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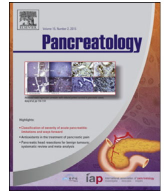

Original article

Metabolic reprogramming and cell fate regulation in alcoholic liver disease

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ABSTRACT

Alcoholic liver disease (ALD) should be defined as a life-style metabolic disease. Its pathogenesis is driven by altered cell fate of both parenchymal and non-parenchymal liver cell types, contributing to different pathologic spectra. A critical turning point in progression of ALD is chronic alcoholic steatohepatitis (ASH) or alcoholic neutrophilic hepatitis (AH), which markedly predisposes patients to most devastating ALD sequela, cirrhosis and liver cancer.

Results: Our research identifies the pivotal roles of unique metabolic reprogramming in M1 activation of hepatic macrophages (HM) and myofibroblastic activation (MF) of hepatic stellate cells (HSC) in the genesis of inflammation and fibrosis, the two key histological features of chronic ASH and neutrophilic AH. For M1 HM activation, heightened proinflammatory iron redox signaling in endosomes or caveosomes results from altered iron metabolism and storage, promoting IKK/NF-kB activation via interactive activation of p21ras, TAK1, and PI3K. For MF cell fate regulation of HSC, activation of the morphogen Wnt pathway caused by the nuclear protein NECDIN or the single-pass trans-membrane protein DLK1, reprograms lipid metabolism via MeCP2-mediated epigenetic repression of the key HSC quiescence gene *Ppar-γ*.

Conclusions: The findings from these studies re-enforce the importance of metabolic reprogramming in cell fate regulation required for the pathogenesis of ALD.

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Metabolic reprogramming of hepatic macrophages

Macrophage vs. neutrophilic inflammation in ALD

Inflammation is a key pathologic turning point for progression of alcoholic liver disease (ALD) and is manifested as chronic alcoholic steatohepatitis (ASH) characterized primarily by mononuclear cell infiltration, perisinusoidal and pericellular fibrosis, and foamy hepatocellular degeneration. Some of these ASH patients develop neutrophilic alcoholic hepatitis (AH) with hepatic and systemic complications leading to the mortality as high as 50–60%. Hepatic macrophages are considered as a central effector for ASH, which undergoes M1 proinflammatory activation via pathways involving endotoxin-TLR4 [1]. In AH, inflammation shifts to neutrophilic infiltration, the histologic hallmark of AH, for reasons that are yet to be defined. This shift is also reproduced in a mouse model which recapitulates the risk factors known for AH patients in the US including binge drinking [2]. It is generally believed that M1 macrophage activation serves as a predisposing condition required for progressive ASH or neutrophilic infiltration in AH triggered by an additional hit. For this reason, the mechanisms underlying M1 macrophage activation remains a focus of active investigation.

Link between macrophage iron and chronic inflammatory diseases

Chronic liver diseases such as ALD [3], non-alcoholic fatty liver disease (NAFLD), and viral hepatitis [4,5], are accompanied by increased hepatic iron content that in turn exacerbates the disease process. In an animal model, chronic alcohol intake increases iron content in both hepatocytes and hepatic macrophages [6]. In a non-alcoholic steatohepatitis (NASH) animal model, erythrophagocytosis and resultant iron loading promote oxidant stress, inflammation, and liver fibrosis [7]. In fact, iron

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accumulation is not restricted to liver diseases but is also evident in other chronic inflammatory diseases including arthrosclerosis [8], pulmonary fibrosis [9] and neurodegenerative diseases such as Parkinson's disease [10] and Alzheimer's disease [11], suggesting iron accumulation is a common consequence or even cause of chronic inflammation and tissue damage. The causal relationship is suggested for liver diseases as an iron reduction therapy by phlebotomy improves the plasma aminotransferase level, the indicator for liver damage, in patients with NAFLD [12] and viral hepatitis [13]. The most prevalent hypothesis for the causal mechanism of iron is the Fenton pathway generating a hydroxyl radical and causing oxidative tissue injury. Thus, it is not surprising that any additional incremental increase in tissue iron content sensitizes the organs for oxidative damage caused by primary etiological factors. This is exemplified by ALD that is clearly exacerbated by dietary iron supplementation in animal model [14] or increased hepatic iron content due to hemochromatosis in man [15].

We proposed 17 years ago, a notion that there must be a more direct mechanism than the Fenton reaction, by which iron promotes inflammation in chronic liver disease via its role in hepatic macrophages (HM). Treatment of rats subjected to bile duct ligation and transection (BDL) with 1,2 dimethyl-3-hydroxypyrid-4-one (L1), a lipophilic iron chelator, markedly attenuated NF-κB activation and TNF-α and IL-6 expression in HM isolated from the model, as well as cholestatic liver damage [16]. HM isolated from a rat model of ALD had a ~80% increase in non-heme iron content and substantially activated NF-κB as compared to HM from pair-fed control rats. Ex *vivo* treatment of HM from the ALD model with L1 eliminated both the increment in non-heme iron content and NF-κB activation [17], suggesting the critical role of an expansion of the chelatable pool of iron in HM in NF-κB activation. We also observed a slight decrease (~15%) in the non-heme iron content of HM from the control rats by L1 treatment, suggesting that there exists a fraction of the chelatable iron pool even in normal HM. In fact, we showed this chelatable pool plays a pivotal role in NF-κB activation in HM from normal rats.

Identification of macrophage iron signaling ([LMW-Fe]i) for NF-κB activation

The molecular basis for the role of chelatable iron pool in HM NF-κB activation was subsequently revealed by identification of a transient rise in intracellular low molecular weight iron complexes ([LMW-Fe]i) at 1–2 min after LPS stimulation prior to IKK activation at 15–30 min and increased p65/p50 binding to the κB element at 30–60 min [18]. The treatment of HM with the iron chelator abolished LPS-stimulated [LMW-Fe]i, IKK activation and NF-κB binding. Loss-of-function approaches disclosed that peroxynitrite (ONNO−) was responsible for LPS-induced [LMW-Fe]i [18], which in turn activated IKK via protein–protein interaction and activation of p21Ras, PI3K, and TAK1 in caveolin1-positive endocytic compartments [19]. For p21Ras and TAK1 activation mediated by [LMW-Fe]i, we showed c-Src activation by PTP2 inactivation and K63-linked polyubiquitination of TRAF6 were critical upstream events, respectively (see a schematic summary shown in Fig. 1A and B). We then tested whether [LMW-Fe]i signaling is relevant to man. For this, we used peripheral blood monocytes isolated from normal human subjects. After purification of monocytes, we treated the cells with PMA overnight to promote macrophage differentiation as assessed by the expression of macrophage marker such as CD14 and CD68. After washing and resting the cells, these macrophages were tested for [LMW-Fe]i stimulated with peroxynitrite, the immediate upstream effector for the signaling. Indeed, macrophages derived from PMA-treated human monocytes, exhibited the [LMW-Fe]i response while monocytes without PMA treatment failed to show this response. More importantly, macrophages with acquired [LMW-Fe]i signaling, released 4–5 fold more TNF-α as compared to monocytes in response to peroxynitrite. Further, the iron chelator treatment (L1) abrogated both [LMW-Fe]i and TNF-α release by macrophages. These results demonstrate that: 1) [LMW-Fe]i signaling is relevant to man and a function acquired by differentiated macrophages; and 2) acquisition of this iron signaling confers the cells the ability to exhibit a maximal cytokine response [20].

Accentuated [LMW-Fe]i in ASH

How does [LMW-Fe]i signaling explain accentuated IKK and NF-κB activation in iron-loaded HM as seen in chronic liver disease? Is [LMW-Fe]i accentuated as a chelatable pool of iron expands in HM? These natural questions were subsequently addressed. Indeed, in HM isolated from the ASH model, an increased chelatable iron pool was directly responsible for enhanced [LMW-Fe]i signaling and NF-κB activation [20]. To further confirm this causal relationship, we artificially increased the non-heme iron content in HM by a single subcutaneous injection of iron dextran which was gradually and relatively selectively taken up by macrophages. HM isolated from mice 2 weeks after a single subcutaneous injection of iron dextran (25 mg/kg or 75 mg/kg), had a 1.7 or 3.8 fold increase in non-heme iron content. This manipulation enhanced LPS or peroxynitrite induced [LMW-Fe]i and TNF-α release by HM *ex vivo*. Further, this treatment given prior to intragastric infusion of ethanol and a high fat diet, markedly aggravated ASH and even induces liver fibrosis within 4 weeks of feeding, supporting the pathologic significance of enhanced [LMW-Fe]i signaling for NF-κB dependent proinflammatory cytokine expression in ALD [20]. One can also enhance [LMW-Fe]i signaling by a genetic manipulation. RAW264.7 cells expressing high level of Nramp1, a late endosome iron transporter, has less non-heme iron content and a reduced chelatable pool of iron as compared to the cells with Nramp1 deficiency and an increased chelatable iron pool [21]. As predicted, the latter cells have a heightened [LMW-Fe]i response, accentuated IKK and NF-κB activation, and more pronounced TNF-α release in response to LPS [18].

One may naturally wonder why iron accumulates in HM in chronic liver disease. Our screening for iron transporters and regulatory molecules in HM from the rat ALD model [20] showed ferroportin-1 (FPN1), a major iron exporter protein was induced in these cells, suggesting this change could not account for the increased non-heme iron content. Instead, FPN1 induction was likely an adaptive response to increased iron content as this major iron exporter is positively regulated by iron loading and erythrophagocytosis in J774 macrophages [22]. Indeed, iron treatment of cultured HM resulted in marked induction of FPN1 mRNA while L1 treatment causes its suppression [20]. We next determined the plasma levels of hepcidin, the most important iron-regulatory hormone primarily expressed by hepatocytes which causes degradation of FPN1 for its suppressive effect on iron efflux from intestinal cell basal membrane. However, the plasma pro-hepcidin levels were not different between alcohol and control diet fed animals. We then examined mRNA expression of transferrin receptor-1 (TfR1), and TfR2, as well as the hemochromatosis gene (Hfe) known to regulate transferrin-mediated iron uptake. This analysis demonstrated a 6-fold induction of TfR1 (a major receptor type in HM) but not of TfR2 and 2-fold induction in Hfe in HM from alcohol-fed animals [20]. TfR1 protein expression was also increased in these cells, suggesting enhanced TfR1-mediated iron uptake as a possible cause of iron accumulation. This notion was tested next by examining Fe59 uptake by HM from alcohol-fed and control animals in serum-containing medium. Indeed, HM from alcohol-fed animals exhibited an enhanced iron uptake rate as compared to the control cells. HFE is believed to upregulate TfR-

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