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REVIEW ARTICLE OPEN

New insights into crosstalk between Nrf2 pathway and ferroptosis in lung disease

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Ferroptosis is a distinctive process of cellular demise that is linked to amino acid metabolism, lipid oxidation, and iron oxidation. The ferroptosis cascade genes, which are closely associated with the onset of lung diseases, are among the regulatory targets of nuclear factor erythroid 2-related factor 2 (Nrf2). Although the regulation of ferroptosis is mostly mediated by Nrf2, the precise roles and underlying regulatory mechanisms of ferroptosis and Nrf2 in lung illness remain unclear. This review provides new insights from recent discoveries involving the modulation of Nrf2 and ferroptosis in a range of lung diseases. It also systematically describes regulatory mechanisms involving lipid peroxidation, intracellular antioxidant levels, ubiquitination of Nrf2, and expression of FSP1 and GPX4. Finally, it summarises active ingredients and drugs with potential for the treatment of lung diseases. With the overarching aim of expediting improvements in treatment, this review provides a reference for novel therapeutic mechanisms and offers suggestions for the development of new medications for a variety of lung disorders.

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FACTS

- Nrf2 plays a pivotal role in the regulation of essential genes involved in ferroptosis and is intimately linked to the progression of lung diseases.
- In lung cancer, the hyperactivation of Nrf2 impedes the induction of ferroptosis in malignant cells, thereby conferring a survival advantage.
- The creation of pharmaceutical agents aimed at either stimulating or impeding the activity of Nrf2 proteins represents a promising strategy for modulating ferroptosis.
- The combined use of Nrf2 inhibitors enhances the sensitivity of lung cancer cells to ferroptosis.

OPEN QUESTIONS

- What are the potential limitations and challenges associated with targeting Nrf2 inhibition to induce ferroptosis as an effective treatment for lung cancer?
- Are there any unexplored potential targets for the crosstalk between Nrf2 and ferroptosis?
- What serves as the key hub connecting Nrf2 and ferroptosis?
- What is the clinical efficacy of drugs targeting Nrf2 and ferroptosis, for the treatment of lung diseases?

INTRODUCTION

Lung diseases are a complex and diverse group of pathological states that severely affect the structure and function of the lungs and have become a major health threat worldwide. Pulmonary diseases include chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILDs), infectious lung diseases, and lung cancer, with the global incidence rates of COPD and lung cancer showing alarming increases year by year [1–3]. Currently, COPD is the third most common fatal disease worldwide, while lung cancer has one of the highest cancer-related mortality rates [4, 5]. Oxidative stress is thought to play a central role in the pathogenesis of these lung diseases. Oxidative stress directly damages lipids, proteins, and DNA in lung tissues, induces an inflammatory response, and also further accelerates the pathological process by inducing iron death in lung tissues [6]. Prolonged exposure to irritants such as tobacco smoke leads to a sustained increase in oxidative stress in the lungs of COPD patients, which in turn inhibits the function of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and weakens the body's antioxidant defences, leading to further damage to alveolar structure, increased airway remodelling, and inflammatory responses, thus driving the pathological progression of the disease [7]. Similarly, in lung fibrosis, inhibition of the Nrf2 pathway is closely associated with elevated levels of oxidative stress in fibrotic tissues, which in turn triggers the abnormal deposition of fibrous components such as collagen, leading to a post-ferroptotic state in lung tissue cells [8, 9]. Additionally, in lung cancer, hyperactivation of Nrf2 enables cancer cells to regulate intracellular iron metabolism more effectively, thereby inhibiting iron-dependent lipid peroxidation and evading ferroptosis [10]. This mechanism not only helps cancer cells survive a hostile environment, it also confers tolerance to treatments such as radiotherapy and chemotherapy, and is recognised as an important cause of drug resistance during lung cancer treatment. It is evident that dysregulation of the Nrf2 pathway and regulation of the inflammatory response and

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ferroptosis play key roles in the pathogenesis of several lung diseases, making Nrf2 a potential therapeutic target. Elucidating the regulatory mechanisms of Nrf2 and ferroptosis in lung diseases could profoundly deepen our understanding of the pathogenesis of these diseases and inspire new research directions for their treatment.

Since its discovery in 1994, Nrf2 has been widely studied and shown to be an essential controller of antioxidant genes. Additionally, we now know the precise molecular makeup and mode of regulation of its pathway partner, Kelch-like ECH-associated protein 1 (Keap1) [11, 12]. Among the seven conserved functional areas referred to as the Nrf2-ECH homology (Neh) domains of Nrf2, Neh1 primarily dimerises and attaches to small Maf (sMAF) proteins before going on to bind to DNA [13, 14]. Neh2 is the key to stable Keap1 binding, while two Neh2 motifs, hinge ETGE and latch DLG, interact with Keap1 in a hinge-and-latch mechanism [15]. Additionally, the Neh2 structural domain contains lysine residues, which are substrates for ubiquitination and are involved in the degradation of the Nrf2 protein [16]. Neh3, Neh4, and Neh5 are involved in transactivation, while Neh6 regulates self-stability [17]. Keap1, as a negative regulator of Nrf2, comprises three main structural and functional domains: BTB, IVR, and Kelch repeat [18]. The BTB domain binds CUL3 and is used to link to E3 ubiquitin ligase, the IVR domain regulates cysteine residue activity, and the Kelch repeat domain is mainly responsible for linking to Nrf2 (Fig. 1) [19, 20].

In the basal state, Nrf2 is mostly found in the cytoplasm of cells, bound to Keap1. Nrf2 relies on proteasomal degradation to maintain low intracellular levels, which is mediated by Keap1. Keap1, in association with CUL3 and Rbx1, forms a functional E3 ubiquitin ligase that ubiquitinates Nrf2, targeting it for degradation [21, 22]. Under oxidative stress conditions, active cysteine residues of Keap1 undergo direct modifications, changing the structure of the active E3 ubiquitin ligase and leading to a breakdown in ubiquitination [23, 24]. Nrf2 then accumulates in the cytoplasm and translocates to the nucleus [25], where the Nrf2-dependent self Neh1 attaches to sMAF transcription factors. Nrf2-sMAF heterodimers ultimately bind to antioxidant response elements (AREs), which control the expression of anti-inflammatory, cytoprotective, and antioxidant proteins.

Since its identification in 2012, the mechanisms underlying ferroptosis have gradually been unravelled. Unlike other forms of regulated cell death, ferroptosis is an iron-dependent, non-apoptotic process [26, 27] characterised by increased reactive oxygen species (ROS) and lipid peroxidation, both of which are driven by the accumulation of intracellular iron [28–30]. Lipid peroxidation, damage to the plasma membrane, fewer mitochondria, diminished mitochondrial cristae, and increased membrane density are the primary characteristics of ferroptosis [31, 32]. Thorough mechanistic investigations have recently revealed that multiple metabolic pathways linked with the process of lipid peroxidation ultimately impact the regulation of ferroptosis (Fig. 2). Among these, the ferroptosis process known as the cyst(e)ine/glutathione (GSH)/glutathione peroxidase (GPX)4 axis is regulated by the classical GPX4. In this mechanism, the GSH-dependent cystine reduction pathway stimulates the production of GSH by reducing the cysteine that system Xc transports into the cell [33–35]. GPX4 requires GSH, a strong reducing agent, as a cofactor to effectively reduce phospholipid hydroperoxides (PLOOHs) to their equivalent alcohols (PLOHs) inside cells. Reducing PLOOH buildup shields cells from ferroptosis, delaying the quick and irreversible destruction to membrane components [36, 37]. Although the main factor in ferroptosis prevention is believed to be GPX4, other crucial players include the GPX4-independent ferroptosis suppressor protein 1 (FSP1) [38]. It was discovered that FSP1 (originally known as AIFM2) shields cells from GPX4-independent ferroptosis brought on by suppression or deletion of GPX4. FSP1 accomplishes this through its ubiquinone oxidoreductase activity, which produces panthenol by decreasing the incomplete oxidation product of ubiquinone (CoQ10), semihydroquinone [39]. This free radical is able to directly lower lipid free radicals and stop lipid autoxidation, or indirectly promote the regeneration of oxidised α-tocopherol free radicals, which are the most potent naturally occurring chain-breaking antioxidants in lipids [40]. Additionally, it has been revealed that GTP cyclohydrolase 1 (GCH1), through its metabolites tetrahydrobiopterin (BH4) and dihydrobiopterin (BH2), is resistant to ferroptosis [41]. BH4 acts both as a direct trap for small molecule free radicals and a cofactor for enzymes involved in CoQ10 synthesis, protecting phospholipids containing two polyunsaturated fatty acid (PUFA) tails from oxidative degradation during ferroptosis.

CROSSTALK BETWEEN NRF2 AND FERROPTOSIS

As an important stress factor that maintains intracellular oxidative homoeostasis, Nrf2 controls the expression of many antioxidant genes. Iron ions are essential for cell metabolism and survival, but excess free iron ions lead to increased intracellular oxidative stress, which promotes cell death, especially ferroptosis [42, 43]. Studies have shown that Nrf2 plays a crucial role in maintaining the levels and distribution of intracellular iron ions by regulating the gene expression of key factors involved in iron metabolism, including transferrin (Tf), ferritin, ferroportin, and FSP1 [44–46]. Activation of the Nrf2 pathway was found to diminish liver injury due to iron overload by regulating the expression of Tf and FTH and reducing the accumulation of cellular iron-free ions, thereby inhibiting oxidative stress and attenuating cell death [47]. Furthermore, Nrf2 activators reduce the extent of neuronal death caused by iron overload, most likely by regulating genes associated with iron metabolism and the synthesis of antioxidants that protect cells from oxidative stress and ferroptosis [48, 49]. One of these Nrf2 targets, haem oxygenase-1 (HO-1), has two purposes in ferroptosis: promotion of ferroptosis via the generation of Fe^{2+} from haem degradation, and deceleration of ferroptosis through the inhibition of oxidative stress. Thus, the dual functions of HO-1 are dependent on the balance between oxidative stress and ferroptosis [50–52]. Additionally, ferroptosis is considered to represent a new approach to anti-tumour therapy, and has been reported in lung cancer. However, deletion of *Keap1* activates high expression of Nrf2, contributing to tumour resistance to treatment [53, 54]. Along with decreasing oxidative stress in tumours, Nrf2 activation increases the expression of downstream genes *FSP1* and *GPX4*, which can shield cancerous cells from iron ptosis [55, 56]. Indeed, many lung cancer therapies are based on reducing Nrf2 expression to induce the sensitisation of lung cancer cells to ferroptosis. Elucidating how Nrf2 preferentially upregulates target genes to avert various forms of oxidative cell death could facilitate the design of new treatments and preventative strategies for iron-associated illnesses.

ROLE OF THE NRF2 PATHWAY AND FERROPTOSIS IN ACUTE LUNG INJURY (ALI)

Novel mechanisms for regulating the Nrf2 pathway and ferroptosis in ALI

ALI is a common pathological state that is induced by a variety of factors, such as infection, trauma, and inhalation of harmful substances [57]. The pathological process of ALI involves extensive lung tissue damage and dysfunction, and is therefore more appropriately regarded as a clinical syndrome of acute lung injury rather than a stand-alone chronic lung disease [58]. In intensive care patients, ALI, especially acute respiratory distress syndrome (ARDS), is characterised by rapid deterioration, resulting in severe respiratory failure, morbidity, and death [59]. Preventive and specific therapeutic options for ALI are lacking, and constitute one

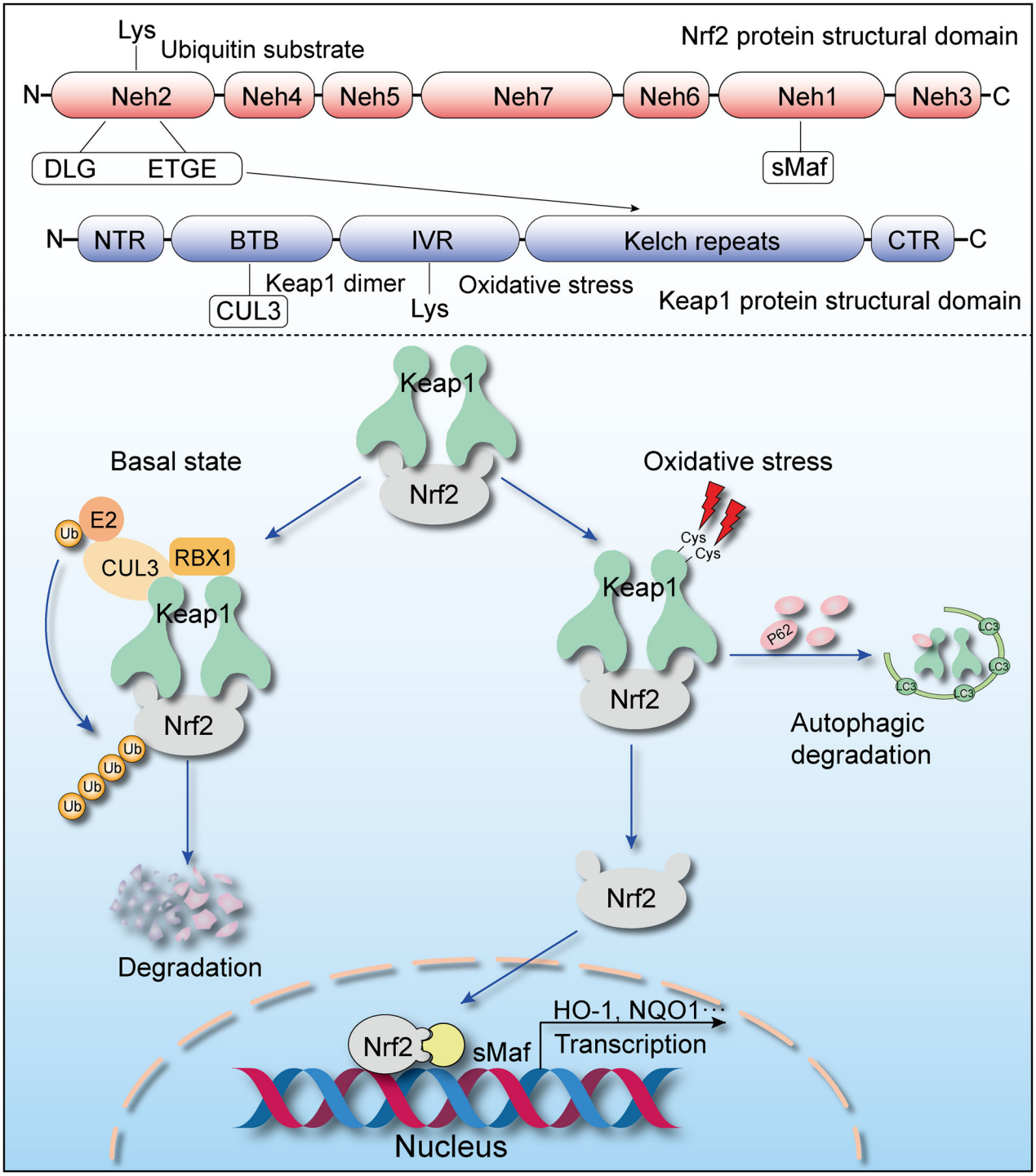

Fig. 1 Keap1-mediated regulation of Nrf2 through its Neh structural domains under normal and oxidative stress conditions.

of the major scientific problems in the field of respiratory critical care [60]. An in-depth study of ALI pathogenesis not only provided a scientific basis for new therapeutic strategies for a wide range of lung diseases, it also revealed the common pathological mechanisms of acute and chronic lung injury, including oxidative stress, inflammatory response, and ferroptosis [61]. Therefore, elucidation of the mechanisms of Nrf2 and ferroptosis in the regulation of ALI could be significant. Studies have shown that Nrf2-regulated ferroptosis plays important roles in the treatment and protection against ALI. In intestinal ischaemia-reperfusion (IIR-ALI)-induced ALI, knockdown of *Nrf2* exacerbated ALI injury, further reducing GPX4 expression and relative GSH content [62]. In contrast, ALI symptoms were lessened by increased expression of Nrf2. Furthermore, it was discovered that solute carrier family 7 member 11 (SLC7A11) adversely regulates the Nrf2/HO-1 pathway in ALI, while Nrf2 defensively restrains ferroptosis in ALI caused by seawater submersion [6]. Further studies have reportedly uncovered additional regulatory mechanisms of Nrf2 and ferroptosis in ALI (Fig. 3). Activation of signal transducer and activator of transcription 3 (STAT3) into its phosphorylated form in IIR-ALI led to increased expression of SLC7A11 [63], mitigating the IIR-ALI. Conversely, inhibition of STAT3 expression decreased SLC7A11

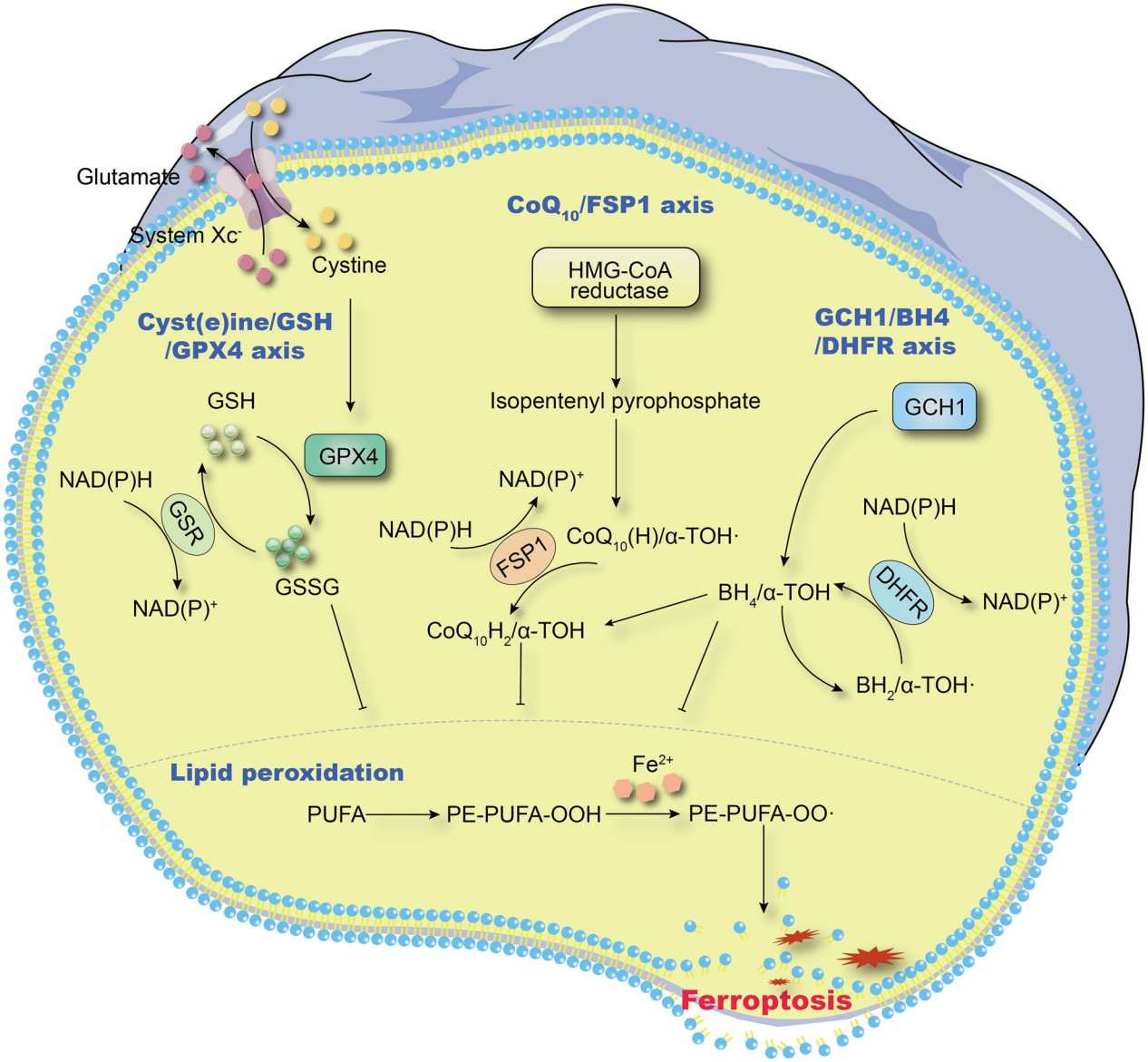

Fig. 2 Activation and regulatory mechanisms of ferroptosis. DHFR, dihydrofolate reductase; GSSG, oxidised glutathione (GSH); GSR, GSH reductase; PE, phosphatidylethanolamine.

expression. Further studies revealed that *Nrf2* knockdown had an activating effect on STAT3, suggesting that Nrf2 and STAT3 co-regulate SLC7A11 to reduce ferroptosis and protect against IIR-ALI. Furthermore, telomerase reverse transcriptase (TERT) with SLC7A11 expression was found to be significantly reduced in lung tissues of *Nrf2*$^{-/-}$ mice with lipid peroxidation accumulation. Conversely, overexpression of TERT led to a reduction in iron accumulation and a notable increase in the levels of ferroptosis-related proteins and SLC7A11. These findings suggest that ferroptosis is regulated by TERT, a crucial factor for telomerase activity [64], within an Nrf2/TERT/SLC7A11 axis, which carries out a protective function against IIR-ALI. Thus, anti-ferroptosis strategies to treat ALI may require stimulation of the Nrf2 signalling pathway. In the same year, it was discovered that the inhibitor of apoptosis-stimulating protein of P53 (IASPP) could be used to treat IIR-ALI. Further investigations demonstrated that IASPP operates as an antioxidant within the cytoplasm, dependent on the translocation of Nrf2 to the nucleus [62]. This mechanism leads to decreased expression of hypoxia-inducible factor (HIF)-1α and Tf while boosting the levels of proteins such as FTH1, NAD(P)H quinone dehydrogenase 1 (NQO1), HO-1, and GPX4. Moreover, this process contributes to the reduction of ferroptosis in IIR-ALI, indicating the potential of IASPP as a drug for the treatment of ALI.

Additionally, in recent studies, deletions of related genes were observed to increase Nrf2 expression and decrease ferroptosis in ALI, providing a protective effect. For example, deletion of the genes encoding BACH1 [65] and JMJD3 [66], negative regulators of Nrf2, upregulated the expression of Nrf2, inhibiting the LPS-induced inflammatory response and ferroptosis, and ameliorating LPS-induced ALI. The mRNA-binding protein Au-rich element RNA-binding factor (AUF1) is essential for inhibiting the inflammatory response and reducing sepsis-related symptoms [67]. Studies have shown that AUF1 overexpression reverses ferroptosis-related indicators and improves the survival rate of sepsis-induced ALI mice. Further studies found that AUF1 interacts with the coding sequence and 3′-untranslated region (UTR) of *Nrf2* to stabilise the gene, whereas AUF1 binding to the 3′-UTR of activating transcription factor 3 (*ATF3*) promotes degradation of the gene, producing an anti-ferroptosis effect and ameliorating ALI [68]. Transmembrane glycoprotein mucin 1 (MUC1) also exhibits Nrf2

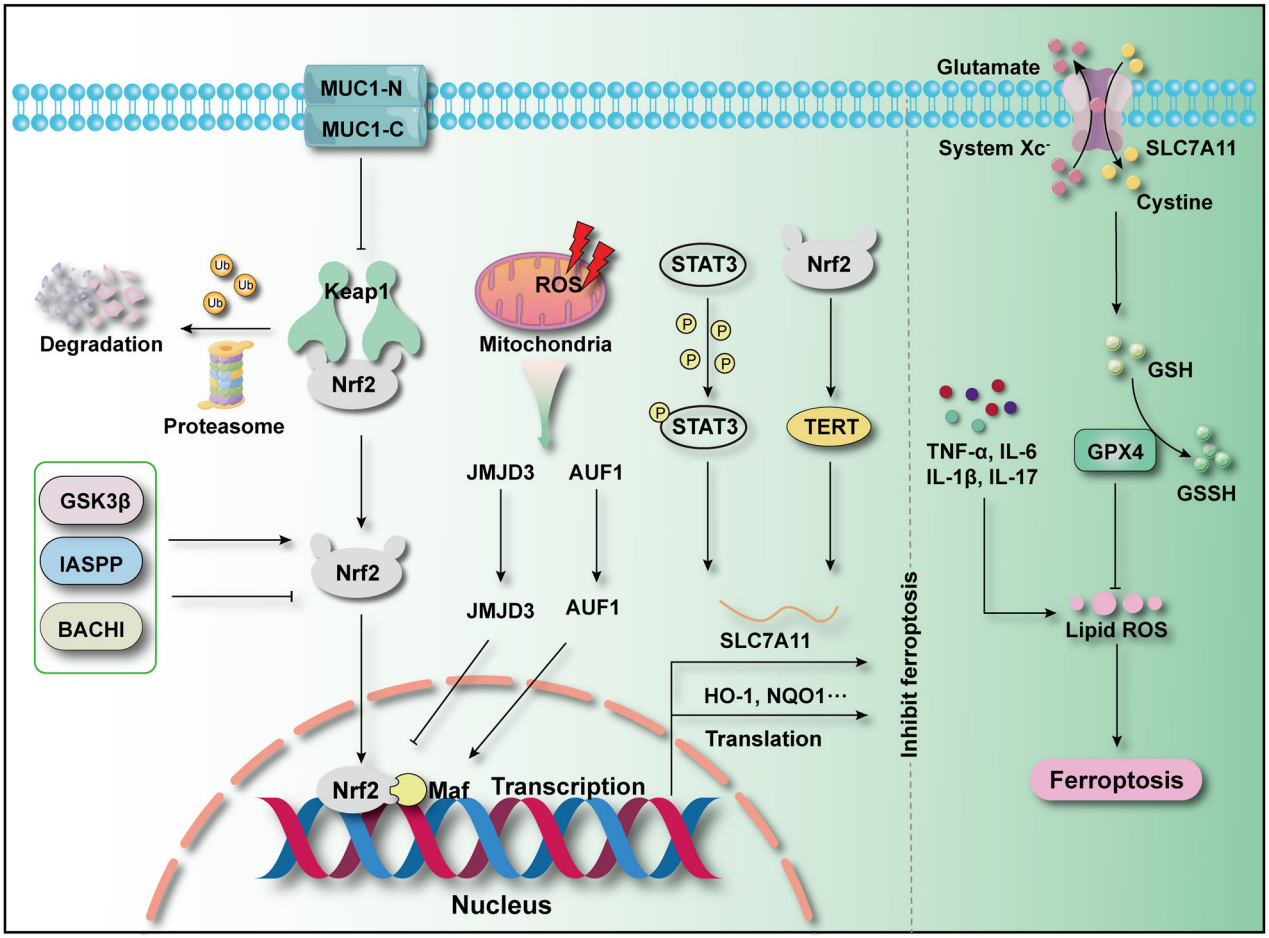

Fig. 3 Mechanisms by which the Nrf2 signalling pathway is regulated to inhibit ferroptosis in ALI.

regulation, specifically through dimerisation of its transmembrane and cytoplasmic domain (MUC1-C), which represses Keap1 expression while promoting phosphorylation of glycogen synthase kinase 3β (GSK3β). The subsequent translocation of Nrf2 into the nucleus leads to upregulation of GPX4 expression. This indicates that MUC1 mitigates ALI by inhibiting ferroptosis via the GSK3β-Keap1-Nrf2-GPX4 signalling pathway [69]. In summary, the Nrf2 signalling pathway and ferroptosis are crucial in ALI, and elucidation of the specific regulatory mechanisms has important potential value for the future treatment of ALI.

Drugs that treat ALI by modulating the Nrf2 pathway with ferroptosis

ALI caused by oxidative stress and inflammation [70] has limited therapeutic options, mainly comprising supportive treatments such as mechanical ventilation and nutritional therapy [71, 72]. In addition to natural remedies, which are essential for both preventing and curing the illness, it is crucial that we develop new medications to treat ALI. Obacunone has been shown to reduces ROS content and MDA formation, increases *HO-1* mRNA expression levels, and inhibits ubiquitination of Nrf2 in lung tissues of mice with ALI. The degradation of Nrf2 is also reduced, prolonging its half-life, and decreasing the occurrence of ferroptosis in ALI [73]. As research continues, more and more active ingredients are being used in the treatment of ALI (Table 1). For example, astaxanthin [74], itaconate [75], and irisin [76] all modify the Nrf2 signalling pathway and reduce ferroptosis to exert preventative or curative effects on ALI. It follows that targeted research into drugs that inhibit Nrf2 ubiquitination will lead to the discovery of new therapeutics for the treatment of ALI.

ROLE OF THE NRF2 PATHWAY AND FERROPTOSIS IN LUNG CANCER

Keap1-Nrf2-FSP1-mediated ferroptosis in lung cancer

Studies on non-small cell lung cancer (NSCLC), both preclinical and clinical, have demonstrated tight relationships among the resistance to chemotherapy, radiation therapy, and other agents, and the loss of function of Keap1 and overexpression of Nrf2. Nrf2 overexpression starts out playing a protective role in cancer, but ultimately encourages disease progression and metastasis, while mutations in *Keap1* have been linked to a poor prognosis in individuals with advanced NSCLC receiving treatment [10]. A study using a three-dimensional tumour sphere model combined with CRISPR-Cas9 screening reported that Nrf2 overactivation was essential for lung tumour proliferation and survival, whereas silencing of Nrf2 predisposed spherical cells to ferroptosis, which was also consistent with clinical observations [77]. Additionally, Nrf2 overexpression was shown to activate FSP1, further reducing lipid free radical production by lowering CoQ10 and inhibiting ferroptosis from occurring in lung cancer, mediating resistance to ferroptosis and radiation in *Keap1*-deficient lung cancer cells. Subsequent investigations demonstrated that FSP1, regulated by Nrf2, significantly inhibited lung cancer cell growth and sensitised *Keap1*-deficient cells to ferroptosis by knockdown or inhibition of FSP1 expression in *Keap1* post-mutant lung cancer [46, 78]. It has been shown that a combination of FSP1 inhibitors can effectively treat cancers caused by mutations in the oncogenic Kirsten rat sarcoma viral oncogene homologue (KRAS) gene [79]. Therefore, combining FSP1 inhibitors may represent an effective therapeutic strategy for ferroptosis in *Keap1*-deficient lung cancer and cancers with radioresistance.

Table 1. Therapeutic agents with the potential to improve ALI by suppressing ferroptosis via Nrf2 pathway activation.

Therapeutic drug	Regulatory mechanism	Experimental model	Reference
Obacunone	Inhibiting the Nrf2 ubiquitination pathway increases cytoplasmic Nrf2 content and reduces ferroptosis	ALI model was created 7 h after IP injection of LPS (10 mg/kg) into C57BL/6 mice	[73]
Astaxanthin	Increasing Nrf2 levels in lung tissue reduces inflammation and inhibits ferroptosis	ALI model was induced in BALB/c mice by IP injection of LPS (5 mg/kg), followed by a 6-h interval	[74]
Itaconate	Increased bodily accumulation of Nrf2 upregulates GPX4 protein expression and reduces lipid peroxidation	ALI models in C57BL/6 and *Nrf2*-KO mice were induced by IP injection of LPS (10 mg/kg) for 12 h	[75]
Irisin	Ferroptosis is decreased following overexpression of GPX4 and the rise in Nrf2 and HO-1 mRNA levels	LIRI mouse model was established by 120 min of reperfusion after 60 min of ischaemia in the left lung of C57BL/6 mice	[76]
Ferulic acid	Activation of the Nrf2/HO-1 pathway reduces Fe^{2+} release, thereby protecting against ALI	ALI model was induced in female BALB/c mice using the caecum ligation and puncture method	[116]
Urolithin A	Reducing Keap1 expression activates the Nrf2/HO-1 pathway, which in turn reduces ferroptosis in ALI	C57BL/6 mice were given LPS (10 mg/kg) by tracheal drip infusion for 24 h to create an ALI model	[117]
Quercetin	Quercetin activates the Sirt1/Nrf2/GPX4 pathway to prevent ferroptosis	ALI model was established by giving C57BL/6 mice a 12-h tracheal infusion of LPS (5 mg/kg)	[118]
Fibroblast growth factor 10 (FGF10)	FGF10 reduces ferroptosis by activating the SIRT1-Nrf2 pathway to reduce the synthesis of lipid peroxidation products	Tracheal drip of LPS (5 mg/kg) for 6 h in C57BL/6 mice was used to establish an ALI model	[119]
Tempol	Activation of Nrf2 expression and upregulation of organismal synthesis of GSH reduce ferroptosis in lung epithelial cells	ALI model was produced in BALB/c mice 1 week following an IP injection of LPS (10 mg/kg)	[120]

IP intraperitoneal, *LIRI* liver ischaemia–reperfusion injury.

Targeting Nrf2 ubiquitination to mediate ferroptosis in lung cancer

The high expression of Nrf2 is essential for the survival of lung cancer cells, thus strategies to reduce Nrf2 expression may be effective for the treatment of lung cancer, in which ubiquitination plays an important role in the Nrf2 protein degradation pathway. In lung adenocarcinoma (LUAD) cells, the E3 ligase MIB1 was shown to induce ubiquitination of Nrf2 in the Neh2 structural domain, following which the ubiquitinated Nrf2 was degraded via the proteasomal pathway. Furthermore, the reduction of Nrf2 increased the susceptibility of the LUAD cells to ferroptosis [80]. In NSCLC, a deubiquitinating enzyme that stabilises Nrf2 expression by deubiquitinating Nrf2, ubiquitin carboxyl-terminal hydrolase 11 (USP11), was positively correlated with Nrf2 expression [81]. The small molecule RSL3 directly binds to USP11 protein to inactivate it, thereby promoting the ubiquitination and degradation of Nrf2 in lung adenocarcinoma cells, making them more susceptible to ferroptosis. This suggests that, by inhibiting the activity of the deubiquitinating enzyme USP11, the level of oxidative stress in LUAD cells can be increased, promoting cellular ferroptosis [82]. Therefore, targeted suppression of the USP11-Nrf2 axis or promotion of Nrf2 ubiquitination to reduce the high expression of Nrf2 may represent effective strategies to reduce drug resistance and increase the susceptibility to ferroptosis of LUAD cells.

Nrf2-mediated regulation of metabolic susceptibility to lung cancer and ferroptosis occurrence

A growing body of research suggests that cysteine deprivation increases tumour susceptibility to ferroptosis, but the exact mechanism is unclear. Overexpression of Nrf2 in NSCLC activates downstream antioxidant factors that protect lung cancer cells from ferroptosis. However, a negative regulatory interaction between Nrf2 and focadhesin (FOCAD), an adhesion plaque protein that enhances the sensitivity of NSCLC cells to ferroptosis under cysteine deprivation conditions, has been discovered [83]. Further studies revealed that replication protein A1 (RPA1) competes with sMAF for binding to Nrf2, activates the cancer-related FOCAD gene, and upregulates focal adhesion kinase (FAK) activity to make NSCLC cells more susceptible to cysteine deprivation-induced ferroptosis, without affecting GPX4 inhibition-induced ferroptosis. Cysteine deprivation-induced ferroptosis has a significant impact on NSCLC cells, particularly in terms of sensitivity. Alternatively, studies have shown that ferroptosis induced by cysteine deprivation in NSCLC cells with high-level expression of Nrf2 exerts a protective effect independent of GSH [84]. High Nrf2 expression increases the catalytic subunit activity of glutamate-cysteine ligase (GCLC). Nrf2 is a critical transcriptional regulator of GCLC. In NSCLC deprived of cysteine, GCLC replaces cysteine with other small uncharged amino acids to produce γ-glutamyl-peptide. Thus, inhibiting glutamate buildup prevents iron prolapse. Additionally, lung cancer cells defective in Keap1 are glucose dependent; when glucose levels are low, high uptake of cystine by lung cancer cells via the Nrf2/SLC7A11 axis stimulates the accumulation of intracellular disulfide bonds and depletion of NADPH. This leads to ferroptosis, but can be reversed by inhibition of Nrf2 [85]. Elucidating the regulatory mechanisms of Nrf2 sensitivity to ferroptosis in lung cancer cells under cysteine or glucose limitation may lead to novel therapeutic strategies in the clinical management of NSCLC.

Drugs that mediate ferroptosis in lung cancer via the Nrf2 pathway

Lung cancer has the highest incidence and mortality rates of all cancer types globally and is still on the rise [86]. China is predicted to have substantially higher rates of incidence and mortality from lung cancer than any other country between 2015 and 2030 [87], and the mortality rate is predicted to rise by ~40%, necessitating the urgent development of new lung cancer treatments, such as those listed in Table 2 [88]. Studies have shown that nuclear Nrf2 is

Table 2. Therapeutic agents with the potential to induce ferroptosis in lung cancer cells via inhibition of Nrf2.

Therapeutic drug	Regulatory mechanism	Experimental model	Reference(s)
RSL3	RSL3 suppresses USP11 expression, which allows Nrf2 protein to be degraded, leading to ferroptosis in KLK lung cancer cells	SC injection of A549 cells into nude mice established xenograft lung cancer models with tumours measuring 100 mm^3	[82]
Ginkgetin	Ginkgetin downregulates the Nrf2/HO-1 pathway, lowering the expression of SLC7A11 and GPX4, and encouraging cellular ferroptosis	Establishment of a nude mouse model of NSCLC transplantation by SC injection of A549 cell tumours (~100 mm^3)	[88]
Manoalide	Ferroptosis is produced via stimulation of the mitochondrial Ca^{2+} overload-driven FTH1 pathway and inhibition of the KRAS-ERK pathway and the Nrf2-SLC7A11 axis	Tumour tissue was taken at 12 weeks for organoid culture after adenovirus infection via tracheal drip	[90]
Trabectedin	Elevations in Fe^{2+} and ROS trigger apoptosis by stimulating the HIF-1/IRP1 axis and transferrin receptor protein 1, and blocking the suppression of the Keap1/Nrf2 axis	A549, H460, PC-9, H1299, and HSAECs cells were selected for mechanistic studies	[91]
ShtIX	Inhibition of the Nrf2/GPX4 pathway in lung cancer cells induces cellular ferroptosis and increases lipid peroxide and Fe^{2+} levels	Xenograft lung cancer model was established by SC injection of A549 cells into nude mice, resulting in tumour xenografts of ~ 100 mm^3 in size	[92]
Erastin/sorafenib	Erastin/sorafenib induces ferroptosis in cisplatin-resistant NSCLC cells through inhibition of the Nrf2/xCT pathway	SC injection of N5CP cells into nude mice and 600 mm^3 xenografted tumours were used to establish a xenograft cisplatin-resistant tumour model	[94]
Cisplatin and PRLX93936	Inhibition of Nrf2 expression promotes ferroptosis in NSCLC cells, synergizing with cisplatin and PRLX93936 to enhance GPX4 inhibition	Cell lines A549 and H23 were selected for mechanistic studies in NSCLC cells	[95]
Acetaminophen	Erastin synergistically inhibits the Nrf2/HO-1 signalling pathway with acetaminophen and promotes lipid peroxidation in A549 cells	SC injection of A549 cells into the right side of the thymus of BALB/c nude mice generated tumours ≤ 80 mm^3, establishing a xenograft lung cancer model	[96]
ZVI-NP	ZVI-NP promotes ferroptosis in lung cancer cells by activating the AMPK/mTOR pathway, which enhances degradation of Nrf2 via the GSK3/β-TrCP pathway	SC implantation of A549 cells in NOD/SCID mice to establish an A549 xenograft model and a spontaneous lung metastasis model in immunodeficient mice	[121]
Isoorientin	Cellular ferroptosis is aided by inhibition of the SIRT6/Nrf2/GPX4 signalling pathway	Six days after SC injection of A549/DDP tumour cells into BALB/c-nu mice, average tumour diameter reached 0.5 cm	[122]
Metformin and eriocitrin	Iron overload in lung cancer cells is facilitated by increased MDA, ROS, and iron ion levels, coupled with reduced expression of GPX4, SLC7A11, Nrf2, and HO-1 proteins	A549 and H1299 cells were selected for mechanistic studies	[123, 124]
Cephaeline	Targeted reduction of Nrf2 expression in lung cancer cells causes lipid peroxidation	Injection of H460 cells into the right dorsal side of BALB/c-nu mice was used to establish a SC tumour model	[114]
Clobetasol propionate	Inhibition of Nrf2 expression makes human lung cancer cells more radiosensitive, increasing mitochondrial ROS and lipid peroxidation	Xenograft tumour model was created by giving NOD/SCID BALB/c female mice SC injections in the right hind leg, producing tumours of ≤ 100 mm^3 in size	[125]

AMPK AMP-activated protein kinase, *β-TrCP* beta-transducin repeat containing protein, *ERK* extracellular signal-regulated kinase, *IRP1* iron regulatory protein 1, *mTOR* mammalian target of rapamycin, *NOD/SCID* non-obese diabetic/severe combined immunodeficiency mutant, *SC* subcutaneous, *ZVI-NP* zero-valent-iron nanoparticle.

overexpressed in 26% of NSCLC tumours [89]. Lung cancer cells become much more susceptible to ferroptosis under Nrf2 silencing. For instance, manoalide and trabectedin have been shown to induce Fe^{2+} overload by modulating the Nrf2/SLC7A11 axis, thereby triggering ferroptosis in lung cancer cells [90, 91]. Additionally, a novel ferroptosis inducer, S-3′-hydroxy-7′, 2′, 4′-trimethoxyisoxane (ShtIX), selectively eliminates NSCLC cells while sparing normal cells. Further research indicated that ShtIX induces ferroptosis in NSCLC cells by blocking the Nrf2/HO-1 signalling pathway [92].

Additionally, *Keap1* mutations are commonly found in NSCLCs such as LUAD and lung squamous carcinoma, and are strongly linked to poor prognosis and resistance to current treatments [55, 56, 93]. In a study using microRNA (miR)-6077-targeted inhibition of *Keap1* expression, the resulting initiation of antioxidant genes by Nrf2 was found to be a key factor in the inhibition of ferroptosis and generating cisplatin resistance in LUAD. Indeed, a combination of drugs targeting the sponging of miR-6077 effectively increased the sensitivity of LUAD cells to cisplatin [93]. Thus, the use of combined medications to address the drug resistance arising from *Keap1* mutations represents a promising novel approach to combat chemotherapy resistance in clinical settings.

Studies have shown that activation of the Nrf2/HO-1 pathway contributes to cisplatin resistance. Ginkgetin disrupts cellular

redox balance in cisplatin-treated cells by increasing ROS levels and suppressing the Nrf2/HO-1 pathway. This results in reduced expression of SLC7A11 and GPX4 [88]. Furthermore, co-administration of ginkgetin and cisplatin enhance cytotoxicity in NSCLC cells, consistent with recent findings indicating that cisplatin-resistant NSCLC cells might also be eliminated effectively with low-dose cisplatin combined with the ferroptosis agonist erastin/sorafenib [94]. Additionally, the erastin analogue PRLX93936 in combination with cisplatin was found to induce ferroptosis of NSCLC cells in a clinical trial. Further studies found that cisplatin and PRLX93936 co-treatment inhibited GPX4 over-expression, which was potentiated by *Nrf2* knockdown [95]. Increasing the sensitivity of cancer cells to erastin may likewise address the problem of erastin-induced resistance to ferroptosis. Both acetaminophen and MT1DP induce ferroptosis in cancer cells by reducing Nrf2 expression, thereby enhancing lipid peroxidation and sensitizing NSCLC cells to erastin [96, 97]. Clearly, Nrf2 plays a significant role in both anti-lung cancer treatment and resistance, indicating that Nrf2 inhibitors combined with other medications could be part of a successful treatment plan for lung cancer.

NRF2 PATHWAY AND THE ROLE OF FERROPTOSIS IN OTHER LUNG DISEASES

Particulate matter-mediated lung injury triggered by the Nrf2 and ferroptosis pathways

One of the most common types of ambient particulate matter is $PM_{2.5}$, which is a type of fine particulate matter with a diameter less than or equal to 2.5 μm that poses a significant threat to human health. Extensive research indicates that $PM_{2.5}$ can infiltrate the human respiratory system, disrupt pulmonary gas exchange, and contribute to the development and progression of respiratory disorders. Recent studies exploring ferroptosis have further revealed that exposure to $PM_{2.5}$ induces oxidative stress in mouse lungs. This oxidative stress is characterised by elevated levels of GSH and MDA, along with reduced expression of antioxidant enzymes such as SOD2, GPX4, and SLC7A11. Additionally, exposure to $PM_{2.5}$ upregulates the expression of fibrosis-related proteins (e.g. α-SMA) and collagen [98]. $PM_{2.5}$ can induce ferroptosis in lung cells, causing lung lesions that are mainly associated with inhibition of the Nrf2 signalling pathway. Thus, therapeutic approaches aimed at controlling the Nrf2 signalling pathway could mitigate $PM_{2.5}$-induced lung injury by alleviating ferroptosis in pulmonary tissues. Astragaloside IV has been shown to be beneficial in attenuating $PM_{2.5}$-induced lung injury. Astragaloside IV exhibits pharmacological effects that include anti-inflammatory and antioxidant properties, and enhances the expression of ferroptosis-related proteins GPX4 and SLC7A11, thereby regulating cellular iron transport and mitigating ferroptosis [99]. Furthermore, Astragaloside IV reduces the levels of pro-inflammatory cytokines interleukin (IL)-6, IL-1β, and tumour necrosis factor-α by modulating the Nrf2 signalling pathway. Melatonin and tectoridin reportedly have the same beneficial effects [100, 101]. Sipeimine and rosavin prevent ferroptosis by reducing the levels of Fe^{2+}, MDA, and inflammatory factors, offering therapeutic benefits in lung injury through phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT)-mediated Nrf2 expression. Research indicates that AKT enhances Nrf2 expression and regulates ferroptosis in lung injury [102]. However, this therapeutic effect is reversed by administration of the PI3K inhibitor LY294002, suggesting that sipeimine combined with rosavin regulates ferroptosis via the PI3K/AKT/Nrf2 pathway, addressing $PM_{2.5}$-induced damage to the lungs [103]. Given the link between $PM_{2.5}$-induced oxidative stress and the onset of ferroptosis in the lungs, enhancing the Nrf2 signalling pathway appears to be crucially important for preventing ferroptosis. Consequently, medications that regulate Nrf2/ferroptosis may 1 day be used to treat lung disorders brought on by $PM_{2.5}$.

Radiation-induced lung injury and pulmonary fibrosis

The most frequent and dangerous side effect of chest radiation therapy is lung damage, leading to conditions such as radiation-induced pulmonary fibrosis [104, 105]. The main mechanism for this condition is a radiation-triggered series of inflammatory responses that ultimately result in cellular demise [106]. Increasing research has revealed that GPX4 expression is dramatically decreased in lung tissues after radiation irradiation, suggesting the occurrence of ferroptosis. However, following administration of the ferroptosis inhibitors liproxstatin-1 or ferrostatin-1, the levels of inflammatory factors and ROS are reduced, endogenous antioxidant pathways related to Nrf2, HO-1, and NQO1 are upregulated, transforming growth factor-β expression is down-regulated, and iron ptosis is reduced in lung tissue [107]. Further studies revealed that p62 could facilitate the nuclear translocation of Nrf2 by interacting with Keap1, a promotional effect that could be cancelled by siRNA against *Keap1* [108]. Therefore, the reduction of ferroptosis through the p62-Keap1-Nrf2 pathway could serve as a useful treatment for radiological lung injury or fibrosis.

Other lung diseases

Nrf2 is implicated in the pathogenesis and progression of various pulmonary diseases, including pulmonary fibrosis (PF), high-altitude pulmonary oedema [107], plateau pulmonary oedema, and chronic obstructive pulmonary disease (COPD) [109]. According to one study [110], lung tissues from COPD patients exhibit ferroptosis due to hypermethylation of the CpG region of the *Nrf2* promoter, which in turn prevents expression of Nrf2/GPX4. Additionally, ferroptosis was found to occur in either plateau-type pulmonary oedema or paraquat-induced PF, whereas regulation of the Keap1/Nrf2/HO-1 pathway significantly upregulated ferroptosis-associated proteins and reversed ferroptosis [109, 111]. An in-depth study found that Nrf2-mediated regulation of ferroptosis may be related to mitochondrial ROS. By blocking mitochondrial ROS production, treatment with Mito-TEMPO successfully lowers RSL3 toxicity, increases cell antioxidant capacity, restores GPX4 expression, and prevents ferroptosis [112]. Although these findings indicate that the regulation of ferroptosis by Nrf2 in lung diseases may be related to the inhibition of mitochondrial ROS, further validation studies are necessary. We anticipate that elucidating the intrinsic link between the Nrf2 pathway and ferroptosis will be the key to treating lung diseases, as illustrated in Fig. 4.

SUMMARY AND DISCUSSION

Nrf2 plays an important role in the regulation of ferroptosis, which exhibits a dual role in lung diseases by modulating ferroptosis [113]. To prevent oxidative stress and the inflammatory response in acute and chronic progressive diseases, approaches to enhance the expression of Nrf2 and thereby inhibit ferroptosis should undoubtedly play a central role in treating ALI, COPD, and idiopathic PF in the future. By contrast, as therapeutic strategies for lung cancer have gradually developed, it has become clear how detrimental Nrf2 overexpression is to the treatment of lung cancer. Furthermore, Nrf2 overexpression raises the expression levels of FSP1, GPX4, SLC7A11, and other related proteins in lung cancer [114, 115], and obstructs the therapeutic process of ferroptosis activators by shielding lung cancer cells from ferroptosis. Therefore, in the treatment of lung tumours with *Keap1* deletion or Nrf2 overexpression, Nrf2 inhibitors should be administered to enhance the susceptibility of lung cancer cells to ferroptosis. Based on currently available research, there are three main mechanisms by which medications interact with Nrf2 to impact ferroptosis in lung disease (Fig. 5): (1) reduction of CoQ10 through the Nrf2-FSP1 axis to inhibit the generation of lipid peroxides, thereby mitigating the occurrence of cellular

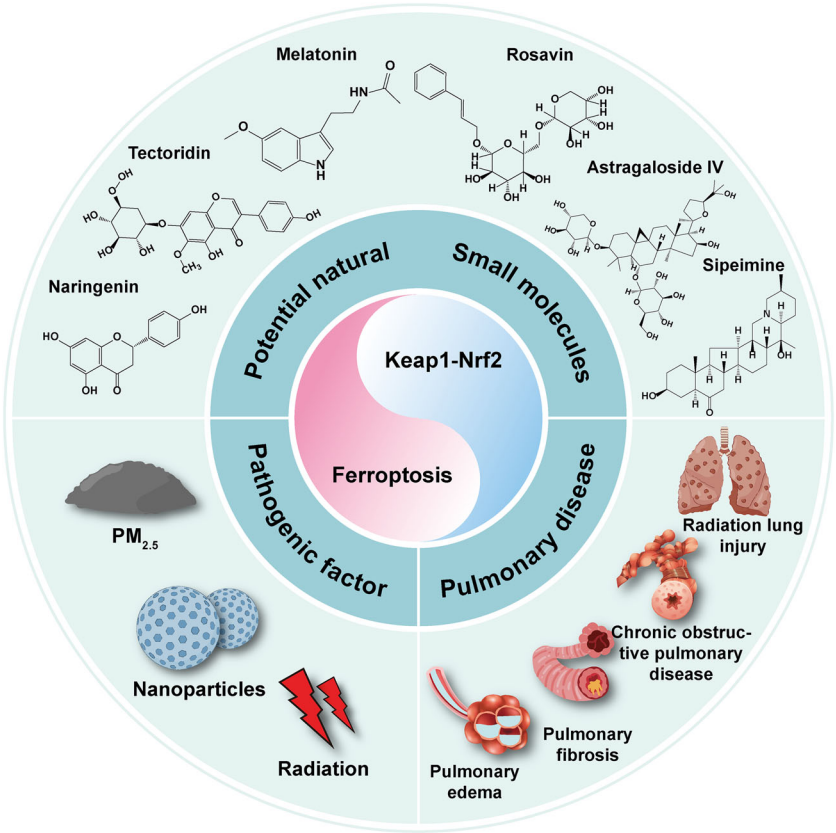

Fig. 4 The interaction of Keap1-Nrf2 and ferroptosis with various lung diseases, and potential therapeutic agents.

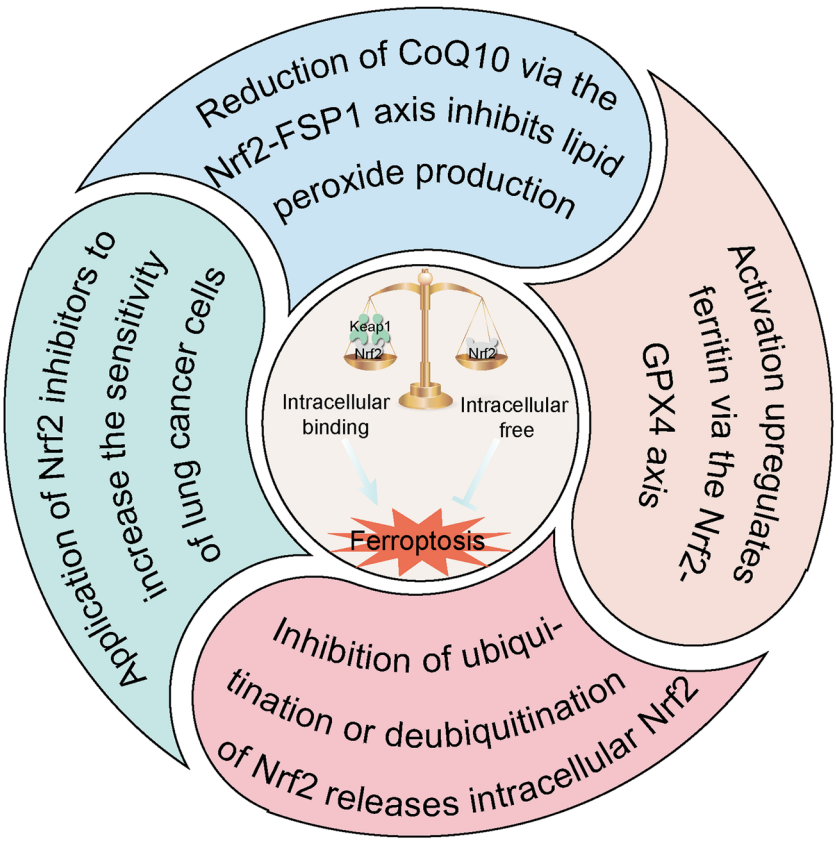

Fig. 5 Mechanisms of drugs that mediate Nrf2 to regulate ferroptosis in the treatment of lung diseases.

ferroptosis; (2) enhancement of antioxidant proteins (e.g. HO-1 and NQO1) via the crucially important Nrf2-GPX4 axis alongside increased protein expression of GPX4 and FTH to counteract ferroptosis; and (3) increased Nrf2 levels in lung tissues to prevent ubiquitination or deubiquitination of Nrf2, thereby facilitating its nuclear translocation and inhibiting ferroptosis. We predict that selective activation or inhibition of Nrf2 (as appropriate for different lung diseases), supplemented by drug therapy, will likely improve drug efficacy while reducing cellular tolerance to ferroptosis, and will become a major treatment approach for lung diseases in the future.

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AUTHOR CONTRIBUTIONS

YC carried out the primary literature search, drafted and revised the manuscript. ZJ helped modify the manuscript. XL revised and edited the final version of the manuscript. All authors read and approved the final manuscript

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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