Iron Metabolism and Leukemia

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Abstract

Iron is an important regulator of cell growth, apoptosis and enzymatic functions. Many cancers, including soft tissue sarcoma, mesothelioma, renal cell carcinoma, colorectal cancer, gastric cancer, lung cancer, hepatocellular carcinoma, and endometriosis have been associated with iron overload. Iron metabolism is also affected in leukemia, and iron chelators can inhibit proliferation of leukemia cells.

Lipocalin 2 (LCN2) is an iron transporter that plays important roles in cellular metabolism, growth and differentiation, and host immune response. Siderophores are small iron-binding molecules that facilitate microbial and mammalian cells iron transport. Type 2 Hydroxy Butyrate Dehydrogenase (BDH2), a member of the short-chain dehydrogenase family, is a rate-limiting factor in the biogenesis of the mammalian siderophores. In our previous studies, we reported that LCN2 is a good prognostic marker in patients with Cyto-genetically Normal Acute Myeloid Leukemia (CN-AML), and BDH2 predicts poor prognosis in CN-AML patients. Expression levels of both LCN2 and BDH2 genes are independent from other well-known gene alterations and clinical characteristics of CN-AML patients.

They may - (pass through does not make sense) induce or inhibit apoptosis during Reactive Oxygen Species (ROS) challenges. We have also demonstrated that higher BDH2 expressions are associated with a greater chance of leukemic transformation in myelodysplastic Syndrome (MDS) patients. Since the level of BDH2 expression directly correlates with the serum ferritin concentration in MDS patients, iron metabolism may have important roles in tumor transformation.

In this review, we summarize evidence of how iron metabolism and iron transporters influence the prognosis of leukemia.

Keywords: Iron metabolism; LCN2; BDH2; Leukemia

Introduction

Iron is a fundamental element for sustaining life [1]. It is an essential component of many proteins and enzymes that are essential for cell growth and replication [2-4], and its depletion causes G1/S arrest and apoptosis [5]. Iron exists in two oxidation states, the ferrous (Fe2+) and the ferric (Fe3+) forms, and plays key roles during the generation of Reactive Oxygen Species (ROS) through the Fenton reaction [6]. The formation of ROS including OH- radicals leads to reactions with DNA, proteins and lipids, thereby inducing mutations and cellular damages [7-9]. Evidence from epidemiological, animal, and cell culture studies support the role of iron in carcinogenesis of several tumors [10]. Here we review the relationship between iron transport and metabolism and leukemia.

Iron Transport

Intestinal epithelial cells have two different iron transporters: one in the apical membrane and one in the basolateral membrane. Once Dcytb, a ferrireductase, converts Fe3+ to Fe2+, it can be transported into the cell through the Divalent Metal Ion Transporters (DMT1) that are expressed on the apical pole of enterocytes in the proximal duodenum [11,12]. Uptake of Fe through DMT1 is regulated by the Iron-Regulatory Proteins 1 and 2 (IRP1 and 2). Both IRP1 and IRP2 are able to recognize and bind to Iron-Responsive Element (IRE), a highly conserved 28-nucleotide sequence motif in the untranslated region of mRNAs encoding proteins involved in the iron metabolism. These IRE-containing mRNAs include the Transferrin Receptor 1 (TIR1), ferritin, and Ferroportin-1 (FPN1) [13,14].

After being transported into enterocytes, these forms of Fe are consolidated to form the intracellular labile Fe pool (LIP) [15]. From the LIP, Fe can be exported into the circulation via FPN1, a major transporter involved in cellular Fe release [16]. FPN1 expressions are regulated by IRP/IRE interactions and hepcidin, a Fe regulatory hormone [17-20].

To avoid high level of free iron, TIR1 binds to free iron and forms a di-ferric Tf-TIR1 complex, which is then transported into cells. Fe3+ is released from Transferrin (Tf) after a decrease in pH in the endosome. The Fe3+ is reduced to Fe2+ by an endosomal ferrireductase, a Six-Transmembrane Epithelial Antigen of the Prostate3 (Steap3), and then transported into the cytoplasm by DMT1 [21, 22]. In the cytoplasm, Fe enters the LIP and is subsequently stored in ferritin or used in the production of Fe-containing proteins [23].

Iron in Carcinogenesis

Carcinogenicity of iron-containing compounds has been clearly demonstrated in animal experiments [24], The first supporting evidence of iron’s carcinogenic property is the induction of pulmonary tumors in mice following exposures of iron oxides [25]. Spindle-cell sarcoma, pleural mesothelioma and renal cell carcinoma have also been induced in mice/rats by iron-containing compounds [24]. In addition, renal cell carcinoma can be induced by intraperitoneal injection of iron chelators.
Lipocalin 2 and Leukemia

Lipocalin 2 (LCN2, 24p3) is a 24-kDa secreted glycoprotein that serves several functions mediated by environmental, metabolic (associated with hyperlipidemia, obesity, and insulin resistance), and developmental factors [48]. Increased LCN2 expression can cause a widespread immune reaction through activation of the innate immune system, while LCN2 knockout mice were significantly more susceptible to bacterial infections than control animals [49-54]. LCN2 functions as an iron transporter, and iron-loaded 24p3 increases intracellular iron concentration without promoting apoptosis. Iron-lacking 24p3 increases intracellular iron concentrations, which induce expression of proapoptotic protein Bim and result in apoptosis [55]. In 2012, Correnti and coworkers proposed an opposite view that LCN2 does not induce cellular iron efflux nor stimulate apoptosis. They showed that stably expressed murine LCN2 FL5.12 and 32D.3 cells undergoing apoptosis in response to the addition of iron chelator, DFO, LCN2 showed protective effect of apoptosis on all of these cell lines [63].

BDH2 and Leukemia

Siderophores (2, 5- dihydroxybenzoic acid, 5, DHBA) are small iron-binding molecules that facilitate microbial and mammalian iron transport. Type 2-hydroxybutyrate dehydrogenase, BDH2, a member of the short-chain dehydrogenase family of reductases, is a rate-limiting factor in the biogenesis of the mammalian siderophore. The key physiologic implication of BDH2 is that iron-mediated post-transcriptional regulation of hBDH2 controls mitochondrial iron homeostasis in human cells [64]. Human BDH2 (DHR56) is also an enzyme that participates in the citric acid cycle metabolism and ketogenesis, which may play crucial roles in promoting tumorgenesis [65-67]. In our previous study, we found that BDH2 is a weak prognostic risk factor, independent of other genes alternation, including NPM1, FLT3-ITD, CEBPA, IDH1/2, DNMT3A, MLL, ERG, NM1, miR-181a and miR-3151 in Cytogenetic Normal AML (CN-AML) patients. A lower level of BDH2 expression in leukemia cell lines results in a greater sensitivity to ROS induced apoptosis [68]. Wharton et al. reported that mitochondrial iron loss from L1210 cells, a mouse lymphocytic leukemia cell line, may be injured by activated macrophages [69]. In normal human cells, a portion of the cytoplasmic free iron pool is composed of the iron-siderophore complex, which is also the form of iron imported into mitochondria. Iron-replete conditions destabilize hBDH2 mRNA, leading to reduced siderophore levels. As a consequence, mitochondrial iron concentrations diminish [64]. Correnti et al. proposed an experiment that there was no apoptosis when 2, 3-DHBA and 5-DHBA were added to stably expressed murine LCN2 FL5.12 and 32D.3 cells culture [56]. Siderophores function as iron transport modulators that are controlled by cytoplasmic iron concentrations and pH levels in cell cytoplasm. It is not known whether they can function equally well extracellularly.

Myelodysplastic Syndrome (MDS) is a disorder of hematopoietic stem cells. In MDS patients, leukemia progression is associated with iron overload. We have shown that MDS patients with a higher level of BDH2 expression exhibited a higher leukemia transformation rate compared with those with lower BDH2 expression (15% vs 3.18%, P=0.017). The BDH2 mRNA expression level also correlated to serum ferritin level (P=0.049). In CN-AML patients, BDH2 functions as
an anti-apoptosis factor through survivin, and BDH2 knock-down leukemia cells showed cell cycle retardant [68,70].

**Conclusion**

Imbalance of iron metabolism has been associated with several cancers including leukemia. LCN2 is an iron transporter and has functions related to metabolism and immune response. BDH2 is a rate-limiting factor in the biogenesis of the mammalian siderophage. Siderophore binding with LCN2 can transport iron between cytoplasm and mitochondria. Lower LCN2 and higher BDH2 expressions are associated with poor survival in CN-AML patients. In contrast, higher rates of leukemia transformation are seen among patients with high BDH2 expression, and the BDH2 mRNA expression correlates with serum ferritin level. Finally, the function of BDH2 and LCN2 in leukemia may depend on intracellular iron concentration.

**References**


