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Iron Metabolism and Leukemia

Wen-Chi, Yang*

Division of hematology and medical oncology, Department of Internal Medicine, Yuan's General hospital, Yuan's General Hospital, Taiwan (R O C)

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 Cytogenetically 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 (TfR1), 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, TfR1 binds to free iron and forms a di-ferric Tf-TfR1 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

***Corresponding author:** Wen-Chi Yang, Division of hematology and medical oncology, Department of Internal Medicine, Yuan's General hospital,Molecular Medicine Lab, Yuan's General Hospital, No.162, Chenggong 1st Rd, Lingya District, Kaohsiung City 802, Taiwan (R.O.C.), Tel: 886-7-3351121-2247; E-mail: wenchi9251103@yahoo.com.tw

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[26-28]. In humans, hepatocellular carcinoma, malignant mesothelioma (iron in asbestos fibers), colorectal cancer, stomach cancer, lung cancer and ovarian endometriosis have been associated with iron overload [10,24,29]. Possible mechanisms of iron carcinogenesis include iron-mediated ROS damage, iron-induced oxidative responsive transcription factors like Activator Protein-1 (AP-1), and Nuclear Factor Kappa B (NFkB), affecting signal-regulate kinases (ERKs) such as Stress-Activated Protein Kinases/c-Jun NH2 terminal Kinases (SAPK/JNK), and p38 Mitogen-Activated Protein Kinase (MAPK) , cell cycle growth and immune system [30-36].

Long-term iron overload are detected in at least 14% of children after therapy for acute lymphoblastic leukemia and 15 to 20% of adults of acute leukemia based on studies with small sample sizes. In acute leukemia and bone marrow transplantation patients, iron overload is related to liver dysfunction [37-39]. Acute myeloid leukemia (AML) is a heterogeneous disease resulting from unrestrained proliferation of undifferentiated myeloblasts [40]. In AML cell lines and primary cells studies, iron chelating therapy induces the differentiation of leukemia blasts and normal bone marrow precursors into monocytes/macrophages in a manner involving modulation of ROS expression and activation of MAPKs. Iron chelating agents induce expression and phosphorylation of the vitamin D3 receptors, and iron deprivation and vitamin D3 act synergistically [41]. Iron depletion by chelators inhibits the proliferation cancer cells, including leukemia cells [42-46]. Ohyashiki et al. reported that K562 cells treated with deferasirox, an oral iron chelator, revealed up-regulation of Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A) encoding p21CIP, genes regulating interferon, Growth Differentiation Factor 15 (GDF-15) and Regulated in Development and DNA Damage Response (REDD1). REDD1 functions up-stream of tuberin to down-regulate the mTOR pathway and thereby inhibits proliferation of leukemia cells [47].

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 transpoter, and iron-loaded 24p3 increases intracellular iron concentration without promoting apoptosis. Iron-lacking 24p3 decreases 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 underwent apoptosis in response to the addition of iron chelator, DFO [56].

Several studies have shown that LCN2 is also related to cancers [57,58]. Yang et al. reported that an increased intensity of LCN2 staining in either the tumor site or the stroma area correlated with advanced stages of breast cancer and the metastatic status. In a Chronic Myeloid Leukemia (CML) cell line, BCR-ABL oncoprotein drives persistent secretion of LCN2, which targets normal hematopoietic cells for apoptosis [59,60]. Leng et al. showed that LCN2 is required for leukemia development, as BCR-ABL-positive bone marrow cells lacking LCN2 expression failed to cause disease in recipient mice with intact bone marrow [61]. The receptor for LCN2 is down-regulated in BCR-ABL-positive leukemia cells [55]. Furthermore, 24p3 (mouse LCN2)-mediated apoptosis has been shown to play a critical role in imatinib-induced cell death [62]. These studies suggest that LCN2 is associated with cancer development.

In our previous study, we found that LCN2 expression is a favorable prognostic factor of overall survival in cytogenetic normal de novo AML patients, independent of FLT3, NPM1 and CEBPA mutation status [63]. The LCN2 expression also increased when patients demonstrated complete remission. In a leukemia cell line study using MV4-11 cells with FLT3-ITD, LCN2 demonstrated protective role under oxidative stress and cytarabine treatment. However, LCN2 overexpression resulted in elevated apoptotic rate among THP1 cells under oxidative stress and cytarabine treatment compared with empty vector transfected control cells. This has also been observed in OCI-AML3, a leukemia cell line with NPM1 mutation [63]. A possible explanation for this phenomenon is that LCN2 works as a pro-apoptosis factor and enhances apoptosis under oxidative stress and cytarabine treatment, as evident by leukemia cells without FLT3-ITD. However, leukemia cells with FLT3-ITD compensate the pro-apoptosis effect of LCN2, resulting in resistance of intensive chemotherapy. When treating with an iron chelator, DFO, LCN2 showed protective effect of apoptosis on all of these cell lines [63].

BDH2 and Leukemia

Siderophores (2, 5- dihydroxybenzoicacid, 2, 5-DHBA) are small iron-binding molecules that facilitate microbial and mammalian cells 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 (DHRS6) is also an enzyme that participates in the citric acid cycle metabolism and ketogenesis, which may play crucial roles in promoting tumorigenesis [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 2, 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 siderophore. 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.

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