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Iron: The Cancer Connection

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Abstract

Iron plays an essential role in normal biological processes: The generation of cellular energy, oxygen transport, DNA synthesis and repair are all processes that require iron-coordinated proteins, either as elemental iron, heme or iron-sulfur clusters. As a transition metal with two major biological oxidation states, iron is also a critical intermediate in the generation of reactive oxygen species that can damage cellular structures and contribute to both aging and cancer. In this review, we focus on experimental and epidemiologic evidence that links iron and cancer, as well as strategies that have been proposed to either reduce or increase cellular iron for cancer therapy.

Keywords

transferrin receptor; ferroportin; metastasis; iron chelator; ferroptosis

1. Introduction

Pathways that govern iron metabolism in non-malignant cells are perturbed in cancer cells. Here, we provide an overview of the links between iron and cancer, specifically the evidence that iron can contribute to the initiation, growth and metastatic spread of tumors. We also discuss targeting iron as a potential anti-cancer strategy. For a more detailed description of iron regulatory pathways in normal cells, the reader is referred to other chapters in this book. We also refer the reader to recent reviews that delve more extensively into particular facets of the relationship between iron and cancer at the cellular and systemic level, including the role of iron in immune metabolism[1] and roles of heme iron[2].

2. Iron as a carcinogen

Iron is an essential nutrient that is required for functions ranging from oxygen transport to respiration to DNA synthesis. However, due to its ability to redox cycle (gain and lose electrons), iron also has the potential to participate in deleterious reactions that produce free radicals. In particular, iron catalyzes the formation of hydroxyl and possibly ferryl radicals[3](Fenton chemistry), two species that can damage DNA, lipids and proteins, and are major contributors to oxidative stress[4–8].

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The ability of iron to catalyze the formation of DNA strand breaks and oxidize DNA bases[9] renders it a potential mutagen. When mutations occur in critical genes that regulate cell growth and proliferation, cancer ensues. In most cancers, it is the accumulation of multiple mutations over time that is thought to drive cancer -- single oncogenic events such as the (9;22)(q34;q11.2) translocation “Philadelphia chromosome” that gives rise to the BCR-ABL1 fusion protein and results in CML[10] are the exception rather than the rule. Thus, we believe that iron can be considered a driver in an oncogenic program: as cancer cells acquire more iron, more radicals are formed, and more mutations are acquired.

3. Experimental links between iron and cancer

What is the evidence for a mutagenic activity of iron? The link between excess iron and cancer was observed decades ago, in studies demonstrating that exposure to iron oxide dust triples the incidence of pulmonary tumors in mice[11], and that intramuscular injection of iron dextran induces sarcoma in rats[12]. Work begun in the 80’s[13] demonstrated that a single injection of iron (ferric nitrilotriacetate) induces oxidative DNA damage in rat kidneys and gives rise to tumors that exhibit a mutational spectrum similar (within limits) to that seen in human kidney cancer[14,15]. Another link between iron and carcinogenic mutations is seen in patients with hemochromatosis, a genetic disease that can lead to iron overload and an increased risk of developing hepatocellular carcinoma[16]. Such patients exhibit an accumulation of p53 mutations[17] and epigenetic changes in the liver[18] that are characteristic of hepatocellular carcinoma, even in non-malignant tissue. Such findings suggest that the link between iron, excess mutation and tumor formation is pertinent to human disease. Although all these examples involve exposure to supra-physiological levels of iron, they demonstrate the potential of iron to foster carcinogenic events in vivo.

As an essential nutrient, iron is also required for tumor growth. Early experimental studies demonstrated the ability of excess dietary iron to enhance tumor growth in mice[19–22]. Tumor incidence in mice that spontaneously develop intestinal tumors due to heterozygosity in the APC tumor suppressor is similarly increased in mice fed a high iron diet and decreased in mice fed an iron-restricted diet[23]. Conversely, iron withdrawal, produced by treatment with small molecule iron chelators or by dietary manipulation, inhibits tumor growth both in spontaneous and xenograft models of cancer[24,25].

A genetically engineered mouse model with tissue-specific deletion of FBXL5 in the mouse liver was recently used to more explicitly demonstrate the effects of hepatic iron overload on cancer[26]. FBXL5 is an ubiquitin ligase that degrades IRP2 (iron regulatory protein 2), a protein that post-translationally controls expression of transferrin receptor (TFR1), ferritin, and ferroportin. In the absence of FBXL5, IRP2 is constitutively expressed, resulting in TFR1 stability (enhanced iron uptake) and repression of ferroportin and ferritin (decreased iron efflux and storage, respectively). Collectively, these molecular events lead to hepatic iron overload[27]. Consistent with the pro-tumorigenic activity of iron, FBXL5-deficient mice exhibit oxidative stress and develop liver tumors late in life. Moreover they exhibit a high hepatic tumor incidence and increased tumor size following exposure to chemical (diethylnitrosamine; DEN) or viral carcinogens (hepatitis C viral transgene[26]).

These and other observations illustrating the pro-tumorigenic effects of iron and the anti-tumorigenic effects of iron depletion form the conceptual foundation for the strategy to use iron chelation in anti-cancer therapy (discussed in Section 8 below).

4. Epidemiology of iron and cancer

Population-based studies have examined the relationships between iron intake and/or stores of iron and human cancer risk. Many, but not all studies have observed a link between high iron and cancer.

Early nutritional surveys demonstrated a significant increase in transferrin saturation (the fraction of transferrin in the blood that is bound to iron) in men who subsequently developed cancer relative to those who remained cancer-free[28–31]. More recent meta-analyses that examine the association between biomarkers of iron status and risk of specific cancers indicate that the association between iron and cancer may be cancer-type specific: in a meta-analysis of 27 studies of women with breast cancer there was an increase in relative risk of breast cancer between highest and lowest levels of iron (RR 1.22; 95% CI 1.01–1.47)[32]. A meta-analysis of hepatocellular carcinoma similarly observed an association between both high serum ferritin and high serum iron and primary liver cancer risk (6 studies, HR 1.49, 95% CI 1.13–1.96 for ferritin; 3 studies, HR 2.47; 95% CI 1.31– 4.63 for serum iron)[33], and approximately three-quarters of 33 studies of colorectal neoplasia supported an association between increased iron intake or increased iron stores with increased risk of colorectal neoplasia[34]. However a meta-analysis of 13 studies found no association between serum iron and lung cancer risk[35]. The association between dietary iron intake and cancer risk has also been examined using food frequency questionnaires, with similarly mixed results. For example, in a large study of over 500,000 participants with 8 years follow-up, individuals in the highest quintile of red meat intake exhibited a significantly increased risk of several malignancies when compared to those in the lowest quintile, including esophageal cancer, colorectal cancer, liver cancer and lung cancer[36]. However red meat intake was not associated with gastric cancer, bladder cancer, leukemia, lymphoma, melanoma, breast or prostate cancer[36]. Overall, the most consistent associations have been between consumption of red meat and colorectal cancer, although there has been a call for better-designed studies to more definitively test this association[37].

There are both technical and biological reasons for the variance in the strength of the association between iron intake or biochemical indices of body iron and cancer. As examples, (1) assessments of iron intake are often derived from questionnaires that depend on recall which is sometimes incomplete or inaccurate; (2) there is a well-established variability in iron absorption after intake; and (3) single short periods of assessment are generally used to infer intake over a long period of time. In addition, although the association between ingestion of specific foods, such as red meat, with increased cancer risk has been attributed to the high iron (heme) content of red meat, it may also be due to other constituents of this complex food. Further, when blood tests are used to assess body iron stores in humans, the tests themselves are subject to factors independent of body iron content that affect results. For example, serum ferritin, a widely used marker of iron status

in humans, can be markedly altered by inflammatory conditions that are independent of the subject's iron status [38].

In addition to assessing the risk associated with increased stores or intake of iron, another approach to evaluate the connection between iron and cancer has been to examine the consequences of diseases that result in systemic iron overload in tissues such as the liver. As discussed above in Section 3, one such disease is hereditary hemochromatosis, which results in iron retention in the liver and other organs. Although hereditary hemochromatosis can result from at least five distinct genetic abnormalities, the most common mutation is in the HFE gene; patients with homozygous mutations have a 20–200 fold increased risk of liver cancer as well as increased cancer risk at other sites[39,40]. In an interesting example of gene/environment interaction, in certain African populations the risk of hepatocellular carcinoma and esophageal carcinoma may be exacerbated by the intake of home-brewed alcoholic drinks contaminated with iron[41,42].

Another link between iron body stores and cancer risk comes from studies in which iron is depleted by blood donation (which reduces body iron by removing red blood cells, a major reservoir of iron) or increased by blood transfusion. A study involving examination of over 800,000 computerized files of Scandinavian individuals reported that cancer risk was increased in recipients of blood transfusions, with elevated incidence ratios of the transfused population versus the general population for cancers of the tongue, mouth, pharynx, esophagus, liver, and respiratory and urinary tracts and for squamous cell skin carcinoma[43]. However, the authors could not rule out the presence of undiagnosed occult cancers that may have produced symptoms necessitating the blood transfusion; possible immunosuppressive effects of transfusions (i.e. transfusion-related immunomodulation (TRIM)) may also have contributed to the observed elevation in cancer risk[44]. Conversely in a study of individuals who were frequent blood donors, cancer risk was significantly decreased (RR) of 0.79 ($p < 0.001$) [45]. A subsequent study of blood donors reported a more limited association: there was a significant trend of decreasing risk for cancers of the liver, lung, colon, stomach, and esophagus ($P(\text{trend}) < .001$[46]), but not other malignancies, between the lowest and highest categories of estimated iron loss from blood donation. Perhaps most compellingly, in a clinical study in which phlebotomy was performed to attempt to reduce peripheral arterial disease, phlebotomy decreased overall cancer risk and cancer-specific mortality[47].

5. Mechanisms of dysregulation of iron in cancer

Once a cancer develops, there is substantial and growing evidence of increased metabolically available iron in the cancer cells themselves. This form of iron is frequently termed the labile iron pool, or LIP, and is believed to represent a small but biologically important fraction of total cellular iron[48]. In addition to the further acquisition of mutations, such excess iron, both in the form of labile iron and heme, supports cancer growth. How does the cancer cell acquire this additional iron?

Upregulation of transferrin receptor 1 (TFR1) is one way. Increases in TFR1, the receptor for transferrin-bound iron that is responsible for cellular iron uptake, have been repeatedly observed in numerous cancers, including breast, lung and bladder cancer, CLL, non-

Hodgkin's lymphoma, and others[49]. The increase in TFR1 can be directly oncogene driven; for example c-myc transcriptionally upregulates TFR1; alternatively, the increase in TFR1 can occur indirectly, for example as a function of FBXL5 reduction[27] or IRP2 upregulation[50,51]. Another mechanism for increasing iron acquisition is upregulation of DMT1 in colorectal cancer[52]. CD44 is a cell surface protein whose expression is increased in cells undergoing the epithelial to mesenchymal transition (EMT) and is frequently used as a cancer stem cell marker. A recent study demonstrated that CD44 is responsible for glycosaminoglycan-mediated endocytosis of iron, suggesting not only that CD44 may play a role in iron acquisition in cancer stem cells, but directly tying iron to regulation of EMT[53].

NGAL (lipocalin 2; gene name *LCN2*), is a 24 kd secreted glycoprotein and member of the lipocalin family of proteins that transport small hydrophobic ligands. NGAL binds iron complexed to a siderophore, and can be internalized by the cell surface receptor 24p3R. NGAL produced by tumor-associated macrophages can deliver iron and promote growth of tumor cells[54]. In addition, NGAL is upregulated in some cancers, and uptake of iron via this pathway has been linked to breast and renal cancer, among others[55,56].

An additional mechanism by which cancer cells acquire excess iron is by inhibiting its efflux. In 2010, our laboratory reported that ferroportin (FPN), a cellular iron efflux pump, is downregulated in breast cancer[57]. We subsequently reported similar results in prostate[58] and ovarian[59] cancer; others have confirmed and expanded these results in other malignancies, including lung cancer[60], multiple myeloma[61] and a subset of patients with AML[62]. Multiple mechanisms for the decrease in ferroportin in cancer cells have been described, including upregulation of IRP2[50,51], which inhibits translation of FPN mRNA; upregulation of hepcidin, which triggers the degradation of FPN protein[58], microRNAs such as miR-20a[60] and miR-485–3p [63], and promoter methylation[64].

Not all cancers use the same pathways to enhance iron acquisition and retention. Even within a single cancer, alternative mechanisms can be engaged. In work in breast cancer, for example, our laboratory showed that two distinct patterns of gene expression could result in the same phenotype of reduced patient survival: (1) Decreased iron export through reduction of ferroportin and overexpression of hepcidin; or (2) increased iron uptake through high expression of the transferrin receptor and reduction of HFE, a negative regulator of TFFR1[65]. This work further demonstrated that an "iron regulatory gene signature" or IRGS, effectively predicts clinical outcome in a cohort of breast cancer patients treated with the same therapy. The IRGS includes ferroportin and transferrin receptor, as well as 14 additional genes of iron metabolism[65]. Clearly, the constellation of modifications in genes that govern iron metabolism in cancer involves much more than TFR1 and ferroportin. Systems biology approaches may be useful in parsing out these differences and identifying key signatures and drivers among them[66–68].

6. Iron addiction

There is evidence that the enhanced uptake and retention of iron in cancer constitutes a metabolic addiction – i.e., that cancer cells develop a dependence on iron that exceeds that of their non-malignant counterparts. Thus cancer cells are more sensitive

to the anti-proliferative effects of a range of chemically distinct iron chelators, including desferoxamine, tachpyridine, the di-2-pyridylketone class of thiosemicarbazones (e.g. Dp44mT and DpC), than non-cancer cells[69,70]. Consistent with these findings, forced expression of ferroportin, which reduces intracellular iron by genetic rather than chemical means, is sufficient to reduce the rate of proliferation of breast, prostate and ovarian cancer cells[57,59,71]. Since the anti-proliferative effect of iron restriction on cancer cells tends to be greater than that on non-cancer cells[59], we have termed this phenomenon “iron addiction”[59].

7. Iron and metastasis

Although data are limited, there is evidence that iron may affect cancer metastasis as well as tumor growth. NDRG1, a metastasis suppressor that is downregulated in numerous cancers[72], is upregulated following treatment with iron chelators[73]. Accordingly, treatment with the iron chelator Dp44mT induced NDRG1 and reduced formation of bone metastasis of human bone metastatic breast cancer cells (MDA-MB231-BoM) in intracardially injected mice[72]. Dp44mT also inhibited the formation of lung tumors in a metastatic model created by injection of osteosarcoma cells in nude mice[74]. Using induction of ferroportin to deplete iron, our group observed a decrease in the number of tumors in a mouse model of metastasis[59]. In this model, ovarian cancer cells were injected directly into the peritoneum (a major site of ovarian cancer metastases). Further, the FPN-mediated decrease in tumor number was associated with a decrease in invasion, IL6, and phosphorylated STAT3[59], a result consistent with results implicating activation of STAT3 in iron-dependent promotion of colorectal tumorigenesis[52]. Finally, the observation that expression of ferroportin and TFR1 predicts survival of breast cancer patients[65] and that disrupted regulation of these pathways is associated with poorer survival of patients with prostate cancer[58] implies a role for iron in human metastasis, since mortality from these cancers is primarily due to metastatic disease.

8. Iron and signaling in cancer

How does iron transmit a signal to induce tumor cell proliferation and metastasis? Our knowledge in this area is incomplete. However, it is clear that iron both regulates and is regulated by signaling pathways in cancer. Generally, the role of iron in tumor cell proliferation and metastasis has been linked to its function as a cofactor, required for the function of proteins essential to these processes, as well as to the ability of iron to impact signaling pathways directly. In turn, oncogenes, tumor suppressors, and growth factor and cytokine-mediated signaling pathways regulate critical proteins in iron metabolism. We provide a few important examples illustrating these principles.

8.1 Regulation of cell signaling by iron.

Iron is essential for the catalytic function of ribonucleotide reductase, the enzyme that converts ribonucleotides to deoxyribonucleotides, a critical step in DNA synthesis and therefore an obligate step in cell replication. Iron in the form of iron-sulfur clusters is also required for the activity of essentially all replicative DNA polymerases as well as proteins involved in genome maintenance and repair[75]. These include helicases such as FancJ and XPD; glycosylases involved in DNA repair; primase, Chir1 and DNA2, involved in DNA

replication; RTEL1 with roles in homologous recombination, and others[75]. In addition, iron depletion by IRP2 knockdown or iron chelation induces the cell cycle regulators p15, p21 and p27, causing accumulation of cells in G0/G1, implying that iron is permissive for cell cycle progression.[50] Mechanisms are still unclear; however, iron-dependent control of p21 by the transcription factor SP1 and its interacting partners ER-α and c-Jun in SK-MEL-28 melanoma cells has recently been described[76], whereas in prostate cancer cells, p53 and KLF6 appear to play a role in iron-dependent regulation of p21[71]. By affecting these processes, iron directly impacts cell proliferation as well as DNA integrity.

Iron also influences the activity of the p53 tumor suppressor, arguably one of the most important barriers to tumor formation in humans. It was demonstrated that iron in the form of heme directly binds to p53, stimulating its degradation and interfering with its interaction with DNA, thus reducing p53's anti-tumor effects[77,78]. However, it has also been reported that supplementation of cell cultures with exogenous inorganic iron reduces levels of MDM2, the ubiquitin ligase responsible for p53 degradation[79,80], which would be expected to increase levels of p53, and in fact did so in one report[80]. The iron-mediated decrease in MDM2 was shown to occur by an IRP2-dependent mechanism, in which stabilization of MDM2 mRNA by IRP2 binding to its 3' UTR was disrupted by excess iron[79]. It is possible that whether iron increases or decreases p53 depends on the form of iron (inorganic iron versus heme), the relative rates of these apparently competing pathways, or the particular cell types involved; however, this requires additional investigation. There is evidence that p53 in turn regulates iron: p53 translationally increases ferritin, reducing the availability of intracellular iron during p53-mediated cell cycle arrest[81]. More recent results suggest that this may occur through direct transcriptional induction of ISCU2 (iron sulfur cluster assembly enzyme) by p53. Upregulation of ISCU2 favors the formation of iron-sulfur clusters in IRP1, diminishing the activity of IRP1 as an RNA binding molecule (i.e. reducing its activity as a translational repressor of ferritin and stabilizer of TFR1 mRNA) and favoring its activity as a cytosolic aconitase[82].

In addition to iron itself, proteins of iron metabolism may also act as signaling molecules. For example, ferritin exists both in intracellular and extracellular compartments[38]. The origin of extracellular serum ferritin has been unclear for decades, but it now appears that macrophages are at least one likely source of secreted ferritin [83,84] In conjunction with the unexpected observation that ferritin can induce NFKB[85], a transcription factor that induces multiple tumor-promoting cytokines including IL6, this suggests a potential role for ferritin in sustaining a pro-tumorigenic microenvironment. Further, since NFKB can also induce ferritin[86], the potential exists for the participation of ferritin in a tumor-promoting feed-forward loop. Such a model would be consistent with the link between elevated ferritin and poor outcome observed in some malignancies, such as AML[87].

8.2 Regulation of iron by oncogenic signaling pathways.

Early evidence of a connection between oncogenic pathways and iron was provided by the observation that adenoviral E1A, a viral oncogene with immortalizing properties similar to those of c-myc, represses ferritin[88]. Subsequently, it was demonstrated that the c-myc oncogene directly and coordinately represses transcription of ferritin while transcriptionally

upregulating IRP2 in EBV-immortalized B cells[89]. These effects increased intracellular iron and were required for cell transformation by c-myc. Consistent with these results, c-myc was later shown to activate TFR1 to enhance proliferation and tumorigenesis in in vitro and in vivo models of B cell lymphoma[90].

WNT and STAT3 signaling have both been implicated in iron signaling in colorectal cancer. Iron loading increased WNT signaling in colorectal cells with mutant APC[91], providing a mechanistic underpinning for the subsequent observation that iron exacerbates tumorigenesis in the background of APC loss[23]. The iron dependence of this pathway was also revealed by a WNT inhibitor screen[92]. Separately, iron-mediated induction of JAK1-STAT3 signaling by CDK1 was recently shown to promote colorectal tumorigenesis[52]. Whether these pathways are differentially triggered in tumors from different individuals and/or are the result of different upstream activation events remains to be determined.

Hepcidin is a peptide hormone produced by the liver that is a master regulator of body iron homeostasis. Cancer cells also produce hepcidin, which binds to ferroportin on the surface of cancer cells and thereby downregulates iron efflux, acting as a mechanism of iron retention[57]. Multiple signaling pathways impinge on the synthesis of hepcidin in cancer. These include BMPs and downstream SMADs, as well as the JAK/STAT3 pathway, which controls hepcidin synthesis in response to inflammatory cytokines. Our laboratory recently demonstrated that hepcidin regulatory pathways are also influenced by the microenvironment: in breast cancer cells grown as spheroids in three-dimensional culture, GDF15 emerged as a potent regulator of hepcidin. Further, inclusion of tumor-associated fibroblasts in the spheroids potentiated hepcidin synthesis through secretion of IL6[93]. These results suggest that it will be necessary to construct new paradigms for tumor-mediated control of iron that takes into account tumor architecture and the tumor microenvironment.

9. Iron: therapeutic approaches

Observations of iron dysregulation in cancer have given rise to several strategies to target this metabolic vulnerability for cancer therapy. These approaches can loosely be grouped into four categories: (1) depleting iron, based on the concept that iron is a metabolite upon which cancers are particularly dependent; (2) using iron mimetics to disrupt iron metabolism; (3) using proteins of iron metabolism that are over-expressed in cancer as targets for the delivery of anti-cancer agents; (4) providing additional iron, based on the concept that the excess iron present in cancer cells renders them oxidatively fragile and increases their susceptibility to iron-mediated oxidative stress.

9.1 Strategies to deplete cancer cells of iron.

This is historically one of the earliest approaches to leverage iron for cancer therapy. Soon after the discovery of transferrin receptor as the mechanism of iron delivery into cells and the demonstration that this receptor is upregulated in multiple cancers, anti-TfR antibodies were developed and shown to inhibit tumor growth[94]. Anti-TfR1 antibodies administered in a phase I clinical trial exhibited some activity, particularly in hematopoetic malignancies,

and modest systemic toxicity[95], encouraging the search for humanized antibodies with improved activity[96,97].

Several different small molecule iron chelators used in the clinical treatment of iron overload, such as desferrioxamine and more recently deferiprone[98,99] and deferasirox[100], were shown to preferentially reduce cancer cell growth in cell culture and reduce tumor burden in animal models when administered either alone or in combination with other anti-cancer drugs. A few small clinical trials, mostly of desferrioxamine, produced encouraging but limited responses[101,102].

9.2 Using iron mimetics to disrupt iron metabolism.

Gallium(III) shares certain chemical characteristics with iron(III) that enables it to interact with iron-binding proteins and disrupt iron-dependent tumor cell growth[103]. This includes inhibition of ribonucleotide reductase and mitochondrial function. Newer gallium ligands such as Tris(8-quinolinolato)gallium(III) (KP46) and gallium maltolate have replaced simple gallium salts such as gallium nitrate, and are undergoing clinical evaluation.

9.3 Exploiting proteins of iron metabolism for targeted delivery.

This strategy has focused largely on TFR1, a cell surface receptor frequently over-expressed in cancer cells that can be co-opted to serve as a delivery vehicle for anti-cancer drugs. Examples include transferrin conjugated to chemotherapeutic drugs such as doxorubicin and cisplatin, toxins such as diptheria toxin and ricin, and anti-neoplastic nucleic acids[49]. Toxicity was an issue in early trials, but the development of improved antibodies holds promise, and this is still an area of active investigation[96,104].

9.4 Leveraging iron to generate cytotoxic oxidative stress in cancer cells.

Although iron chelators are generally used to deplete iron, iron chelators of the appropriate chemical structure[3] can also bind iron (and copper) in a fashion that promotes redox cycling and consequently the generation of toxic free radicals. Examples of iron chelators of this class, such as the thiosemicarbazones DpC and Dp44mT, have shown substantial promise as anti-cancer and anti-metastatic agents in preclinical studies and progressed to evaluation in clinical trials[105]. In selected cancer cells, iron itself may have pro-oxidant cytotoxic effects: a recent finding that leukemic cells from a subset of patients with AML exhibit low levels of ferroportin led to the observation that ferumoxytol (Feraheme), an FDA-approved iron oxide nanoparticle used in treatment of iron deficiency, can induce oxidative stress and reduce tumor burden in a murine leukemia model[62].

Finally, ferroptosis is a recently-described mechanism of cell death notable for its iron-dependence[106]. Ferroptosis is triggered by an accumulation of peroxidized membrane phospholipids, which distinguishes ferroptosis mechanistically from other forms of regulated cell death. Since the formation of lipid radicals is fostered by iron, cancer cells with excess iron may be particularly susceptible to drugs that induce ferroptosis. In line with this prediction, we observed that ovarian cancer stem cells could be effectively targeted in vitro and in vivo by erastin, a preclinical drug that induces ferroptosis[59]. Salinomycin, a drug with efficacy against cancer stem cells, may also act by inducing ferroptosis:

salinomycin sequesters lysosomal iron, resulting in an iron depletion response that triggers lysosomal degradation of ferritin, production of ROS, and a death pathway resembling ferroptosis[107]. Conversely, prominin2 protects cells from ferroptosis by stimulating efflux of ferritin and its associated iron in endosomes and multivesicular bodies[108]. The ongoing effort to discover new ferroptosis-inducing agents to treat cancer[109], and the entry of these agents into early stage clinical trials in cancer patients (ClinicalTrials.gov NCT01695590), suggests that this may be a promising venue for further study.

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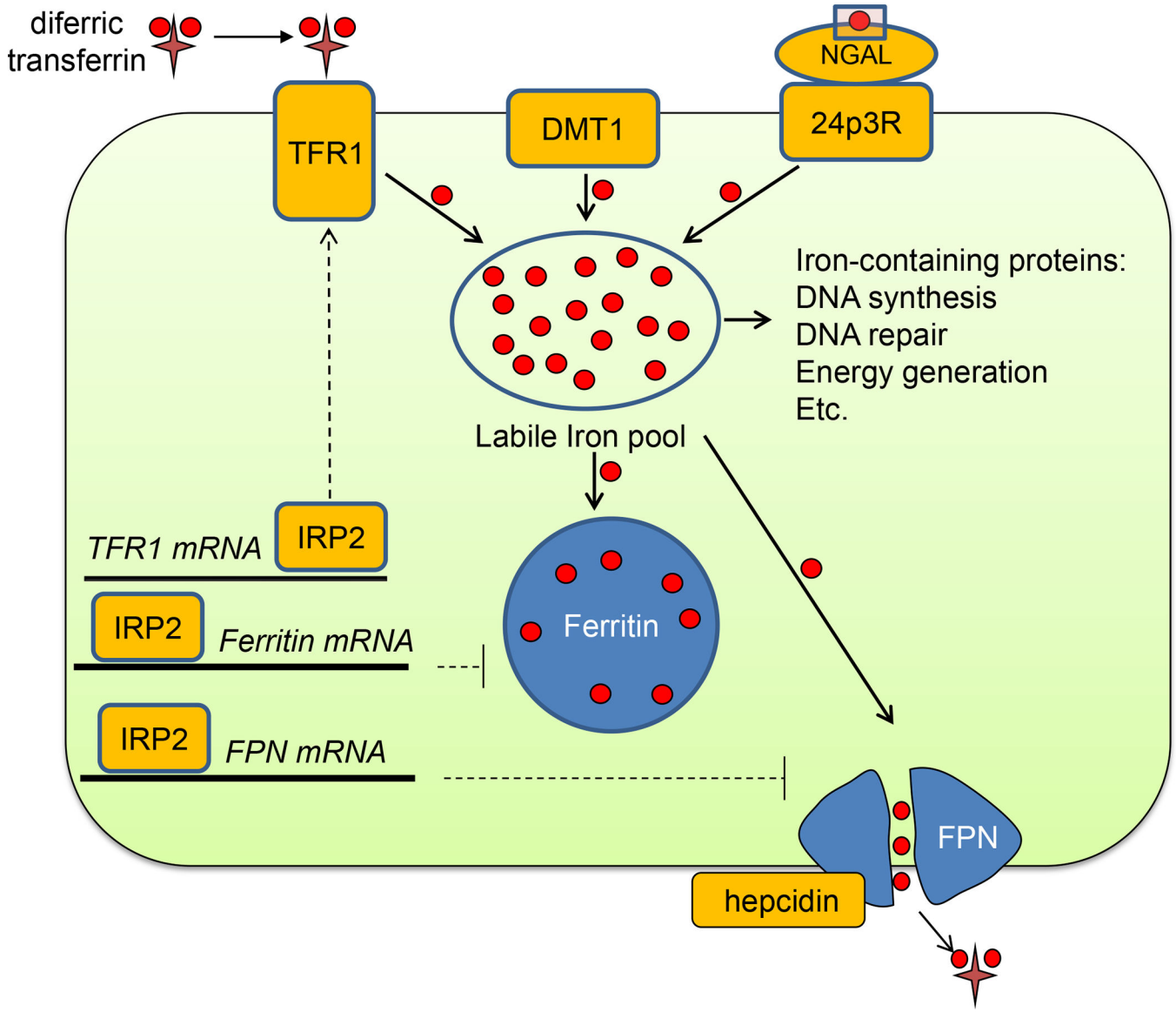

Figure:

Examples of iron trafficking proteins altered in cancer. Small red circles represent iron. Proteins colored in orange are increased in most cancer cells when compared to non-malignant cells; proteins colored in blue are decreased. Upregulation of proteins involved in iron import, such as TFR1, DMT1 and 24p3R increase the labile iron pool; downregulation of ferritin shifts more iron to the labile iron pool; reduction of ferroportin increases iron retention by decreasing iron efflux. Hepcidin degrades ferroportin – more hepcidin is associated with decreased iron efflux. Upregulation of IRP2 is one of several mechanisms underlying these changes: IRP2 stabilizes TFR1 mRNA by binding to the 3'UTR of its mRNA; IRP2 also binds to the 5' UTR of the ferritin and ferroportin mRNA to repress their translation. (IRP1 also functions as a translational regulator of TFR1, ferritin, and ferroportin; however it does not appear to exert a similar pro-tumorigenic effect). Ferritin consists of H and L subunits that are similarly regulated by IRP2; for simplicity these

subunits are both represented as “ferritin”. Note that these changes are not observed in all cancers and are not necessarily present simultaneously.