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Correlation between RNA N6-methyladenosine and ferroptosis in cancer: current status and prospects

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N^6-methyladenosine (m^6A) is the most abundant chemical modification in eukaryotic cells. It is a post-transcriptional modification of mRNA, a dynamic reversible process catalyzed by methyltransferase, demethylase, and binding proteins. Ferroptosis, a unique iron-dependent cell death, is regulated by various cell metabolic events, including many disease-related signaling pathways. And different ferroptosis inducers or inhibitors have been identified that can induce or inhibit the onset of ferroptosis through various targets and mechanisms. They have potential clinical value in the treatment of diverse diseases. Until now, it has been shown that in several cancer diseases m^6A can be involved in the regulation of ferroptosis, which can impact subsequent treatment. This paper focuses on the concept, function, and biological role of m^6A methylation modification and the interaction between m^6A and ferroptosis, to provide new therapeutic strategies for treating malignant diseases and protecting the organism by targeting m^6A to regulate ferroptosis.

KEYWORDS

N6-methyladenosine, ferroptosis, cancer, correlation, regulation

Introduction

N6-methyladenosine (m^6A) is a frequent post-transcriptional modification in many eukaryotic mRNAs, and was first reported in 1974 (Fu et al., 2014). This modification is a highly dynamic and reversible process involving the installation of methyltransferases called "writers," the removal of demethylases called "erasers," and the recognition of binding proteins called "readers." m^6A can regulate mRNA processing events such as translation, export, selective splicing, and stability. A growing body of evidence suggests that m^6A modification is involved in carcinogenesis. For example, it regulates cell metastasis, proliferation, stem cell differentiation, and homeostasis in cancer and represents a promising biomarker for cancer detection (Qing et al., 2021; Zhao et al., 2021).

Ferroptosis, a novel form of cell death discovered recently, plays a vital role in clearing malignant cells. It is caused by iron-dependent lipid peroxidation and excessive accumulation of reactive oxygen species. It is distinguished from apoptosis, necrosis, pyroptosis, and autophagy, mainly characterized by lipid peroxidation, glutathione peroxidase 4 (GPX4) deficiency, and mitochondrial membrane density concentration

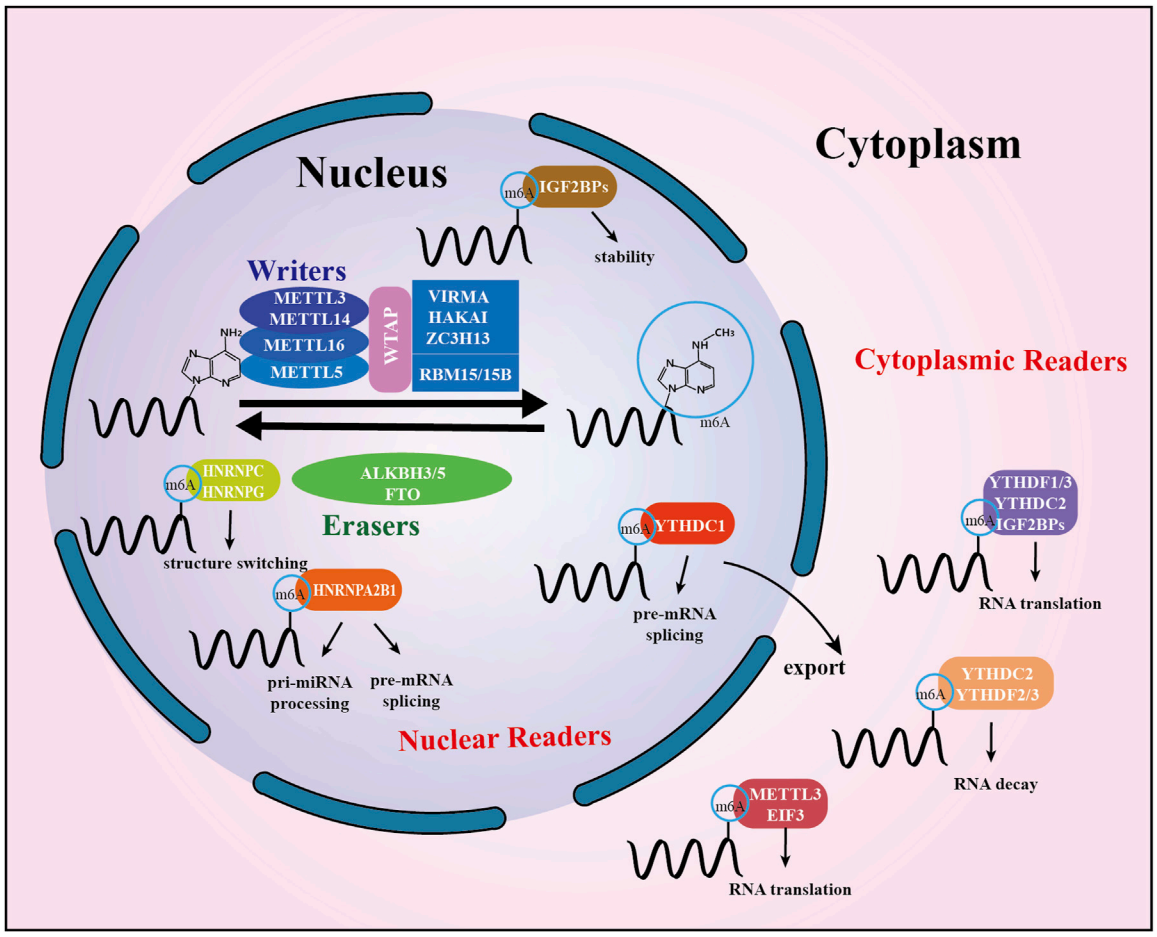

FIGURE 1
Summary of m^{6}A modification machinery. The m^{6}A methyltransferase complex composed of METTL3, METTL14, and WTAP, probably also of VIRMA and RBM15, serves as m^{6}A "writer", demethylases (FTO and ALKBH5) serve as m^{6}A "erasers". A set of m^{6}A-binding proteins serve as m^{6}A "readers" that determine the fate of target m^{6}A-modified mRNA transcripts. Mature RNAs modified by m^{6}A in the nucleus are recognized by readers, which subsequently mediate subcellular localization. In the cytoplasm, m^{6}A is identified by cytoplasmic readers. It modulates RNA stability, translation, and binding capacity.

(Chen et al., 2021b). Ferroptosis has important implications for diseases such as cancer, aging, neurodegenerative diseases, and ischemia-reperfusion injury. The related signaling pathways have been identified as therapeutic targets in several investigations (Sun et al., 2019).

Recently, many researchers have focused on ferroptosis, investigating whether changes in the critical m^{6}A enzyme can directly or indirectly induce ferroptosis, resulting in various disease problems. In this review, we explore how m^{6}A methylation is involved in the initiation and progression of ferroptosis and the prospects of using m^{6}A methylation as a new diagnostic biomarker and therapeutic target for disease treatment.

m^{6}A modification and its regulators

The m^{6}A "writers," "erasers," and "readers" are proteins that can add, remove, or recognize m^{6}A modification sites, altering critical biological processes in the process. The members of each class of regulators work together in a coordinated manner to maintain a stable balance of m^{6}A levels in the cell. The specific details are described below, and a summary is presented in Figure 1.

Methyltransferase: m^{6}A writers

The methylation of m^{6}A is catalyzed by a multicomponent methyltransferase complex, which is mediated by the methyltransferase complex (MTC). The first characteristic component of the m^{6}A methyltransferase complex is METTL3, an S-adenosyl-methionine (SAM) binding protein (Bokar et al., 1997). Another active component of the m^{6}A methyltransferase complex, METTL14, co-localizes with METTL3 in the nuclear speckle and forms a stable heterogeneous complex in a 1:1 ratio with METTL3 (Liu et al., 2014). WTAP (Wilms tumor 1-associated protein) is the complex's third key component (Wang et al., 2016). RBM15 and its analog RBM15B were later discovered to be members of a complex that facilitates their recruitment to specific sites on RNA molecules (Patil et al., 2016). Recently, researchers have identified vir-like m^{6}A methyltransferase-associated proteins

VIRMA (also known as KIAA1429), HAKAI and zinc finger protein 13 (ZC3H13) to interact with other components of the complex to form a large multi-component complex (Yue et al., 2018). In addition to this, METTL16, a homolog of METTL3, is thought to be a regulator of cellular SAM levels (Zhang et al., 2019). It can catalyze m^{6}A modification in small nuclear RNAs, U6 snRNAs, and other non-coding RNAs (lncRNAs) (Warda et al., 2017). METTL5 has a similar function (van Tran et al., 2019) (Figure 1).

Demethylases: m^{6}A erasers

In 2011, the first m^{6}A demethylase, Fat mass and obesity-associated protein (FTO) were identified, indicating that m^{6}A RNA methylation is reversible and dynamic (Jia et al., 2011). A second RNA demethylase, α-ketoglutarate-dependent dioxygenase homolog 5 (ALKBH5), which is predominantly expressed in the testis, was soon discovered in 2013 (Zheng et al., 2013; Ueda et al., 2017). The recently discovered demethylase ALKBH3, which appears to demethylate tRNA preferentially, is also commonly thought to be a DNA repair enzyme (Beharry et al., 2016) (Figure 1).

Methylation recognition protein: m^{6}A readers

The m^{6}A methylation recognition protein activates downstream signaling pathways by selectively recognizing bases where m^{6}A modifications occur, which regulates mRNA export, translation, metabolism, and stability. The m^{6}A methylation recognition proteins can be broadly classified according to their functions: YTHDF2, YTHDF3, and YTHDC2, which promote mRNA degradation; IGF2BP1/2/3, which maintain mRNA stability; and YTHDF1, YTHDF3, YTHDC2 and IGF2BP1/2/3, which promote translation of target mRNAs(Huang et al., 2018); YTHDC1, on the other hand, may affect mRNA splicing and export from the nucleus (Wang et al., 2014). Members of the heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNPA2B1, HNRNPC and HNRNPG) are potential m^{6}A methylation recognition proteins that play a crucial role in regulating the processing and maturation of RNA substrates and gene expression (Lin et al., 2016). In addition, METTL3 in the cytoplasm can act as a reader protein and promote the translation of certain specific cellular mRNA types (Alarcon et al., 2015). Eukaryotic initiation factor 3 (EIF3), proline-rich coiled-coil protein 2A (PRRC2A), and other recognition proteins have also been reported (Wu et al., 2019) (Figure 1).

Biological functions of m^{6}A modifications

As a widely distributed RNA modification with many recognition proteins, m^{6}A mediates various biological functions involved in the regulation of mRNAs, the direction of differentiation of stem cells, the regulation of development, the development of neurological diseases and the progression of tumors.

RNA m^{6}A modification appears to be transcription-independent. However, a recent study revealed that chromosome-associated regulatory RNAs (carRNAs), can be modified by m^{6}A to cause carRNA attenuation via YTHDC1, influencing chromatin state and downstream transcription (Liu et al., 2020). In mammals, m^{6}A modifications can regulate the pathway of pre-mRNA splicing. For example, the m^{6}A recognition protein HNRNPG may interact with RNA polymerase II and nascent pre-mRNA co-transcription using the Arg-Gly-Gly motif to control selective splicing (Zhou et al., 2019). Additionally, YTHDC1 can direct pre-mRNA splicing factors to bind to certain mRNAs and regulate mRNA splicing (Xiao et al., 2016). There is also evidence that m^{6}A can alter RNA structure and thus affect RNA-protein interactions in cells. In addition, it was found that m^{6}A is involved in regulating biological development and plays a vital role in sex determination (Haussmann et al., 2016), spermatogenesis (Xu et al., 2017), epithelial cell differentiation (Wang et al., 2017) and other functions (Huang et al., 2020).

According to a study, lung cancer patient's circulating tumor cells (CTCs) of considerably increased the m^{6}A modification. This suggests that upregulating the m^{6}A RNA methylation in CTCs may assist monitor and preventing tumor spread (Huang et al., 2016). In addition, R-2HG exhibited anti-leukemic effects as it increased m^{6}A modification in sensitive cells by inhibiting FTO proteins (Su et al., 2018). Not coincidentally, the modification of m^{6}A regulators in cancer has also been reported. Investigators found that METTL3 was modified by SUMO1, and significantly inhibited its m^{6}A methyltransferase activity, resulting in reduced m^{6}A levels in mRNA. These results suggest that modifying m^{6}A regulators may be a novel molecular mechanism for regulating m^{6}A methylation (Du et al., 2018).

Ferroptosis

Ferroptosis is an iron-dependent, unique kind of programmed cell death separate from apoptosis, cell necrosis, and cell autophagy initially postulated by Dr. Brent R. Stockwell at Columbia University in 2012 (Dixon et al., 2012; Yang et al., 2014). The specific flow chart is shown in Figure 2.

The following features mainly characterize ferroptosis: (i) The accumulation of significant levels of iron ions, lipid peroxidation, increased ROS, and alterations in specific genes that regulate iron homeostasis and lipid peroxidation metabolism, are all associated with cell death. (ii) In the fine structure of the cell, smaller than average mitochondria will appear, and the mitochondrial membrane will be wrinkled. In contrast, the mitochondrial cristae will be reduced or disappear, and the outer membrane will be broken, but the morphological changes in the nucleus are not apparent (Cosialls et al., 2021).

Regulation of ferroptosis

Ferroptosis is a regulated form of cell death characterized by accumulating iron-mediated lipid peroxidation of polyunsaturated fatty acid (PUFA) to lethal levels. Sensitivity to ferroptosis is closely related to many biological processes, including amino acid, iron, and polyunsaturated fatty acid metabolism (Stockwell et al., 2017). Current studies have shown that the accumulation of PUFA oxide is a marker of ferroptosis. Its accumulation process mainly

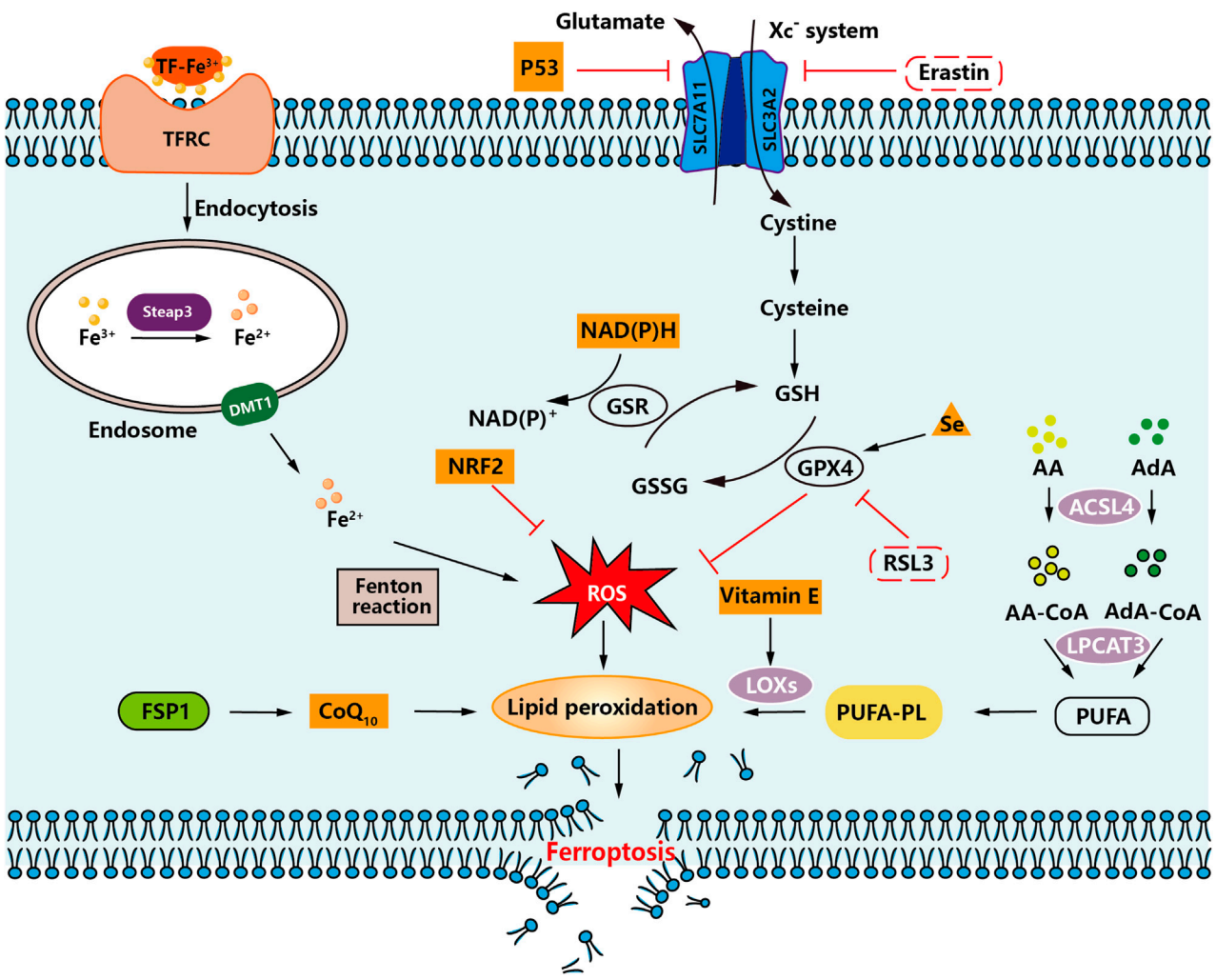

FIGURE 2
An overview of ferroptosis. An illustration demonstrating how intracellular and intercellular signaling events can influence ferroptosis by regulating cellular metabolism and ROS levels.

involves deoxygenation inhibition (mainly GPX4 and ferroptosis suppressor protein 1 (FSP1)) and enhanced peroxidation catalyzed by iron and a series of enzymes. A detailed diagram is shown in Figure 2.

Among the amino acid metabolism pathways, the regulatory systems involved in ferroptosis are mainly the Xc^- system (SLC7A11/SLC3A2 complex) and the lipid repair enzyme glutathione peroxidase 4 (GPX4) system (Ursini and Maiorino, 2020). When the Xc^- system is inhibited, cystine uptake decreases and so does the amount of glutathione (GSH), leading to the accumulation of lipid radicals. After GPX4 inactivation, lipid radicals are converted to toxic lipid peroxides catalyzed by iron, which leads to the rupture of PUFA of cell membrane lipids and induces ferroptosis (Doll and Conrad, 2017). Therefore, when the cystine transport protein (Erastin) is inhibited, intracellular GSH is depleted, which eventually leads to the inactivation of GPX4, leading to the accumulation of lipid peroxidation, which can induce cell death. Inhibition of GPX4 enzymes, such as RSL3, can also directly contribute to this effect. Therefore, inhibition of Xc^- system, insufficient or depleted GSH synthesis, and inactivation of GPX4 all lead to the accumulation of lipid peroxides in the cell, and ultimately to ferroptosis (Cao et al., 2022).

In the lipid metabolism pathway, arachidonic acid (AA) and adrenaline (AdA) can be esterified by acyl-CoA synthetase long-chain family member 4 (ACSL4) to lipid coenzyme a derivatives, and then recombinant lysophosphatidyl-choline acyltransferase 3 (LPCAT3) promotes the incorporation of PUFA into phospholipids to form polyunsaturated fatty acid phospholipids (PUFA-PL) (Yang et al., 2016; Doll et al., 2017). PUFA-PLs are susceptible to oxidation triggered by free radicals mediated by lipoxygenases (LOXs). This oxidation eventually disrupts the lipid bilayer and affects membrane function, thereby promoting ferroptosis (Wu et al., 2019). Thus, activation of ACSL4, LPCAT3, and LOXs leads to excessive lipid peroxidation, resulting in the development of ferroptosis.

Among the pathways associated with iron metabolism, Fe^{3+} enters the blood and binds to transferrin (TF) to form TF-Fe^{3+}, which binds to the transferrin receptor (TFRC) on the cell surface. The intracellular metal reductase STEAP3 reduces Fe^{3+} to Fe^{2+} and then releases Fe^{2+} into the dynamic iron pool of the cytoplasm via

divalent metal transporter protein 1 (DMT1) (Gao et al., 2015). Under pathological conditions, Fe^{2+} accumulates in the cell. It undergoes the Fenton reaction, generating a large amount of ROS, which will generate lipid peroxides by a series of peroxidation reactions with PUFA on the cell membrane, leading to the destruction of the cell membrane structure and eventually causing ferroptosis (Yu et al., 2019).

Other factors that affect ferroptosis sensitivity include coenzyme Q10 (CoQ10) (Bersuker et al., 2019), reduced coenzyme II (Nicotinamide Adenine Dinucleotide phosphate, NADPH) (Guo et al., 2020), selenium (Alim et al., 2019), p53 (Jiang et al., 2015)., nuclear factor E2-related factor 2 (NRF2) (Sun et al., 2016), and Vitamin E (Imai et al., 2017).

Biological functions of ferroptosis

Susceptibility to ferroptosis is tied to many biological processes, and excess iron can lead to tissue damage and an increased risk of cancer. It has also been associated with pathological cell death associated with mammalian neurodegenerative diseases (such as Alzheimer's disease, Huntington's chorea and Parkinson's syndrome), stroke, cerebral hemorrhage, traumatic brain injury, local ischemia-reperfusion injury and renal failure (Jiang et al., 2021). In addition, ferroptosis is a potential weapon against the development of many cancers, such as colorectal (Liu et al., 2022b), pancreatic (Yamaguchi et al., 2018), gastric (Zhang et al., 2020), lung (Wang et al., 2019), liver (Capelletti et al., 2020), renal cell (Yang et al., 2019) and ovarian (Wang et al., 2021) cancers.

Compared with normal cells, cancer cells are more metabolically active, with dysfunctional mitochondria and more ROS accumulation, which increases the sensitivity of cancer cells to ferroptosis. Tumors are more sensitive to ferroptosis induction, namely, when they undergo epithelial-mesenchymal transition or when they acquire "stemness" and become tumor stem cells (Zhang et al., 2018). In brief, induction of ferroptosis may not only be a new means of inhibiting tumor cell growth, but also provides a new promising pathway for reversing tumor drug resistance.

Meanwhile, several studies have demonstrated the role of ferroptosis in neurodegenerative and cardiovascular diseases, suggesting the therapeutic potential of ferroptosis inhibition. Iron chelators have been tested in different experimental systems for stroke and neurodegeneration (Hambright et al., 2017). Elevated iron levels have been detected in patients with aging and degenerative diseases such as Parkinson's disease (PD), Huntington's disease and Alzheimer's disease (AD) (Buijs et al., 2017). Multiple lines of evidence suggest that the GSH-GPX4 antioxidant pathway is significantly abnormal in both AD and PD patients and that using antioxidant drugs may alleviate symptoms of AD and PD pathology (Yan et al., 2021).

m^6A modification induces ferroptosis pathway

In recent studies, multiple iron metabolism-related pathways have been found to play an essential role in the progression of tumor development, which may provide ideas for developing new therapies. However, two main pathways affect ferroptosis: exogenous (transporter protein-dependent) and endogenous (enzyme-regulated) pathways, and modifications of m^6A are present in these cases (Chen et al., 2021a). The details are shown in Figure 3.

Exogenous (transporter protein-dependent) pathway

The exogenous pathway enables initiation by inhibition of cell membrane transport proteins such as cystine/glutamate reverse transporter proteins (Xc^- system), or activation of iron transport proteins. Increasing iron uptake, decreasing iron storage and limiting iron efflux lead to increased iron accumulation, which then promotes ferroptosis through a series of signaling pathways.

In a recent study, high expression of YTHDC2 was found to induce ferroptosis in lung adenocarcinoma (LUAD) cells. SLC7A11 mRNA is modified by m^6A and binds to YTHDC2 to inhibit the antioxidant function of LUAD cells by accelerating the decay of SLC7A11 mRNA (Ma et al., 2021a). Another subunit of the Xc^- system, SLC3A2, is equally essential for YTHDC2-induced ferroptosis. HOXA13 acts as a transcription factor to stimulate the expression of SLC3A2. Thus, YTHDC2 inhibits SLC3A2 by repressing HOXA13 indirectly through m^6A (Ma et al., 2021b). Similarly, METTL3-mediated m^6A modification stabilizes SLC7A11 mRNA and promotes its translation, thereby promoting LUAD cell proliferation and inhibiting ferroptosis. This is because the m^6A reader YTHDF1 is recruited by METTL3 to enhance the modification of SLC7A11 m^6A (Xu et al., 2022). Not coincidentally, in the modification of SLC7A11 by METTL3, IGF2BP1 promoted the stability of SLC7A11 mRNA and upregulated its expression by inhibiting the process of demethylation thereby suppressing the sensitivity of hepatoblastoma to ferroptosis before leading to disease progression (Liu et al., 2022a). Exogenous overexpression of NKAP protects glioblastoma cells from ferroptosis by positively regulating SLC7A11, promoting cell resistance to ferroptosis inducers (Alarcon et al., 2015).

As an m^6A demethylase, FTO downregulates SLC7A11 through m^6A demethylation, regulating ferroptosis in papillary thyroid carcinoma (PTC), thereby inhibiting the development of PTC (Ji et al., 2022). FTO removes m^6A modification of OTUB1 transcripts and promotes the expression of OTUB1. By stabilizing the interaction between OTUB1 and SLC7A11, FTO inhibits radiation-induced cell ferroptosis and ultimately triggers radiotherapy resistance in nasopharyngeal carcinoma (Huang et al., 2023). ALKBH5 eliminated the m^6A modification on SLC7A11 mRNA, reduced the stability of SLC7A11 mRNA, and further reduced the expression of SLC7A11, thus promoting ferroptosis in CRC cells (Luo et al., 2023). Using drugs to induce ferroptosis is a popular strategy. Curdione activates ferroptosis by enhancing MELL14 and the methylation of SLC7A11 mRNA and HOXA13 mRNA, reducing the stability of the reading protein YTHDF2, leading to the expression of SLC3A2. These results provide references or new ideas for the study of ferroptosis in colorectal cancer (Wang et al., 2023). Inhibition of METTL14 is triggered in an HIF-1α-dependent manner under hypoxia

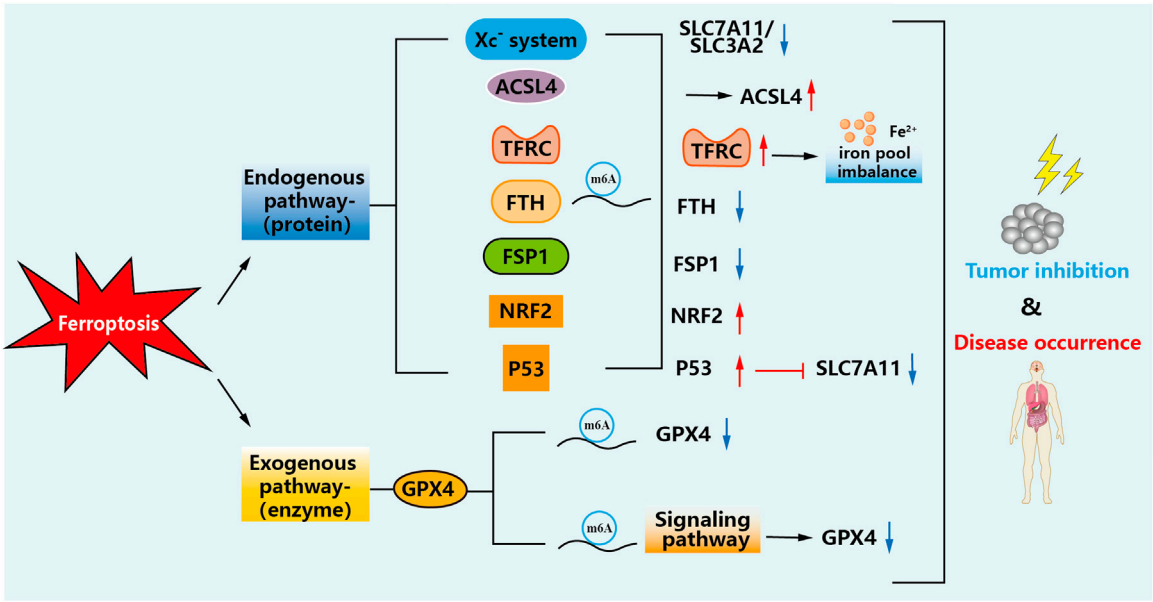

FIGURE 3
Mechanisms of m^{6}A-modified ferroptosis pathways. m^{6}A modification can change the metabolic course of ferroptosis in cells, regulate the changes of these factors, increase lipid peroxidation and iron accumulation in the tumor cell microenvironment, and thus inhibit the occurrence and development of tumors or reduce damage to the body.

conditions, and SLC7A11 was found to be a direct target of METTL14. METTL14 induces m^{6}A modification of SLC7A11 mRNA at 5′UTR, and its degradation depends on a YTHDF2-dependent pathway, which can effectively eliminate ferroptosis in HCC cells (Fan et al., 2021). At the same time, a potential m^{6}A modification site on SLC7A11 mRNA was also found in another study, and YTHDF2 can bind to SLC7A11 mRNA in an m^{6}A dependent manner. YTHDF2 promotes the degradation of SLC7A11 mRNA, thereby reducing its mRNA stability. Therefore, YTHDF2 accelerates the ferroptosis of endothelial cells in cerebrovascular atherosclerosis (Li et al., 2023). KIAA1429, a key component of the m^{6}A methyltransferase complex, targets SLC7A11 during ferroptosis in Hepatocellular carcinoma (HCC) cells. It protects HCC cells against ferroptosis and provides a new insight into abnormally regulated external transcriptomics in the HCC context (Wang et al., 2023). The resulting discovery of a vital role for m^{6}A modification in Xc$^-$system-mediated ferroptosis provides a potential strategy for treating the disease by blocking the m^{6}A- Xc$^-$ system axis.

ACSL4 is a member of the long chain family of acyl-CoA synthetase proteins and is one of the core factors of lipid peroxidation during ferroptosis after myocardial I/R injury. Inhibition of ACSL4 can prevent ferroptosis and reduce myocardial and kidney I/R damage (Qiu et al., 2023). The LPCAT3 protein can also interact with ACSL4, and its upregulation inhibits the expression of ACSL4. *In vitro* models, ACSL4 was identified as a target for LPCAT3 to inhibit mitochondrial damage. Methylation regulation of LPCAT3 improves osteoarthritis by regulating ACSL4 to inhibit chondrocyte ferroptosis (Habaxi et al., 2024).

The transferrin receptor (TFRC) is essential for the uptake of the transferrin - iron complex into cells. It has been shown that in head and neck squamous cell carcinomas (HNSCCs), the YTH structural domain of the m^{6}A reader YTHDF1 interacts with the 3′UTR and 5′UTR of TFRC mRNA. It positively regulates the translation of m^{6}A-modified TFRC mRNA. The high expression of YTHDF1 may increase iron metabolism by promoting the accumulation of intratumoral iron (Jung et al., 2019). From a therapeutic perspective, targeting YTHDF1 and TFRC-mediated iron metabolism to promote iron homeostasis imbalance may be a promising strategy for treating HNSCC. Meanwhile, upregulation of METTL3 lactation enhanced the stability and expression level of METTL3 protein in hemin-treated PC12 cells. After METTL3 silencing, the occurrence of ferroptosis can be inhibited by regulating the m^{6}A level of TFRC mRNA, which is a method to treat cerebral hemorrhage (Zhang et al., 2023).

Ferritin (FTH) is a key regulator of ferroptosis. Downregulated YTHDF1 inhibited cell proliferation, migration and invasion. FTH has been identified as a key target for YTHDF1. In addition, overexpression in YTHDF1 deficient cells partially restored the inhibition. Thus, YTHDF1 upregulation promotes lung cancer by accelerating ferritin translation in an m^{6}A-dependent manner (Diao et al., 2023). Other studies have shown that LncRNA CACNA1G-AS1 can upregulate the expression of FTH1 through the IGF2BP1 axis, thereby inhibiting ferroptosis by regulating FTH phagocytosis, and ultimately promoting the proliferation and migration of ovarian cancer cells (Jin et al., 2023).

FSP1 is a necessary ferroptosis inhibitor. High levels of miR-4443 inhibit cisplatin induced tumor death by reducing the expression level of METTL3 and increasing the level of FSP1, suggesting that miR-4443 plays an important role in cisplatin resistance in NSCLC through the METTL3/FSP1 mediated ferroptosis (Song et al., 2021). Downregulation of YTHDC1 promotes lung tumor progression and leads to ferroptosis resistance through m^{6}A mediated upregulation of

FSP1 protein levels, providing a treatment option for lung cancer with high YTHDC1 levels associated with ferroptosis (Yuan et al., 2023). The upregulation of METTL3 and FSP1 induced by fear stress increases the m^{6}A level of glioma tumor tissue, providing a new understanding of glioma development by inhibiting the tumor progression caused by ferroptosis (Bu et al., 2023).

NRF2 plays a crucial role in the regulation of cellular antioxidant molecules. It has been reported that there is a significant m^{6}A modification site on the 3′UTR, and WTAP can install its methylation. In addition, YTHDF1 identifies the m^{6}A site on NRF2 mRNA and enhances its mRNA stability, thereby accelerating the progression of bladder cancer malignancies (Wang et al., 2023). In another study, the action mechanism and detailed mechanism of SNAI3-AS1/SND1/NRF2 in glioma ferroptosis were elucidated. lncRNA SNAI3-AS1 interfered with SND1's m^{6}A recognition of NRF2 mRNA, thereby reducing the stability of NRF2 mRNA and promoting the occurrence of ferroptosis (Zheng et al., 2023). NRF2 has also been found to be a target of FTO, which demethylates m^{6}A in NRF2 mRNA, thereby impairs the stability of NRF2 mRNA. Therefore, the results of this study illustrate the important role of FTO in Parkinson's disease (PD) through the ferroptosis (Pang et al., 2024).

p53 can inhibit cystine uptake by down-regulating the expression of SLC7A11, thereby inducing ferroptosis. Erianin significantly increased the m^{6}A modification level of the 3′UTR of ALOX12 and P53 mRNA in Human renal cancer stem cells (HuRCSCs). By promoting modification of m^{6}A, kidney cancer stem cells can be induced by ferroptosis, and finally have therapeutic effect (Shen et al., 2023). Silencing KIAA1429 promoted erastin -induced NSCLC cell ferroptosis, activated the p53 signaling pathway, and inhibited its proliferation, migration, and invasion. This also suggests that m^{6}A may be a molecular target for a promising therapeutic strategy for the treatment of NSCLC (Wu et al., 2023).

Endogenous (enzyme-regulated) pathways

The endogenous pathway is activated by blocking intracellular antioxidant enzymes (e.g., GPX4). Lipid peroxide accumulation is a marker of ferroptosis, GPX4 reduces cytotoxic lipid peroxides (L-OOH) to the corresponding alcohol (L-OH), and inhibition of GPX4 activity leads to the accumulation of cell membrane lipid peroxides (Conrad and Pratt, 2019). Studies have shown that FTO can directly regulate the m^{6}A modification of GPX4 mRNA at site 193, while YTHDF2 regulates AKT inhibitation-induced ferroptosis by recognizing and degrading the m^{6}A methylation modification site on GPX4 mRNA (Zhang et al., 2023). RUNX1-IT1 can directly bind to IGF2BP1, resulting in IGF2BP1 occupying more of GPX4 mRNA and increasing the stability of GPX4 mRNA. Targeting the previously unappreciated RUNX1-IT1/IGF2BP1/GPX4 regulatory axis may be a promising treatment for breast cancer patients (Wang et al., 2023). METTL16 epigenetically enhances GPX4 expression through m^{6}A modification and promotes breast cancer progression by inhibiting ferroptosis (Ye et al., 2023). By demethylating the m^{6}A modification of ACSL3 and GPX4 mRNA, FTO reduces its stability and inhibits the expression of ACSL3 and GPX4. Ferroptosis activation of high levels of FTO in Oral squamous cell carcinoma (OSCC) may be a potential therapeutic target (Wang et al., 2023) found that METTL3 was involved in high glucose and palmitic acid (HGPA)-induced osteoporosis through upregulation of the ASK1/p38 signaling pathway, and that activation of the ASK1/p38 pathway was associated with ferroptosis induction. This study suggests that high glucose and high fat (HGHF) induces ferroptosis in diabetic osteoporosis by activating the METTL3/ASK1-p38 pathway (Lin et al., 2022).

m^{6}A modification regulates the occurrence of ferroptosis

Ferroptosis inducers have been shown to enhance the antitumor effects of radiation, but ferroptosis inhibitors have been developed to attenuate radiation-induced organ damage and hematopoietic damage. Therefore, finding the linkage between m^{6}A and ferroptosis in diseases where they are jointly involved, and delving into the regulatory ferroptosis pathway to maximize the clinical benefit in treatment are crucial questions that deserve further investigation. As shown in Figure 4.

m^{6}A as an inducer of ferroptosis occurrence

Tumors are the number one problem in the world, and in the treatment of oncological diseases, the most crucial purpose of m^{6}A involvement in the biology of ferroptosis is to promote the occurrence of ferroptosis in tumor cells. Combined with the above description, the effect of eliminating malignant tumors can be achieved by activating the metabolic pathway of ferroptosis. For example, both subunits of the Xc^-system in the development of lung adenocarcinoma are indispensable for YTHDC2 induced ferroptosis (Ma et al., 2021b).

In addition, METTL3-mediated m^{6}A modification can stabilize SLC7A11 mRNA and promote its translation, thereby promoting the proliferation of LUAD cells and inhibiting ferroptosis. Down-regulating METTL3 can inhibit this process (Xu et al., 2022). Similarly, miR-30c-5p promotes the ferroptosis of cervical cancer by targeting the METTL3/KRAS axis, and inhibits the growth and metastasis of xenografts of cervical cancer. Targeting this process can be effectively treated (Gong et al., 2024).

WTAP-mediated m^{6}A modification on circCMTM3 inhibits ferroptosis in hepatocellular carcinoma by recruiting IGF2BP1 to increase PARK7 stability (Chen et al., 2023). WTAP also can regulate NUPR1 m^{6}A modification to upregulate LCN2, thereby promoting the proliferation, migration and invasion of breast cancer (Tan et al., 2023). Meanwhile, WTAP accelerates bladder cancer malignancy by targeting NRF2 through YTHDF1-m^{6}A dependent ferroptosis regulation (Wang et al., 2023). Each of these pathways can play a therapeutic role by inhibiting WTAP.

One study found that ALKBH5 leads to impaired stability of NFE2L2/NRF2 mRNA and reduced expression in hypopharyngeal squamous cell carcinoma (HPSCC) through an m^{6}A-IGF2BP2-dependent mechanism. Therefore, ferroptosis as an anti-cancer treatment may help treat HPSCC patients with high ALKBH5 expression (Ye et al., 2022). EGFR blocks the nuclear output of ALKBH5, increases the clearance function of m^{6}A, and protects glioblastoma from ferroptosis by producing GSH. ALKBH5 inhibitors enhance the antitumor efficacy of EGFR or GSH inhibitors (Lv et al., 2023). However, ALKBH5 expression is decreased in

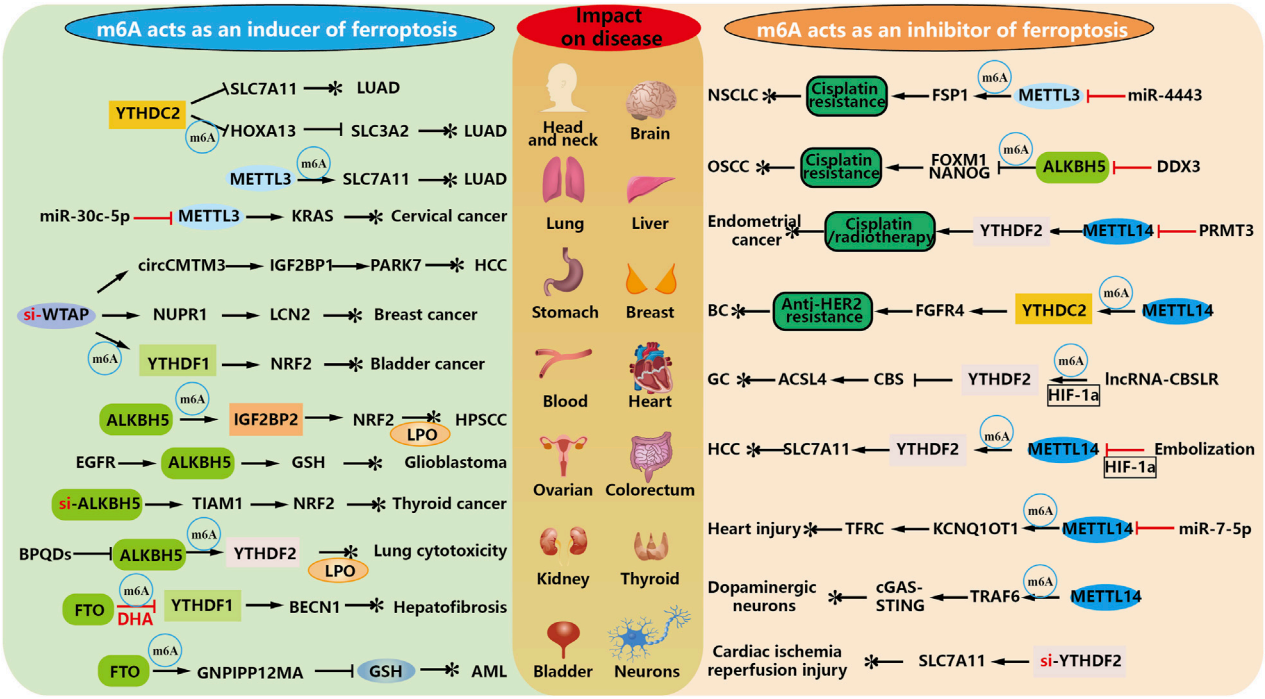

FIGURE 4
m^{6}A modification regulates the inhibition and occurrence of ferroptosis. As an inducer of modified regulated ferroptosis, m^{6}A elucidated that exogenous drugs or high expression of m^{6}A in tumors promoted ferroptosis and thus played an anticancer role. At the same time, m^{6}A methylation regulates RNA, which can affect the drug resistance of some diseases, thus producing essential side effects for its treatment.

thyroid cancer, and ferroptosis can be induced by overexpression of ALKBH5 along the m^{6}A-TIAM1-NRF2/HO-1 axis, thereby inhibiting the progression of thyroid cancer, suggesting that ALKBH5 may be a potential target molecule for the treatment and diagnosis of thyroid cancer (Li et al., 2023). In contrast, in studies of nanoengineering for disease, black phosphorus quantum dots (BPQDs) significantly increased m^{6}A levels and decreased levels of the demethylase ALKBH5 in lung cells. YTHDF2 recognizes these m^{6}A-modified mRNAs, which leads to their decay in the cytoplasm. Ultimately, ferroptosis is triggered by biological processes including mitochondrial dysfunction, lipid peroxidation and iron overload (Ruan et al., 2021).

DHA treatment increased autophagy levels in HSCs, and upregulated m^{6}A modification was essential for DHA to activate autophagy by reducing FTO (Shen et al., 2022). It ultimately plays an anti-fibrotic role by inhibiting the activation of hematopoietic stem cells (Shen et al., 2021). Self-assembled FTO inhibitor-loaded GSH bioimprinted nanocomposites (GNPIPP12MA) enhance improved GSH depletion and enhanced anti-leukemic chemo-immunotherapy. GNPIPP12MA selectively targets AML cells in the myeloid ecotone and induces ferroptosis by depleting intracellular GSH to achieve a therapeutic effect (Cao et al., 2022).

m^{6}A as an inhibitor of ferroptosis occurrence

It is believed that a significant obstacle to cancer treatment is chemotherapy resistance. Therefore, identifying new mechanisms of chemoresistance may improve clinical outcomes.

In a study of non-small cell lung cancer (NSCLC), high expression of miR-4443 was found to negatively regulate the m^{6}A modification of FSP1 induced by methyltransferase METTL3 to inhibit cisplatin-induced ferroptosis, thereby conferring cisplatin resistance in NSCLC. Therefore, researchers have proposed a novel anticancer strategy to restore METTL3/FSP1-mediated ferroptosis in tumor cells (Song et al., 2021). Some investigators also found that DDX3 reduces tumor stem cell populations by inhibiting the expression of FOXM1 and NANOG. The m^{6}A demethylase ALKBH5 was also directly regulated by DDX3, leading to reduced m^{6}A methylation in FOXM1 and NANOG nascent transcripts, resulting in chemoresistance. In a patient-derived cell xenograft model of chemo-resistant OSCC, ketorolac restores cisplatin-mediated ferroptosis and significantly reduces tumor burden (Shriwas et al., 2020). PRMT3 inhibitor-mediated METTL14 overexpression promotes methylation through m^{6}A-YTHDF2-dependent mechanism, reduces the stability of low GPX4 mRNA, increases lipid peroxidation levels, and accelerates ferroptosis. Thus, blocking PRMT3 may improve the progression of endometrial cancer after cisplatin and radiotherapy (Wang et al., 2023). Moreover, m^{6}A hypermethylation resulting from METTL14 modification and YTHDC2 modulation led to the upregulation of FGFR4, which inhibited ferroptosis and conferred anti-HER2 resistance to breast cancer. Further inhibition of FGFR4 in drug-resistant cells revealed that the expression of SLC7A11 and GPX4 was significantly reduced, which promoted ferroptosis to inhibit tumorigenesis, thus restoring the sensitivity of drug-resistant breast cancer cells to anti-HER2 (Zou et al., 2022). In addition, Yang H et al. found that CBSLR, a long-stranded non-coding RNA activated

by HIF-1α reverse transcription, is upregulated in gastric cancer and that inhibition of CBSLR under hypoxic conditions leads to chemoresistance. It was shown that lncRNA-CBSLR recruits YTHDF2 protein and CBS mRNA to form a CBSLR/YTHDF2/CBS complex, reducing the stability of CBS mRNA in an m^{6}A-dependent manner. It protects GC from ferroptosis in the hypoxic tumor microenvironment, thus revealing a potential therapeutic target for refractory hypoxic tumors (Yang et al., 2022). Fan et al. found that METTL14 targets m^{6}A methylation under normoxic conditions at the 5′UTR of SLC7A11 mRNA. m^{6}A-modified SLC7A11 mRNA is recognized by YTHDF2 and then sent to the P-body for degradation. Depleting SLC7A11 leads to reduced input of cystine, cysteine and GSH accumulation, which ultimately stimulates ROS production and induces ferroptosis. In contrast, interventional embolization-induced hypoxia inhibits METTL14 in a HIF-1α-dependent manner and subsequently blocks METTL14/YTHDF2/SLC7A11/ROS axis-mediated ferroptosis, promoting HCC progression. This also suggests that targeting the HIF-1α/METTL14/YTHDF2 signaling axis may synergistically affect HCC interventions (Fan et al., 2021).

Of course, in treating malignant tumor diseases, the ultimate goal of studying the mechanisms involved in inhibiting ferroptosis by m^{6}A is still to induce its occurrence to inhibit the development of tumor cells. And in the process of traumatic repair, there is also the action of chemotherapeutic drugs causing the malignant growth of normal tissues, which requires the inhibition of ferroptosis. miR-7-5p could effectively inhibit the expression of METLL14 and TFRC and selectively inhibit METTL14/KCNQ1OT1/miR-7-5p positive feedback loop-mediated ferroptosis, which could be used for the treatment of doxorubicin (DOX)-induced cardiac injury, and the approach was able to inhibit the activation of death without necessarily impairing its anticancer activity (Zhuang et al., 2021). METTL14 downregulates the expression of TRAF6 and inactivates the cGAS-STING pathway, thereby alleviating mitochondrial dysfunction and ferroptosis in dopaminergic neurons (Shao et al., 2023). The cardioprotective effect of silencing YTHDF2 is achieved by increasing the stability and expression of SLC7A11, reducing ferroptosis, and providing a new potential therapeutic target for the treatment of ischemic heart disease (Pang et al., 2023).

Taken together, these findings suggest that ferroptosis due to m^{6}A modification is essential for regulating cellular homeostasis. m^{6}A modification leading to ferroptosis promotes or inhibits malignant cells depending mainly on the level of m^{6}A (dynamically regulated by writers and erasers), the function of downstream targets, and changes in target RNA after methylation (depending on the readers), which in turn affects lipid peroxidation or antioxidant enzymes. These findings support the identification of m^{6}A regulators involved in aberrant expression in the ferroptosis pathway and as promising biomarkers to predict the prognosis of different cancers.

Future and prospects

The m^{6}A methylation is the most epistatic modality for mRNA modification in mammals and has played a vital role in various biological processes, such as tissue development and stem cell differentiation. And the critical impact of m^{6}A in multiple types of cancer is being widely recognized. As a novel regulatory cell death mode different from cell necrosis, apoptosis, and autophagy, ferroptosis has promising applications in tumor therapy. In this paper, we analyze the mechanism of m^{6}A in regulating the life process of ferroptosis through writers, erasers, and readers, and have specific effects on various diseases, and propose some correlations between them. It also suggests future research directions that still need to be further explored.

Although some progress has been made in identifying the relevant regulatory mechanisms, the exact link between m^{6}A modification and ferroptosis under various pathological conditions remains to be further investigated. Current studies have focused on the regulatory factors of m^{6}A, and the readers involved are mainly recognition proteins of the YTH structural domain; then, whether other kinds of readers are involved in the ferroptosis pathway and what role they play need to be further explored. Also, specific mechanisms in drug resistance and side effects of therapeutic approaches still need to be elucidated. m^{6}A and ferroptosis-related genes are highly expressed in some cancers and may also cause other programmed cell death, which together exert anti-tumor effects. For example, in DHA-induced ferroptosis in HSCs, the interaction of m^{6}A modification with BECN1 mRNA promoted the degradation of autophagic ferritin, which ultimately induced ferroptosis (Shen et al., 2022).

In a word, m^{6}A, as the most common RNA modification, enhances the malignant biological behavior of some tumor cells. And tumor cells have a relatively strong sensitivity to ferroptosis, providing a new direction for m^{6}A methylation modification of ferroptosis to adjuvant treat malignant tumors. Therefore, targeting m^{6}A to induce ferroptosis disease may be a promising therapeutic strategy. Also, inhibition of ferroptosis after m^{6}A modification also provides important guidance for studying the damage of chemotherapeutic drugs on the organism.

Author contributions

QL, LL, XC, JZ, JL, and XX carried out the most work. QL, LL, and XC wrote the original draft. JZ, JL, and LY analyzed the data and prepared the Figures. XX, CZ, and HZ conceived the idea and designed the research. QL, LL, and XC wrote the manuscript. XX, CZ, and HZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AA	Arachidonic acidc
ACSL4	Acyl-CoA synthetase long-chain family member 4
AD	Alzheimer's disease
AdA	Adrenaline acid
ALKBH5	α-ketoglutarate-dependent dioxygenase homolog 5
AML	Acute myeloid leukemia
BC	Breast cancer
BPQDs	Black phosphorus quantum dots
carRNAs	chromosome-associated regulatory RNAs
CoQ10	Coenzyme Q10
CRC	Colorectal cancer
CTCs	Circulating tumor cells
DHA	Dihydroartemisinin
DMT1	Divalent metal transporter protein 1
EIF3	Eukaryotic translation initiation factor 3
FSP1	Ferroptosis suppressor protein 1
FTO	Fat mass and obesity-associated protein
GC	Gastric cancer
GPX4	Glutathione peroxidase 4
GSH	Glutathione
GSR	Glutathione reductase
GSSG	oxidized Glutathione
HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
HGPA	High glucose and palmitic acid
HNSCCs	Head and neck squamous cell carcinomas
HPSCC	Hypopharyngeal squamous cell carcinoma
HSCs	Hematopoietic stem cells
HuRCSCs	Human renal cancer stem cells
lncRNA	long non-coding RNA
I/R	Ischemia/reperfusion
LOXs	Lipoxygenases
LPCAT3	Lysophosphatidyl-choline acyltransferase 3
LUAD	Lung adenocarcinoma
m6A	N6-methyladenosine
SLC3A2	Solute carrier family 3 member 2
METTL14	Methyltransferase-like 14
METTL16	Methyltransferase-like 16
METTL3	Methyltransferase-like 3
METTL5	Methyltransferase-like 5
MTC	Methyltransferases complex
NADPH	Nicotinamide Adenine Dinucleotide phosphate
NRF2	Nuclear factor E2-related factor 2
NSCLC	Non-small cell lung cancer
OSCC	Oral squamous cell carcinoma
PD	Parkinson's disease
PRRC2A	Proline rich coiled-coil 2A
PUFA	Polyunsaturated fatty acids
PUFA-PL	Polyunsaturated fatty acid phospholipids
RBM15/15B	RNA binding motif protein 15/15B
ROS	Reactive oxygen species
Se	Selenium
SLC7A11	Solute carrier Family 7 member 11
SOD	Superoxide dismutase
TF	Transferrin
TFRC	Transferrin receptor
VIRMA	Vir like m6A methyltransferase associated
WTAP	Wilms' tumor 1-associating protein
ZC3H13	Zinc Finger CCCH-Type Containing 13