

## IRON, INFLAMMATION AND INVASION OF CANCER CELLS

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### Abstract

*Chronic inflammation is associated with the metastasis of tumor cells evolving from a benign tumor to disseminating cancer. Such a metastatic progression is fostered by the angiogenesis propelled by various mediators interacting at the site of tumor growth. Angiogenesis causes two major changes that are assisted by altered glycosylation and neo-antigen presentation by the cancer cells. The angiogenesis-promoted pathological changes include enhanced inflammation and degradation of tissue matrices releasing tumor cells from the site of its origin. The degraded tumor cells release the neo-antigens resulting from altered glycosylation. Presentation of neo-antigens to T cells escalates metastasis and inflammation. Inflammasome activation and inflammation in several infections are regulated by iron. Based on the discrete reports, we propose a link between iron, inflammation, angiogenesis and tumor growth. Knowing the link better may help us formulate a novel strategy for cancer immunotherapy.*

**Keywords:** iron metabolism, cancer, hepcidin, targeted therapy

### Introduction

Iron is an essential element that promotes growth and differentiation of cells and modulates the cell-mediated immunity including cytokine production. Because iron is involved in many physiological processes but its overload is toxic, the iron level in the body is controlled in a complex but finely tuned manner [1]. The first is of course the intestinal absorption, followed by hepatic regulation and redistribution in different tissues, particularly in the reticulo-endothelial system. The reticulo-endothelial system implements intricate strategies to control iron metabolism in general and the handling of the metal within immune cells. Cytokines such as IL-6 and IL-10, immune-cell-derived radicals such as reactive oxygen species and nitric oxide, and acute-phase proteins contribute to iron

homeostasis at different levels ranging from transcriptional interference with iron regulating genes to modulation of iron transport capacities of transmembrane iron channels [2]. Thus, during inflammation, iron is diverted from the circulation to the reticulo-endothelial system causing restricted erythropoiesis and anemia, termed anemia of inflammation or chronic diseases [1]. However, such reactions may have some beneficial effects: first, proliferation of tumor cells and invading microbes is impaired, and secondly, the cell-mediated immunity against the invading pathogens is strengthened [3]. Therefore the study of iron metabolism holds the key for future therapeutic developments for the treatment of cancer, characterized as a chronic inflammatory disease.

### Cancer and iron

That iron is intimately associated with cancer

Manuscript received: 11.06.2015

Accepted: 30.06.2015

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becomes apparent with the correlation between hepatocellular carcinoma (HCC) in chronic liver diseases and the lack of iron within the tumor tissue in the liver [4]. Expression for most of the iron-regulatory genes, including hepcidin, transferrin receptor 2 (TfR2), transferrin (Tf), ceruloplasmin (Cp) and iron regulatory protein 1 (IRP1) were significantly down-regulated in the tumoral tissues of HCC patients compared to the adjacent non-tumoral liver tissues and normal liver controls [4]. Interestingly, although IRP-1 was shown to be down-regulated in the tumor tissue in HCC, individual siRNA-mediated knockdown of IRP-1 or IRP-2, which binds to iron-responsive elements (IREs) in the untranslated regions of mRNAs, encoding proteins of iron storage, uptake and transport [5]. Five percent of normal cellular levels do not completely abolish the ferritin H or TfR1 response to iron challenge, demonstrating an extensive excess capacity of the IRP system, which is the master regulator of cellular iron metabolism [5]. Similarly, studies on the mRNA levels of hepcidin (HAMP), HFE, neogenin (NEO1), transferrin receptor 1 (TFRC), transferrin receptor 2 (TFR2), and hemojuvelin (HFE2) in normal human brain, brain tumors, and astrocytoma cell lines suggested that several iron-related genes were expressed in normal brain, and that their expression might be dysregulated in brain tumors [6]. Likewise, in a study of 65 oral cancer patients and 85 matched controls, it was found that mild iron deficiency and low GSH levels, which are associated with increased oxidative stress, increased the risk of oral cavity cancer [7]. Thus, iron is associated with cancer and oxidative stress, which often results from chronic inflammation.

Molecular epidemiology of oxidative stress or chronic inflammation and the incidence of cancer suggest that oxidative stress is one of the major causes of carcinogenesis. The reactive oxygen and nitrogen species inflict epigenetic changes upon the genome causing mutations in hot spots and eventual suppression of the tumor suppression genes or activation of the proto-oncogenes. Either of the changes is able to induce uncontrolled cellular proliferation which may further evolve to give rise to metastasizing tumors [8]. As far as the role of iron is concerned, it is shown that ferric nitrilotriacetate directly causes site-specific DNA damage in the presence of  $H_2O_2$ . Iron catalyzes reactive oxygen species (ROS) generation from various organic carcinogens, resulting in oxidative DNA damage. It can perhaps cause DNA damage through indirect mechanisms such as inflammation, as well as suggesting important roles for metal-mediated oxidative DNA damage in chemical carcinogenesis [9]. Indeed, in a murine model of hepatocellular carcinoma (HCC), where the transgenic mice express hepatitis C virus polyprotein, it was observed that hepatic tumors including HCC developed in 5 of 11 (45%) transgenic mice fed the excess-iron diet but not in control mice after 12 months of dietary iron over-loading [10]. The study suggested that iron overload

induces mitochondrial injury and increases the risk of HCC development in chronic hepatitis C virus infection [10]. Supporting these observations, in parts of sub-Saharan Africa, dietary iron overload has been correlated with increased incidence of HCC [11]. The mechanisms of iron-induced malignant transformation are yet to be fully characterized, but chronic necrotic inflammatory hepatic disease is suggested to contribute to the malignant transformation. Increased hepatic iron may also be directly carcinogenic perhaps due to the generation of reactive oxygen intermediates and the resultant chronic oxidative stress. Taken together, these observations suggest that iron homeostasis plays a significant role in tumorigenesis and its malignant transformation. A recently discovered hepatic hormone called hepcidin plays significant roles in iron homeostasis and has been implicated in the control of tumor formation.

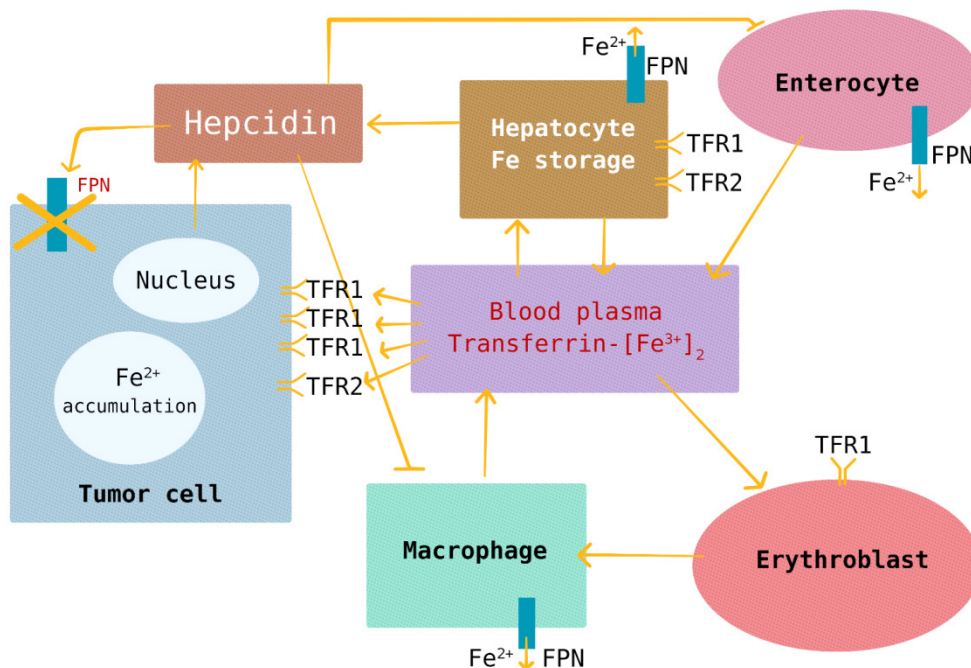
### Hepcidin and tumorigenesis

Iron is a micronutrient and an essential component of metabolism. While iron deficiency leads to anemia, overload of the same element induces oxidative stress to tissues, leading to inflammation, cell death, and system dysfunction including cancer. Thus, maintaining normal iron balance is necessary and is performed primarily by hepcidin (Figure 1), a recently characterized hepatic hormone that regulates duodenal iron absorption and iron efflux from enterocytes, macrophages, and hepatocytes [12]. In tumor cells, transferrin receptors expression is increased, and more, hepcidin blocks ferroportin causing iron accumulation in the cell [3]. This antimicrobial peptide is produced in the liver and released into the circulation in response to iron, oxygen and inflammatory signals, the pathways implicated being BMP/SMAD, JAK/STAT, mTOR and Ras-RAF [13]. Hepcidin levels are controlled through hepatocyte cell surface proteins including HFE, transferrin receptor 2, hemojuvelin, TMPRSS6 and the IL-6R [2]. Hepcidin binds to ferroportin that serves as a transmembrane iron channel enabling iron efflux from cells. The hepcidin-ferroportin complex is then degraded in lysosomes and iron is locked inside the cells (mainly enterocytes, hepatocytes and macrophages). This leads to lowering of iron absorption in the intestine and to a decrease in serum iron concentration. Thus, low hepcidin causes iron overload whereas increased hepcidin expression plays an important role in the anemia of inflammation (AI) by restricting intestinal iron absorption and macrophage iron release. During inflammation, infection and possibly also in cancer, iron is shifted from circulation into cellular stores in hepatocytes and macrophages, making it less available for invading microorganisms and tumor cells [14]. Indeed, in HCC patients, hepcidin mRNA expression is strikingly suppressed in cancerous, but not in non-cancerous tissues, irrespective of ferroportin or TfR2 expression and thus, associating with the development of HCC [15]. The factors

that regulate hepcidin expression are being defined but is still far from complete [16].

The association of hepcidin with tumorigenesis is also evident from other observations. The perturbation of the tumor-suppressor p53, a transcriptional regulator

stimulating DNA synthesis as well as by enhancing c-myc expression, an association between c-myc translocation and iron-dependent cell cycle regulatory mechanism has been proposed [18]. The same mechanism is operative in IL-6 enhanced hepcidin expression [19]. Indeed, stimulation of



**Figure 1.** A scheme for iron absorption, regulation and distribution in normal *versus* tumor cells.

of the genes involved in cell cycle and survival, is a hallmark of the majority of human cancers. A putative p53 response-element (p53RE) is contained in the hepcidin gene (HAMP) promoter. Chromatin immunoprecipitation, reporter assays and the use of a temperature-sensitive p53 cell-line system demonstrated p53 binding and activation of the hepcidin promoter. Consistent with this observation, p53 activation increased hepcidin expression, while p53 silencing decreased hepcidin expression in human hepatoma cells. Thus, it is possible that hepcidin up-regulation by p53 is part of an anti-cancer defense mechanism through iron deprivation and that p53-induced hepcidin might be involved in the anaemia accompanying cancer [17]. Similarly, a STAT3 binding motif located at position -64/-72 of the hepcidin promoter is also required for its transcriptional upregulation. siRNA-mediated RNA knockdown of STAT3 strongly reduces hepcidin mRNA expression. Likewise, the cellular proto-oncogene c-myc is an important transcription factor that plays a role in several cellular activities such as proliferation, differentiation, and apoptosis and its amplification or aberrant translocation can lead to malignant cell growth and tumor progression. Because iron can increase cell proliferation, mainly by

hepcidin expression in the human hepatoma cell line Huh7 with interleukin-6 promoted a significant approximately 30% decrease in <sup>59</sup>Fe efflux from the <sup>59</sup>Fe-transferrin pre-loaded THP1 cells. Similar results were obtained with HepG2 cells transfected with a hepcidin cDNA [20] suggesting a crucial role for hepcidin in the inflammation-induced control of macrophage iron homeostasis. In fact, it has been suggested that increased hepcidin concentration can exacerbate tumor-associated anemia [21]. The role of hepcidin-ferroportin signaling promotes tumor growth and metastasis in breast [22], prostate [23] and colon [24, 25] cancer. Thus, iron's association with tumorigenesis via hepcidin or the proteins that control hepcidin expression including the inflammatory mediators paves the way for iron-targeted anti-tumor therapy [26].

#### Iron-targeted anti-tumor therapy

During the last decade, the field of iron metabolism has been revived with the discovery of several new proteins-transferrin receptor 2, frataxin, hephaestin, hepcidin and hemojuvelin- involved in the homeostatic control of this critical nutrient. Studies on the role of iron in the regulation of cell cycle progression and angiogenesis opened a new

vista for iron-targeted anti-proliferative therapy. There are targets that are affected by iron depletion, such as molecules involved in cell cycle control, angiogenesis and metastasis suppression. These include hypoxia-inducible factor-1 alpha (HIF-1 alpha), vascular endothelial growth factor-1 (VEGF1), p21(CIP1/WAF1), cyclin D1 and the protein product of the N-myc downstream regulated gene-1 (Ndrgl). Some of these approaches are discussed below.

Heme oxygenase-1 (HO-1) catalyzes the oxidation of heme to biologically active products: carbon monoxide (CO), biliverdin, and ferrous iron, and prevents endothelial cells apoptosis, promoting angiogenesis and vasculogenesis. Since angiogenesis is one of the pre-requisites for tumor cell metastasis, HO-1 may play a role in carcinogenesis influencing the tumor cell metastasis of by promoting angiogenesis. Thus, HO-1 inhibition is now suggested as a potential therapeutic approach to enhance the anti-tumor effect of radiation, chemotherapy, or photodynamic therapy [27,28].

Chronic inflammation may contribute to carcinogenesis through increase in cell proliferation, angiogenesis, and metastasis and is marked by over-expression of cyclooxygenase-2 (COX-2). COX-2 is also up-regulated in a variety of cancers. Studies with desferrioxamine (DFX), an iron chelator, suggest that iron metabolism modulates cyclooxygenase-2 signaling pathway [29]. Another marker of inflammation is NF- $\kappa$ B activation. It has been shown that NF- $\kappa$ B inhibition down-regulates ferritin heavy chain expression [30] that leads to an increase in free intracellular iron, which, in turn, induces

massive generation of reactive oxygen species. In a murine T-cell lymphoma model, we show that inhibition of NF- $\kappa$ B and subsequent down-regulation of ferritin heavy chain significantly delays tumor growth in vivo. Thus, ferritin heavy chain is a potential target for effective therapy in lymphomas with aberrant NF- $\kappa$ B signaling [30]. Ferritin is also shown to bind to a 22-aa sub-domain of cleaved high molecular weight kininogen (HKA) that is critical for its anti-angiogenic activity and to oppose HKA's anti-angiogenic effects in a human prostate cancer xenograft, restoring tumor-dependent vessel growth [31]. Thus, controlling angiogenesis by a ferritin-targeted therapy may prove useful.

The other physiological factor that controls angiogenesis in response to hypoxic stress is vascular endothelial growth factor (VEGF). The VEGF pathway is directly involved in tumor angiogenesis and growth in multiple myeloma via a paracrine VEGF loop. This provides a further indication that the VEGF pathway and its signaling proteins may be appropriate targets in the management of multiple myeloma [32]. Because angiogenesis is a major factor in tumor metastasis, small molecule VEGF receptor tyrosinase kinase inhibitors are tested for their anti-angiogenic responses in tumors. Using magnetic resonance imaging and superparamagnetic nanoparticles for measuring relative vascular volume fraction (rVVF) in a drug-resistant colon carcinoma model, it has been shown that such small molecules can effectively decrease tumor angiogenesis [33]. However, whether these results are comparable with anti-VEGF antibody treatment remain to be confirmed.

**Table I.** Recent clinical trials on cancer treatment that include iron supplementation or iron chelation.

Clinical trial identifier	Cancer type	Drug
<b>Iron supplementation</b>		
NCT01435200	Gynecologic Cancers	Intravenous iron
NCT00401544	Non-Myeloid Malignancies	Iron dextran
NCT00661999	Leukemia, Lymphoma	Sodium ferric gluconate complex
NCT01953107	Ovarian-, cervical- and uterine Cancers	Ferrous Fumarate
NCT00199277	Colorectal neoplasm	Iron sucrose
<b>Iron chelation</b>		
NCT02222363	Refractory advanced solid tumors	VLX600
NCT01159067	Leukemia and lymphoma patients after allogeneic stem cell transplant	Deferasirox
NCT00602446	Breast cancer, leukemia, lymphoma, multiple myeloma, plasma cell neoplasm, myelodysplastic syndrome, neuroblastoma, ovarian cancer	Deferasirox
NCT01273766	Leukemia, lymphoma	Deferasirox
NCT00990587	Leukemia, myelodysplasia, Hodgkin's disease	Ciclopirox Olamine
NCT00382330	Vulvar cancer	Ciclopirox
NCT00004213	Solid tumors	Triapine
NCT01835171	Uterine cervix and vaginal cancer	Triapine
NCT00054015	Prostate cancer	Triapine
NCT00024323	Advanced solid tumors	Triapine
NCT00390052	Metastatic solid tumors	Triapine
NCT00288093	Pancreatic cancer	Triapine



Iron excess is associated with tumorigenesis because it is the source of mutagenic hydroxyl radical formation that interferes with DNA repair and affects the signal transduction in cancer cells, acting as a nutrient for proliferating tumors [34]. The other groups of compounds used for iron-targeted anti-tumor therapy are the iron chelators. Because iron is critical for cell-cycle progression and DNA synthesis, it is a potential molecular target for the design of new anticancer agents. Therefore, many iron chelators are on trial (Table I) and of these di-2-pyridylketone-4,4,-dimethyl-3-thiosemicarbazone (Dp44mT) and desferrioxamine are found to be promising. Dp44mT caused up-regulation of the Fe-responsive tumor growth and metastasis suppressor NdrG1 in the tumor but not in the liver, indicating a potential mechanism of selective anticancer activity [35]. Gene expression studies with desferrioxamine revealed that the N-myc downstream-regulated gene 1 (NdrG1) was specifically up-regulated by iron chelation. NdrG1 markedly slows tumor growth and acts as a potent metastasis suppressor. Iron repletion reversed the anti-proliferative functions of chelators. NdrG1 up-regulation after chelation occurred at the transcriptional level and was mediated by hypoxia inducible factor-1 alpha (HIF-1alpha)-dependent and -independent mechanisms [36]. Although many functions of NdrG-1 in differentiation, proliferation and angiogenesis are reported, its molecular targets remain scant. Whole genome gene array revealed one significant target- thiamine triphosphatase (Thtpa)- in the majority of tumor cell models. Because Thtpa is known to decrease the levels of the energy currency molecule, thiamine triphosphate, iron chelation may work through up-regulation of NdrG-1 that in turn up-regulates Thtpa to implement the anti-proliferative effects of iron chelators such as desferrioxamine. On the other hand, NdrG-1-effected reduced expression of cathepsin C that plays a role in invasion also suggests the anti-metastatic functions of iron chelation [37].

By using hepcidin antagonists for a pharmacological control of hepcidin expression, several regulatory steps have been targeted. This category includes hepcidin sequestering agents, ferroportin stabilizers, SMAD or IL6/STAT3 pathway inhibitors [38].

The other aspect in iron-targeted anti-tumor therapy is the development of drug delivery vehicles. Current nanoparticle-based therapeutic strategies for cancer treatment are primarily aimed at the delivery of chemotherapeutic agents to induce apoptosis or DNA/siRNA to regulate oncogene expression. In a recent development, a nanoparticle system is designed for alternative mode of cancer treatment but combined with the properties for magnetic resonance imaging and optical imaging contrast. The nanoparticle is made of an iron oxide nanoparticle core conjugated with an amine-functionalized poly(ethylene glycol) silane and a small peptide, chlorotoxin. The latter substantially enhances

cellular uptake and inhibits cancer cell invasion perhaps by inducing deactivation and internalization of the membrane-bound matrix metalloproteinase 2 (MMP-2). Since MMP-2 upregulation of activity have been observed in many tumors, this nanoparticle system can potentially be used for non-invasive diagnosis and treatment of a variety of cancer types [39].

Iron homeostasis is altered in tumorigenesis; thus, besides the iron supplementation in anemic cancer patients, many efforts of scientists aim at repurposing the iron-chelator drugs such as deferasirox, ciclopirox and triapine for cancer therapy, and this resulted in several in vitro and in vivo studies, but also clinical trials [3].

### **Conclusion**

As the tumor mass grows, the core suffers from hypoxic stress resulting in the expression of hypoxia-responsive genes. Many of these genes such as hypoxia-induced factor-1 and VEGF promote angiogenesis through a variety of mechanisms. These events result in chronic inflammation and increased tumor cell metastasis. The inflammation caused in the process induces hepcidin and other proteins that dysregulate iron metabolism and further promote tumor growth. On the other hand, tumor hypoxia induces resistance to treatment in cancer cells affecting the clinical efficacy of the treatment [40,41]. This review has summarized how we can target the angiogenesis and iron to develop novel anti-tumor therapy that also addresses the resistance of tumor cells to chemotherapy.

### **Acknowledgements**

The work is financially assisted by the Department of Biotechnology, Government of India. This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776. We acknowledge the support of Romanian UEFISCDI Grant for Exploratory Research Project PN-II-ID-PCE-2011-3-1057, 250/2011. We wish to express our gratitude to graphic artist Oana Coheci.

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