors; TRAFs, TNFR-associated factors.

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1. Introduction

Kupffer cells (KCs) are known as liver-derived macrophages and account for 20–35% of all non-parenchymal cells in the liver and 80–90% of tissue macrophages present in the body (Li et al., 2014c; Zeng et al., 2013). They are important members of the innate and adaptive immune systems, and they reside in the hepatic sinusoid and serve as a first line of defense against bacteria, microbial debris and endotoxins derived from the gastrointestinal tract. KCs recognize danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by expressing pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), mannose receptors, and NOD-like receptors (NLRs) (Kawai and Akira, 2009). In addition, as primary phagocytic cells, KCs are highly poised for the clearance of particles, as well as dead and dying erythrocytes and cells in the hepatic parenchyma, from systemic circulation [4]. Moreover, as a type of antigen-presenting cell (APC), KCs provide a bridge between the innate immune system and the adaptive immune system. Many phagocytosable particles and soluble substances can activate KCs (Bilzer et al., 2006). The activated KCs play an important role in inflammatory responses, the immune response during endotoxin tolerance (ET), liver transplantation and nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). In this review, we summarize our research findings and combine with other significant studies to describe the biological characteristics and the contributions of KCs in host defense and hepatic diseases.

2. The origin and polarization of KCs

The origin of KCs has been thought to involve two mechanisms: replenishment by local self-proliferation and recruitment from circulating bone marrow (BM) derived monocytes (Davies et al., 2013). Recent evidence suggests that Murine KCs originate from the yolk sac in a colony-stimulating factor-1/receptor (CSF-1/R)-dependent and Myb-independent way. This type of KCs accumulation can be sustained by local proliferation, in particular, during inflammation sustained by T-helper (Th) 2 cells. Ginhoux et al. found that the called precursor cells of macrophage in the body have been seeded in the corresponding tissue before birth (Ginhoux and Jung, 2014). These precursor cells have the ability to differentiate into tissue inherent macrophages which also maintain number and function of corresponding tissue macrophages. Moreover, BM-derived cells can also differentiate into KCs. Two subsets of F4/80highCD11lowKCs have been identified as radiosensitive and radioresistant respectively, the former type cells participating in immunoinflammatory reactions (Klein et al., 2007).

Similar with TH1- TH2 polarization, macrophages undergo M1 and M2 activation states, also called classical and alternative activation, in response to different signals. When stimulated by IFNγ alone or in concert with cytokines (eg TNF and GM-CSF) or microbial stimuli (eg LPS), macrophages undergo M1 activation. Other cytokines including IL-4, IL-13 and IL-33 induce M2 activation of macrophage. In general, the M1 cells present an IL-12^{high}IL-23^{high}IL-10^{low}phenotype, which is characterized by up-regulation of proinflammatory cytokines, high levels of reactive nitrogen and oxygen intermediates, facilitating Th1 response, and strong antimicrobial and antineoplastic effect. In contrast, the M2 cells share IL-12^{low} IL-23^{low} IL-10^{high} phenotype, which are involved inpolarized Th2 responses, parasite containment, production of ornithine and polyamines via the arginase pathway, the suppression of inflammation, tumour progression and immunoregulation. They are characterized by efficient phagocytic activity, high expression of scavenger, galactose and mannose-type receptors (Mantovani et al., 2013). Moreover, M1 and M2 macrophages present distinct chemokinome profiles, different iron, glucose, and amino acid metabolism (Biswas and Mantovani, 2012).

Macrophage polarization is controlled by different mechanisms that include signaling pathways, transcription factors, microRNAs (miRNAs) and epigenetic modifications. The balance between STAT1 and STAT3/STAT5/STAT6 activation finely regulates polarization and activity of macrophage. A predominance activation of NF-κB, STAT1, IRF3, IRF5, and IRF8 promotes M1 macrophage polarization, leading to cytotoxic and pro-inflammatory functions. Whereas, a predominance activation of STAT3, STAT5, and STAT6 in favour of M2 macrophage polarization (Sica et al., 2014). Epigenetic modifications and miRNAs were also involved in macrophage polarization. For instance, IL-4 promotes M2 genes expression and inhibit M1 genes via up-regulating the histone demethylase Jumonji D3 which alters chromatin modifications in mouse macrophages (Satoh et al., 2010). Moreover, over-expression of miRNA let-7c promotes M2 and inhibits M1 macrophage polarization (Banerjee et al., 1950), while expression of miR-19a-3p facilitates M2 macrophage polarization and upregulation of the Fra-1 proto-oncogene (Yang et al., 2014).

3. The activation mechanism of Kupffer cells

A large number of phagocytosable particles and soluble substances can activate KCs by binding to specific receptors on the cytomembrane. The most important activators of KCs include lipopolysaccharide (LPS), complement C3a and C5a, fungi with beta glucan, and bacteria. LPS can directly activate KCs through TLR4 signaling pathways, leading to the upregulation of TNF-α, IL-1β, IL-6, IL-12, IL-18, IL-10, and IFN-γ (Xu et al., 2008). TLR4 engagement by LPS induces a large multiprotein complex formation at the cytoplasmic face of the plasma membrane that contains the myeloid differentiation factor MyD88, TNFR-associated factors (TRAFs), interleukin-1 receptor-associated kinases (IRAKs), and TGF-beta-activated kinase 1 (TAK1). Furthermore, the JNK, p38 mitogen-activated protein kinases (MAPKs) and NF-κB signaling pathway were activated. Activated TLR4 also translocates to an endosomal compartment, and this leads to the recruitment of TIR domain-containing adaptor proteins inducing IFN-β (TRIF), TRAM, TRAF3 and other proteins. This results in the phosphorylation of interferon regulatory factor 3 (IRF3) and induces the type I interferon (IFN) response. LPS can also bind TLR2 on KCs; this process requires the participation of LPB and CD14. TLR2 was found to be upregulated in KCs isolated from endotoxemic mice, which suggested that this receptor plays a role in the innate immune system in the liver (Dixon et al., 2013; Tsutsui and Nishiguchi, 2014). In addition, the high concentration of LPS in the portal or in the systemic circulation is able to activate KCs indirectly through the complement system (Bilzer et al., 2006).

A recent study uncovered a novel mechanism that the cytoplasmic LPS can activate macrophage via TLR4-independent pathway that results in activation of the inflammatory enzyme caspase-11 (Kayagaki et al., 2013). Shi et al. showed that caspase-11 serves as a receptor which directly binds to cytosolic LPS and was activated through oligomerization upon interaction with LPS (Shi et al., 2014). T Then, caspase-11 cleaves the precursor form of Gsdmd to generate the N-terminal fragment which triggers an inflammatory cell death response called “pyroptosis” and NLRP3-dependent caspase-1 activation that plays a key role in cytokine processing (IL-1β and IL-18) (Aachoui et al., 2013; Kayagaki et al., 2015; Kayagaki et al., 2011; Rathinam et al., 2012). This alternative mechanism for caspase-1 activation is called the “non-canonical inflammasome pathway”. Given that KCs constitute 80–90% of tissue macrophages, a key issue not yet addressed is whether cytoplasmic LPS triggers similar events in KCs (Fig. 1).