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Mini-review

Iron and lung cancer

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ABSTRACT

Iron is an essential trace element in the human body, and its deficiency or excess induces diverse biological processes. Iron dysregulation is closely associated with the initiation and development of several malignant tumors, including lung cancer. Emerging evidence suggests a particularly important role for iron in lung cancer. Moreover, iron plays a prominent part in multiple forms of cell death, making it important for the development of potential strategies for lung cancer therapy. Here we review the function and characteristics of iron and new therapeutic opportunities in lung cancer.

1. Iron metabolism and function

Dietary iron is mainly ferric iron (Fe^{3+}), which is reduced to ferrous iron (Fe^{2+}) and absorbed into cells through the coordination of reductases such as duodenal cytochrome *b* (DCYTB) and divalent metal transporter 1 (DMT1) on intestinal epithelial cells. Absorbed Fe^{2+} is discharged from intestinal epithelial cells through ferroportin on the basolateral surface, and the oxidase hephaestin oxidizes it to Fe^{3+}, which binds to transferrin (TF) and is transported to various tissues and organs. Circulating TF-Fe^{3+} is absorbed into cells through transferrin receptor 1 (TFR1). Fe^{3+} is released in the endosome, reduced to Fe^{2+} by Six-transmembrane epithelial antigen of prostate 3 (STEAP3), and transferred into the cytoplasm through DMT1. Fe^{2+} in the cytoplasm, termed the labile iron pool, is metabolically active and plays a role in a variety of biological functions. Excess iron can be stored in ferritin or be discharged from the cell through ferroportin, where it is oxidized into Fe^{3+} and binds to TF in the bloodstream (Fig. 1) [1].

Excess systemic iron induces hepcidin secretion by the liver. Hepcidin binds to ferroportin and triggers its degradation, decreasing iron efflux from cells. Conversely, when systemic iron levels are low, hepcidin secretion is decreased and iron efflux is increased [2]. Cellular iron homeostasis is mainly regulated post-transcriptionally. Iron-responsive element-binding proteins (IRP1 and IRP2) bind to iron-responsive elements (IREs) in either the 5′ or 3’ untranslated region of mRNA. Thus, the corresponding protein synthesis is controlled. Proteins involved in iron import (TFR1, DMT1), iron storage (FT), and iron export (ferroportin) are regulated in this manner [1].

Iron is an essential trace element for the activity of many proteins and enzymes. Iron-containing proteins are essential for diverse biological processes, including cellular respiration, oxygen sensing, oxygen transport and metabolism, energy metabolism, DNA synthesis and repair, and signaling [3]. In addition, iron increases intracellular generation of reactive oxygen species (ROS) via the Fenton reaction, which is a chemical reaction between ferrous iron and hydrogen peroxide that produces a hydroxyl radical (Fig. 1). Ferric iron generated by the Fenton reaction can be reduced to ferrous iron by superoxide, which is a by-product of cellular respiration, and undergoes further Fenton reaction. Lipid ROS formation can also be catalyzed by iron. ROS generation is closely associated with initiation and development of cancer and multiple forms of cell death [2].

2. Iron in lung cancer

Previous studies reported that iron dysregulation is closely associated with the initiation and development of lung cancer. Systemic iron dysregulation is commonly seen in cancer patients [4]. Interleukin 6 (IL-6), which is reportedly elevated in lung cancer patients and associated with lung carcinogenesis and poor patient survival [5–9], can upregulate hepcidin, decreasing iron efflux from cells and inducing cancer-related anemia [4]. Iron restriction by IL-6 may induce intracellular iron accumulation. This accumulation occurs frequently in cancer cells via alterations in iron metabolism, including increased iron import and storage, decreased iron export, or both (Fig. 2A) [2]. Expression of TFR1 and ferritin is reportedly elevated in 88% and 62% of NSCLC patients, respectively. An elevated serum ferritin level was observed in both NSCLC and SCLC patients [10,11]. Somatic mutation in

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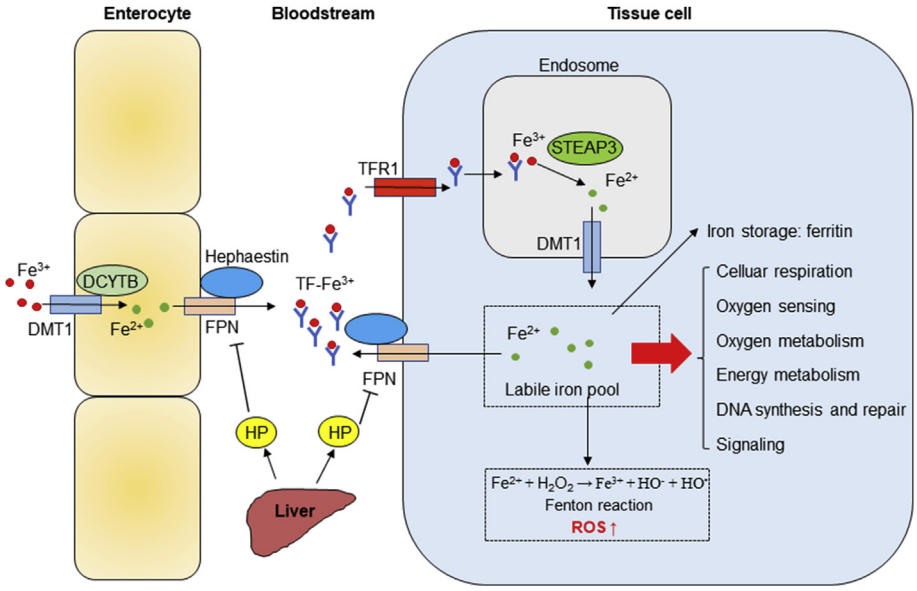

Fig. 1. Iron metabolism

Dietary iron mainly comprises ferric iron (Fe^{3+}), which can be reduced to ferrous iron (Fe^{2+}) and absorbed into cells through the coordination of reductases, such as duodenal cytochrome *b* (DCYTB), and divalent metal transporter 1 (DMT1), present on intestinal epithelial cells. Absorbed Fe^{2+} is discharged from the intestinal epithelial cells through ferroportin (FPN) on the basolateral surface, and the oxidase hephaestin oxidizes Fe^{2+} to Fe^{3+}, which then binds to transferrin (TF) and is transported to various tissues and organs. Circulating TF-Fe^{3+} is absorbed into cells through transferrin receptor 1 (TFR1), Fe^{3+} is released into the endosome and reduced to Fe^{2+} by STEAP3, and then transferred into the cytoplasm through DMT1. The Fe^{2+} in the cytoplasm are metabolically active (labile iron pool). Fe^{2+} in the labile iron pool have a variety of biological functions. Excess iron can be stored in ferritin or can be discharged out of the cell through FPN, oxidized into Fe^{3+}, and then bound to TF in the bloodstream. Excess systemic iron induces hepcidin (HP) secretion by the liver. HP binds to FPN and triggers its degradation, thus decreasing iron efflux from cells. In addition, iron increases intracellular generation of reactive oxygen species (ROS) via the Fenton reaction, which is a chemical reaction between ferrous iron and hydrogen peroxide producing a hydroxyl radical.

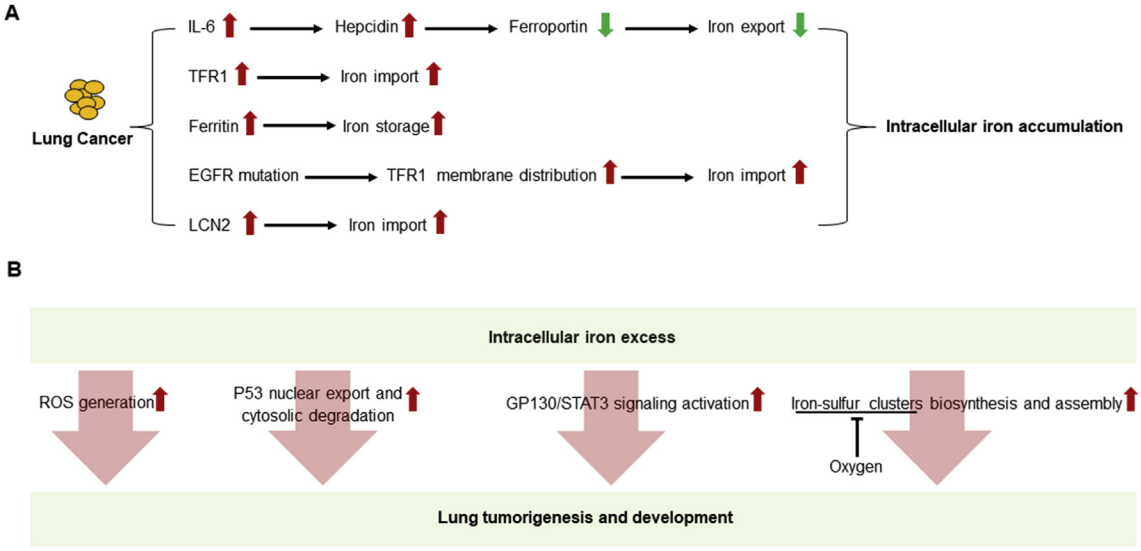

Fig. 2. Iron in lung cancer

(**A**) Interleukin-6 (IL-6), which is reportedly elevated in lung cancer, upregulates hepcidin, decreasing ferroportin and iron export. Transferrin receptor 1 (TFR1) and lipocalin-2 (LCN2) are upregulated in lung cancer, increasing iron import. *EGFR* mutation commonly occurs in non-small cell lung cancer, and regulates redistribution of TFR1, increasing iron import. Ferritin is upregulated in lung cancer, increasing iron storage. Owing to the above characteristics, intracellular iron accumulation is commonly observed in lung cancer. (**B**) Intracellular iron excess has the potential for promoting lung tumorigenesis and tumor development: Iron increases generation of reactive oxygen species (ROS); iron triggers P53 nuclear export and cytosolic degradation; iron promotes activation of GP130/STAT3 signaling; iron is involved in the biosynthesis and assembly of iron-sulfur clusters, and oxygen can trigger the degradation of iron-sulfur clusters.

EGFR frequently occurs in NSCLC [12–14]. It was recently reported that EGFR regulates iron homeostasis though redistribution of TFR1, increasing cellular iron import and promoting the development of lung cancer. EGFR activation is positively correlated with membrane TFR1 expression and iron level in NSCLC [15]. Besides cellular iron import by TF-TFR1, there is an alternative mechanism of iron acquisition mediated by lipocalin-2 (LCN2). LCN2 forms a complex with mammalian siderophores and binds to its receptor to deliver iron into cells [16]. It was reported that LCN2 expression is significantly increased in NSCLC and might be used as a potential biomarker of early stage lung carcinogenesis [17]. In addition, LCN2 is associated with radioresistance of lung cancer [18].

There are some controversies in epidemiological studies of iron and lung cancer risk (Table 1). Chen et al. showed serum iron levels had no significant association with lung cancer risk [19]. Muka et al. showed high intake of iron was associated with reduced risk of lung cancer [20]. Conversely, many epidemiological studies reported that high dietary iron intake significant increased the risk of lung cancer [2,21–27]. These disagreements might be attributed to different populations and different clinical stages of lung cancer. As previously mentioned, intracellular iron accumulates in lung cancer; however, this does not exclude systemic iron reduction at advanced stages of lung cancer. All these factors could impact analysis of the relationship between iron and lung cancer risk. The iron level and iron related parameters at early stages of lung cancer should be assessed in the future. Consistent with most epidemiological data, many experimental studies

Table 1
Epidemiological studies of iron and cancer.

Reference	Number and type of studies	Observation target	Summary relative risk or odds ratio (95% confidence interval) for cancer incidence
KNEKT et al. [21]	1 cohort study	TIBC	Men: 0.69 (0.52–0.91) Women:0.19 (0.02–1.51)
		Transferrin saturation	1.51 (0.98–2.32)
Yang et al. [22]	23 case–control and 11 cohort studies	Red meat intake	1.34 (1.18–1.52)
Xue et al. [23]	6 cohort and 28 case–control studies	Red meat intake	1.44 (1.29–1.61)
Gnagnarella et al. [24]	14 prospective studies	Red meat intake	1.24 (1.01–1.51)
Fonseca-Nunes et al. [25]	1 case–control and 3 prospective studies	Heme iron intake	1.12 (0.98–1.29)
Sukiennicki et al. [26]	1 case–control study	Serum iron	2.38 (1.26–4.51)
		Ferritin	2.65 (1.39–5.03)
		TIBC	2.32 (1.31–4.11)
Ward et al. [27]	1 case–control and 1 prospective study	Heme iron intake	1.16 (1.02–1.32)
Muka et al. [20]	1 prospective study	Iron intake	0.58 (0.37–0.92)

have found a close association between iron and cancer. It was reported that a high-iron diet promotes spontaneous colorectal tumorigenesis and mammary tumor growth in mice [28,29]. In contrast, a low-iron diet decreased tumor growth in mice [30]. Iron chelators inhibited human lung tumor xenografts [31]. In addition, a low-iron diet or the use of iron chelators protected cigarette-smoke-induced chronic obstructive pulmonary disease (COPD) [32], which is related to a 4.5-fold higher incidence of lung cancer than in the general population [33].

Some mechanism studies revealed a relationship between iron and lung cancer (Fig. 2B). Iron reportedly induces cancer stem cells and aggressive phenotypes through ROS generation in human lung cancer cells [34]. Shen et al. found that iron-excess-associated tumorigenesis may be attributed to heme-p53 interaction. Iron polyporphyrin heme binds to p53, triggering nuclear export and cytosolic degradation, promoting tumorigenesis [35]. Our group found that iron promotes lung carcinogenesis via GP130/STAT3 signaling. Iron promotes cyclin-dependent kinase 1 (CDK1) activity and triggers 4E-BP1 phosphorylation, promoting GP130 cap-dependent translation and activation of downstream STAT3 signaling [36]. Furthermore, Fe^{2+} from the labile iron pool is transported into the mitochondria and is involved in the biosynthesis of iron-sulfur clusters, which are essential for the activity of diverse proteins. It was recently reported that the iron-sulfur cluster biosynthetic enzyme NFS1 is particularly important for lung tumor growth and survival [37]. Compared with the 3–8% oxygen concentration typical of most tissues, lung tumors suffer at a higher oxygen concentration, which triggers the degradation of iron-sulfur clusters and increases the demand for their biosynthesis. NFS1 suppression in lung tumors inhibits cell proliferation because the biosynthetic machinery cannot meet the increased demand caused by oxygen-mediated damage to iron-sulfur clusters [37]. In addition, cytosolic iron-sulfur assembly is also reportedly associated with lung tumorigenesis. Cytosolic iron-sulfur assembly pathway inhibition reduces the activity of DNA repair enzymes, decreasing DNA repair capacity, increasing mutational burden, and contributing to lung tumorigenesis [38].

3. Iron and cell death

Iron plays a prominent role in multiple forms of cell death, including apoptosis, necroptosis, ferroptosis, and ascorbate-mediated death (Fig. 3) [2].

Iron deprivation induced by iron chelators or IRP2 knockdown reportedly induces apoptosis [39–41]. Intriguingly, iron excess also induces apoptosis [42]. Iron increases ROS generation via the Fenton reaction; ROS may contribute to the release of cytochrome *c* in response to apoptotic stimuli via oxidizing cardiolipin in mitochondria [43]. Furthermore, mitochondrial ROS generation may amplify apoptotic signaling through caspase activation [44]. Iron can also regulate the extrinsic apoptosis pathway through Serine/arginine-rich splicing factor 7 (SRSF7)-mediated alterative splicing of Fas, which is a critical death receptor. Excess iron suppresses the activity of SRSF7, inducing production of soluble and antiapoptotic Fas through alterative splicing [2].

Necroptosis is a programmed form of cell death, characterized by cellular swelling and plasma membrane rupture [45]. Excess iron induces necroptosis [46,47]. In addition, similarly to apoptosis, necroptosis can also be induced by Fas-FasL binding [48], suggesting that iron can also regulate necroptosis through SRSF7-mediated alterative splicing of Fas.

Ferroptosis is an iron-dependent form of cell death induced by lipid peroxide generation, which might be exploited to selectively destroy RAS-mutant tumor cells [49,50]. Intracellular iron depletion by the iron chelator DFO or ROS inhibition by Fer-1 can inhibit ferroptosis [50]. Conversely, ferric ammonium citrate, iron chloride hexahydrate, or iron-bound TF increase intracellular iron levels and the sensitivity of ferroptosis [50,51]. Studies have already revealed that ferroptosis is regulated by amino acids (e.g., cysteine, α-ketoglutarate), lipid metabolism (e.g. Long-chain-fatty-acid–CoA ligase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3)), iron metabolism (e.g., nuclear receptor coactivator 4 (NCOA4) and IREB2), and several other metabolic pathways (e.g., coenzyme Q10 and NADPH) [49]. However, the role and mechanism of iron in ferroptosis is still unclear. Although iron can induce ROS generation via the Fenton reaction and contribute to lipid ROS generation, increased ROS generation by other mechanisms, such as H_2O_2, does not induce ferroptosis [50]. Numerous questions regarding the mechanism of action and application of iron in ferroptosis remain unanswered.

Ascorbate-mediated death is similar to ferroptosis in several ways, including iron dependency, production of ROS, lipid peroxidation, caspase independency, and the possible involvement of autophagy [52]. Iron therefore plays an important role in ascorbate-mediated death, similar to ferroptosis. However, ascorbate-mediated death is still distinct from ferroptosis, as selective inhibitors of ferroptosis failed to inhibit ascorbate-mediated death [52].

4. Iron and lung cancer therapy

Based on the above-mentioned characteristics of iron in lung cancer and the relationship between iron and different forms of cell death, it is conceivable that there are primarily three iron-related tumor therapy strategies: iron deprivation, iron overload, and iron homeostasis (Table 2).

Iron is an essential trace element, and iron deprivation induces apoptosis [39–41]. However, iron chelators are reportedly ineffective in treating many types of tumors, especially solid tumors [2]. In a cohort of 12 patients with advanced non-small-cell lung cancer, the iron chelator triapine was ineffective in initial combination with gemcitabine, the DNA synthesis inhibitor, or in patients with prior exposure to gemcitabine [53,54]. These clinical data are inconsistent with experimental data showing that a low-iron diet or iron chelators suppress tumors, though the reason is unclear [28–31].

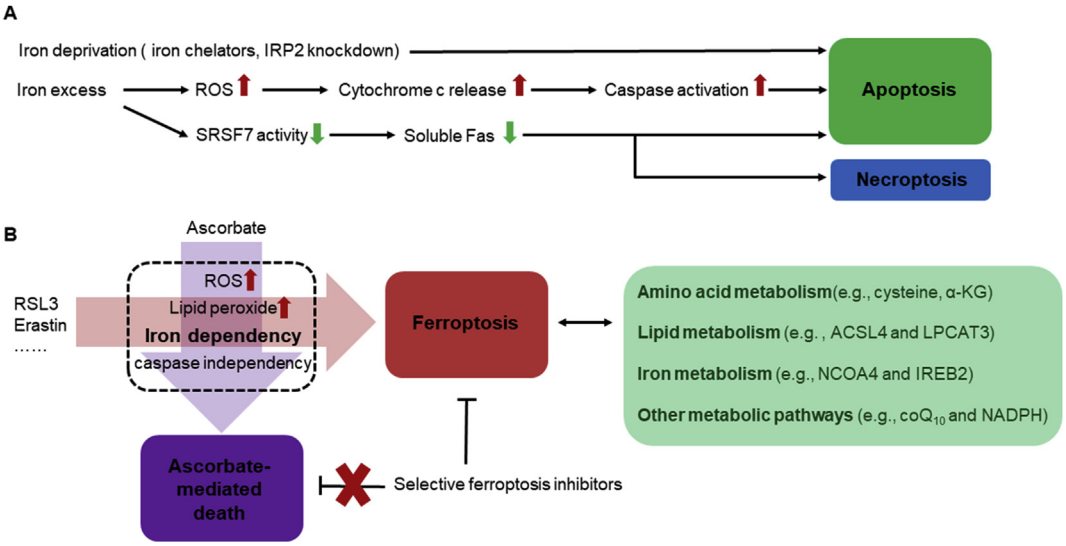

Fig. 3. Iron and cell death

(**A**) Iron deprivation induces apoptosis. Furthermore, iron excess induces apoptosis via reactive oxygen species (ROS)-mediated and SRSF7-mediated mechanisms. Iron excess can also induce necroptosis via an SRSF7-mediated mechanism. (**B**) Ferroptosis is an iron-dependent form of cell death induced by lipid peroxide generation. Ferroptosis is regulated by metabolism of amino acids (e.g., cysteine, α-ketoglutarate (α-KG)), lipids (e.g., ACSL4 and LPCAT3), and iron (e.g., NCOA4 and IREB2) and several other metabolic pathways (e.g., coQ_{10} and NADPH). Ascorbate-mediated death is similar to ferroptosis in several features, including iron dependency, production of ROS, and lipid peroxidation. However, ascorbate-mediated death is still distinct from ferroptosis because selective inhibitors of ferroptosis fail to inhibit ascorbate-mediated death.

Table 2
Potential Iron-associated lung cancer therapy.

Strategy	Drug	Effect	Reference
Iron deprivation	Triapine	Iron chelation	53,54
Iron overload	Ascorbate	Ascorbate-mediated cell death	55–58
	sorafenib	Ferroptosis	59
	Sulfasalazine	Ferroptosis	60,61
	Artesunate	Ferroptosis	62,63
	C′ dot	Ferroptosis	65
	Ferumoxytol	Pro-inflammatory macrophage polarization	66
Iron homeostasis	42/6 monoclonal antibody	TF antibody	67
	Tf-CRM107 et al.	TF-conjugated chemotherapeutic drugs	68

Another therapeutic strategy for cancers involves elevated iron levels or iron-dependent cytotoxicity. Pharmacologic ascorbate induces cell death through an iron-dependent mechanism and is clinically effective alone or in combination with treatments [55–57]. Moreover, ascorbate increases radiosensitivity in NSCLC [58]. In addition, many studies are looking for appropriate drugs to induce ferroptosis for cancer therapy. Due to their pharmacological properties, the most frequently studied ferroptosis inducers, erastin and RSL3, are not suitable for cancer therapy [2]. Several FDA-approved drugs have been shown to induce ferroptosis, including sorafenib, sulfasalazine, and artesunate [59–63]. FDA-approved nanoparticles (C' dots) are not only used in human cancer diagnostics [64] but also selectively kill cancer cells by inducing ferroptosis [65]; ferumoxytol nanoparticles can inhibit tumor growth by inducing pro-inflammatory macrophage polarization in tumor tissues [66]. However, further studies are needed to verify the clinical utility of these ferroptosis inducers.

Iron dysregulation is closely associated with the initiation and development of several malignant tumors. Considering the elevated expression of TF and its receptor TFR1 in many types of tumors, some studies used TF antibody or TF-conjugated chemotherapeutic drugs for cancer therapy [67,68]. However, no effective clinical therapeutic strategies have been found by these studies. Chemotherapy reportedly increases serum iron levels, which is associated with chemotherapy-induced nausea and vomiting. Iron chelation might be a novel antiemetic therapy in patients undergoing chemotherapy [69]. In addition, miR-20 reportedly decreases iron export by regulating ferroportin expression, inducing intracellular iron accumulation, and promoting proliferation [70]. Further studies regarding the mechanism of action and application of iron metabolism in lung cancer remain to be developed.

5. Perspectives and future directions

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality among males and females worldwide [71]. Iron is an essential trace element in the human body and is required for activity of many proteins and enzymes. Iron dysregulation is closely associated with the initiation and development of several malignant tumors, including lung cancer. Emerging evidence suggests a particularly important role of iron in lung cancer. Moreover, iron plays a prominent part in multiple forms of cell death, making it important for the development of potential strategies for lung cancer therapy. However, studies on the role and application of iron in lung cancer are scarce and numerous questions remain unanswered.

The oxygen concentration in the lung is much higher than other tissues, which causes faster degradation of iron-sulfur clusters. Sufficient iron-sulfur clusters are required for multiple essential functions of tumor cells. Therefore, lung tumors may need more iron-sulfur clusters than tumors in other tissues. The iron–sulfur cluster biosynthetic enzyme NFS1 undergoes positive selection in lung tumors, and insufficient iron-sulfur clusters increase ferroptosis sensitivity in lung tumors through activating the iron-starvation response [37]. Hence, further studies regarding iron-sulfur cluster biosynthesis and ferroptosis would provide a new avenue for development of lung cancer therapies.

Iron deprivation by iron chelators suppresses tumors *in vitro*, *in vivo*, and in preclinical studies. However, clinical data showed that iron chelators are ineffective in many types of cancer, including lung cancer. This may be due to limited pharmacokinetic access of iron chelators to solid tumors [2] and may be related to decreased oxygen concentration

in advanced NSCLC tissues. Therefore, we cannot exclude the possibility that iron chelators might have therapeutic effects in patients with early stage lung cancer.

KRAS mutation occurs frequently in lung cancer [72], and attempts to target KRAS for clinical benefit have been unsuccessful. Ferroptosis was first proposed in the study of oncogenic RAS-selective lethal small molecule drugs [50]. Both ascorbate-mediated cell death and ferroptosis may be promising as anticancer therapies in KRAS-mutant lung cancer. We believe that with the continued emergence of iron-relevant research in lung cancer, its application potential is unlimited.

Declaration of interests

The authors declare no competing interests.

Acknowledgments

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