

Review

Anti-ferroptosis: A Promising Therapeutic Approach in Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) is a kind of malignant tumour originating from the mucosal epithelium of the nasopharynx, which has apparent regional distribution characteristics, and its incidence is increasing yearly. At present, the primary treatment method for nasopharyngeal carcinoma is radiotherapy, but radioresistance has become a complex problem to overcome to improve the therapeutic effect. Recently, ferroptosis has been proposed as a new type of iron-dependent programmed cell death, distinct from apoptosis, cell necrosis and autophagy. Many studies have shown that ferroptosis is involved in the occurrence, development, invasion and metastasis of nasopharyngeal carcinoma cells, and promoting the occurrence of ferroptosis of the same cells is a promising treatment method that should be written in the prospect. Therefore, this paper summarizes the mechanism of action of ferroptosis and its role in treating the same as above.

Keywords: nasopharyngeal carcinoma; ferroptosis; treatment; diagnosis; prognosis

1. Introduction

As mentioned above, nasopharyngeal carcinoma is a malignant tumour originating from the mucosal epithelium of the nasopharynx and often occurs in the pharyngeal recess. At present, its incidence is gradually on the rise [1]. Although the overall incidence of nasopharyngeal cancer is not high in the world, it is more common in some parts of Southeast Asia and North Africa, especially southern China [2]. The incidence of nasopharyngeal carcinoma may be related to genetics, Epstein-Barr virus infection, chronic nasopharyngeal infection for a long time and other factors [3]. Since most patients are diagnosed at an advanced stage and the current treatment strategies are difficult to achieve the expected therapeutic effect, early diagnosis and treatment of nasopharyngeal carcinoma can improve its survival rate [4]. At present, the treatment methods for nasopharyngeal carcinoma include radiotherapy, chemotherapy, surgery, biological therapy, etc. Radiotherapy is the main treatment method [5]. In recent years, it has been found that radioresistance can lead to local tumour recurrence, which is the main reason for the treatment failure of nasopharyngeal carcinoma [6]. Therefore, it is particularly significant to find advanced therapeutic method and directions to reduce the disease burden of nasopharyngeal carcinoma, improve patients' standard of living, and provide a new scheme for the treatment of nasopharyngeal carcinoma. Ferroptosis treatment differs from the traditional treatment proposed in the New Year. Ferroptosis is a new type of cell death that has

been proposed in recent years. Different from other classical programmed cell death modes, ferroptosis is regulated by iron content dependence and shows the main characteristics of death due to excessive accumulation of lipid peroxides, which has broad prospects in cancer treatment [7]. The study of ferroptosis in the treatment of nasopharyngeal carcinoma is still controversial. This paper reviews the relevant studies on the relationship between nasopharyngeal carcinoma and ferroptosis.

2. Overview of Nasopharyngeal Carcinoma (NPC)

2.1 The Incidence of NPC

Nasopharyngeal carcinoma is a malignant tumor with low incidence and is affected by many factors. There are considerable regional differences in the incidence of nasopharyngeal carcinoma globally, among which is relatively high in Southeast Asia, North Africa, southern China and other regions. This is related to local eating habits, smoking rate and Epstein-Barr virus infection rate [8]. Long-term intake of unhealthy foods high in salt, oil and smoke can increase the risk of nasopharyngeal cancer. Long-term smoking and excessive alcohol consumption are major risk factors for nasopharyngeal cancer and can significantly increase the likelihood of developing the disease; Epstein-Barr virus (EBV) infection is considered to be an essential factor in nasopharyngeal carcinoma, especially in southern China. Family genetic predisposition may also in-



crease the risk of nasopharyngeal cancer [9]. In general, various factors affect the incidence of nasopharyngeal cancer, including environmental factors, lifestyle, genetic factors, and so on; early detection and change of risk factors can reduce the risk of disease. China is one of the countries with the most significant number of nasopharyngeal cancer patients, and the incidence and mortality are higher than the global level. In recent years, the death rate of nasopharyngeal cancer among Chinese residents has decreased, but the incidence is still on the rise. With the aging of Chinese society, the disease burden of nasopharyngeal cancer will further increase, and it is urgent to formulate effective prevention and treatment programs [10].

2.2 Clinical Staging of NPC

According to the Union for International Cancer Control (UICC/American Joint Committee on Cancer/AJCC), TNM (Tumor - Lymph node - metastasis) staging The eighth edition of the staging system, which was updated in 2017, nasopharyngeal cancer is clinically divided into five stages, including stage 0, I, II, III and IV, of which stage IV includes stage IVA and stage IVB. Stage 0 is the primary tumour and cannot be evaluated. Stage I and II were confined to the nasopharynx and adjacent soft tissues (including parapharyngeal space, intralygoid muscle, and lateral pterygoid muscle), with or without a few proximal lymph node metastases. The boundary between stage III and stage III was mainly whether the nasopharyngeal cancer had bone invasion and destruction, including the skull base, cervical spine, pterygoid plate, paranasal sinuses, and cervical spine, and whether the lymph node metastases further expanded to bilateral cervical lymph nodes at the lower margin of cartilage. Stage IV developed distant metastases that further invaded the intracranial, cranial nerves, hypopharynx, orbit, parotid glands, and extensive soft tissues outside the lateral pterygoid muscle with or without it. According to the different scopes of tumour invasion and distant metastasis, it can be further divided into IVA and IVB stages, and the progression is gradually aggravated.

2.3 Diagnosis and Treatment of NPC

The early symptoms of nasopharyngeal carcinoma patients are not typical, and the individual differences are significant; it is not easy to pay attention to patients and doctors in the early stages of the tumour, and early detection and diagnosis are very difficult. In the areas with a high incidence of nasopharyngeal carcinoma, the overall situation presents the characteristics of high incidence, poor prognosis and low survival rate. More than 70% of nasopharyngeal carcinoma patients are in the advanced stage upon diagnosis, resulting in poor treatment effects and poor prognosis for most patients [11]. Therefore, given nasopharyngeal cancer, we should take adequate measures to achieve early detection, diagnosis, and treatment of the prevention and control effects. For people with high incidence, the

commonly used early detection methods include nasal endoscopy, imaging examination and detection of Epstein-Barr (EB) virus-associated antigens and antibodies, which are quite significant for the early diagnosis of nasopharyngeal carcinoma [12]. Over the years, with the rapid development of medical imaging technology, computed tomography (CT) imaging technology, multi-modal magnetic resonance imaging (MRI) technology, and positron emission computed tomography (PET) technology, ⁹⁹Tcm-HL91 anoxic imaging technology has been gradually widely used in the diagnosis and evaluation of the curative effect after treatment of nasopharyngeal carcinoma, providing solid help for the diagnosis and treatment of nasopharyngeal carcinoma patients. Pathological examination emphasizes the nasopharyngeal biopsy, which can be used as the gold standard for the diagnosis of nasopharyngeal carcinoma. Sometimes, clinical symptoms and imaging examinations support pathological diagnosis, but they do not. Immunohistochemistry or *in situ* hybridization can be used to assist in pathological biopsy for suspicious masses that cannot be biopsied, or the results are not ideal. Nasopharyngeal carcinoma cells are susceptible to ionizing radiation, so intensity-modulated radiotherapy (IMRT) is recommended for the treatment of non-metastatic nasopharyngeal carcinoma. In contrast, IMRT can be used for metastatic nasopharyngeal carcinoma. Tumor immunotherapy is also a promising therapeutic approach [1].

3. Ferroptosis in NPC

Ferroptosis is a novel form of programmed cell death through the process of phospholipid peroxidation, which relies on the metabolites reactive oxygen species (ROS), polyunsaturated fatty acid chain containing phospholipids (PUFA-PL), and transition metal iron and is affected by cell signal transduction to regulate cell metabolism and ROS levels [13]. Morphologically, unlike other classical cell death, ferroptosis does not show typical cell death features, such as nuclear and cytoplasmic changes and apoptotic body formation, but is characterized by mitochondrial atrophy and reduction in the number of mitochondrial cristae. Technologically, ferroptosis is characterized by the inability of antioxidant capacity to resist reactive lipid oxides, which leads to cell death, in contrast to other cell death mediated by cell death executive proteins [14]. Many cancer cells have expressed specific sensitivity to ferroptosis, including breast, pancreatic, lymphatic, and renal cancer cells [15]. It is worth mentioning that ferroptosis is inhibited in several cancer cells, such as breast cancer, thereby contributing to cancer cell proliferation and metastasis. Therefore, increasing the degree of ferroptosis in cells benefits chemotherapy and radiotherapy resistance [16]. An increasing number of signalling pathways, regulatory genes, and small molecule inducers have been demonstrated to achieve the therapeutic effect of cancer through the ferroptosis mechanism. For nasopharyngeal

Table 1. Factors in NPC and their potential as biomarkers.

Proteins/medicine/genes	Detection methods	Cohort size/subtype	Sample source	Ref
GSTM3	qRT-PCR, western blot	tumor tissues (n = 36), normal tissues	Tissues	[26]
MIF	qRT-PCR, Immunohisto-chemistry, western blot	tumor tissues (n = 30), normal tissues	Tissues	[28]
ASCL4	qRT-PCR, western blot	tumor tissues (n = 20), normal tissues	Tissues	[27]
PKC β II	qRT-PCR, western blot	tumor tissues (n = 49), normal tissues	Tissues	[30]
SOD2	western blot	-	Tissues	[35]
DHODH	western blot	-	Tissues	[34]
ATG5	qRT-PCR	tumor tissues (n = 504), normal tissues (n = 44)	Tissues	[38]
P4HA1	qRT-PCR, western blot	tumor tissues (n = 103), normal tissues (n = 6)	Tissues	[24]
CAPRIN2	qRT-PCR, western blot	tumor tissues (n = 54), normal tissues (n = 59)	Tissues	[39]
SLC7A11	qRT-PCR, western blot	tumor tissues (n = 6), normal tissues (n = 6)	Tissues	[40]
BBR	western blot, qRT-PC	-	Tissues	[21]
CuB	western blot	tumor tissues (n = 20), normal tissues	Tissues	[22]
Icaritin	western blot	tumor tissues (n = 24), normal tissues	Tissues	[23]
DSF/Cu	qRT-PCR, western blot	tumor tissues (n = 20), normal tissues	Tissues	[31]
Ent-halimane diterpenoid	qRT-PCR, western blot	tumor tissues, normal tissues	Tissues	[41]
MTDH	qRT-PCR, western blot	tumor tissues (n = 291), normal tissues	Tissues	[29]
HMOX1	qRT-PCR, western blot	tumor tissues (n = 45), normal tissues	Tissues	[33]
lncRNAs	qRT-PCR, western blot	tumor tissues (n = 535), normal tissues (n = 59)	Tissues	[36,37]
Others	Detection methods	Cohort size/subtype	Sample source	Ref
EVs	qRT-PCR	tumor tissues, normal tissues	Tissues	[32]
EBV	qRT-PCR, immunoblotting	tumor tissues (n = 181), normal tissues	Tissues	[25]

GSTM3, Glutathione S-transferase mu 3; MIF, Macrophage migration inhibitory factor; ACSL4, Acyl-CoA Synthetase Long Chain Family Member 4; PKC, protein kinase; SOD2, Superoxide dismutase 2; DHODH, dihydroorate dehydrogenase; ATG5, autophagy-related gene 5; P4HA1, Prolyl 4-hydroxylase; CAPRIN2, Caprin family member 2; SLC7A11, Solute Carrier Family 7 Member 11; BBR, Berberine; CuB, Cucurbitacin B; DSF, Disulfiram; *MTDH*, metadherin; *HMOX1*, heme oxygenase 1; lncRNAs, long noncoding RNAs; EVs, extracellular vesicles; EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma; PKC β II, protein kinase C beta type II.

carcinoma, it has been clarified that the effects of inducers Erastin and sulfasalidine promote glutathione depletion [17], the related regulator *p53* acts on Solute Carrier Family 7 Member 11 (SLC7A11) to cause the inhibition of cysteine-glutamate reverse transport system (Xc- system) [18], and miRNA regulates ferroptosis to affect the proliferation, invasion and differentiation of nasopharyngeal carcinoma cells [19]. Among them, it is worth noting that SLC7A11 is a solute transporter that participates in the extracellular uptake of cystine and glutamate release, promotes the synthesis of glutathione, protects cells from oxidative stress damage, and thus prevents cell death caused by lipid peroxidation, which plays a crucial role in ferroptosis [20]. Here, we discuss the possible therapeutic value and clinical significance of some regulatory factors and molecular inducers in nasopharyngeal carcinoma (NPC) cells (Table 1, Ref.[21–41], Table 2, Ref. [21–29,32,34–49]).

3.1 The Role of Regulating Ferroptosis via Glutathione Peroxidase 4 (GPX4) Pathway in the Treatment of Nasopharyngeal Carcinoma

Glutathione Peroxidase 4 (GPX4) is considered to be an essential regulator of ferroptosis and has the function of transforming lipid peroxides [50]. The ferroptosis propensity of cells is affected by the expression level of GPX4 in tumor cells, which in turn affects tumor progression by promoting radiation resistance and metastasis. High expression of GPX4 is associated with poor clinical outcomes in nasopharyngeal carcinoma and other cancer types. Currently, several well-studied and commonly used ferroptosis inducers, such as RAS synthetic lethal 3 (RSL3) and Sorafenib, are direct GPX4 inhibitors, which regulate the glutathione (GSH)/GPX4 axis to target cell ferroptosis. These drugs have shown great potential in cancer cell therapy [51,52]. In addition, there are also newly identified ferroptosis inducers, such as Tubastatin A, which also acts on

Table 2. Effects of factors in NPC.

Proteins/medicine/genes	Functions	Molecular mechanisms	Refs
GSTM3	<i>in vivo</i> : ↓ tumor progression	USP14, FASN, GPX4	[26]
MIF	<i>in vivo</i> : ↑ immune cell infiltration (TMB/TME/HLA), ↑ proliferation	JAB1/JNK, ERK, PI3K/Akt, p53	[28]
ASCL4	<i>in vivo</i> : ↓ proliferation/invasion/migration abilities	PUFA/Acyl-CoA	[27]
SOD2	<i>in vitro</i> : ↓ tumor growth, ROS accumulation	ROS, ATP	[35]
DHODH	<i>in vitro</i> : ↓ tumor growth, ROS accumulation	GPX4, ROS	[34]
FTH1	<i>in vivo</i> : ↓ prognostic survival <i>in vitro</i> : ↑ tumor growth	-	[46]
FTO	<i>in vivo</i> : ↓ prognostic survival <i>in vitro</i> : ↑ radioresistance	OTUB1/SCL7A11	[47]
ATG5	<i>in vitro</i> : ↓ prognostic survival	PD-L1/PD-L2, G2M	[38]
P4HA1	<i>in vitro</i> : ↑ tumor growth	MVA/HMGCR/HMGCS1	[24]
CAPRIN2	<i>in vivo</i> : ↑ proliferation/invasion/migration abilities	LINC00941/CAPRIN2/HMGCR	[39]
SLC7A11	<i>in vitro</i> : ↑ tumor growth <i>in vivo</i> : ↑ proliferation	MAPK, GSH, p38, ERK	[40]
BBR	<i>in vivo</i> : ↓ proliferation/invasion/migration abilities	HIF-1 α , VEGF, Xc/GSH/GPX4	[21]
CuB	<i>in vitro</i> : ↓ tumor growth, cell cycle progression <i>in vivo</i> : ↓ proliferation/invasion/migration abilities	STAT3, Raf/MEK/ERK	[22]
Icaritin	<i>in vitro</i> : ↓ tumor growth, cell cycle progression	ROS, γ -H2AX/p-CDC25C/B1, ACSL4, GPX4	[23]
Cephalosporins	<i>in vitro</i> : ↓ tumor growth <i>in vivo</i> : ↓ proliferation	ErbB-MAPK-p53, HMOX1	[49]
Itraconazole	<i>in vitro</i> : ↓ radioresistance	Fe, GSH, LPO	[48]
Isoquercetin	<i>in vitro</i> : ↓ tumor growth <i>in vivo</i> : ↓ proliferation/invasion/migration abilities	NF- κ B, AMPK, IL-1 β , ROS	[43,44]
DSF/Cu	<i>in vitro</i> : ↑ necroptosis	ROS, MAPK, p53, ROS-JNK	[42]
Lupeol	<i>in vitro</i> : ↑ necroptosis	AMPK, p-IkB α , NF- κ B, p65	[45]
Ent-halimane diterpenoid	<i>in vivo</i> : ↓ proliferation/invasion/migration abilities	JAK2/STAT3	[41]
MTDH	<i>in vivo</i> : ↑ proliferation/invasion/migration abilities	-	[29]
lncRNAs	<i>in vivo</i> : ↑ immune cell infiltration (TMB/TME/HLA)	-	[36,37]
Others	Functions	Molecular mechanisms	Refs
EVs	<i>in vivo</i> : ↑ proliferation/invasion/migration abilities	ITGB3 and MAPK/ERK/ATF4/Nrf2	[32]
EBV	<i>in vivo</i> : ↑ tumor progression	p62-Keap1-Nrf2/MAPK-JNK/NF κ B	[25]

↑ means the corresponding protein, gene, or medicine promotes a certain process, whereas ↓ represents inhibition/suppression. USP14, Ubiquitin-specific proteases14; FASN, Fatty acid synthase; GPX4, Glutathione Peroxidase 4; JAB1, c-Jun activation domain binding protein-1; JNK, c-Jun N-terminal kinase; ERK, extracellular regulated protein kinases; PI3K, Phosphatidylinositol 3-kinases; Akt, protein kinase B; PUFA, polyunsaturated fatty acid; Acyl-CoA, Acetyl-CoA; ATP, Adenosine triphosphate; OTUB1, OTU Deubiquitinase, Ubiquitin Aldehyde Binding 1; PD-L1, Programmed cell death ligand 1; PD-L2, Programmed cell death ligand 2; ROS, Reactive oxygen species; FTH1, Ferritin Heavy Chain 1; FTO, Fat mass and obesity-associated protein; MVA, Mevalonate pathway; VEGF, vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; HMGCR, HMG-CoA reductase; GSH, glutathione; ITGB3, Integrin Subunit Beta 3; ERK, extracellular regulated protein kinases; HIF-1 α , Hypoxia-inducible factor 1; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; Xc, Cystine/glutamate antiporter system; ErbB, Erythroblastic Leukemia Viral Oncogene Homolog; LPO, Lipide Peroxide; AMPK, Adenosine 5-monophosphate (AMP)-activated protein kinase; IL-1 β , Interleukin-1 β ; NF κ B, nuclear factor kappa-B; JAK2, Janus kinase-2; FRGs, Ferroptosis-Related Genes; ATF4, activating transcription Factor 4; Nrf2, Nuclear factor erythroid 2-related factor 2; p62, Sequestosome 1; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase.

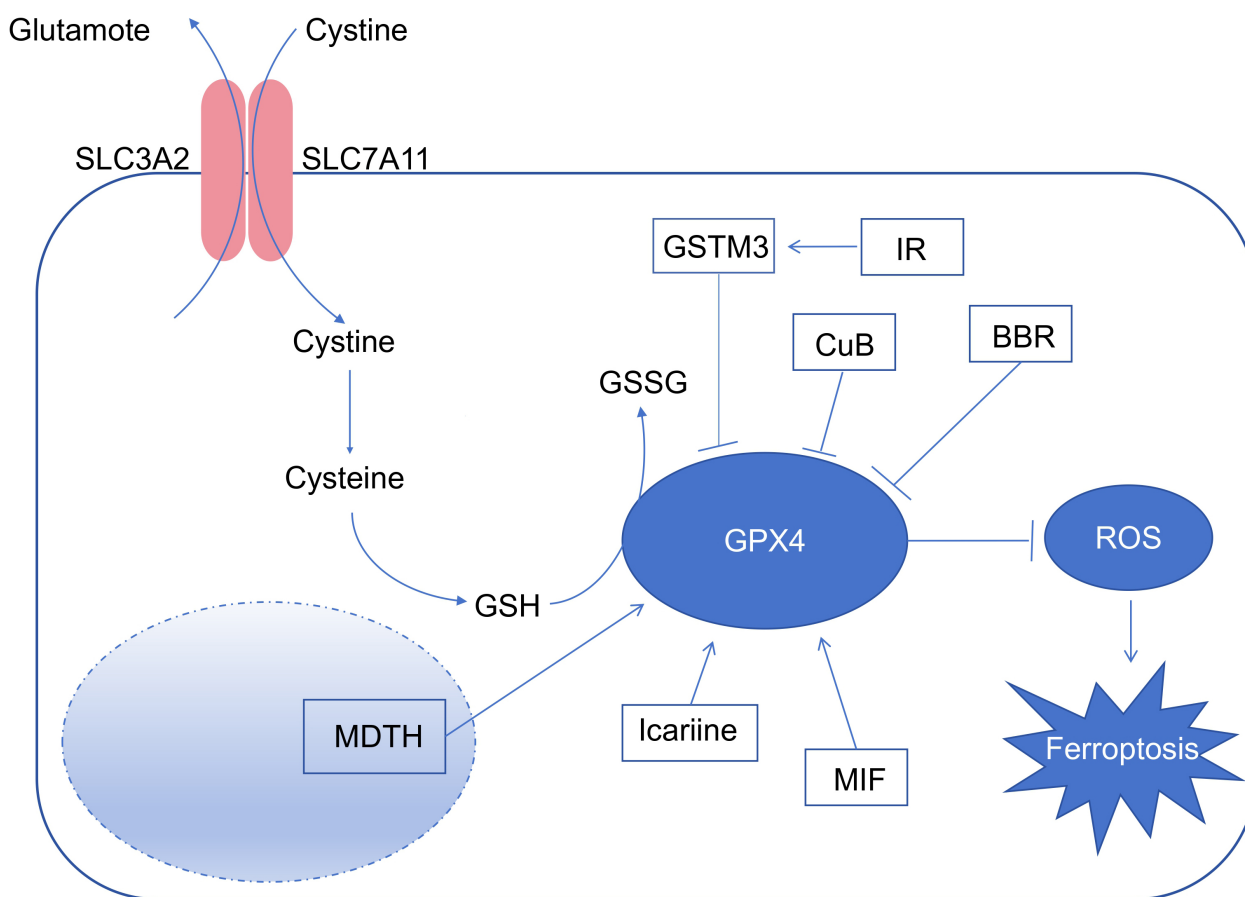


Fig. 1. Possible mechanism of targeting Glutathione Peroxidase 4 (GPX4) pathway in the treatment of nasopharyngeal carcinoma. GSTM3, Glutathione S-transferase mu 3; IR, Ionizing radiation; GSSG, glutathione (oxidized form); GSH, glutathione; GPX4, Glutathione Peroxidase 4; BBR, berberine; CuB, cucurbitacin B; ROS, reactive oxygen species; MDTH, Methylenetetrahydromethanopterin dehydrogenase; MIF, migration inhibitory factor.

GPX4. However, the clinical therapeutic effects of cancer need to be further investigated [53]. Recently, many studies have tried to clarify the mechanism of action of some new drug-active molecules, cytokines, and gene loci on tumor progression by exploring the level of GPX4 expression, such as berberine (BBR), cucurbitacin B (CuB), icaritin, Glutathione S-transferase mu 3 (GSTM3), macrophage migration inhibitory factor (MIF), oncogene *MTDH* and so on (Fig. 1).

Berberine (BBR) is a natural isoquinoline alkaloid derived from protoberberine, which has various pharmacological effects, including the inhibition of distant metastasis of nasopharyngeal carcinoma cells. However, the mechanism is still unclear [21]. Recently, Wu *et al.* [54] suggested that BBR exerted its anti-metastatic effect on NPC by inhibiting the systemic Xc/GSH/GPX4 axis. BBR induces ferroptosis in nasopharyngeal carcinoma cells by increasing reactive oxygen species, lipid peroxidation, and iron content in cells and significantly inhibits the expression of GPX4, a key inhibitor of lipid peroxidation, at the protein and mRNA levels. At the same time, overexpression of GPX4 can reverse BBR induced ferroptosis [55].

Cucurbitacin B (CuB) is a tetracyclic triterpenoid natural product and active ingredient in natural herbal medicine with an antitumor pharmacological effect [22]. CuB was found to induce extensive lipid peroxidation, down-regulate GPX4 expression, and initiate ferroptosis. Alternatively, CuB showed antitumor effects *in vitro* by inhibiting cell microtubule polymerization, arresting the cell cycle, and inhibiting migration and invasion. In conclusion, CuB can be used as a promising therapeutic agent for nasopharyngeal carcinoma by inducing ferroptosis [56]. Icaritin is the active ingredient of the traditional Chinese medicine *Epimedium*, which has inhibitory effects on a variety of tumor cells, such as lung cancer, breast cancer, and ovarian cancer [57–59]. Studies have shown that icaritin treatment can significantly promote reactive oxygen species (ROS) production and Gamma H2AX (γ -H2AX) expression in NPC cells. Combined treatment leads to cell cycle arrest in the G2 phase, down-regulation of cell division cycle 25C (CDC25C) and cyclin B1 expression, up-regulation of p-CDC25C expression, increased apoptosis, and enhanced ferroptosis protein ACSL4 expression. The expression of GXP4 is decreased, and the effect of enhance-

ing the radiotherapy effect of nasopharyngeal carcinoma cells is finally realized [23].

Recently, it has been found that prolyl 4-hydroxylase (P4HA1) is a novel regulator of ferroptosis. PAHA1 protects NPC cells from ferroptosis inducer Erastin by activating 3-Hydroxy-3-Methylglutaryl-CoA Synthase 1 (HMGCS1), a key enzyme in the mevalonate pathway. The P4HA1/HMGCS1 axis promotes the proliferation of nasopharyngeal carcinoma cells *in vitro*. Knockdown of the P4HA1/HMGCS1 axis inhibited the xenograft growth of NPC cells and enhanced the inhibitory effect of Erastin on tumor growth. Up-regulation of the P4HA1/HMGCS1 axis promotes NPC cells' resistance and survival rate to ferroptosis [24].

In addition to these drugs and genetic loci that can achieve therapeutic effects through ferroptosis, Epstein-Barr Virus (EBV) has also been shown to achieve ferroptosis escape mechanism of NPC through the SLC7A211-GPX4 pathway, resulting in a worse prognosis of EBV-infected NPC. It is involved in the Nuclear erythroid 2-related factor 2 (Nrf2)/kelch-like ECH-associated protein 1 (Keap1) signaling pathway. This signaling pathway plays a crucial role in cancerous and non-cancerous cells, such as non-alcoholic liver disease and non-small cell lung cancer. By over-activating the Nrf2/Keap1 pathway, cancer and non-cancer cells enhance antioxidant defense mechanisms and regulatory cell death resistance, thereby promoting their proliferation and survival [60–62]. EBV enhances the resistance of NPC cells to ferroptosis by activating the p62-Keap1-NRF2 signaling pathway and increasing the expression of SLC7A11 and GPX4. GPX4 further interacts with the transforming growth factor- β (TGF- β)-activated kinase 1 (TAK1)-TAK1-binding protein-1 (TAB1)/TAK1-binding protein-3 (TAB3) complex to regulate TAK1 kinase activity. This process further activates the downstream mitogen-activated protein kinase (MAPK)-c-Jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF- κ B) pathways. This process not only revealed the mechanism of ferroptosis escape promoted by chemotherapy resistance caused by EBV infection but also more clearly identified GPX4 as a potential therapeutic target for nasopharyngeal carcinoma [25].

Glutathione S-transferase mu 3 (GSTM3), a member of the glutathione S-transferase family, plays a vital role in the progression of various malignant tumors [63]. Ionizing radiation (IR) promotes lipid peroxidation and induces ferroptosis in nasopharyngeal carcinoma cells. The expression of GSTM3 is increased after IR treatment, which is related to IR-induced ferroptosis and can reduce the radioresistance of nasopharyngeal carcinoma. Further studies have shown that GSTM3 inhibits ubiquitination and subsequent fatty acid synthase (FASN) decomposition by stabilizing ubiquitin-specific peptidase 14 (USP14), interacts with GPX4, inhibits GPX4 expression, and eventually leads to ferroptosis of cells to achieve radiosensitization

(Tables 1,2) [26]. Macrophage migration inhibitory factor (MIF) is an inflammatory factor that inhibits macrophage migration and is involved in the progression of various cancers [27]. However, MIF tightly links various cells together in the tumour microenvironment (TME). It was found that GPX4 expression was decreased with inhibition of MIF function in M0, M1, or M2 macrophages. MIF is highly expressed in nasopharyngeal carcinoma cells. MIF secreted by nasopharyngeal carcinoma cells can be absorbed by macrophages, thereby inhibiting macrophage ferroptosis and promoting the metastasis of nasopharyngeal carcinoma [28].

The oncogene Metadherin (*MTDH*), also known as *AEG-1*, is considered an oncogene because of its association with promoting cancer progression, invasion and enhancing radioresistance [42,64]. Recently, Cao *et al.* [29] constructed ferroptosis-related features, including IL6, *NCF2*, metadherin (*MTDH*), and *CBS*. *MTDH*, which promotes ferroptosis by inhibiting GPX4, has a very potent effect on ionizing radiation-induced ferroptosis, thereby increasing radiosensitivity, and has been identified as a potential therapeutic target for radioresistant HNSCC patients [29].

3.2 The Therapeutic Role of Promoting Lipid Peroxide Accumulation in Ferroptosis in Nasopharyngeal Carcinoma

Excessive accumulation of lipid peroxides is the most important inducer of ferroptosis, which involves the regulation of many enzymes, including long-chain acyl-coa synthetase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) (Fig. 2). ACSL4 is a lipid metabolic enzyme that can cause ROS accumulation leading to ferroptosis [27]. Photosynthesis microcapsules (PMCs), a novel ferroptosis inducer, directly lead to the excessive production of ROS by constructing a hyperoxic environment to achieve ferroptosis of tumour cells and achieve therapeutic effects [65]. The ferroptosis regulated by ACSL4 plays an essential role in the progression of nasopharyngeal carcinoma and is considered as a therapeutic target for ferroptosis induction [66]. ACSL4 inhibits cancer cell growth in NPC by ferroptosis and regulates tumour-associated macrophage (TAM) polarization. The expression level of ACSL4 is low in NPC patients and CNE-2 and 5-8F cells. Using ferroptosis inducers Erastin and ACSL4 increased lipid peroxidation, reduced cell viability, colony formation, cell proliferation, migration, and invasion, and inhibited epithelial-mesenchymal transition (EMT). In addition, Erastin and ACSL4 also promoted the polarization of M2 macrophages to M1 macrophages and inhibited the growth of cancer cells [55].

Protein kinase C (PKC), as a protein kinase, contains a variety of isoforms, including α , β I, β II and γ subclasses. As one of the isoforms of PKC, protein kinase c beta type II (PKC β II) is an essential marker of lipid peroxidation.

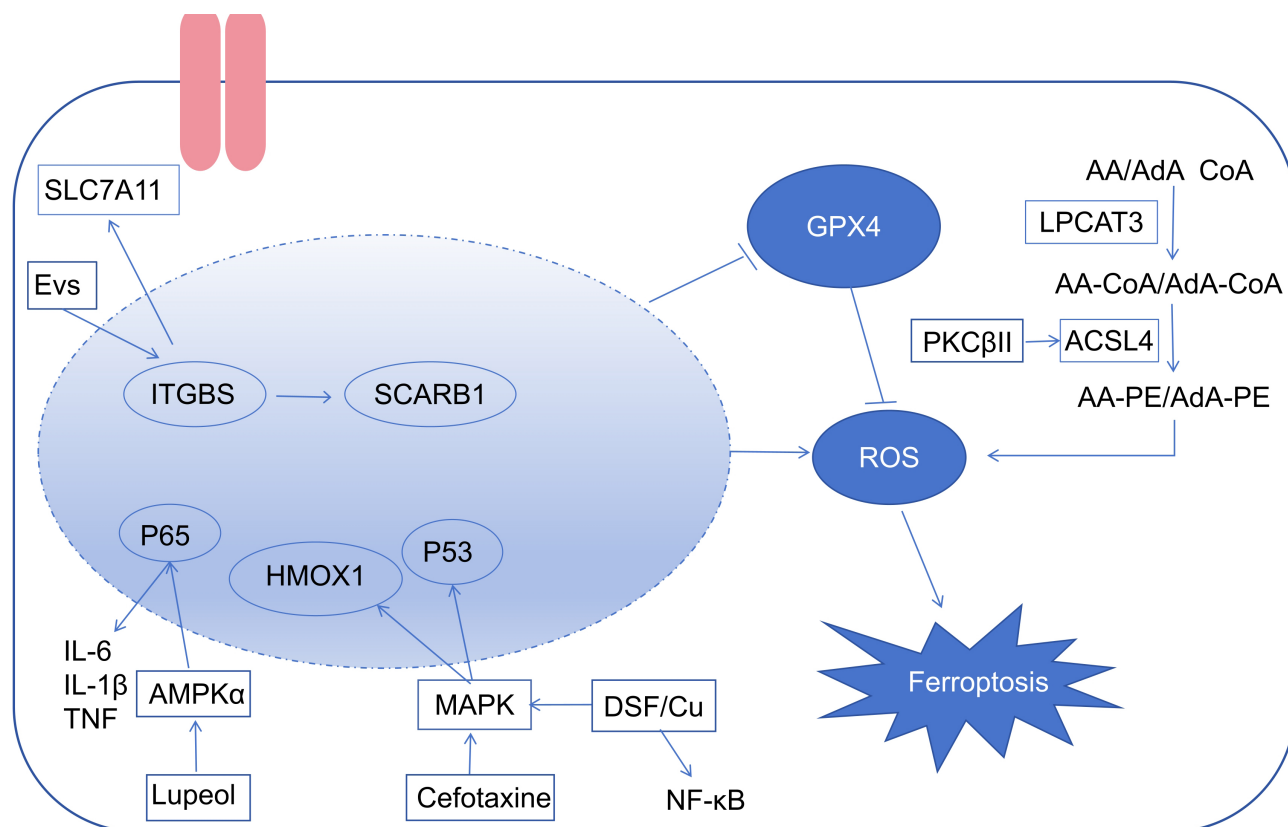


Fig. 2. Possible mechanism of promoting lipid peroxide accumulation in ferroptosis in nasopharyngeal carcinoma. LPCAT3, lysophosphatidylcholine acyltransferase 3; ACSL 4, acyl-CoA synthetase long chain family member 4.

PKC β II detects initial lipid peroxides by phosphorylating and activating ACSL4 and enlarges lipid peroxides associated with ferroptosis (Tables 1,2). Activated ACSL4 catalyzes the biosynthesis of lipids containing multiple unsaturated fatty acids, promotes the accumulation of lipid peroxidation products, and eventually leads to ferroptosis while attenuating PKC β II-ACSL4 pathway can effectively block ferroptosis *in vitro* and interfere with ferroptosis related cancer immunotherapy *in vivo* [30].

Isoquercetin (quercetin-3-O- β -D-glucopyranoside) is a kind of flavonoid compound with abundant therapeutic value, including anti-cancer and antioxidant [43]. Isoquercitrin significantly inhibits the NF- κ B pathway, adenosine 5-monophosphate (AMP)-activated protein kinase (AMPK) pathway and the expression of interleukin (IL)-1 β , enhances ROS production and lipid peroxidation, and significantly reduces cell viability and proliferation, thereby inhibiting tumor growth and enhancing lipid peroxidation and ferroptosis *in vivo* [44].

Disulfiram (DSF) is an anti-alcoholic drug that inhibits aldehyde dehydrogenase and can even treat some cancers [67,68]. DSF/Cu has a strong cytotoxic effect on nasopharyngeal carcinoma cells, irreversibly reducing the activity of nasopharyngeal carcinoma cells and promoting cell apoptosis and necrosis through an aldehyde dehydrogenase (ALDH) independent pathway. In addition, DSF/Cu

showed anti-tumour activity on nasopharyngeal carcinoma cells by producing reactive oxygen species (ROS), activating MAPK and p53 signalling pathways, and mediating ferroptosis (Fig. 2). The combination of DSF/Cu with cisplatin could significantly inhibit the growth of nasopharyngeal carcinoma tissues [31]. In addition, lupeol significantly increased the phosphorylation of AMPK α , decreased the levels of NF-kappa-B inhibitor alpha (I κ B- α) and NF- κ B p65, inhibited inflammation, induced apoptosis, enhanced oxidative stress, and suppressed immune response in NPC cells. These changes were characterized by increased apoptosis rate, increased expression of BCL2-Associated X (Bax) and cleaved caspase-3, increased ROS production and malondialdehyde (MDA) level, and decreased levels of Bcl-2, Matrix metalloproteinases (MMP), superoxide dismutase, TNF- α , IL-6, and interleukin-1 β (IL-1 β). In addition, lupeol can also promote iron secretion and lipid peroxidation and induce ferroptosis in nasopharyngeal carcinoma cells [45].

Extracellular vesicles (EVs) are essential membrane-wrapped transport carriers for transporting various cellular substances. A study has proved that extracellular vesicles are involved in tumour progression, incredibly distant metastasis [69]. Platelet-derived extracellular vesicles can inhibit ferroptosis and promote distant metastasis of nasopharyngeal carcinoma by up-regulating the inte-

grin subunit $\beta 3$ gene (ITGB3). In patients with nasopharyngeal carcinoma, distant metastasis is positively correlated with the expression level of ITGB3 in extracellular vesicles derived from platelets. In addition, P-EVs up-regulate ITGB3 expression, which increases the expression level of SLC7A11 by enhancing protein stability and activating the MAPK/ERK/ATF4/Nrf2 axis that inhibits ferroptosis, thus promoting distant metastasis [32]. In addition to up-regulating the expression level of ITGB3 and affecting the distant metastasis of nasopharyngeal carcinoma, nasopharyngeal-evs can also be taken up by macrophages and change the polarization of macrophages. The genes related to these regulatory functions include *SCARB1*, *HAAO*, and *CYP11B1*. Scarb1-rich evs promote ferroptosis of M1 macrophages to reduce M1 macrophage infiltration by up-regulating *HAAO* levels and reduce phagocytosis of M2 macrophages by up-regulating *CYP11B1* levels. *SCARB1* binds to the gene *KLF9*, which is involved in the transcription of *HAAO* and *CYP11B1*. *SCARB1*-EVs promote metastasis by jointly regulating the function of M1 and M2 macrophages [70].

3.3 Radiosensitization and Chemotherapy Sensitization of NPC Through Ferroptosis Pathway

As mentioned above, radiotherapy remains the primary treatment for nasopharyngeal carcinoma, but overcoming radioresistance is essential for enhancing therapeutic outcomes [33]. Notably, ferroptosis plays a significant role in the radiosensitivity of nasopharyngeal carcinoma cells. Antioxidant enzymes that mitigate the accumulation of reactive oxygen species (ROS) or reduce phospholipids in the peroxidized membrane can effectively inhibit ferroptosis [71]. Two critical enzymes in this context are superoxide dismutase 2 (SOD2) and dihydroorotate dehydrogenase (DHODH) [34,72]. When SOD2 is depleted, the balance of intracellular ROS is disrupted, resulting in an accumulation of superoxide that induces ferroptosis. This depletion also impairs the cells' ability to form colonies in both ionizing and non-ionizing radiation settings.

In contrast, the DHODH inhibitor reduced the fluorescence intensity of malondialdehyde and oxidized C11 BODIPY, adenosine triphosphate (ATP) levels, and mitochondrial oxygen consumption (Tables 1,2). Cell viability and colony formation were also rescued. Therefore, SOD2 depletion can enhance the radiosensitivity of NPC cells, and the whole process is also regulated by DHODH inhibitors [35].

Recent research has indicated that elevated levels of ferritin heavy chain (FTH1) are linked to poor survival outcomes in head and neck squamous cell carcinomas (HNSCCs). Additionally, reducing FTH1 expression can enhance cell death in these cancers. FTH1 is a key component of ferritin, which is involved in regulating iron metabolism [46,51]. In nasopharyngeal carcinoma cells (CNE-2), which exhibit high FTH1 levels and low epider-

mal growth factor receptor (EGFR) levels, there is a lack of sensitivity to ferroptosis induction and EGFR inhibition. The ferroptosis inducer RSL3 is combined with the EGFR monoclonal antibody cetuximab to disrupt cell survival, with FTH1 playing a critical role in this process [73]. N6-methyladenosine (m6A) is a prevalent modification of mRNA that influences gene expression within cells, and its dysregulation is associated with cancer. In tissues and cells of radiation-resistant nasopharyngeal carcinoma (NPC), the mRNA demethylase fat mass and obesity-associated protein (FTO) was found to be upregulated. FTO removes the m6A modification from the OTU deubiquitinase, ubiquitin aldehyde binding 1 (OTUB1) transcript, which subsequently enhances OTUB1 expression. This mechanism inhibits radiation-induced ferroptosis, ultimately contributing to the radioresistance observed in NPC. However, the FTO inhibitor FB23-2 and the ferroptosis activator Erastin modified the sensitivity of NPC cell lines and patient-derived xenografts to radiotherapy [47].

In addition to radiotherapy, chemotherapy alone or in combination is an additional therapeutic modality for NPC patients [74]. Anticancer antibiotics are considered an important chemotherapy modality. It has been reported that cephalosporin antibiotics can achieve a radiosensitizing effect by causing mitochondrial dysfunction and increasing intracellular ROS accumulation resulting in DNA damage. Research has demonstrated that cephalosporin antibiotics possess a highly specific and selective anticancer effect against nasopharyngeal carcinoma CNE2 cells, exhibiting lower toxicity. Cefotaxime sodium notably modulated 11 genes associated with cancer in CNE2 cells in a concentration-dependent manner. Notably, the apoptosis and ErbB-MAPK-p53 signaling pathways were significantly enriched, and the *HMOX1* gene was markedly upregulated, leading to the induction of ferroptosis in nasopharyngeal carcinoma cells and enhancing radiosensitivity as a therapeutic outcome [49].

In addition to cephalosporin antibiotics, itraconazole also has some therapeutic effects on NPC cells. Itraconazole is a triazole antifungal medication that targets a crucial enzyme involved in the production of ergosterol—specifically, lanosterol 14 α -demethylase (14DM). This inhibition results in a reduction of ergosterol levels and an increase in methylsterols within the membranes of fungal cells. Many studies have shown that itraconazole has different therapeutic effects on different cancer cells, including melanoma, breast cancer cells, lung cancer cells, and epithelial ovarian cancer cells [75–78]. However, a recent study found that spheroids formed by NPC cells have stem-like properties and exhibit a degree of radioresistance and ferroptosis resistance, as indicated by decreased iron concentration in lysosomes and lipid peroxides and increased glutathione (GSH) levels. However, itraconazole can induce ferroptosis by chelation of iron in lysosomes, which is manifested as the increase of iron concentration and oxygen

content of lipid peroxides, the decrease of GSH level, and the decrease of cell viability of spheroids [48].

3.4 Prognostic Features of NPC Based on Ferroptosis

It cannot be ignored that ferroptosis-related genes, regulators, lncRNAs, and metabolic markers are involved in the progression and prognosis of nasopharyngeal carcinoma, which provides an essential reference for the diagnosis and treatment of nasopharyngeal carcinoma. Among them, the relationship between ferroptosis-related genes (FRGs) and the prognosis of NPC still needs to be fully understood. A recent study has screened and identified some FRGs different from normal tissues in nasopharyngeal carcinoma tissues, including ABCC1, GLS2, CS, and HMG-CoA reductase (HMGCR) [79]. ABCC1 is involved in poor prognosis and radiosensitivity, GLS2 is involved in glutamine catabolism and is a direct target gene of P53. These mechanisms are involved in the ferroptosis process to varying degrees [36,37]. These FRGs are associated with poor prognosis of NPC patients, which may be related to the regulation of the tumour microenvironment (TME) [79]. Other studies have shown that ATG5 is a critical ferroptosis-related gene in NPC cells. The expression level is high in nasopharyngeal carcinoma cells and is positively correlated with overall survival and the expression of programmed cell death ligand 1/programmed cell death ligand 2 (PD-L1/PD-L2). Patients with high ATG5 expression showed poor response and shorter survival after immune checkpoint blockade. In addition, ATG5 is closely related to the G2M checkpoint pathway, and patients with high ATG5 expression have a lower IC50 with G2M checkpoint inhibitor drugs. Therefore, ATG5 can be an essential target for treating ferroptosis in NPC cells [38].

Liu *et al.* [80] evaluated the ferroptosis regulation mode of nasopharyngeal carcinoma samples based on 113 ferroptosis regulators, identified three different ferroptosis subtypes, and used a Gaussian mixture finite model to make ferroptosis regulatory factor-related scoring system to predict the prognosis and immunotherapy effect of nasopharyngeal carcinoma. Subtypes 1 and 3 are consistent with the immune activation phenotype, which has the immune-activated tumour microenvironment (TME) phenotype and has better progression-free survival (PFS) and lower risk of recurrence and metastasis. However, subtype 2 is consistent with the immunosuppressive phenotype, and the tumour microenvironment phenotype is immunosuppressive with a poor survival rate [80].

Based on the biological information analysis of ferroptosis-related lncRNAs, Dai and Zhong [81] constructed a prediction model for the prognosis of nasopharyngeal carcinoma after clinical treatment. The researchers identified 14 differential long non-coding RNAs (lncRNAs) associated with ferroptosis prognosis. These include *ALOX15*, *ATP5MC3*, *CISD1*, *DPP4*, *FANCD2*, *GCLC*, *GLS2*, *GSS*, *SCL7A11*, *PHKG2*, *ACSL3*, *PEBP1*, *ABCC1*

and *PGD*. Based on these findings, the prognostic model can effectively predict the prognosis of NPC patients. These ferroptosis-related lncRNAs may be associated with the level of immune infiltration in model construction, suggesting their potential as therapeutic targets [81].

In the metabolomic study by Liao *et al.* [82], 1230 metabolites were found in serum and urine of NPC patients, of which 181 showed significant changes. These 181 metabolites were mainly concentrated in 16 metabolic pathways, including unsaturated fatty acid biosynthesis, cholesterol metabolism and ferroptosis. Among them, 179 metabolites were significantly changed, mainly involving 8 pathways, including tricarboxylic acid (TCA) cycle and caffeine metabolism. In addition, seven metabolites, such as creatinine and paraxanthine, were found to exhibit significant changes in both serum and urine samples. The changes of these metabolites provide important reference for the diagnosis and treatment of nasopharyngeal carcinoma [82].

Distant metastasis is the leading cause of death in patients with nasopharyngeal carcinoma, and inhibition of nasopharyngeal carcinoma cell proliferation and distant metastasis is an effective treatment [83]. Recently, a study has demonstrated that specific protein molecules and compounds exert undiscovered anticancer effects. In previous studies, Caprin family member 2 (CAPRIN2) was only shown to be an RNA-binding protein that plays a role in central defence and eye development [84]. Recently, CAPRIN2 was found to play a role in anti-ferroptosis and survival promotion in ECM-isolated NPC cells and is a positive regulator of migration and invasion of NPC cells. Under the upstream regulator LINC00941 regulation, CAPRIN2 is abnormally activated in NPC. HMGCR is a critical downstream molecule of CAPRIN2 and mediates CAPRIN2 regulation of ferroptosis, survival, migration, and invasion of NPC cells. Therefore, CAPRIN2/HMGCR can be a potential clinical therapeutic target for nasopharyngeal carcinoma cells (Tables 1,2) [39]. SLC7A11 is a transporter on the cell membrane and plays a vital role in glutathione synthesis [27]. NPC cells depend on SLC7A11 for cystine import for glutathione biosynthesis and maintenance of intracellular REDOX balance. Targeting SLC7A11 limits glutathione biosynthesis, leading to intracellular reactive oxygen species accumulation, lipid peroxidation, ferroptosis, and apoptosis. As a commonly used ferroptosis inducer, elastin can induce ferroptosis in various ways, including inhibiting SLC7A11 and GSH depletion [17]. Moreover, targeting SLC7A11 altered the cellular mitogen-activated protein kinase pathway, including activation of p38 and inhibition of extracellular regulated protein kinases (ERK), limiting the proliferation of NPC cells [40].

Wang *et al.* [41] discovered an enhalane diterpenoid that exhibits sensitivity in CNE cells. This compound inhibits the activation of the JAK2/STAT3 signal-

ing pathway by binding to Gln326 of STAT3 in CNE cells, thereby reducing cell migration, invasion, and epithelial-mesenchymal transition. Additionally, it induces ferroptosis in CNE cells in a dose-dependent manner [41].

4. Conclusion

Ferroptosis is a novel cell death mode characterized by the structural damage of the cell membrane caused by uncontrolled lipid peroxidation, which is influenced by the content of reactive oxygen species, lipid peroxidation level, antioxidant system and transcription factors. Changes in the metabolism of nasopharyngeal carcinoma cells and disruption of the REDOX balance increase their dependence on antioxidants, making nasopharyngeal carcinoma cells vulnerable to ferroptosis induction. With the deepening of the research, it is found that ferroptosis plays an essential role in the progression of nasopharyngeal carcinoma. However, the research on tumour immunity still needs to be made more explicit. Although the relationship between the two has not been fully revealed, the mechanism of ferroptosis is an excellent direction to apply in clinical treatment. Targeted therapy of ferroptosis, in particular, would offer a potentially practical approach to the limitations of current therapies. There are a few examples of Ferroptosis-related therapy used to treat nasopharyngeal cancer. In the future, we can develop targeted drugs related to ferroptosis in clinical work and study the crosstalk between ferroptosis and other types of cell death. Furthermore, in nasopharyngeal cancer, FRGs are associated with ferroptosis sensitivity and are involved in the progression and prognosis of nasopharyngeal cancer, which provides potential directions for precision medicine strategies.

Author Contributions

RH and XL designed the research study. TL and FL performed the research. ZS and JY provided help and advice on acquiring and analyzing literature. RH and TL wrote the manuscript. EF and XY collected and sorted references. YR designed and drew the figures and tables. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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