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MINI REVIEW

Shaping macrophages function and innate immunity by bile acids: Mechanisms and implication in cholestatic liver diseases

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Summary The liver is selectively enriched in innate immune cells, macrophages (Kupffer cells), natural killer, and natural killer T cells. These cells release an array of mediators with cytotoxic, pro- and anti-inflammatory, angiogenic, fibrogenic, and mitogenic activity that function to fight infections, limit tissue injury, and promote wound healing. The diverse activity of macrophages is mediated by distinct subpopulations that develop in response to signals within their microenvironment. Understanding the mechanisms and role of the microenvironment contributing to modulation of macrophage populations is crucial for comprehension of the pathophysiology of liver injury in diverse conditions. Several studies initiated in the 1990s have shown that bile acids modulate innate and adaptive immunity. In the last decade, bile acids turned into hormones and signalling molecules involved in many metabolic and inflammatory processes. Biological properties of bile acids are thought to be mediated mainly through activation of the nuclear receptor FXR, the membrane receptor TGR5, as well as PK, ERK, MAP kinases signalling pathways. FXR and TGR5 agonists are currently under development for clinical purpose. This review analyses the mechanisms involved in the immunomodulatory effects of bile acids on the macrophage and discuss their implications in the pathophysiology of cholestasis, primary biliary cirrhosis and primary sclerosing cholangitis.

Abbreviations: BEC, biliary epthelial cells; CA, cholic acid; CBP, CREB-binding protein; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; FXR, farnesoid X receptor; GR, glucocorticoid receptor; ISG, IFN-stimulated gene; PBC, primary biliary cirrhosis; PKI, PKA inhibitor; PSC, primary slerosing cholangitis; SP1R2, sphingosine-1-phosphate receptor 2; TGR5, G-protein-coupled bile acid receptor; TLC, taurolithocholic acid; TLR, Toll/IL-1R (TIR) domain-containing adapter-inducing IFN-β; TUDC, tauroursodeoxycholic acid.

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Introduction

The liver is selectively enriched in innate immune cells, macrophages (Küpffer cells), natural killer, and natural killer T cells. These cells release an array of mediators with cytotoxic, pro- and anti-inflammatory, angiogenic, fibrogenic, and mitogenic activity that function to fight infections, limit tissue injury, and promote wound healing. The diverse activity of macrophages is mediated by distinct subpopulations that develop in response to signals within their microenvironment. Understanding the mechanisms and role of the microenvironment contributing to modulation of macrophage populations is crucial for comprehension of the pathophysiology of liver injury in diverse conditions. Several studies initiated in the 1990s have shown that bile acids modulate innate and adaptive immunity [1—11]. In the last decade, bile acids turned into hormones and signalling molecules involved in many metabolic and inflammatory processes. Biological properties of bile acids are thought to be mediated mainly through activation of the nuclear receptor FXR, the membrane receptor TGR5, as well as PK, ERK, MAP kinases signalling pathways. FXR and TGR5 agonists are currently under development for clinical purpose.

This review analyses the mechanisms involved in the immunomodulatory effects of bile acids on the macrophage and discuss their implications in the pathophysiology of primary biliary cirrhosis.

Macrophages diversity and plasticity

Macrophages are professional phagocytic cells that play crucial roles in host defense, regulation of the inflammatory response and maintenance of tissue homeostasis [12,13]. Macrophages present striking heterogeneity in their functions. Some functions are pro-inflammatory, such as the release of reactive toxic species or cytokine and chemokine production. These functions are crucial for efficient elimination of pathogens and communication with other components of the immune system. In contrast, macrophages may participate in the resolution of inflammation, wound healing and maintenance of peripheral self-tolerance. Thus, macrophages can display different specialized forms of activation (so called 'macrophage polarization') and plasticity in response to host homeostatic signals or external environmental challenges.

One functional subset is the classically activated macrophage (M1) that develops in response to interferon gamma (IFNγ) released by Th1 cells or microbial components (such as bacterial lipopolysaccharide, LPS). M1 macrophages produce inflammatory cytokines, microbicidal species and favor antigen presentation and cellular immunity. M1 responses are therefore essential to combat intracellular infections such as Mycobacterium tuberculosis and HIV. A second subset is M2- or wound healing-type macrophages [14]. This phenotype, induced by stimulation of macrophages with IL-4 and/or IL-13, is characterized as CCL18- and CD206-positive, and high expression of CD86 and CD163. In contrast, the phenotype of classically M1 activated macrophages is characterized as CD206neg, CCL18neg, CD86low, and CD163low. M2 macrophages have an immunosuppressive phenotype due to their active production of IL-10 and TGF-β and other anti-inflammatory mediators [15]. ''Mixed'' macrophage phenotypes are also observed in chronic pathologies, such as foam cells in atherosclerosis, tumor-associated macrophages in cancer, adipose tissue macrophages during obesity/T2D or activated microglia in models of Parkinson's/Alzheimer's diseases [16—18].

Macrophages recognize the presence of pathogens through Pattern Recognition Receptors (PRRs)

PRRs detect conserved molecular structures of pathogens, the Pathogen Associated Molecular Patterns (PAMPs). Recognition of PAMPs by PRRs activates signaling cascades that initiate innate immunity, which constitutes the first line of defense against microorganisms and represents an important interface with adaptive immunity [19]. The best-known family of PRRs is the Toll-like Receptor (TLR) family, comprising 10 members of membrane-bound receptors in humans. TLR4 recognizes lipopolysaccharide (LPS), an outer-wall component of gram-negative bacteria. LPS-binding results in activation of downstream signaling, which is mediated via the recruitment of adapter proteins, including MyD88. MyD88 recruitment induces the production of inflammatory cytokines through activation of transcription factors, mainly NF-κB and AP-1, a heteromeric complex comprising cFos and cJun. TLR4 also triggers a delayed MyD88-independent signal transduction leading to the release of type I interferon (IFN) via activation of IFN regulatory factor 3 (Fig. 1). The activation of these transcription factors as well as the IL-10-mediated resolution of the inflammatory response are orchestrated further by effector kinases of the p38MAPK pathway.

Bile acids PKA-dependently reduce pro-inflammatory capability of human macrophages

In a recent study, Haselow et al. [20], afford new data on the mechanisms involved in the immunoregulatory effects of bile acids in human macrophages. Whereas IL-4 robustly induced alternative activation of human macrophages, with a clear switch toward M2-type macrophages, stimulation with taurolithocholate (TLC) did not result in an M2-like expression pattern in terms of cytometry. Basal and LPS-stimulated phagocytic activity was significantly decreased in the presence of TLC. The LPS-induced expression of IL-6, TNF-α, and IFN-β and the p40 subunit of IL-12 (IL-12B) was inhibited in response to TLC on mRNA and protein levels, whereas the production of the anti-inflammatory cytokine IL-10 remained unaffected. This effect of TLC was mimicked by induction of cAMP by forskolin or 8Bromo-cAMP. The effect of bile acids on the cytokine response of macrophages was not restricted to the TLR4 ligand LPS but was also be observed upon activation with ligands to TLR2, -3, -7, or -9. In particular, expression of TNF-α, which was induced by all of the TLR ligands tested, was suppressed in the presence of TLC, irrespective of the inducing TLR ligand.