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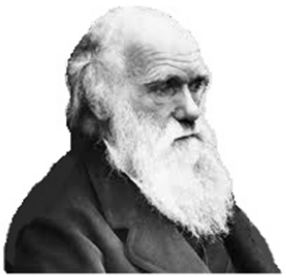

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Anticancer Activities of Ferrous and Ferric Ions in Progression, Proliferation, Angiogenesis, Invasion and Metastasis against Cancer and Tumor Cells

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ABSTRACT

The process of ferroptotic death is characterized by the overwhelming, iron-depending accumulation of lethal lipid ROS. Unlike other forms of apoptotic and non-apoptotic death, this requirement for ROS accumulation appears to be universal. Redox cycling is a characteristic of transition metals such as iron (Ferritin Fe^{3+} ⇄ Ferrous Fe^{2+}). Iron via the Fenton reaction can exacerbate the consequences of hydrogen peroxide (H_2O_2) production, leading to the generation of hydroxyl radicals. The superoxide ion can participate in regenerating ferrous iron that is required for the Fenton reaction. An excess of iron is toxic due to its ability to engage in redox cycling and promote free radical formation. Super oxide anion generation; $O_2 \rightarrow \cdot O_2^-$. Hydrogen peroxide production; $\cdot O_2^- + 2H^+ + e\text{-} \rightarrow H_2O_2$. Haber-Weiss reaction; $H_2O_2 + O_2^- \rightarrow \cdot OH + OH^- + O_2$. Fenton reaction; $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$. Reduction to Fe(II); $Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2$. Ferritin is stable in iron-rich conditions, whereas it is rapidly degraded under conditions of iron starvation and ferritin degradation can be led. New blood vessel formation in angiogenesis is fundamental to tumor growth, invasion, and metastatic dissemination. Iron deficiency will lead to the dysfunction of immune system, metabolic disorders, myasthenia and anemia, whereas, excess iron also damages several vital organs. Thus, iron is essential for multiple cell functions, but is also potentially deleterious reasons of its ability to generate free oxygen radicals, iron balance by continuously recycling and reusing cellular iron, storage in ferritin, and export through ferroportin protecting cells from free iron toxicity. However the exact molecular mechanism involved on iron imbalance in development for tumor cells and the iron overload-mediated induction of apoptosis are required to be explored in future.

***Keywords*:** Ferrous and ferric ions, Ferroptosis, Ferritin, ROS, Iron deficiency and overload, Angiogenesis, Invasion and metastasis, Cancer and tumor cell death

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Abbreviations: ART = artesunate, **CRC** = colorectal cancer, **BMSCs** = bone marrow mesenchymal stem cells, **DEP** = deferiprone, **DFO** = desferoxamine, **DFT** = desferrithiocin, **DFX** = deferasirox, **DMT** = divalent metal transporter, **EMT** = epithelial to mesenchymal transition, **FAC** = ferric ammonium citrate, **FPN** = ferroportin, **FTL** = ferritin light chain, **FTH** = ferritin heavy chain, **HCC** = hepatocellular carcinoma, **HIF-1α,2α** = hypoxia inducible factor-1,2α, **HK** = high molecular weight kininogen, **IC_{50}** = half maximal inhibitory concentration, **MAPK** = mitogen-activated protein kinase, **MCF-7** = Michigan cancer fund 7, **MSCs** = mesenchymal stem cells, **NAF-1** = nutrient-deprivation autophagy factor 1, **Ndrg-1** = N-myc downstream regulated gene-1(iron-regulated Ndrg-1), **NRF2** = nuclear factor (erythroid-derived 2)-like 2, **p53** = proteins 53, **SCD** = sickle cell diseases, **TNBC** = triple negative breast cancer, **TNF-α** = tumor necrosis factor-**α, TfR** = transferrin receptor, **RAS** = rat sarcoma, **ROS** = Reactive oxygen species, **VEGF** = vascular endothelial growth factor.

1. INTRODUCTION

Iron is the most abundant transition metal in the human body of approximately 2～6 g. Of this, about 2.5 g is contained in the hemoglobin needed to carry oxygen through the blood, and most of the rest within approximately 2 g in adult men, and somewhat less in woman of childbearing age is contained in ferritin complexes that are present in all cells, but most common in bone marrow, liver, and spleen. Of the body's total iron content, about 400 mg is devoted to cellular proteins that use iron for important cellular processes like storing oxygen (myoglobin) or performing energy-producing redox reactions (cytochromes). A relatively small amount of 3～4 mg circulates through the plasma, bound to transferrin [1, 2]. Under physiological conditions, iron mainly exists in one of two readily interconvertible redox states; the reduced Fe^{2+} ferrous form (acts as an electron donor) and the oxidized Fe^{3+} ferric form (acts as an electron acceptor). Iron plays an important role in oxidative tissue damage and subsequent carcinogenesis.

Clinical features of iron overload are typical in hemochromatosis, iron induced carcinogenesis having expanded enormously. Iron is also potentially toxic, because, under aerobic conditions, it catalyses the propagation of reactive oxygen species (ROS) and the generation of highly reactive radicals through Fenton chemistry [3]. Studies with complicated problems occurring between iron and cancer that the role of iron in the cancer development, tumor microenvironment, iron deficiency and overload, etc., have been carried out, in which these new insights resolved may ultimately provide new therapeutic opportunities for treating cancer. In this review, firstly, the role of iron homeostasis, ferroptosis, ferritin in cancer is described. Secondly it will serve to elucidate prevention, malignant growth cell, inflammation and differentiation, angiogenesis, invasion and metastasis in cancer and tumor cells. Finally, it has become apparent that iron induced cancer and tumor cell death have been led.

2. IRON HOMEOSTASIS IN CERCINOGENESIS AND TUMORIGENESIS

Iron may function in tumor initiation, tumor growth, tumor microenvironment, and metastasis. Cellular iron homeostasis is controlled by iron uptake at the plasm membrane, eliciting balanced iron distributions among cellular compartments and iron export. In cancer cells, pathways involved in iron acquisition, trafficking, storage and regulation are all perturbed, in which iron metabolism is important for tumor cell survival. Additionally, iron can also contribute to DNA replication and repair processes, as well as cell cycle control in

cancer cells [4]. Iron has a pivotal role in homeostasis due to its participation in virtually all of the body's oxidation-reduction process, that redox cycling of iron is closely associated with the generation of ROS, in which non-protein-bind 'free' or 'catalytic' iron functions damage biomolecules. Iron is an essential nutrient utilized as a cofactor in enzymes for oxygen transport, oxidative phosphorylation, and metabolite oxidation. Therefore, biological utilization of iron is a tightly regulated process. The nuclear factor (erythroid-derived 2)-like 2 (NRF2) transcription factor, which can respond to oxidative and electrophilic stress, regulates several genes involved in iron metabolism [5]. Iron plays an important role for oxidative tissue damage and subsequent carcinogenesis, in which excess iron is a risk for cancer, presumably via generation of reactive oxygen species and clinical features of iron overload are typical in hemochromatosis [6]. Both deficiency and overload may cause such serious conditions in human as anemia and hemochromatosis.

Iron-induced oxidative tissue damage and subsequent carcinogenesis may be thought to be several iron transporters and hepcidin, a fine control of body iron stores, a peptide hormone regulating iron metabolism, and iron reduction by phlebotomy decreased cancer risk in the apparently normal population. These results warrant reconsideration of the role of iron for the carcinogenesis and the cancer prevention [6].

In homeostasis and tumorigenesis, a crucial feature of the biological activity of iron is the possibility to readily switch in a one-electron oxidation-reduction reaction between the ferrous form, Fe(II), and the ferric form, Fe(III). Under aerobic conditions, Fe(II) is readily oxidized in solution to Fe(III), which is virtually insoluble at physiological pH. Systemic iron levels and local increase in iron accumulation in tumors significantly impacts the progression of colorectal cancer (CRC), that is the third most common cause of cancer-related deaths in industrialized countries in which understanding the mechanisms of growth and progression of CRC is essential to improve treatment [7]. Thus, anti-TfR1 antibody for antitumor activity through inhibiting iron uptake, systemic decrease of iron for exacerbated anemia, the higher iron utilization by cancer cells for reducing iron content in the colon to limit the progression of colon tumor, and iron accumulation and progression in colon tumors are required to understand, in which these complicated facts can specifically restrict iron in the colon, and the development of pharmacological methods to modulate colon iron could have the potential to impact human CRC [7].

3. ROLE OF IRON FOR CANCER THERAPY AS FERROUS IRON IN CANCER AND FERROTOXIC DISEASE

Iron plays an important role in oxidative tissue damages and subsequent carcinogenesis. Clinical features of iron overload are typical in hemochromatosis, iron induced carcinogenesis having expanded enormously. Fine control of body iron stores would be a wise strategy for cancer prevention. Considering the recent report that iron reduction by phlebotomy decreased cancer risk in a supposedly normal population, complete understanding of iron-induced carcinogenesis should be considered a high priority for efficient cancer prevention [6]. The other, iron-chelators such as desferrithiocin (DFT) advance in iron-chelation therapy for the treatment of iron-overloaded diseases and cancer, as well as neurodegenerative and chronic inflammatory diseases [8]. DFT, a tridentate siderophore, is an orally effective iron chelator.

Iron also is target for cancer therapy and prevention, in which iron chelators are natural or synthetic small molecules that bind iron with a high affinity. Several iron chelators, such as desferoxamine (DFO), deferiprone and deferasirox are used clinically for the treatment of patients with iron overload disorders [9]. The avidity of cancer cells for iron has led to the question of whether iron chelators could be used in cancer therapy. The development of iron chelators or other iron-restrictive strategies as chemopreventives represents additional opportunities. Curcumin that is commonly used in curry and with a long history of use in traditional Indian Ayurvedic medicine, is a cancer chemopreventive and some of its activity may be attributable to its ability to chelate iron [9]. Curcumin has also served as potentially more potent synthetic chemopreventive agents and may account for its ability to prevent oral tumors [9]. High ferritin expression can enhance cell growth and improve resistance to oxidative stress in metastatic melanoma cells by interfering with their cellular antioxidant system.

4. FERROPTOSIS

Ferroptosis is a recently characterized form of non-apoptotic cell death, in which the oncogenic RAS-selective lethal small molecule erastin triggers a unique iron-dependent form of non-apoptotic cell death that we term ferroptosis [10]. The ferroptosis is dependent on intracellular iron, but not other metals, and is morphologically, biochemically and genetically distinct from apoptosis, necrosis and autophagy. The activation of ferroptosis by iron induced oxidative death due to creating a void in the antioxidant defenses of the cell results in the non-apoptotic destruction of certain cancer cells. While, inhibition of this process may protect organisms from neurodegeneration [10]. The process of ferroptotic death is characterized by the overwhelming, iron-depending accumulation of lethal lipid ROS. Unlike other forms of apoptotic and non-apoptotic death, this requirement for ROS accumulation appears to be universal [11].

Redox cycling is a characteristic of transition metals such as iron (Ferritin Fe^{3+} ⇄ Ferrous Fe^{2+}) and copper (Cupric Cu^{2+} ⇄ Cuprous Cu^{1+}). Iron is an essential metal involved in oxygen transport mediated by hemoglobin in mammals and the activity of various enzymes including catalase. Iron via the Fenton reaction can exacerbate the consequences of hydrogen peroxide (H_2O_2) production, leading to the generation of hydroxyl radicals. The superoxide ion can participate in regenerating ferrous iron that is required for the Fenton reaction. An excess of iron in the body is toxic due to its ability to engage in redox cycling and promote free radical formation.

Super oxide anion generation; $\mathbf{O_2 \rightarrow \cdot O_2^-}$
Hydrogen peroxide production; $\mathbf{\cdot O_2^- + 2H^+ + e^- \rightarrow H_2O_2}$
Haber-Weiss reaction [12]; $\mathbf{H_2O_2 + O_2^- \rightarrow \cdot OH + OH^- + O_2}$
Fenton reaction [3]; $\mathbf{Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH}$
Reduction to Fe(II); $\mathbf{Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2}$

Information on iron metabolism in breast cancer may also be used to improve breast cancer therapy [13]. Molecular biology of breast cancer plays a critical role in selecting the

optimal therapy for treating breast cancer patients. Breast cancer cells increase levels of intracellular iron through multiple pathways, including increased uptake and decreased efflux. The dependence of breast cancer on iron presents rich opportunities for improved prognostic evaluation and therapeutic intervention [13]. The other, the activation of apoptosis in nutrient-deprivation autophagy factor 1(NAF-1) becomes a major player in the metabolic regulation of breast cancer cells through its effects on cellular iron ions distribution, mitochondrial metabolism and the induction of apoptosis [14]. Ferroptosis is a new form of programmed cell death characterized by iron dependent increased in reactive oxygen species (ROS) [15]. Autophagy an intracellular catabolic process involving lysosomes that could lead to programmed cell death through extensive degradation of intracellular structures or organelles [15]. Iron is a requisite metal in almost all biological systems. It is required for numerous critical processes such as DNA synthesis, heme and iron-sulfur cluster synthesis. The levels of iron in the cell need to be tightly balanced, as an excess of iron can have damaging effects due to the generation of ROS. Exogenous application of iron oxide nanoparticles to cells in culture can lead to induction of autophagy due to ROS generation, in which addition of reactive iron also leads to increased ROS and autophagy. At 24 hours after treatment iron levels are increased corresponding to increased ROS and autosis [15]. Iron is required ferroptosis and iron mediated ROS could also lead to elevated and prolonged autophagy leading to autosis, where ferritin was partially dependent upon autophagy degradation [15]. Thus, ferroptosis and autophagy induced cell death occur independently, but both are mediated by iron dependent ROS generation in breast cancer cells.

5. FERRITIN

5. 1. Role of ferritin in cancer cells

Ferritin is a major iron storage protein essential to iron homeostasis. Ferritin plays a key protective role against oxidative stress due to its ability to sequester iron, and can protect normal and cancer cells. In cancer patients, elevated levels of ferritin are detected in the serum, and very high levels correlate with aggressive disease and poor clinical outcome. Ferric iron (Fe^{3+}) released from ferritin and hemosiderin is reduced to ferrous iron (Fe^{2+}) which, in presence of super oxide and hydrogen peroxide (H_2O_2), can catalyze the formation of the hydroxyl radical (·OH). ·OH is a powerful oxidizing agent which can promote lipid peroxidation, mutagenesis, DNA strands breaks, activation of oncogenes, and tumor suppressor gene inhibition. Recently, ferritin detected is involved in cell proliferation, angiogenesis, immunosuppression, iron delivery and iron storage.

In mammalian cells, the major iron storage protein is ferritin. Ferritin is a hollow, spherical-structured protein complex composed of 24 subunits. The H-ferritin subunit exhibits ferroxidase and antioxidant activity, which converts toxic ferrous ions into less toxic ferric ions. The other hand, L-ferritin has no ferroxidase activity but can modify the microenvironment to facilitate iron storage, in which the iron uptake process requires the cooperation of both H- and L-subunits. H-ferritin is abundant in muscle, brain, and heart, while L-ferritin is rich in liver and spleen [16]. The link between ferritin and many pathways related with cancer, such as cell proliferation, growth suppressor evasion, cell death inhibition, immortalization, immune-modification, angiogenesis, invasion and metastasis. Elevated ferritin in cancer cells may be related with cancer progression, resistance to

therapies, or poor prognosis. The roles of ferritin in cancer biology have been demonstrated that are sustaining proliferative signaling, resisting cell death, evading growth suppressors, inducing angiogenesis, immunosuppressive and microenvironment modification, enable replicative immortality, and activating invasion and metastasis [16]. An antagonistic role of ferritin in tumor necrosis factor-**α** (TNF-**α**) induced apoptosis, in which in cancer cells, both H- and L-ferritin were induced in response to TNF-**α** treatment. TNF-**α** -induced apoptosis in cancer cells was accompanied by a 2-fold increase in H- and L-ferritin and a decrease in transferrin receptor, two indices of increased iron availability [17]. The receptor for transferrin (Tf), referred to as TfR1 (also known as CD71), is ubiquitously expressed at low levels in most normal human tissues [18]. Iron supplementation and overexpression of H-ferritin or its mutant with an inactivated ferroxidase center reduced by about 50% the number of apoptotic cells after TNF**α**-treatment, while overexpression of L-ferritin was ineffective [17]. Anthracyclines as potent antitumor agents cause cardiotoxicity at high cumulative doses, owing to be attributed to their ability to avidly bind Fe iron. The effect of anthracyclines at inhibiting the ferritin iron mobilization pathway had been investigated, resulting in marked Fe accumulation within the molecule [19]. Thus, this response may have consequences in terms of the cytotoxic effects of anthracyclines.

5. 2. Ferritin degradation

Ferritin functions as the major iron storage protein in mammals and consists of 24 protein subunits that can store up to 4,500 atoms of iron per ferritin. There are two subunits of ferritin, ferritin heavy chain (FTH) and ferritin light chain (FTL). FTH has a ferroxidase function that can catalyze extracellular iron into nontoxic ferric iron form and store this form of iron in the ferritin complex. Ferritin is stable in iron-rich conditions, whereas it is rapidly degraded under conditions of iron starvation. Ferritin has been degraded either in lysosomes or by the proteasomes depending on the cellular stimulants [20]. Artesunate (ART) that is an anti-malaria drug and has shown to exhibit anti-tumor activity, is required for ART-induced cancer cell death [20], in which one major source of iron for the cytotoxicity of ART is attained from the degradation of ferritin by lysosomes. Thus, ART-induced cell death by focusing on lysosomal activation and ferritin degradation can be led.

5. 3. Ferritin heavy chain and ferritin light chain

Ferritin is a protein that binds to and stores iron. Ferritin serves as a critical component of iron homeostasis and requires the participation that is composed of the two subunits, the ferritin light chain (FTL, L-subunit, 19 kDa) and the ferritin heavy chain (FTH, H-subunit 21 kDa) [21]. The L-subunit facilitates stable iron storage in the ferritin core, while the H-subunit has ferroxidase activity, it is essential and sufficient for rapid iron uptake. It is differentially overexpressed in several malignancies including breast cancer, liver cancer, lymphoma, and pancreatic cancer. In breast tumor tissues, L-ferritin levels are 6-fold higher than surrounding benign breast tissue.

FTL was found to be an independent predictor for breast cancer and present in TAMs, in which TAMs are rich in ferritin and this has led to the hypothesis regarding the contribution of ferritin in cancer cell. Ferritin inhibition induces the sensitization of MCF-7 cells to doxorubicin, in which MCF-7 cells were treated with FTL and FTH siRNA [21]. Thus, ferritin exhibits proliferative activity in MCF-7 cells by promoting cell growth,

inhibiting doxorubicin-induced ROS formation, and suppressing the p21Cip/WAF1 expression with a high level-ferritin in the serum of breast cancer patients. The other, ferritin heavy chain of the ferritin complex has recently been identified as a favorable prognostic protein for triple negative breast cancer (TNBC) patients [22]. FTH1 is localized in both the cytoplasm and/or nucleus of cancer cells. High cytoplasmic FTH1 was associated with favorable prognosis, whereas nuclear FTH1 staining was associated with adverse prognosis. Blockade of cytoplasm-to-nucleus switching of FTH1 may suppress tumor metastasis and therefore serve as a potential therapeutic target for TNBC [22]. Furthermore, recently, FTH has been shown to be involved also in the control of cancer cell growth that analysis of public microarray databases in ovarian cancer revealed a correlation between low FTH expression levels and shorter survival, in which using a human cancer cell line SKOV3, the cancer proliferation, migration, and ability to cells with stem cell like properties (CSCs) propagation were monitored for a new role for FTH as a repressor [23]. Thus, new function of FTH is exerted through the regulation of a subset of miRNAs involved in cell migration and control of epithelial to mesenchymal transition (EMT).

5. 4. Transferrin (Tf) cell death

Transferrin receptor **(**TfR) displays multiple desirable characteristics for use in the targeting of cytoxic agents to cancer tissue in which TfR1 is a single pass type-Ⅱ transmembrain protein expressed at basal levels in most tissues. The TfR is an attractive molecule for the targeted therapy of cancer since it is upregulated on the surface of many cancer types and is efficiently internalized. These targeted therapies can cause cytotoxic effects including growth inhibition and induction of apoptosis in malignancies. The TfR also could be targeted for different therapeutic approaches, including the purging of cancer cells for autologous transplantation and for passive immunotherapy through agents that are directly cytotoxic or through the delivery of anticancer agents through receptor-mediated endocytosis [18]. Moreover, TfR in cancer cells has been essential role in cell growth and proliferation, and its overexpression by cancer cells, in which among the therapeutic agents used to target TfR1, antibodies stand out due to their remarkable specificity and affinity [24]. The therapies targeting TfR1 as direct therapeutics or delivery conduits remain an attractive alternative for the treatment of cancers that overexpress the receptor [24].

5. 5. Serum Ferritin

Serum ferritin is relatively iron-poor, that despite the absence of a conventional secretary, signal on ferritin L, it appears and serum ferritin L, and tissue ferritin L are encoded by the same gene, in which ferritin L was secreted from hepatocytes transfected with ferritin L cDNA via a classic secretory pathway [25].

Ferritin secretion into the medium of cultured cells is increased by iron and the cytokines interleukin-1-β （IL-1） and tumor necrosis factor-**α** (TNF-**α**). This enhanced secretion was blocked by co-treatment with dichlorofuranosylbenzimidazole (DRB), a specific transcriptional inhibitor, suggesting that these cytokines transcriptionally upregulate ferritin and its secretion [26]. Serum ferritin in malignant histiocytosis consists mainly of ferritin H. In neuroblastoma, an increase in serum ferritin has been directly linked to secretion of ferritin by the tumor. The amount or composition of ferritin secreted by tumors is not sufficient to change the overall composition of serum ferritin [25].

6. CANCER PREVENTION AND IRON CHELATION THERAPY

Prospects for the use of iron chelators in the treatment and prevention of the diseases appear greater that the iron chelators may be an effective therapy for prevention of the disease in which optimization of the use of dietary iron and iron supplements to block their iron-chelation activity, as well as careful balancing of overall nutritional demands and promising the use of iron chelation or iron mediated oxidative assault for the treatment or prevention of cancer [26]. Intracellular iron chelation prevents new DNA synthesis with inhibiting cell proliferation [27]. Structures of possible iron chelators are that tridentate ligands have three donor atoms and hexadentate ligands have six atoms, in which the coordinated iron requires six donor atoms in an octahedral configuration with the metallic ion in the middle [28]. Major iron chelators are desferrioxamine (DFO), deferasirox (DFX), deferiprone (DEP), and desferrithiocin (DFT) [28].

Fe^{3+} chelator DFO is known as inhibition of ability of ribonucleotide reductase to reduce ribonucleotides intact cells at concentrations in the micromolar range [27] that the use of iron chelation or iron mediated oxidative assault for the treatment or prevention of cancer appears. Iron-chelation therapy has its origins in the treatment of iron-overload syndromes that for many years, the standard for this purpose has been deferoxamine. Iron-overload generally occurs when total body iron excess 5 g that excess accumulation and storage of iron and iron-induced ROS production are occurred on increased risk of cancer. Carcinogenetic effects of excess iron are indicated that ROS of overproduction promote and maintain the oncogenic phenotype of cancer cells, and that ROS-activated signal-transduction pathways include the mitogen-activated protein kinase (MAPK) pathway, and the nuclear factor-**κ**B(NF-**κ**B) pathway, which impress transcription of genes involved in transformation and cell growth [29]. Hence, iron deprivation can be induced by iron chelators which play a role in the prevention and treatment of cancer in patients with iron overload. An iron deficiency-mediated pro-angiogenic environment could contribute to the high recurrence of breast cancer in young patients, and iron accumulation-associated pro-oxidant conditions could lead to the high incidence of breast cancer in older woman [30].

Understanding the role of this iron imbalance in breast cancer could lead to adjuvant therapeutic treatments, and potentially benefit patients by decreasing recurrence and increasing overall survival [31]. Practical chelation therapy is often used to remove excess stored iron and to reverse related complications [32], in which iron therapy is focused on treatment of patients with transfusional iron overload, however, a wider prospective is being taken with the use of DFX being investigated in a number of other conditions including hereditary haemochromatosis, characterized by progressive iron loading through increased intestinal iron absorption [32]. Iron chelators of intestinal HIF-2**α**/divalent metal transporter-1(DMT-1), chronic hepatitis B (CHB), iron and ferritin of iron overload, aurintricarboxylic acid (ATA) and DFO inhibit decreasing tissue-iron accumulation, the liver cell, mesenchymal stem cells(MSCs), and MCF-7 in accumulation, disorder, of excess iron via the induction of ferritin [33-36]. However, in order to avoid both the iron deficiency and the iron overload, iron availability is tightly regulated at both the cellular and systemic levels that the hepcidin-ferroportin (FPN) axis is essential to maintaining iron homeostasis, in which the liver peptide hepcidin controls iron flux to plasma from enterocytes and macrophages through degradation of the cellular iron exporter FPN [37].

7. MALIGNANT CELL GROWTH, INFLAMMATION, PROLIFERATION AND DIFFERENTIATION

Iron and its homeostasis are intimately tied to the inflammation. The key roles of iron and iron proteins in cell proliferation make them potential targets for cancer therapy. However, clinical trials directed toward perturbation of tumor iron homeostasis by iron chelation have been limited to the use of deferoxamine (DFO). A novel iron chelator 311 (2-hydroxy-1-naphthyladehyde benzoyl hydrazone) inhibited the growth of CCRF-CEM cell in a time- and concentration-dependent fashion with half maximal inhibitory concentration IC_{50} that was about 20-fold lower than that of DFO, in which 311 also inhibited the growth of breast, bladder, and head and neck cancer cell lines [38]. This iron chelator of the pyridoxal isonicotinoyl class inhibits malignant cell growth. Increased dietary iron intake and elevated systemic iron levels are associated with increased cancer risk, in which a molecular explanation for the tumor-promoting effects of iron is provided as an unexpected link between intracellular iron accumulation and pro-inflammatory signaling [39]. Identifying divalent metal transporter 1 (DMT1) as important modifier of the inflammatory response during colonic tumorigenesis provides further support for the rationale to target signaling pathways such as Janus kinase/Signal Transduction and Activator of Transcription (JAK/STAT3) in colorectal cancer (CRC) therapy. Moreover, DMT1 represents an attractive targetable candidate to inhibit cell proliferation and to prevent the formation of an inflammatory microenvironment in sporadic cancers that arise in the absence of an overt chronic inflammation [39]. Serum ferritin is an important inflammatory disease marker that arises from damaged cells, and is thus a marker of cellular damage, in which the level of serum ferritin correlates with numerous inflammatory and degenerative diseases [40].

Anemia is a common complication in patients with inflammatory diseases and cancer that focuses on the controversies around management with the Erythropoietic Stimulating Agents (ESAs) and the adjuvant use of iron in anemia management [41]. Anemia of inflammation also and inflammatory chronic diseases are profoundly influenced by iron status, in which increased iron stores are correlated with markers of chronic inflammation and other well-established risk factors of diabetes, obesity, and metabolic syndrome [42]. Thus, potential benefits of treatment to ameliorate the hypo- ferremic condition promoted by inflammation are considered [42].

8. ANGIOGENESIS

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a pathophysiological process necessary for tumor growth and metastases, in which it is a carefully orchestrated process that is regulated by the balance between pro- and antiangiogenetic factors [43]. Increasing the intracellular iron levels will have an opposite, anti-angiogenic effect, in which perturbing iron homeostasis in endothelial cells using a unique form of iron, Ferric Ammonium Citrate (FAC). FAC is a cell-permeable form of iron, and inhibits VEGF-induced endothelial cell proliferation, migration, tube formation and spouting, that cell-permeable iron attenuates Vascular Endothelial Growth Receptor-2 (VEGR-2) mediated signaling and inhibits tumor angiogenesis [43]. Ferritin, which is elevated during inflammation and malignancy, may play a role in regulating the levels of

angiogenesis in these conditions, in which exhibits high-affinity binding to 2-chain high molecular weight kininogen (HKa) that is markedly different in structure and function from its parent protein high molecular weight kininogen (HK) [44]. Ferritin binds to a 22-aa subdomain of HKa that is critical to its antiangiogenic activity. Ferritin opposed HKa's antiangiogenic effects in a prostate cancer xenograft, restoring tumor-dependent vessel growth, in which ferritin-mediated regulation of angiogenesis represents a new angiogenic regulatory pathway, and identifies a new role for ferritin in cell biology [44]. Iron deficiency contributes to the poor outcome by promoting the hypoxia inducible factor-1**α** (HIF-1**α**) and VEGF formation. Cellular iron deficiency increased HIF-1, VEGF, and angiogenesis, suggesting that systemic iron deficiency might play an important part in the tumor angiogenesis and recurrence in this young age group of breast cancer patients [45]. Iron deficiency and overload on angiogenesis play important roles in menopause-related breast cancer outcomes. Iron deficiency that significantly promotes VEFG by stabilizing hypoxia HIF-1, conversely, high iron levels increase oxidative stress and sustain mitogen-activated protein kinase (MAPK) activation, which are mechanisms of known significance in breast cancer development [30]. Thus, an iron deficiency-mediated pro-angiogenic environment could contribute to the high recurrence of breast cancer in young patients, and iron accumulation-associated pro-oxidant conditions could lead to high incidence of breast cancer in older woman.

Baicalein containing a strong chelator for iron Fe(II) with a stoichiometry of ∼3:2 as enzyme, acts initiated at the level of HIF-specific hydrolases, and its proangiogenic effects, that confirm the feasibility of a novel approach for therapeutic angiogenesis in which neovascularization is achieved by use of a small molecule. Thus, this baicalein suppresses ubiquitination of HIF-1α, promotes new blood vessel formation, and leads to induction of HIF-1-mediated reporter gene activity and target gene transcription in tissue culture cells [46]. The spread of cancer cells and growth of localized tumors beyond a few millimeters in size requires local angiogenesis in which tumor cells produce new blood vessels by releasing pro-angiogenic chemical signals that tumors like brain, lung, and liver can co-opt and grow along existing vessels without evoking new vessel growth. Local neovascularization supplies growing tumors with oxygen and essential nutrient, supports tumor extension and invasion into nearby normal tissue, and is essential to distant metastasis. Effective inhibition of tumor angiogenesis might arrest or halt tumor progression but would not eradicate the tumor as a stand-alone therapy, especially with a single mechanism anti-angiogenic agent, in which the combination of an angiogenesis agent and chemotherapy might be essential for effective tumor treatment [47]. New blood vessel formation in angiogenesis is fundamental to tumor growth, invasion, and metastatic dissemination. The vascular endothelial growth factor (VEGF) signaling pathway plays pivotal roles in regulating tumor angiogenesis in which the current status of tumor therapeutic agents targeting to VEGF and the applications of VEGF related molecular imaging are summarized [48].

9. INVASION AND METASTASIS

Tissue invasion is an important determinant of angiogenesis and metastasis that constitutes an attractive target for cancer therapy in which the identified agents inhibit invasion by mechanism other than inhibition of cell attachment or cytotoxicity. The novel

concept of stromal therapy, namely the protection of stromal cells against the dominating influence of tumor cells in tumor-stroma interaction by antioxidants and micronutrients, may form the basis for prevention of mesenchymal-mesenchmal transition (MMT) in strategies for chemoprevention of tumor invasion [49]. Molecular tissue invasion and metastasis have been studied as explored potential targets in tackling metastasis and also potential methods, including phytochemicals, small molecule inhibitors and natural compounds in devising new strategies for treating metastasis [50].

A recently identified metastasis suppressor, N-myc downstream regulated gene-1(iron-regulated Ndrg-1) has been shown to reduce the invasion and metastasis of breast, colon, prostate and pancreatic cancer. This iron-regulated metastasis suppressor Ndrg-1 reduces the protein level of cathepsin C which plays a role in invasion, indicating a potential mechanism of its anti-metastatic role in pancreatic cancer cells, suggesting a potential pathway for the anti-proliferative effects [51].

Further, novel thiosemicarbazone iron chelators induce up-regulation and phosphorylation of the metastasis suppressor N-myc down-stream regulated gene-1 and inhibit the growth of pancreatic cancer xenografts that molecular effectors of a novel and potent antitumor agent could be useful for pancreatic cancer treatment [52]. The iron chelator Dp44mT up-regulated Ngrg-2, suppressed epithelial-mesenchymal transition(EMT) and inhibited tumor metastasis in hepatocellular carcinoma (HCC) having high metastatic potential [53], as used a promising therapeutic approach in HCC.

10. IRON INDUCED CANCER CELL DEATH

A new form of cell death, ferroptosis, was recently discovered, in which ferroptosis results from iron-independent liquid peroxide accumulation and is characterized mainly by cell volume shrinkage and increased mitochondrial membrane density without typical apoptotic and necrotic magnification [54].

Ferroptosis is a form of iron-dependent cell death involving the production of reactive oxygen species. Specific mechanism involved in ferroptosis, including depletion of glutathione and inhibition of glutathione peroxidase 4, have been uncovered. Ferritinography is a newly identified mechanism for degradation of the iron storage protein ferritin [54]. The apoptosis pathways elicited by tumor necrosis factor (TNFα) in HeLa cells involve modifications of cellular iron homeostasis, and that H-ferritin participates in the pathways independently from its ferroxidase activity [17].

Tumor hypoxia has long been associated with resistance to radiation therapy. Moreover, the expression of hypoxia inducible factors HIF1α and HIF2α correlates with poor prognosis in many tumors, in which specifically, inhibiting HIF2α expression augments p53 activity, increases apoptosis, and reduces donogenic survival of irradiated and non-irradiated cells [55]. Artesunate (ART) that has been shown to exhibit anti-tumor activity, accumulates in lysosomes and promotes lysosomal function and ferritin degradation, leading to mitochondria reactive oxygen species production and eventually cell death [20].

Ferroptosis is significantly distinct at morphological, biochemistal, and genetic levels from other form of cell death such as apoptosis and necrosis [56]. Although increased intracellular iron levels can promote proliferation, iron can promote cell death, however, the mechanism remains unclear.

Ru360 of an inhibitor of the mitochondrial calcium uniporter reversed mitochondrial changes and restored cell survival in ovarian carcinoma cells treated with iron, that cells treated with Ru360 and iron also had induced autophagic punctae with increased lysosomal numbers, implying cross-talk between these compartments. Iron in modulating cell survival in a mitochondria-dependent manner in ovarian cancer cells, in which intercellular iron can promote cell death [57].

The other hand, ferroptosis and autophagy induced cell death occur independently, but both are mediated by iron dependent ROS generation in breast cancer cells, in which siramesine and lapatinib initially induced ferroptosis but changes to an autophagy induced cell death after 24 hours. Furthermore, decreased expression of the iron storage protein, ferritin was partially dependent upon autophagy degradation and the intracellular iron level increased in a time dependent manner following treatment accompanied by an increase in ROS [6615]. Tumor cell death mechanism has a molecular basis for the conserved tumoricidal effect of nucleotide-binding proteins as Human Alpha-lactalbumin Lethal to Tumor cells (HAMLET) targets, suggesting that dysregulation of the ATPase/kinase/GTPase machinery contributes to cell death, following the initial, selective recognition of HAMLET by tumor cell [58]. Iron deficiency will lead to the dysfunction of immune system, metabolic disorders, myasthenia and anemia, whereas, excess iron also damages several vital organs such as the liver, heart and bone.

In clinical studies, iron overload is associated with numerous diseases such as hemochromatosis, liver injury, diabetes, mellitus, cardiovascular diseases and arthritis [59]. Iron overload contributes to the dysfunction of these organs that melatonin may prevent its toxicity and exposure to increased concentrations of ferric ammonium (FAC) induced a gradual increase of intracellular iron level in bone marrow mesenchymal stem cells (BMSCs). Melatonin protects BMSCs against FAC-induced apoptosis and necrosis, and intracellular ROS increase by iron overload [59]. The effects of transfused sickle cell diseases (SCD) [60], osteoblastic cell death [61], apoptotic cell death [62], and molecular fibrogenesis [63] could be promoted and relieved by iron overload process, however the exact molecular mechanism involved in the iron overload-mediated induction of apoptosis in such as osteoblasts etc. have not been explored.

Thus, iron is essential for multiple cell functions, but is also potentially deleterious reasons of its ability to generate free oxygen radicals that owing to the lack of an active excretory mechanism, iron balance in mammals is maintained by limiting its intestinal uptake and by continuously recycling and reusing cellular iron, in which binding to chaperone proteins, storage in ferritin, and export through ferroportin (FPN) protect cells from free iron toxicity. Recently, important roles of the FPN-hepcidin [64, 65] and FPN-zinc finger protein[66] have been affecting cancer growth and metastasis due to inhibition of cellular efflux of iron by binding to FPN and causing its subsequent degradation, providing new evidence to understand the contribution of cancer cell death.

As mentioned-above, it is represented in **Table 1** that anti-cancer activity reactions of ferrous and ferric ions in initiation, progression, proliferation, angiogenesis, invasion, and metastasis against cancer and tumor cells are summarized by redox reaction of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions through ROS generation.

Table 1. Anti-cancer activities of iron-induced initiation, progression, proliferation, angiogenesis, invasion, and metastasis by redox reaction of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions against cancer and tumor cells

Fe^{2+}, Fe^{3+} Ions	**Progression and Growth of Cancer and Tumor Cells**				
	Prevention	Promotion	Progression	Proliferation and Invasion	Metastasis Angiogenesis
	Carcinogenesis	Tumorigenesis-initiation	Oncogenes Malignant cell formation	Angiogenesis Invasive growth Cell migration	Transendothelial migration
Fe^{3+} →	Fe^{3+} or Fe^{2+}	Fe^{3+}, Fe^{2+} O_2^-, H_2O_2	Fe^{2+}, Fe^{3+} O_2^-, ·OH, H_2O_2 , OOH^-	Fe^{3+}, Fe^{2+} O_2^-, ·OH, H_2O_2 Anti-angiogenesis	Fe^{2+}, Fe^{3+} ·OH, H_2O_2 Anti-angiogenesis
or			·ROS product ·Ferritin degradation inhibits tumor progression ·Malignant cell killing via ROS	·ROS product ·Anti-angiogenesis by cell-permeable iron ·Autophagy and fusion protein ·DNA damage ·ROS generation to inhibit tumor invasive growth ·Ferritin inhibits blood vessel formation & tumor angiogenesis	·ROS product ·Inhibitor of angiogenesis and anti-metastatic effects by ferritin Fenton reaction
Fe^{2+}	·Fe^{3+}-chelator DFO prevention ·Green tea and iron overload	·ROS product ·Activation of ferrotopsis inhibits initial tumor formation and growth ·$O_2 + e \rightarrow O_2^-$ ·$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$ ·$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$	·Haber-Weiss reaction: ·$H_2O_2 + O_2^- \rightarrow$ ·OH + OH^- + O_2 ·Fenton reaction: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- +$ ·OH	·$H_2O_2 + O_2^- \rightarrow$ ·OH + OH^- + O_2 ·$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$	·$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- +$ ·OH ·$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$ Iron-regulated Ndrg-1, iron chelator Dp44mT reduce the invasion and metastasis of breast, colon, prostate and pancreatic cancer.

11. CONCLUSIONS

The ferroptosis is dependent on intracellular iron, but not other metals, and is morphologically, biochemically and genetically distinct from apoptosis, necrosis and autophagy. The activation of ferroptosis by iron induced oxidative death due to creating a void in the antioxidant defenses of the cell results in the non-apoptotic destruction of certain cancer cells. While, inhibition of this process may protect organisms from neurodegeneration. The process of ferroptotic death is characterized by the overwhelming, iron-depending accumulation of lethal lipid ROS. Unlike other forms of apoptotic and non-apoptotic death, this requirement for ROS accumulation appears to be universal. Redox cycling is a characteristic of transition metals such as iron (Ferritin Fe^{3+} ⇄ Ferrous Fe^{2+}). Iron is an essential metal involved in oxygen transport mediated by hemoglobin in mammals and the activity of various enzymes including catalase. Iron via the Fenton reaction can exacerbate the consequences of hydrogen peroxide (H_2O_2) production, leading to the generation of hydroxyl radicals. The superoxide ion can participate in regenerating ferrous iron that is required for the Fenton reaction. An excess of iron in the body is toxic due to its ability to engage in redox cycling and promote free radical formation.

Super oxide anion generation; $\mathbf{O_2 \rightarrow \cdot O_2^-}$

Hydrogen peroxide production; $\mathbf{\cdot O_2^- + 2H^+ + e^- \rightarrow H_2O_2}$

Haber-Weiss reaction; $\mathbf{H_2O_2 + O_2^- \rightarrow \cdot OH + OH^- + O_2}$

Fenton reaction; $\mathbf{Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH}$

Reduction to Fe(II); $\mathbf{Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2}$

Ferritin is stable in iron-rich conditions, whereas it is rapidly degraded under conditions of iron starvation. Ferritin has been degraded either in lysosomes or by the proteasomes depending on the cellular stimulants. Artesunate (ART) that is an anti-malaria drug and has shown to exhibit anti-tumor activity, is required for ART-induced cancer cell death, in which one major source of iron for the cytotoxicity of ART is attained from the degradation of ferritin by lysosomes.

The spread of cancer cells and growth of localized tumors beyond a few millimeters in size requires local angiogenesis in which tumor cells produce new blood vessels by releasing pro-angiogenic chemical signals, that tumors like brain, lung, and liver can co-opt and grow along existing vessels without evoking new vessel growth. Local neovascularization supplies growing tumors with oxygen and essential nutrient, supports tumor extension and invasion into nearby normal tissue, and is essential to distant metastasis. New blood vessel formation in angiogenesis is fundamental to tumor growth, invasion, and metastatic dissemination. A recently identified metastasis suppressor, N-myc downstream regulated gene-1(iron-regulated Ndrg-1) has been shown to reduce the invasion and metastasis of breast, colon, prostate and pancreatic cancer. This iron-regulated metastasis suppressor Ndrg-1 reduces the protein level of cathepsin C which plays a role in invasion, indicating a potential mechanism of its anti-metastatic role in pancreatic cancer cells, suggesting a potential pathway for the anti-proliferative effects.

Iron deficiency will lead to the dysfunction of immune system, metabolic disorders, myasthenia and anemia, whereas, excess iron also damages several vital organs such as the liver, heart and bone. Iron overload contributes to the dysfunction of these organs that melatonin may prevent its toxicity and exposure to increased concentrations of ferric ammonium (FAC) induced a gradual increase of intracellular iron level in bone marrow mesenchymal stem cells (BMSCs). Melatonin protects BMSCs against FAC-induced apoptosis and necrosis, and intracellular ROS increase by iron overload. The effects of transfused sickle cell diseases (SCD), osteoblastic cell death, apoptotic cell death, and molecular fibrogenesis could be promoted and relieved by iron overload process, however the exact molecular mechanism involved in the iron overload-mediated induction of apoptosis in such as osteoblasts etc. have not been explored. Further, research on iron imbalance in development and progression for cancer and tumor cells should become necessary in future.

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