Research progress on the regulation of ferroptosis in NPC (Review)

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Abstract. Ferroptosis is a novel form of iron-dependent programmed apoptosis, characterized by dysregulated iron metabolism, impaired antioxidant defense systems and accumulation of lipid peroxidation products. Nasopharyngeal carcinoma (NPC) cells exhibit marked susceptibility to ferroptosis, and its induction can effectively suppress tumor progression, offering a potential therapeutic strategy for NPC. At the molecular level, ferroptosis-related genes [such as Solute Carrier Family 7 Member 11 (SLC7A11), Glutamate-Cysteine Ligase Modifier Subunit (GCLM) and Glutamate-Cysteine Ligase Catalytic Subunit (GCLC)] are notably upregulated in NPC tissues compared with normal tissues, and their overexpression associates with poor patient prognosis, suggesting their utility as diagnostic or prognostic biomarkers. The present review systematically summarizes the molecular mechanisms of ferroptosis, elucidates its role in NPC pathogenesis and discusses ferroptosis-targeted therapeutic approaches for NPC.

Contents

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the mucosal epithelium of the nasopharynx, exhibiting distinct geographical distribution patterns. It is highly prevalent in regions such as South China (for example, Guangdong, Guangxi, Fujian and Hunan), Southeast Asia and North Africa (1). The pathogenesis of NPC involves genetic susceptibility, environmental factors and Epstein-Barr virus (EBV) infection, with EBV being a well-established oncogenic driver (1). Currently, the standard treatment for NPC primarily consists of radiotherapy combined with cisplatin-based concurrent chemoradiotherapy. However, chemotherapy resistance and severe side effects notably limit clinical efficacy (2). Consequently, there is a need to develop novel therapeutic strategies that are more effective, less toxic and capable of overcoming drug resistance.

In 2012, Dixon *et al* (3) first described ferroptosis as a novel iron-dependent form of programmed cell death, distinct from apoptosis, necrosis and other cell death modalities (4,5). In recent years, ferroptosis has garnered notable attention in cancer therapeutics, demonstrating particular promise in NPC research (6-13). Accumulating evidence indicates that ferroptosis participates in NPC progression regulation through multiple signaling pathways. Notably, NPC cells exhibiting resistance to conventional therapies or possessing highly metastatic characteristics often demonstrate increased susceptibility to ferroptosis (14). Consequently, targeting ferroptosis and its key regulatory proteins may represent a breakthrough therapeutic strategy for NPC.

Ferroptosis is a novel form of iron-dependent programmed cell death that is distinct from apoptosis and autophagy (15,16). Its core mechanism involves the catalysis of lipid peroxidation (LPO) in membrane polyunsaturated fatty acids (PUFAs) by ferrous iron (Fe^{2+}) or lipoxygenases (LOXs), leading to membrane damage and subsequent cell death. Characteristic morphological features include mitochondrial shrinkage and increased membrane density, while nuclear structure typically remains intact (17-19). Currently identified regulatory pathways of ferroptosis include: The system

cystine/glutamate transporter (Xc)-/glutathione (GSH)/GSH peroxidase 4 (GPX4) axis; guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4) pathway; dihydroorotate dehydrogenase (DHODH)-mediated pathway; membrane-bound O-acyltransferase 1/2 (MBOAT1/2)-monounsaturated fatty acid (MUFA) regulation; Nrf2 signaling; LPO mechanisms and apoptosis-inducing factor mitochondria-associated 2 (FSP1 otherwise known as AIFM2) pathway. The present review systematically examines the molecular mechanisms and key signaling pathways of ferroptosis. By integrating the epidemiological characteristics and risk factors of NPC, the present review elucidates the relationship between ferroptosis and NPC pathogenesis. Furthermore, the present review discusses the potential therapeutic value of targeting ferroptosis in NPC treatment, providing a theoretical foundation for developing novel anti-tumor strategies.

2. Molecular mechanisms and regulatory pathways of ferroptosis

Ferroptosis has emerged as a prominent research focus in cell biology as a distinct form of programmed cell death. A precise understanding of its definition and characteristics forms the essential foundation for in-depth investigation of this cell death mechanism. Defined as an iron-overload and reactive oxygen species (ROS)-dependent cell death process driven by lipid peroxide accumulation, ferroptosis reveals two key pathogenic factors: Iron ions and ROS (20-24). Morphologically, ferroptosis exhibits unique ultrastructural features: Markedly shrunken mitochondria with increased membrane density, reduced or vanished mitochondrial cristae, outer mitochondrial membrane rupture and loss of plasma membrane integrity (25-27). These characteristics distinctly differentiate ferroptosis from other cell death modalities such as apoptosis and necroptosis. Notably, nuclear morphology typically remains intact during ferroptosis, contrasting with classical apoptotic nuclear fragmentation.

These distinctive features suggest that ferroptosis is regulated through specific molecular mechanisms. In the following sections, the present study systematically elaborates on the key metabolic pathways and molecular mechanisms governing ferroptosis regulation.

Iron metabolism pathway. Iron is important for human survival, participating in physiological activities in the forms of Fe^{3+} and Fe^{2+}: It is not only a key participant in the electron transport chain during oxidative phosphorylation but also the core of heme in hemoglobin, responsible for oxygen transport in the blood. The majority of iron in the body is bound to proteins or stored by ferritin, with only a small amount of free iron forming the labile iron pool (LIP) (28). The transport, metabolism and storage of iron are tightly regulated because free Fe^{2+}, with its redox activity, can promote the generation of ROS through the Fenton reaction, exacerbating LPO (29-32). Extracellular Fe^{3+} first binds to transferrin and enters cells via endocytosis mediated by transferrin receptor 1. Within the endosome-lysosome system, as the pH decreases, Fe^{3+} dissociates and is reduced to Fe^{2+} by the metal reductase STEAP3, then transported to the cytoplasm by the divalent metal transporter 1 (33,34). In the cytoplasm, Fe^{2+} can be reduced and stored as Fe^{3+} by ferritin, exported out of the cell via ferroportin (FPN1/SLC40A1), involved in the synthesis of iron-containing proteins or exist as part of the transient LIP (35). Iron homeostasis is vital for cell survival and iron overload disrupts this balance, thereby inducing ferroptosis (Fig. 1).

LPO. Lipids are the core structural components of cell membranes and organelle membranes. Under normal physiological conditions, lipid oxidation and reduction maintain a dynamic balance, but cellular carcinogenesis or external stimuli can disrupt this equilibrium (36). Ferroptosis, a novel form of cell death, is characterized by oxidative damage to PUFA-containing phospholipids in cell membranes (37,38). PUFAs are the primary substrates of LPO and their oxidation severely disrupts membrane structure and function. By contrast, MUFAs can antagonize ferroptosis by inhibiting LPO (39-41). Thus, PUFA levels regulate both LPO and susceptibility to ferroptosis.

At the molecular level, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are key enzymes regulating PUFA incorporation into phospholipids. Inhibition or loss of their activity confers resistance to ferroptosis (42-44). Specifically, ACSL4 and LPCAT3 work synergistically to esterify arachidonic acid (AA) or adrenic acid (AdA) into phosphatidylethanolamine (PE). Subsequently, LOXs catalyze the formation of lipid hydroperoxides. The breakdown products of these peroxides attack proteins, induce plasma membrane rupture and ultimately drive ferroptosis (45-47) (Fig. 1).

System Xc-/GSH/GPX4 pathway. System Xc^- is composed of SLC7A11 (light chain) and SLC3A2 (heavy chain). As an important antioxidant defense mechanism in cells, it carries out a central role in regulating ferroptosis (48-51). Due to the limited ability of cells to synthesize cysteine intracellularly, they mainly rely on the Xc^- system to uptake extracellular cystine, this transporter effluxes intracellular glutamate and uptakes cystine at a 1:1 ratio and the latter is reduced to cysteine after entering the cell (52-54).

As a key precursor, cysteine, together with glutamate and glycine, is catalyzed by glutamate-cysteine ligase and GSH synthetase in sequence to synthesize GSH. GSH is an essential cofactor for GPX4, a selenium-dependent enzyme that can reduce toxic lipid peroxides (PL-PUFA-OOH) to harmless lipid alcohols (PL-PUFA-OH), maintaining redox homeostasis (49,50,55).

In addition, GSH reductase can regenerate oxidized GSH into reduced GSH, thereby maintaining the activity of GPX4 and blocking ferroptosis triggered by LPO (50,51,56). Therefore, the targeted regulation of the three-level defense network of cystine uptake, GSH synthesis and GPX4 function is an effective strategy for intervening in ferroptosis (Fig. 1).

The GCH1/BH4 pathway. GCH1-BH4 pathway is central to the regulation of ferroptosis (57). BH4 is generated from GTP through three enzymatic steps: GTP GCH1 catalyzes the formation of an intermediate, which then undergoes a cascade reaction involving 6-pyruvoyltetrahydropterin synthase and dihydrobiopterin (BH2) reductase to produce

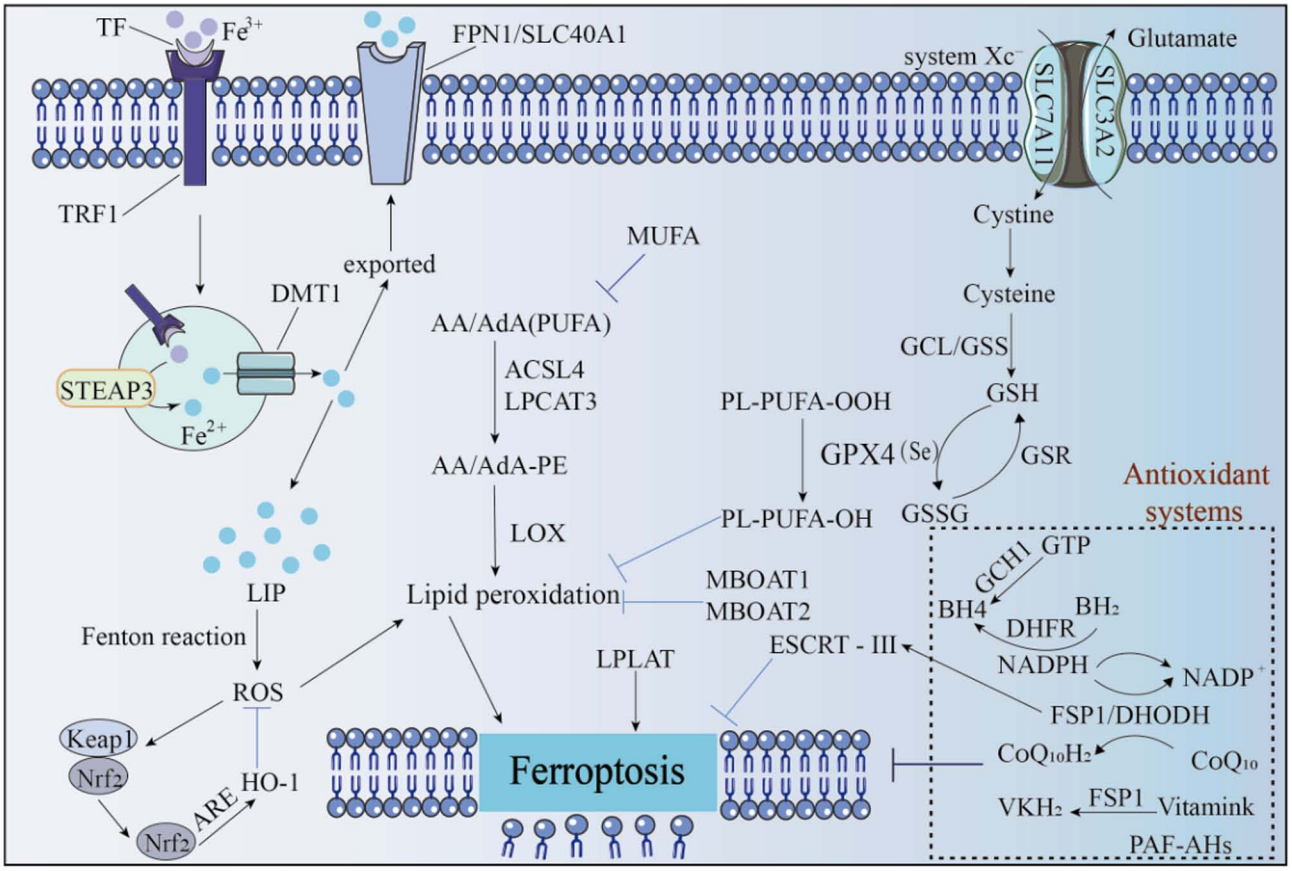

Figure 1. Ferroptosis pathway. Schematic depicts the global ferroptosis regulatory network, integrating antioxidant systems (such as, GSH-GPX4 and FSP1-CoQ10), iron/lipid metabolism molecules, MBOAT1/2, and antioxidant/membrane repair factors to cover key pro- and anti-ferroptosis links. GSH, glutathione; GSSG, GSH oxide; GPX4, GSH peroxidase 4; GSR, GSH reductase; FSP1, ferroptosis inhibitory protein 1; CoQ10, ubiquinone; CoQ10H2, ubiquinol; DHODH, dihydroorotate dehydrogenase; GTP, phosphohydrolases; GCH1, cyclohydrolase-1; BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; ACSL4, acyl-CoA synthetase long-chain family member 4; LOX, lipoxygenase; LPCAT3, lyso-phosphatidylcholine acyltransferase 3; PUFA, polyunsaturated fatty acids; CoA, coenzyme A; PL-PUFA, acids-polyunsaturated polyunsaturated fatty; HO-1, heme oxygenase 1; TRF1, transferrin receptor; DMT1, divalent metal transporter 1; Keap1, Kelch-like ECH associated protein 1; MBOAT1/2, o-acyltransferase 1/2; ESCRT, endosomal sorting complex, required for transport; CHAM5/6, charged multivesicular proteins 5 and 6; Glu, glutamic acid; PE-PUFA, unsaturated fat phospholipids; FPN, ferroportin; ARE, antioxidant response element; Se, Selenium; PL-PUFA-OOH, lipid hydroperoxide; VK, vitamin K; VKH2, hydroquinone; CoQ10, ubiquinone; CoQ10H2, ubiquinol; LPLAT, Lys phospholipid acyltransferase.

the final product. BH4 exhibits notable antioxidant activity and can directly neutralize lipid peroxides. As a rate-limiting enzyme, the expression level of GCH1 determines the sensitivity of cells to ferroptosis, its inhibition leads to impaired BH4 synthesis, triggering ROS accumulation and ferroptosis (58); conversely, overexpression promotes BH4 production, reduces ROS and confers resistance to ferroptosis (59,60).

BH4 and BH2 form a redox cycle that synergistically scavenges oxygen-free radicals to inhibit ferroptosis (61). This cycle is regulated by dihydrofolate reductase (DHFR), which uses NAD(P)H as a cofactor to reduce BH2 to BH4. Elevated BH4 levels can induce cellular lipid remodeling, reducing the proportion of phospholipids containing di-polyunsaturated fatty acyl groups (diPUFA) and thereby blocking ferroptosis (62).

Furthermore, BH4 enhances the biosynthesis of coenzyme Q10 (CoQ10) by promoting the synthesis of 4-hydroxybenzoic acid, associating the GCH1-BH4-DHFR pathway to the FSP1-CoQ10 axis and forming a synergistic anti-ferroptosis network (Fig. 1).

DHODH pathway. DHODH is another pathway involved in the resistance to ferroptosis (63). As a flavin-dependent protein, DHODH is located in the inner mitochondrial membrane. It can convert dihydroorotate into orotate, simultaneously reduce ubiquinone to ubiquinol and generate lipophilic antioxidants, thereby inhibiting the accumulation of LPO and carrying out an inhibitory role against ferroptosis (64). It is worth noting that there is a considerable synergistic effect between DHODH and GPX4 in mitochondria. The two work together to effectively reduce the degree of LPO and prevent ferroptosis from occurring in the inner mitochondrial membrane (57,65).

In the biosynthetic pathway of pyrimidine nucleotides, DHODH occupies a key position and carries out an indispensable role in the synthesis of DNA and RNA. Once DHODH is inhibited, this biosynthetic pathway will be disrupted, resulting in abnormal or even terminated synthesis of pyrimidine nucleotides (66). This further leads to a decrease in the availability of pyrimidine nucleotides, making the purine-pyrimidine base pairing process unable to proceed normally and ultimately severely hindering the synthesis of RNA (67). Since RNA is a cofactor of GSH, a decrease in the

amount of RNA will lead to an increase in the amount of GSH. At this time, GPX4 can reduce the peroxidized lipids back to their original state. As the level of LPO decreases, the process of ferroptosis is inhibited and the incidence of ferroptosis also decreases accordingly (68,69) (Fig. 1).

MBOAT1/2-MUFA pathway. Liang *et al* (70) revealed that membrane-bound proteins MBOAT1 and MBOAT2 are novel sex hormone-dependent inhibitors of ferroptosis. As members of the lysophospholipid acyltransferase (LPLAT) family, they can specifically select MUFAs as substrates, catalyze their binding to lysophosphatidylethanolamine, increase intracellular PE-MUFA levels and reduce PE-PUFA levels.

PE-PUFAs are the preferred substrates for LPO, and their content directly affects the degree of LPO and cellular sensitivity to ferroptosis. Thus, MBOAT1 and MBOAT2 regulate the composition of unsaturated fatty acids in membrane phospholipids, reducing oxidizable PE-PUFAs and increasing stable PE-MUFAs, to form a defense against ferroptosis, effectively inhibiting its occurrence (71). Further studies showed that their expression and function are specifically regulated by sex hormone receptors: MBOAT1 is regulated by estrogen receptors, with activity related to estrogen signaling; MBOAT2 is regulated by androgen receptors, with function dependent on androgen signal activation. This makes their ferroptosis-inhibiting effect sex hormone-dependent, providing a new perspective for analyzing the differential regulation of ferroptosis under different sex or hormonal microenvironments (70,72,73). This mechanism does not rely on classical pathways (70) such as GPX4 or AIFM2, but acts by directly remodeling the fatty acid composition of membrane phospholipids, adding new insights into the complexity and diversity of the ferroptosis regulatory network (Fig. 1).

FSP1-COQ10-NAD(P)H pathway. FSP1, a type II nicotinamide adenine dinucleotide-H (NADH): quinone oxidoreductase (NDH-2) with N-terminal hydrophobic/membrane (aa 1-27), NADH oxidoreductase (aa 81-285) and FAD (aa 286-308) domains (74), is a key anti-ferroptosis factor. Its GSH-independent antioxidant pathway, parallel to GPX4, regulates iron metabolism and protects against iron-dependent death (75).

Guo *et al* (76-78) showed FSP1 inhibits ferroptosis by generating antioxidant CoQ, reducing intracellular oxidized CoQ; exogenous CoQ fails to reverse ferroptosis in FSP1-deficient cells, indicating an endogenous role for CoQ. FSP1 mediates the NAD(P)H pathway, reducing membrane-bound NAD(P)H-dependent ubiquinone (oxidized CoQ) to ubiquinol (reduced CoQ) (79) (Fig. 1).

Vitamin K, a lipophilic molecule with 2-methyl-1,4-naphthoquinone and polyisoprene side chains (plant-derived phylloquinone K1; animal/bacterial menaquinone K2), converts to hydroquinone (VKH2) for the vitamin K cycle (79,80-82). FSP1 acts as a vitamin K reductase, consuming NAD(P)H to produce VKH2, which inhibits ferroptosis by blocking LPO (83,84) (Fig. 1).

Additionally, FSP1 enhances membrane repair via the ESCRT-III-dependent pathway (CoQ-independent) to inhibit ferroptosis (85). Ferroptosis inducers trigger FSP1 to suppress tumor cell ferroptosis; FSP1 knockout blocks RSL3-induced plasma membrane expression of CHMP5/6, while CHMP5 overexpression reverses inducer- and FSP1 knockout-induced cell death (86-89) (Fig. 1).

The Nrf2 pathway. Nrf2, the core of cellular antioxidant responses, binds to antioxidant response elements (AREs) to promote downstream gene transcription (90). It carries out a key role in regulating ferroptosis as an important transcription factor against it, involved in iron, lipid and amino acid metabolism (91). Its regulated antioxidant effectors [such as heme oxygenase-1 (HO-1) and GSH] which contain AREs (92). Elevated ROS activate the p62-Keap1-Nrf2 pathway: Nrf2 dissociates from Keap1, translocates to the nucleus, binds to AREs, initiates transcriptional cascades and upregulates downstream antioxidant genes, which is important for maintaining redox balance and inhibiting ferroptosis (77) (Fig. 1).

Additionally, cytoplasmic platelet-activating factor (PAF) acetylhydrolase (II) specifically inhibits short-chain fatty acid oxidation, blocks oxidized phospholipid (such as PAF) accumulation by interfering with cellular redox capacity, thus inhibiting ferroptosis (78). whereas LPLAT disrupts lipid bilayers, increases membrane permeability and triggers ferroptosis (93) (Fig. 1).

3. The incidence status and risk factors of NPC

NPC is a malignant tumor originating from the mucosal epithelium of the nasopharynx. Its incidence shows obvious regional characteristics and is particularly high in Southeast Asia and North Africa (79). The pathogenesis of this disease is multifactorial, involving the complex interaction of various risk factors such as genetic susceptibility, environmental exposure, EBV infection and lifestyle (79).

Genetic and environmental risk factors

Genetic factors. Genetic factors carry out an important role in the pathogenesis of NPC. Epidemiological studies have shown that NPC exhibits notable familial aggregation. The risk of disease in first-degree relatives is markedly compared with that in the general population, indicating the key role of genetic susceptibility in the occurrence of this disease (80-82). Currently, it is considered that specific gene polymorphisms (such as the HLA gene cluster), mutations in tumor susceptibility genes (such as TP53) and epigenetic changes may jointly affect the susceptibility of an individual to NPC. In addition, genetic factors may interact with environmental factors (such as EBV infection), further increasing the risk of developing the disease (Table I).

Environmental factors. Environmental exposure is one of the important risk factors for NPC. Long-term exposure to air pollutants (such as PM2.5, sulfur dioxide and nitrogen oxides) can lead to chronic inflammation of the nasopharyngeal mucosa and DNA damage, thus promoting malignant transformation (94). In addition, occupational exposure to certain chemical carcinogens (such as formaldehyde or benzo(a)pyrene) may also increase the risk of NPC. Viral infection carries out a central role in the development of NPC, especially EBV infection. EBV can infect nasopharyngeal epithelial cells. By expressing latent membrane proteins (LMP) 1 and 2 and oncogenic proteins such as EBV nuclear antigen 1 (EBNA1),

Table I. Summary of possible risk factors for NPC.

Factor classification	Specific factors	Associated with NPC morbidity
Hereditary factor	Familial aggregation	Notably higher risk
Environmental factor	Air pollutant	DNA damage and mutation
Occupational exposure	Exposure to chemical carcinogens	Increase of risk
Living habit	Smoke	The risk of mucosal injury and canceration increases
Excessive drinking	The formation of DNA adducts intensifies the risk	
Dietary factor	Pickled food	The formation of carcinogens increases the risk
High-temperature cooking	Smoke causes cancer and promotes tumor occurrence	
EBV infection	Core pathogenic factors	Oncogenic protein expression, genomic instability
Genomic instability	Key mechanism	Gene mutation, deletion and tumor occurrence and development

NPC, nasopharyngeal carcinoma.

it can interfere with the regulation of the cell cycle and induce genomic instability (86,95) (Table I).

Lifestyle habits. Unhealthy lifestyles are modifiable risk factors for NPC. Smoking can notably increase the risk of developing the disease. Carcinogens in tobacco, such as nitrosamines and polycyclic aromatic hydrocarbons, can directly damage the nasopharyngeal mucosa and promote the oncogenic effect of EBV (87,88). Excessive alcohol consumption may induce the formation of DNA adducts through metabolites (such as acetaldehyde), exacerbating mucosal damage (89). Dietary factors also play a key role. Long-term consumption of pickled foods (such as salted fish and cured meat) may increase the risk of NPC because they are rich in nitrites, which can be converted into the potent carcinogen N-nitroso compounds in the body (85). In addition, heterocyclic amines and polycyclic aromatic hydrocarbons produced by high-temperature cooking (such as grilling and smoking) may also promote tumorigenesis (Table I).

The influence of EBV infection on NPC. EBV belongs to the gammaherpesvirus family and is widely prevalent in the human population, with >90% of adults having been infected. It can establish a lifelong latent state in epithelial cells and B cells. EBV is closely associated with a variety of lymphoid malignancies, such as Burkitt's lymphoma, Hodgkin's lymphoma, B-cell lymphoma, NK/T-cell lymphoma, as well as two types of epithelial cancer: NPC and gastric cancer (96). EBV exhibits two distinctly different life cycle states: lytic (productive) and latent (persistent). During primary infection, EBV first replicates in nasopharyngeal epithelial cells, then crosses the epithelial layer of the nasopharyngeal lining, infects naive B cells and continues to replicate, and finally establishes a stable latent state in host cells in the form of histone-associated episomes. To maintain latent viruses and serve as a stable reservoir for EBV-induced tumorigenesis, latent viruses need to be periodically reactivated. In NPC, the prevalence of type 2 and type 3 EBV reaches 100%, and high-level viral reactivation is a risk factor for EBV-associated NPC (97). The interaction between EBV infection, environmental factors, and genetic factors is the core of the pathogenesis of NPC. Recent studies have shown that abortive lytic infection promotes the establishment of the latent state during primary infection and the development of EBV-associated tumors. In-depth exploration of the mechanisms by which EBV viral products drive the development of NPC will help design more effective EBV-targeted therapies (98,99).

During the latent period, the virus only expresses a small number of genes key for genome maintenance and regulation. Based on late gene expression profiles, EBV latency can be divided into four types (100,101). In NPC, EBV infection is largely in type 2 latency, during which EBNA1, LMP1 and LMP2 protein are expressed. At the same time, some non-coding RNAs are also expressed, such as EBV-encoded RNA (EBER), BamHI A rightward transcript (BART), and BART miRNA. These expressed viral genes provide signals necessary for the maintenance of replication and survival of both EBV and host cells. However, EBV lytic phase proteins, such as BGLF5 (DNase) and BALF3, cause host genome instability and play an important role in the tumorigenesis of NPC (100).

Regulation of ferroptosis in NPC by EBV. Ferroptosis is a novel form of programmed cell death, characterized by iron-dependent accumulation of lipid peroxides, which ultimately leads to cell death (102,103). The occurrence of ferroptosis is associated with the balance of intracellular iron metabolism, lipid metabolism and antioxidant systems. In the field of tumor research, abnormal regulation of ferroptosis is associated with the occurrence, development and therapeutic sensitivity of tumors (104-106). The regulatory role of EBV

infection on ferroptosis in NPC is an important content that urgently needs to be supplemented and improved in current research. In the type 2 latency of EBV infection in NPC, the expressed EBNA1, LMP1, LMP2 proteins and non-coding RNAs such as EBER, BART and BART miRNA may carry out key roles in regulating the ferroptosis process (107-109).

EBNA1, as an important nuclear antigen during EBV latency, not only participates in the replication and maintenance of the viral genome but also affects the physiological functions of host cells by regulating intracellular signaling pathways. Studies have shown that EBNA1 can affect the expression of intracellular antioxidant-related genes by activating the NF-κB signaling pathway. The activation of the NF-κB signaling pathway can promote the expression of GPX4 (110-113). As a key inhibitor of ferroptosis, GPX4 can inhibit the occurrence of ferroptosis by reducing LPOs to non-toxic alcohols. Therefore, EBNA1 may upregulate the expression of GPX4 by activating the NF-κB signaling pathway, thereby inhibiting ferroptosis in NPC cells and providing favorable conditions for the survival of cancer cells (114).

As a transmembrane protein, LMP1 can mimic the signal transduction function of members of the tumor necrosis factor receptor family and activate a variety of intracellular signaling pathways, such as MAPK and PI3K/Akt (115,116). Among them, the activation of the PI3K/Akt signaling pathway can promote the degradation of intracellular iron regulatory protein 2 (IRP2). IRP2 can bind to the mRNAs of ferritin heavy chain (FTH1) and ferritin light chain (FTL), inhibiting their translation and thus reducing the synthesis of intracellular ferritin (117,118). Ferritin is an important protein for intracellular iron storage; a decrease in ferritin content leads to an increase in intracellular free iron levels, which in turn promotes the occurrence of ferroptosis. However, after LMP1 activates the PI3K/Akt signaling pathway, it can increase the expression of FTH1 and FTL by promoting the degradation of IRP2, thereby increasing the intracellular ferritin content and reducing free iron levels, which inhibits ferroptosis in NPC cells (119,120). In addition, LMP1 can also upregulate the expression of SLC7A11 by activating the MAPK signaling pathway. SLC7A11 is an important component of the Xc-, which can promote the entry of cystine into cells and provide raw materials for the synthesis of GSH. GSH is an important coenzyme for GPX4 to exert its antioxidant effect; an increase in GSH content can enhance the activity of GPX4 and further inhibit the occurrence of ferroptosis (121-124).

LMP2 protein mainly includes two subtypes: LMP2A and LMP2B, among which LMP2A carries out an important role in the occurrence and development of NPC. LMP2A can activate signaling pathways such as PI3K/Akt and MAPK by mimicking the signal transduction of the B-cell receptor and its regulation of ferroptosis may be similar to that of LMP1. In addition, studies have found that LMP2A can affect the expression of intracellular iron metabolism-related genes, such as downregulating the expression of TFR1 (125-128). TFR1 is an important receptor for iron uptake by cells; a decrease in TFR1 expression reduces iron uptake by cells, lowers intracellular iron levels and thereby inhibits the occurrence of ferroptosis.

EBER is a small non-coding RNA encoded by EBV, mainly including two types: EBER1 and EBER2. Although EBER does not encode proteins, it can regulate the physiological functions and signaling pathways of cells by interacting with a variety of host cell proteins. Studies have shown that EBER can induce the production of IFNs by activating the toll-like receptor 3 signaling pathway and IFN can affect the balance of intracellular iron metabolism and antioxidant systems. In addition, EBER can also interact with RNA-activated protein (RIG-I) to activate downstream signaling pathways and regulate the expression of associated genes, which may further affect ferroptosis. For example, after EBER activates the RIG-I signaling pathway, it can promote the production of pro-inflammatory cytokines and some pro-inflammatory cytokines can upregulate the expression of SLC7A11 and inhibit the occurrence of ferroptosis.

Regulation of ferroptosis by EBV lytic phase-related proteins. EBV lytic phase proteins, such as BGLF5 and BALF3, not only cause host genome instability but also may regulate ferroptosis in NPC cells (103). BGLF5 is a DNase expressed during the EBV lytic phase, which can degrade the DNA of host cells and viruses, leading to genome instability. Genome instability causes an increase in intracellular oxidative stress levels and oxidative stress is one of the important inducers of ferroptosis (129-131). By degrading DNA, BGLF5 may increase intracellular ROS levels; ROS can attack intracellular lipid molecules, trigger LPO reactions and thereby promote the occurrence of ferroptosis. In addition, BGLF5 may also regulate the cellular stress response by affecting the expression of intracellular DNA damage repair-related genes, further influencing the process of ferroptosis. For example, BGLF5 can inhibit the expression of DNA damage repair proteins, preventing cells from effectively repairing DNA damage, leading cells to be in a continuous stress state and increasing their sensitivity to ferroptosis (132,133).

BALF3 is a DNA helicase expressed during the EBV lytic phase and is involved in the replication and packaging of viral DNA. In the process of exerting its biological functions, BALF3 may affect the intracellular redox balance and iron metabolism. Studies have shown that BALF3 can interact with certain intracellular antioxidant proteins, inhibiting their activity, reducing the antioxidant capacity of cells and thereby increasing the sensitivity of cells to ferroptosis (134-136). In addition, BALF3 may also regulate the expression of iron metabolism-related genes, such as upregulating the expression of TFR1, increasing iron uptake by cells, raising intracellular iron levels and promoting the occurrence of ferroptosis (137,138).

In addition to BGLF5 and BALF3, the EBV lytic phase also expresses a variety of other proteins, such as ZEBRA (BZLF1) and RTA (BRLF1). These proteins carry out key roles in initiating EBV lytic infection and may also regulate ferroptosis. For example, ZEBRA can regulate the expression of intracellular oxidative stress and iron metabolism-related genes by activating a variety of signaling pathways, thereby influencing the occurrence of ferroptosis (139,140). RTA can also interact with host cell proteins, affecting the physiological functions and signaling pathways of cells, which may indirectly affect ferroptosis (141,142).

In summary, EBV can regulate the ferroptosis process of NPC cells from multiple aspects, including iron metabolism, lipid metabolism and antioxidant systems, through its

latency-related molecules and lytic phase-related proteins. In-depth study of the mechanism by which EBV regulates ferroptosis in NPC can not only improve the research on the pathogenesis of EBV and NPC but also provide new targets and strategies for the treatment of NPC (102,143,144). For example, designing corresponding inhibitors or antagonists targeting key molecules or signaling pathways involved in EBV-regulated ferroptosis may enhance the sensitivity of NPC cells to ferroptosis and improve the therapeutic effect of NPC (145,146) (Table I).

The influence of genomic instability on NPC. Genomic instability refers to an increased tendency for errors in DNA replication or repair, leading to changes such as mutations and deletions in the genome. Causes for genomic instability include endogenous abnormal cellular processes and exogenous environmental factors (such as radiation, chemicals and viruses) (147). There is evidence indicating that genomic instability is key in the development of NPC and several factors can promote the genomic instability of NPC. For example, EBV can cause DNA damage, inhibit the DNA repair mechanism of infected cells and increase the risk of mutations and chromosomal abnormalities. Exposure to environmental factors such as tobacco smoke, alcohol, formaldehyde and nitrosamines is associated with DNA damage and genomic instability, which can trigger NPC (148-150). Genetic factors (such as mutations in tumor suppressor genes or DNA repair genes) can also increase the susceptibility to NPC by impairing the ability of a cell to maintain genomic stability.

As a malignant tumor, NPC has complex and diverse clinical manifestations and early diagnosis is difficult. The clinical manifestations of NPC vary with the progression of the disease course. In the early stage, NPC may have no obvious symptoms. Some patients with NPC may have mild symptoms such as blood in nasal discharge or nasal bleeding. These symptoms are often ignored by patients, thus delaying the best treatment opportunity. As the disease progresses, the symptoms of NPC gradually become more obvious, including nasal bleeding, ulcers or cauliflower-like masses, tinnitus, hearing loss, nasal congestion, persistent unilateral headache or eye symptoms (151,152). Currently, radiotherapy alone or in combination with chemotherapy is the main treatment method for NPC; however, a large number of patients succumb to NPC due to recurrence and tumor metastasis. Distant metastasis is an important cause of treatment failure and mortality in patients with NPC. Previous studies have shown the key role of ferroptosis in tumor metastasis, emphasizing the importance of ferroptosis in tumor growth and metastasis (13,153-155). Determining new anti-cancer strategies and discovering new drugs that induce ferroptosis will be beneficial for improving the cure rate of advanced patients with NPC (Table I).

4. The role and mechanism of ferroptosis in the occurrence of NPC

Role of abnormal iron metabolism in NPC. NPC development is associated with abnormal iron metabolism. Cancer cells, with higher iron demand, accumulate intracellular iron by increasing Trf for enhanced uptake and regulating genes to reduce iron transport/storage (156). High iron levels trigger Fenton reactions, leading to LPO accumulation, membrane damage and exacerbated ferroptosis (possibly via antioxidant system inhibition). Iron imbalance also fuels proliferation, oxidative stress and DNA damage, accelerating progression (Fig. 2).

Role of SLC7A11 in NPC. As a key Xc^- component, SLC7A11 mediates cystine uptake and glutamate efflux; cystine is reduced to GSH synthesis, resisting ROS. In NPC, overexpressed EGFR stabilizes SLC7A11 (kinase-independently) to inhibit ferroptosis. SLC7A11 knockdown induces ROS accumulation, ferroptosis-related protein upregulation and subcellular changes (157). Sorafenib can activate the ATF4-CHOP signaling axis to upregulate the expression of CHOP protein; CHOP directly inhibits the expression of SLC7A11 (a key subunit of the cystine/glutamate antiporter system), ultimately enhancing cellular sensitivity to ferroptosis (158) (Fig. 2).

Role of the Nrf2 signaling pathway in NPC. Ferroptosis interacts with other pathways in regulating NPC, such as the FGF5/FGFR2/Nrf2 pathway inhibits ferroptosis and reduces cisplatin sensitivity. Cancer-associated fibroblasts (CAFs)-secreted FGF5 binds FGFR2, activating Nrf2 to inhibit ferroptosis (159), indicating a role for CAFs and potential targets (Fig. 2).

Role of GPX4 in NPC. GPX4, a key antioxidant enzyme converting lipid peroxides to inactive forms, has higher positivity in nasopharyngeal carcinoma (NPC) tissues than normal nasopharyngeal tissues (102). Its expression associates with clinical features of NPC: Higher in stage III-IV vs. I-II NPC, poorly vs. well-differentiated tumors, patients with vs. without lymph node metastasis, and those with poor vs. good radiotherapy response. Moreover, GPX4-positive NPC cases have lower 5-year survival rates than GPX4-negative cases (160), indicating high GPX4 as a poor prognosis marker for NPC (Fig. 2).

5. The application of ferroptosis in the treatment of NPC

PRMT4 reduces erastin-induced ferroptosis in cisplatin-resistant NPC cells via the Nrf2/GPX4 pathway. The protein arginine methyltransferase (Prmt) family catalyzes the methylation of arginine residues in both histones and non-histone proteins. As a key post-translational modification, arginine methylation is widely involved in regulating various cellular processes. Prmt4, also known as coactivator-associated arginine methyltransferase 1, is the first identified member of the PRMT family. It can catalyze the asymmetric dimethylation of arginine residues in protein substrates, carries out a key role in the regulation of gene transcription and participates in the modulation of multiple cellular processes (161).

Studies have shown that Prmt4 is overexpressed in a variety of tumors, including breast cancer, prostate cancer and colorectal cancer (162-164). Its overexpression activates key factors of multiple oncogenic signaling pathways, such as FOS, E2F1, Wnt/β-catenin and nuclear receptor coactivator 3 (NCOA3/AIB1), thereby creating a favorable microenvironment for tumor growth, invasion and metastasis. A study

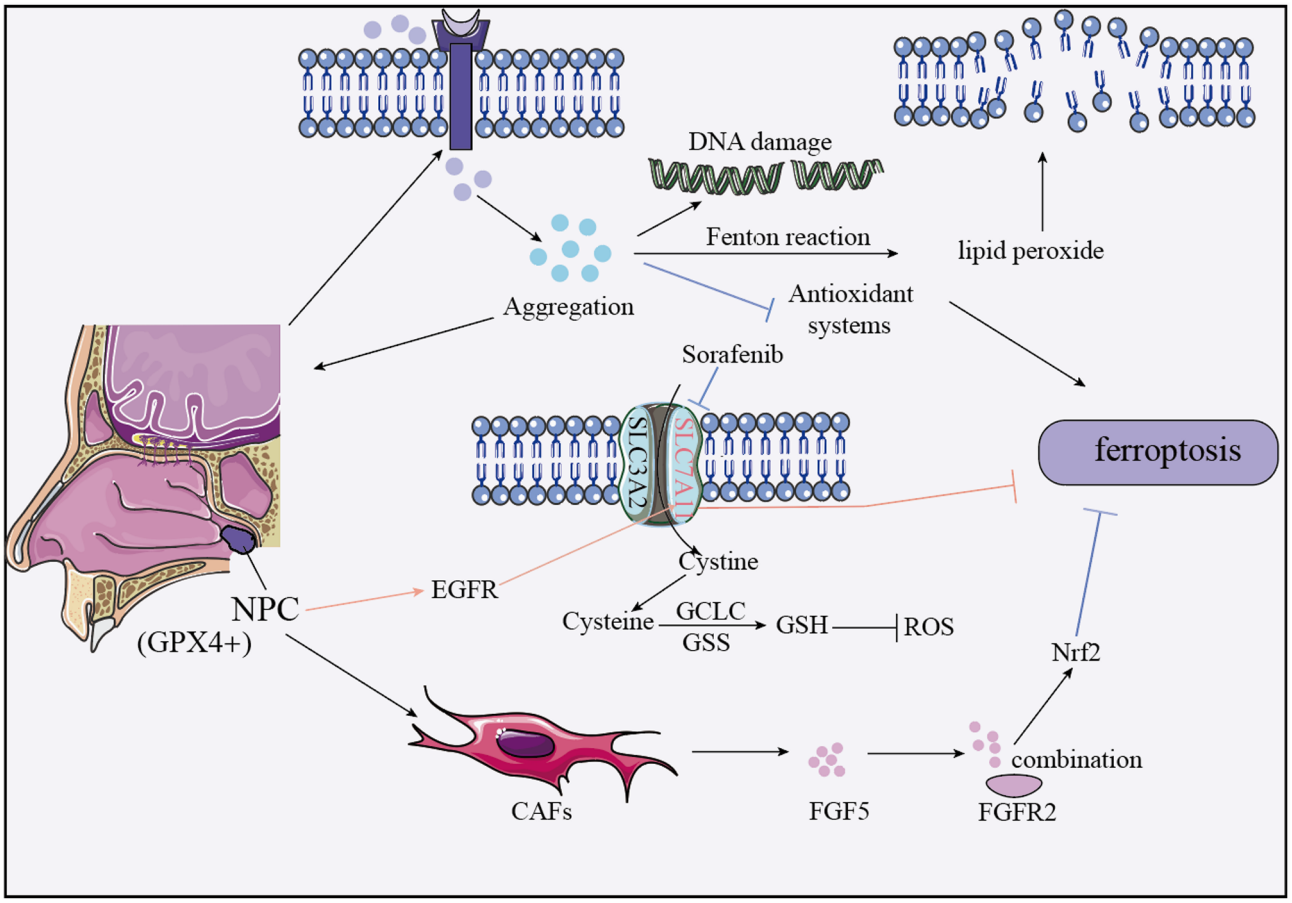

Figure 2. The ferroptosis pathway associated with NPC. The schematic illustrates the core ferroptosis regulatory pathway in NPC, involving the GSH-GPX4 axis, SLC7A11/SLC3A2-mediated cystine uptake and ROS balance, as well as the regulatory role of FGF5 secreted by CAFs in the tumor microenvironment. NPC, nasopharyngeal carcinoma; GSH, glutathione; GSS, GSH oxide; GPX4, GSH peroxidase 4; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; ROS, reactive oxygen species; CAFs, cancer-associated fibroblasts; FGF5, fibroblast growth factor.

by Pu *et al* (161) further revealed that the upregulation of PRMT4 reduces the sensitivity of cisplatin-resistant NPC cells to erastin-induced ferroptosis through mitochondrial damage; additionally, the interaction between PRMT4 and Nrf2 promotes the enzymatic methylation activity of PRMT4. These findings indicate that m6A methylation enhances the stability of PRMT4 in cisplatin-resistant NPC cells, thereby affecting the erastin-induced ferroptosis process.

Currently, research on PRMT4 is mainly in the preclinical stage. Although notable achievements have been made in cellular and animal experiments, progress in clinical trials is relatively slow. The application of PRMT4 as a therapeutic target for tumors faces numerous challenges in clinical practice. Firstly, due to the complexity of the human physiological environment, PRMT4-targeted drugs are difficult to act precisely and tend to interfere with the normal physiological functions of healthy cells, leading to adverse reactions such as myelosuppression and liver injury. Secondly, tumor cells exhibit high heterogeneity, and there are key differences in PRMT4-related characteristics (including expression level, activity and associated signaling pathways) among tumor cells from patients with different types of cancer or even within the same cancer type, making it difficult to develop a unified and effective treatment regimen. Thirdly, long-term use of PRMT4 inhibitors may lead to tumor drug resistance; tumor cells can evade the effects of drugs through alternative pathways or gene mutations, thereby impairing therapeutic efficacy (161). Therefore, to promote the translational application of PRMT4-targeted tumor therapy in the future, it is necessary to optimize the specificity of drugs and reduce their toxic and side effects by leveraging structural biology and targeted delivery technologies; establish personalized diagnosis and treatment regimens through multi-omics stratification and predictive models; and clarify the mechanisms of drug resistance while exploring the combined use of PRMT4 inhibitors with ferroptosis inducers (such as erastin) and chemotherapeutic drugs (such as cisplatin) to reverse drug resistance (Table II).

α-Solanine induces ferroptosis in NPC by targeting the HSP90α/p53 axis. Cui *et al* (165) subcutaneously injected HK-1 cells into BALB/c nude mice, and continuously administered α-solanine for 15 days after tumor formation (administration group). Analysis revealed that compared with the tumor-bearing non-drug-administered group, α-solanine was effective in inhibiting the growth rates of tumor volume and tumor weight. To determine whether the administered dose of α-solanine was toxic to the mice, the researchers also evaluated its effects on the body weight and internal organs of the mice. Treatment with α-solanine had no effect on the body weight of the mice and the detection of relevant

Table II. Analysis table of therapeutic-related elements and experimental effects.

Therapeutic factor	Signaling pathway	Key molecule	*In vitro* results	*In vivo* results	Therapeutic effect	(Refs.)
PRMT4	The Nrf2/GPX4 pathway	Upregulates PRMT4, Nrf2 and GPX4	Reduces ferroptosis induced by erastin	Reduce the susceptibility of cisplatin-resistant cells in NPC to ferroptosis	Prevents the development of NPC	(161)
α-Solanine	The HSP90α/p53 axis	No effect: HSP90α Upregulates: p53 Downregulates: GPX4, SLC7A11	Inhibits cell proliferation	Inhibits the growth of tumor volume and weight and is non-toxic to mice	Induces ferroptosis in nasopharyngeal carcinoma cells	(165)
GSTM3	Regulates GPX4	Overexpression of GSTM3, upregulates: GPX4 and 4-HNE	Promotes radiation-induced ferroptosis in cells	Overexpression of GSTM3 combined with IR treatment markedly reduced the size and weight of the tumor	Enhances the radiosensitivity of NPC	(160)
BBR	The Xc-/GSH/GPX4 axis	Downregulates: GPX4, SLC7A11 and SLC3A2	Inhibits cell metastasis	The metastatic lesions decreased, and the protein expression of GPX4, SLC7A11 and SLC3A2 increased	Inhibits the metastasis of NPC	(187)
Isoquercitrin	AMPK/NF-κB pathway	Downregulates: p-p65/p65, p-IκB/IκB, IL-1β and p-AMPK/AMPK	Induces ferroptosis	Reduces tumor weight and decreases the expression of ferroptosis-related markers	Inhibits the occurrence of NPC	(204,209)
CuB	Directly targets ferroptosis-related molecules	Downregulates: GPX4	The contents of iron and lipid peroxides in cells increase	The tumor volume shrank and no toxic or pathological changes were observed in the major organs	Induces ferroptosis in NPC cells	(227)
Disulfiram/copper	ROS/MAPK and ferroptosis pathway	Upregulates: p53, p21, BAX and ROS	Cell death	Tumor growth was inhibited, but there was no change in the body weight of the mice	Induces the death of NPC cells	(228)
P4HA1	Activates HMGCS1	Upregulates: HMGCS1	Enhances ferroptosis resistance	Promotes the proliferation and survival of NPC cells	Promotes the progression of NPC	(248)
Icaritin	Regulates ferroptosis	Upregulates: ACSL4 Downregulates: GPX4	Promotes ROSaccumulation, leading to DNA damage and G2 phase arrest of NPC cells		Increases the sensitivity of NPC cells to radiotherapy	(255)

PRMT4, protein arginine methyltransferase 4; Nrf2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; HSP90α, heat shock protein 90 αfamily class A member 1; p53, tumour suppressor gene TP53; SLC7A11, recombinant solute carrier family 7, member 11; GSTM3, glutathione-S-transferase mu 3; 4-HNE, 4-hydroxynonenal; BBR, berberine; SLC3A2, recombinant solute carrier family 3, member 2; AMPK/NF-κB, AMP-dependent protein kinase/nuclear factor-κB; p-p65/p65, phosphorylated p65/NF-κB p65; p-IκB/IκB, phosphorylated IκB/NF-κB kinase; IL-1β, interleukin-1β; p-AMPK/AMPK, phosphorylated AMP-activated protein kinase/AMP-activated protein kinase; CuB, cucurbitacin B; p21,cyclin-dependent kinase inhibitor 1; BAX, Bcl-2-associated X protein; ROS, reactive oxygen species; P4HA1, prolyl 4-hydroxylase subunit α1; HMGCS1,3, -hydroxy-3-methylglutaryl coenzyme A synthetase 1; ACSL4, Acyl-CoA synthetase long-chain family member 4.

indicators of the important organs (heart, liver and kidney) of the mice also showed no notable differences between the model group and the administration group, indicating that the drug was non-toxic. At the same time, the researchers further measured ferroptosis-related indicators of the mice after the administration of α-solanine. Consistent with the results of *in vitro* experiments (specifically, the *in vitro* experiments on HK-1 nasopharyngeal carcinoma cells treated with α-solanine, which were conducted as part of the same study to verify the regulatory effect of α-solanine on ferroptosis-related proteins), compared with the model group (tumor-bearing non-drug-administered group), GPX4 and SLC7A11 in the administration group were markedly downregulated. Moreover, α-solanine had no effect on the expression level of HSP90α in the xenograft tumors, while increasing the level of p53. This implies that α-solanine stimulates LPO *in vivo*, further confirming that α-solanine mainly induces the death of NPC cells through ferroptosis. In terms of clinical research progress, the anti-cancer potential of α-solanine has gradually attracted attention. Currently, studies have explored the potential value of belladonna extract combined with chemotherapy for advanced solid tumors, and preliminary results have shown that this combination regimen exhibits good tolerability and anti-angiogenic activity (165-167). In addition, α-solanine has demonstrated adjuvant therapeutic effects in chemotherapy experiments on breast cancer animal models (168). Meanwhile, research has also found that α-solanine exerts certain positive effects in the combined treatment studies of various types of cancer such as liver cancer and nasopharyngeal carcinoma, but the relevant applications have not yet entered the clinical trial phase (169-173) (Table II).

GSTM3 promotes radiation-induced ferroptosis by regulating GPX4 and enhances the radiosensitivity of NPC. GSH S-transferase mu 3 (GSTM3) is a member of the GSH S-transferase family and has multiple effects on the progression of various malignant tumors (160). To investigate the effect of GSTM3 on ionizing radiation (IR; induced ferroptosis *in vivo*, researchers subcutaneously injected GSTM3-overexpressing stable 5-8F cells into nude mice, leading to the formation of palpable tumors (174,175). Subsequently, the mice bearing xenograft tumors received conventional IR treatment. The results showed that the body weight of the mice remained stable throughout the treatment period (176,177). Compared with the control group, in the xenograft model, GSTM3 overexpression alone did not exhibit any effect on tumor growth, while IR effectively inhibited tumor growth. Notably, compared with the group treated with IR alone, the combination of GSTM3 overexpression and IR treatment led to a notable reduction in tumor size and weight. 4-Hydroxy-2-nonenal (4-HNE) serves as a ferroptosis marker reflecting the level of LPO. Immunohistochemical staining showed that IR moderately increased the contents of GSTM3 and 4-HNE (178-180). In addition, GSTM3 overexpression combined with IR treatment resulted in a marked increase in the signal level of 4-HNE (181,182). Overall, these results indicate that GSTM3 enhances IR-mediated ferroptosis and improves the radiosensitivity of NPC.

To the best of our knowledge, currently, clinical research on GSTM3 is relatively limited. Expression of GSTM3 is associated with the inhibition of breast cancer stem cell phenotypes and favorable clinical prognosis (183,184). Additionally, chemotherapeutic drugs can inhibit GSTM3 expression, which promotes the enrichment of breast cancer stem cells and ultimately leads to tumor recurrence and metastasis (182,185). In clinical application, due to the functional redundancy of the GSTM3 family and high heterogeneity of tumor cells, single-target intervention on GSTM3 shows poor efficacy, and it is difficult to develop a unified targeted treatment plan. In the future, it is necessary to analyze the functional cooperation mechanism between GSTM3 and its family members, and construct a patient stratification model using multi-omics technology to promote the translation of GSTM3-related targeted strategies from basic research to clinical practice, thereby providing a new direction for improving tumor treatment efficacy (186) (Table II).

Berberine (BBR) inhibits the metastasis of NPC through ferroptosis mediated by the Xc-/GSH/GPX4 axis system. Ferroptosis is triggered by LPO and is strictly regulated by SLC7A11 and SLC3A2, which are key components of the cystine-glutamate antiporter (187). Due to the inhibition of LPO, the downregulation of GPX4 can directly or indirectly trigger ferroptosis. To determine the specific molecular mechanism of BBR-induced ferroptosis, Wu *et al* (187) treated NPC cells with different concentrations of BBR and detected the mRNA and protein levels of GPX4, SLC7A11 and SLC3A2. The results showed that the protein levels of GPX4, SLC7A11 and SLC3A2 in S18 and 5-8F NPC cells decreased in a dose-dependent manner. Meanwhile, the mRNA levels of GPX4, SLC7A11 and SLC3A2 also decreased (188-190). Moreover, the use of deferoxamine (DFO) and Fer-1 reversed the expression levels of proteins and mRNAs associated with BBR-induced ferroptosis. In addition, the results of the study on the *in vivo* anti-metastatic effect of berberine (BBR) on nasopharyngeal carcinoma (NPC) cells (using a nude mouse xenograft model) showed that the number of metastatic lesions in the BBR treatment group was reduced compared with that in the control group (191). Moreover, compared with the control group, the proteins of GPX4, SLC7A11 and SLC3A2 were elevated, which was consistent with the *in vitro* results of the downregulation of the expression of GPX4, SLC7A11 and SLC3A2 in the BBR treatment group (190,192). These findings indicate that BBR considerably inhibits NPC metastasis both *in vitro* and *in vivo*. In conclusion, GPX4 is a major molecule and the Xc-/GPX4 axis system carries out an important role in BBR-induced ferroptosis of NPC cells (189,193).

In terms of clinical trial progress, studies have shown that BBR can inhibit high glucose-induced ferroptosis in cells associated with diabetic retinopathy by activating the Nrf2/HO-1/GPX4 pathway (194-196), providing a theoretical basis for its application in the treatment of associated diseases. Although *in vitro* and animal experiments have confirmed that BBR can inhibit tumor cell growth and induce ferroptosis (197-200), its clinical application in NPC still faces challenges. Specifically, the complex human physiological environment leads to differences in the pharmacokinetics of BBR between *in vivo* and *in vitro* settings, making it difficult to ensure that BBR acts precisely on NPC cells to induce ferroptosis while avoiding damage to normal cells. Additionally, NPC cells exhibit high heterogeneity, patients vary in their

sensitivity to BBR and the expression of molecules related to the Xc^-/GPX4 axis, which hinders the development of a unified and effective clinical treatment regimen (201-203). In the future, more large-scale, multi-center clinical trials are needed to investigate the safety and efficacy of BBR in humans, explore personalized treatment strategies and promote the translation of BBR from basic research to clinical application in NPC treatment (Table II).

Isoquercitrin promotes ferroptosis and oxidative stress in NPC through the AMPK/NF-κB pathway. Numerous studies have shown that the NF-κB pathway carries out an important role in the regulation of oxidative stress and ferroptosis (204-208). Based on this, Luo *et al* (209) speculated that isoquercitrin might play a promoting role in the oxidative stress and ferroptosis processes of NPC cells by regulating the NF-κB pathway (210,211). By detecting the expression levels of proteins associated with the NF-κB pathway, it was found that isoquercitrin markedly reduced the ratios of phosphorylated (p)-p65/p65 and p-IκB/IκB and simultaneously inhibited the expression of IL-1β. These results indicate that isoquercitrin can inhibit the activation of the NF-κB pathway (212,213).

In addition, as a key molecule regulating various metabolic processes (including oxidative stress), the activity of AMPK is also affected by isoquercitrin. Zhang *et al* (214) showed that isoquercitrin markedly reduced the ratio of p-AMPK/AMPK, indicating that it has an inhibitory effect on the activity of AMPK. These results suggest that isoquercitrin may carry out a role in NPC by inhibiting the AMPK/NF-κB p65 signaling axis. To further verify this mechanism, Luo *et al* (209) established a xenograft tumor model. Analysis revealed that isoquercitrin markedly reduced tumor weight, however, had no obvious effect on the body weight of the mice. At the same time, the level of LPO in the isoquercitrin treatment group was notably increased, while the expressions of ferroptosis-related markers (such as ATF4, xCT, GPX4 and HO-1) were considerably decreased, indicating that isoquercitrin can induce ferroptosis *in vivo* (215,216). In conclusion, isoquercitrin may inhibit tumorigenesis of NPC *in vivo*, enhance oxidative stress and promote ferroptosis by inhibiting the AMPK/NF-κB p65 signaling pathway (209,217).

To the best of our knowledge, to date, there are no publicly available dedicated clinical studies on isoquercitrin for NPC. However, research has explored its potential in other diseases and tumor types: for instance, in early clinical observations of colorectal cancer, isoquercitrin combined with chemotherapy showed a synergistic effect in inhibiting tumor growth without notably increasing adverse reactions, initially demonstrating its safety and potential for combined therapy (218). In small-sample trials for ulcerative colitis (a chronic inflammation-related disease), isoquercitrin alleviated intestinal inflammation by regulating the NF-κB pathway (219,220), this mechanism shares commonality with the 'NF-κB pathway inhibition' observed in NPC research (221), providing an indirect reference value. Nevertheless, to promote the application of isoquercitrin in NPC treatment, targeted Phase I and II clinical trials are still needed to verify its pharmacokinetic characteristics, the efficacy of monotherapy or combined therapy and long-term safety. Additionally, it is necessary to clarify the differences in efficacy across patients with NPC with different molecular subtypes, so as to provide a basis for formulating subsequent clinical protocols (222-226) (Table II).

The molecular mechanism and therapeutic potential of cucurbitacin B (CuB) in inducing ferroptosis of human NPC cells. As a key element in the mitochondrial respiratory chain, iron carries out an important role in the process of ferroptosis. Lipid hydroperoxides are considered to be the main driving force and marker of ferroptosis. To explore the mechanism of action of CuB, Huang *et al* (227) detected the concentrations of intracellular iron and lipid peroxides. The results showed that after treatment with CuB, the contents of intracellular iron and lipid peroxides increased considerably in a dose-dependent manner, and this effect could be effectively reversed by inhibitors such as DFO, CPX and Fer-1. In addition, GPX4, as a key regulatory factor of ferroptosis, its expression level decreased markedly after CuB treatment, further supporting the role of CuB in inducing ferroptosis.

To further verify the anti-tumor effect of CuB, Huang *et al* (227) established a human nasopharyngeal carcinoma (NPC) xenograft model using BALB/c nude mice. The experimental results showed that, compared with the control group, the tumor volume of the mice in the CuB treatment group was notably reduced, and there was no obvious change in the body weight of the mice, indicating that CuB has good tolerance. Through H&E staining observation of the main organs such as the heart, liver, spleen, lung and kidney, and analysis of blood biochemical indexes, it was found that all the mice treated with CuB did not show visceral organ toxicity or obvious pathological morphological changes. These results indicate that CuB has potential application value in the treatment of NPC and is a promising ferroptosis inducer.

To the best of our knowledge, there are currently no publicly available clinical trial data on CuB for NPC, and it has not yet entered the formal clinical trial phase, with only some preliminary explorations conducted. To promote the clinical translation of CuB in the future, targeted Phase II and III clinical trials are still needed to evaluate the objective response rate, progression-free survival, and long-term safety (especially the effects on the hematopoietic system and liver/kidney function) of its monotherapy or combined therapy regimens, thereby providing sufficient clinical evidence (Table II).

Disulfiram (DSF)/copper (Cu) induces antitumor activity against NPC cells and CAFs through ROS/MAPK and ferroptosis pathways. DSF is a drug clinically used for the treatment of alcoholism, which exerts its effect by inhibiting the activity of aldehyde dehydrogenase (228). Studies have shown that DSF has potential application value in cancer treatment. The combined action of DSF and Cu can induce the aggregation of NPL4, leading to complex cellular phenotypes and ultimately triggering cell death (229-231). Experiments have shown that DSF/Cu treatment upregulates the expression of p53 protein and its downstream targets p21 and BAX, and this effect can be reversed by the p53 inhibitor Pifithrin-α (232). In addition, DSF/Cu markedly increases the level of lipid ROS in 5-8F cells, and the ROS scavenger N-acetylcysteine can partially reverse this phenomenon. In the 5-8F xenograft model, DSF/Cu markedly inhibits tumor growth without causing changes in

the body weight of the mice (233-235). These results indicate that DSF/Cu carries out an important role in the treatment of NPC by inducing ROS-mediated ferroptosis and has the potential to be used as an adjuvant therapeutic drug in clinical practice (236,237).

Although DSF/Cu shows promising prospects in NPC treatment research, its clinical application faces challenges: DSF has a short half-life and is easily metabolized into inactive substances after oral administration, making it difficult to maintain effective concentrations (238,239); the complex human physiological environment and pronounced individual differences in pharmacokinetics complicate the determination of precise dosages; additionally, tumor cell heterogeneity increases the difficulty of personalized treatment (240,241). In the future, it is necessary to deepen basic research to clarify the molecular mechanism of DSF/Cu-induced ferroptosis and differences across NPC subtypes, conduct Phase I-III clinical trials to verify its pharmacokinetics, efficacy and safety, screen patients sensitive to DSF/Cu with precision medicine technologies (such as genetic testing and liquid biopsy), and explore innovative drug delivery systems to improve pharmacokinetic properties of DSF, all to promote its development as a clinical adjuvant treatment for NPC (242,243) (Table II).

P4HA1 activates HMGCS1 to promote ferroptosis resistance and progression of NPC. P4H is a heterotetramer composed of P4HA subtypes (P4HA1, P4HA2 and P4HA3) and P4HB, forming P4H1, P4H2 and P4H3 holoenzymes respectively. It carries out a key role in the proline hydroxylation of procollagen, catalyzing the formation of hydroxyproline from the proline residues in the Xaa-Pro-Gly triplet, which is essential for the folding of procollagen into a stable triple-helix structure and its secretion out of the cell (244,245). In addition, P4H also regulates the hydroxylation modification of proteins containing collagen-like sequences (246,247) (such as AGO2).

Previous studies have found that P4HA1 is a novel regulator of ferroptosis. Its overexpression enhances the ferroptosis resistance of NPC cells by activating HMGCS1 (248,249). Meanwhile, the P4HA1/HMGCS1 regulatory axis also promotes the proliferation of NPC cells, as well as the survival and ferroptosis resistance of NPC cells that are separated from the extracellular matrix (248,250,251).

Currently, relevant research on P4HA1 is mostly in the stages of basic research and model validation, but preliminary attempts have been made in other cancer fields: A retrospective study on non-small cell lung cancer revealed that high expression of P4HA1 is associated with poor prognosis in patients, providing indirect evidence for its potential as a prognostic marker and therapeutic target (252,253); In early preclinical trials for pancreatic cancer, small-molecule inhibitors of P4HA1 were able to inhibit tumor growth without obvious toxicity, laying a foundation for research on P4HA1 in NPC (254). In the future, it is first necessary to conduct large-scale retrospective studies to clarify the association between P4HA1 expression and the prognosis, staging and treatment response of patients with NPC. On this basis, Phase I/II clinical trials of P4HA1 inhibitors should be advanced to evaluate their safety, pharmacokinetic characteristics and efficacy, thereby providing evidence for clinical translation (Table II).

Icaritin increases the radiosensitivity of NPC cells by regulating ferroptosis. Icaritin has a variety of pharmacological effects, including antioxidant effects, prevention and treatment of osteoporosis, improvement of cardiovascular function and protection against neurodegenerative damage (255,256). In terms of anti-tumor effects, icaritin has been proven to inhibit the proliferation and induce apoptosis of a variety of tumor cells. These effects make icaritin a potential anti-tumor drug.

Studies have shown that icaritin can regulate the expression of proteins associated with ferroptosis. For example, In NPC cells, the expression of ACSL4, a marker protein of ferroptosis, is upregulated, while the expression of GPX4 is downregulated. Similarly, when icaritin is combined with radiotherapy, it can markedly promote the accumulation of ROS in NPC cells (255,257,258). The accumulation of ROS will further lead to DNA damage, such as the upregulation of the expression of γ-H2AX (259,260). These damages will exacerbate the death of NPC cells, thereby improving the effect of radiotherapy. In addition, icaritin can also cause NPC cells to arrest in the G2 phase. This arrest will further affect the proliferation and division ability of cells, thus enhancing the killing effect of radiotherapy on NPC cells. The aforementioned studies indicate that icaritin may enhance the radiosensitivity of NPC cells by promoting the occurrence of ferroptosis (261,262).

However, there are still challenges in applying icariin to the clinical treatment of NPC: It remains unclear whether the mechanism by which icariin regulates ferroptosis and enhances radiosensitivity in experiments is fully applicable in the complex human environment (263,264). Additionally, there is a lack of clinical data to support balancing efficacy and adverse reactions (such as mucosal damage and myelosuppression) when combined with radiotherapy (256,266). To address these issues in the future, breakthroughs can be made in three aspects: Conducting clinical sample studies on NPC to verify the effect of icariin on ferroptosis-related pathways and the impact of molecular subtypes; developing local formulations for the nasopharynx (such as nano-sprays) to increase drug concentration in tumor tissues; and advancing small-sample Phase I/II clinical trials to explore the safe dosage and administration timing of icariin combined with radiotherapy (267) (Table II).

6. Summary and future prospects

Nasopharyngeal carcinoma (NPC) is a head and neck malignant tumor, with >70% of new cases occurring in East Asia and Southeast Asia (268-270), and its treatment has been a major focus of clinical and research attention (271). Traditional treatment methods, such as radiotherapy and chemotherapy, have achieved curative effects, but present side effects and drugs that need to be addressed. In recent years, with the in-depth study of the mechanism of cell death, ferroptosis, as a new type of programmed cell death, has provided a new perspective and strategy for the treatment of NPC (13,272-274).

Ferroptosis, also referred to as iron-dependent LPO-mediated cell death, is a unique form of cell death driven by iron ions and LPO. Its core characteristic is the intracellular accumulation of iron ions coupled with an uncontrolled LPO reaction, which ultimately results in cell membrane rupture and subsequent cell death. Compared with traditional cell death methods such

as apoptosis and necrosis, ferroptosis has its own uniqueness in morphological, biochemical and genetic characteristics.

Numerous studies have shown that ferroptosis carries out an important role in the occurrence, development and treatment of NPC (10,275-278). Conversely, the abnormal iron metabolism and increased LPO levels in NPC cells make them more sensitive to ferroptosis. On the other hand, some chemotherapeutic drugs, such as cisplatin, have been shown to be able to induce ferroptosis in NPCnuo cells (279-281), thereby exerting an anti-tumor effect. Based on the important role of ferroptosis in NPC, researchers have begun to explore the application of ferroptosis inducers in the treatment of NPC. For example, Erastin, as a small molecule compound that can induce ferroptosis in a variety of cancer cells, has been proven to enhance the sensitivity of traditional anti-cancer drugs to NPC cells (161,282). In addition, some new chemotherapeutic drugs and targeted therapeutic drugs are also being developed. They induce ferroptosis in NPC cells by regulating ferroptosis-related signaling pathways, such as GPX4 and SLC7A11. Although ferroptosis inducers have shown great potential in the treatment of NPC, ferroptosis inhibitors also carry out a role that cannot be ignored. A number of studies have shown that ferroptosis inhibitors can protect normal cells from ferroptosis, thereby reducing the side effects of chemotherapeutic drugs (283-285). In addition, ferroptosis inhibitors can also be used in combination with ferroptosis inducers. By regulating the degree and speed of ferroptosis, a more precise therapeutic effect can be achieved.

Although the application of ferroptosis in the treatment of NPC has made progress, there are still several issues that remain to be solved. For example, how to precisely regulate the degree and speed of ferroptosis to achieve the best therapeutic effect; how to overcome the problem of drug resistance and improve the sensitivity of ferroptosis inducers; how to develop safer and more effective ferroptosis inducers and inhibitors and new treatment methods all need to go through clinical trials and evaluations to ensure their safety and effectiveness. In the future, with the in-depth study of the mechanism of ferroptosis and the development of new drugs, it is considered that ferroptosis will carry out a greater role in the treatment of NPC, and it is expected to achieve more precise and effective therapeutic effects.

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Competing interests

The authors declare that they have no competing interests.

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