Role of CELF2 in ferroptosis: Potential targets for cancer therapy (Review)

JIAHAO LI, LEI XIAN, ZIFENG ZHU, YANG WANG, WENLEI ZHANG, RUIPENG ZHENG, WANG XUE and JIARUI LI

Department of Interventional Therapy, The First Hospital of Jilin University, Changchun, Jilin 130021, P.R. China

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Abstract. Ferroptosis is a novel form of regulated cellular necrosis that plays a critical role in promoting cancer progression and developing drug resistance. The main characteristic of ferroptosis is iron-dependent lipid peroxidation caused by excess intracellular levels of reactive oxygen species. CUGBP ELAV-like family number 2 (CELF2) is an RNA-binding protein that is downregulated in various types of cancer and is associated with poor patient prognoses. CELF2 can directly bind mRNA to a variety of ferroptosis control factors; however, direct evidence of the regulatory role of CELF2 in ferroptosis is currently limited. The aim of the present review was to summarise the findings of previous studies on CELF2 and its role in regulating cellular redox homeostasis. The present review may provide insight into the possible mechanisms through which CELF2 affects ferroptosis and to provide recommendations for future studies.

Contents

Correspondence to: Professor Jiarui Li, Department of Interventional Therapy, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jilin 130021, P.R. China
E-mail: ljr@jlu.edu.cn

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1. Introduction

Ferroptosis is a novel form of cell death discovered in recent years, and is characterised by an excessive accumulation of cellular levels of lipid peroxide, caused by elevated levels of reactive oxygen species (ROS) owing to a severe imbalance in the intracellular redox state. This process is closely linked to intracellular iron homeostasis, where an accumulation of the strongly oxidising ferrous ion, which becomes a labile iron pool, can generate ROS via the Fenton or Haber-Weiss reaction, thereby initiating the ferroptosis process. Ferroptosis is classified as a form of regulatory necrosis, a class of genetically regulated cell death. Its similarity to necrosis is the disruption of plasma membrane integrity and the release of cytoplasmic contents, which usually leads to a potent inflammatory response (1,2). However, unlike necrosis, the unregulated decadence process resulting from extreme adverse conditions, different types of regulated necrosis have different downstream execution mechanisms and stimulatory molecular pathways (1,2). Ferroptosis is regulated by a variety of factors, such as the glutathione peroxidase 4 (GPX4) antioxidant system, dihydroorotate dehydrogenase (DHODH), the ferroptosis suppressor protein 1 (FSP1)-mediated ferroptosis protection mechanism and the lipoxygenase trigger mechanism, which are independent of each other and together influence the occurrence of ferroptosis (3). An increasing number of studies have revealed that ferroptosis is a key mechanism involved in the development and progression of cancer, as well as in the development of drug resistance. Therefore, it is crucial to elucidate the regulatory mechanisms that underlie ferroptosis.

CUGBP ELAV-like family (CELF) proteins are a family of RNA-binding proteins (RBPs) that, similar to the majority of RBPs, play broad and diverse roles in RNA regulation. CELF2 is the second member of this family and has been found to play a critical role in cancer development. CELF2 functions as a tumour suppressor in a variety of tumours, and its downregulation is associated with a poor patient prognosis (4,5). The tumour-suppressive effects of CELF2 are dependent on the post-transcriptional regulation of various genes, such as heme

oxygenase-1 (*HO-1*) and cyclooxygenase 1 (*COX-1*) (6,7), and its inhibition of various cellular signalling pathways.

The present review discusses in detail the possible mechanisms through which CELF2 regulates the mitogen-activated protein kinase (MAPK) signalling pathway, PI3K/AKT signalling pathway, endoplasmic reticulum (ER)-associated protein degradation (ERAD) pathway, autophagy and the Wnt/β-catenin pathway. Subsequently, the role of these pathways in influencing ferroptosis was further summarized. It was hypothsized that the tumour-suppressive effects of CELF2 may be partially dependent on ferroptosis mechanisms.

2. CELF2 affects ferroptosis through the MAPK signalling pathway

Association of MAPK signalling pathway with ferroptosis. MAPK is an intracellular signalling pathway that has been extensively studied. This cascade is activated by a sequence of three to five hierarchical layers of protein kinases known as the MAPK kinase kinase kinase (MAPKKKK) class, MAPK kinase kinase (MAPKKK) class, MAPK kinase (MAPKK) class, MAPK and MAPK-activated protein kinase (MAPKAPK) (8). The first three layers are considered the basic core units that recognise and conduct various signals inside and outside the cell via phosphorylation. MAPK activation is a critical step in the MAPK signalling pathway that mainly involves the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 protein families. These proteins can activate a variety of MAPKAPKs, thereby regulating the expression of downstream genes or proteins and allowing cells to respond to intra- and extracellular signals including proliferation, differentiation, apoptosis, senescence and carcinogenesis (9,10). Targeting the MAPK pathway, which is the most commonly mutated signalling pathway in human cancers, has long been considered a promising strategy for cancer therapy. An increasing number of recent studies have demonstrated that influencing the ferroptosis process is a key mechanism by which the MAPK signalling pathway promotes tumour development (11-14). The role of CELF2 in the MAPK signalling pathway and its possible role in ferroptosis is illustrated in Fig. 1.

ERK1/2, two key members of the ERK/MAPK pathway, are normally found in the cytoplasm and, when activated, can enter the nucleus and regulate the activity of various transcription factors and gene expression, playing a crucial role in cell differentiation and proliferation (15). Additionally, ERK1/2 activation can regulate ferroptosis in cancer cells via multiple pathways.

The ERK/MAPK pathway causes resistance to ferroptosis in cancer cells by inhibiting F-box and WD repeat domain-containing 7 (FBW7). FBW7 is a target of the ERK/MAPK signalling pathway, and ERK1 can directly bind and phosphorylate the Thr205 site of FBW7, which promotes the ubiquitinated degradation of FBW7 in a Pin1-dependent manner, thereby inhibiting FBW7 expression (16). FBW7 is an E3 ubiquitin ligase that ubiquitinates target substrates, usually via K11 or K48 linkages, and consequently degrades target proteins that include a number of crucial human cancer proteins (17,18). Thus, FBW7 functions as a tumour suppressor; its expression is downregulated in several tumours and is associated with patient prognosis (16,18). As previously reported, FBW7 induces cancer cell death by promoting ferroptosis. For example, FBW7 has been shown to reduce the binding of nuclear receptor subfamily 4 group A member 1 to the promoter of stearoyl-CoA desaturase 1 (*SCD1*), an enzyme that converts saturated fatty acids to monounsaturated fatty acids, and to inhibit its transcription via an unknown mechanism, thereby promoting ferroptosis in pancreatic cancer cells (19). Furthermore, FBW7 has been found to be able to recognize and ubiquitinate c-Myc in a manner dependent on Thr58 and Ser62 phosphorylation, thereby regulating the level of c-Myc in cancer cells and likely influencing the process of ferroptosis in cancer cells (20,21).

c-Myc, a component of the ERK/MAPK pathway, is a key regulator of ferroptosis. c-Myc is located downstream of the ERK/MAPK signalling pathway. In addition to indirectly regulating c-Myc levels through FBW7, ERK1/2 directly phosphorylates Ser62 of c-Myc and activates its transcription under conditions of oxidative stress (22). Moreover, p38a, another MAPK parallel to ERK, promotes c-Myc expression by directly phosphorylating Ser64 and Ser67 and inhibiting its proteasome-dependent degradation (23), or transcriptionally activating c-Myc by directly binding and phosphorylating β-catenin (24). c-Myc is considered an oncogenic transcription factor that binds to the promoters of various oncogenes to promote their transcription. It has been reported that c-Myc is able to transcriptionally activate a variety of ferroptosis suppressor genes, conferring cancer cells the ability to resist ferroptosis. For example, c-Myc is enriched at the solute carrier family 7 member 11 (*SLC7A11*) and γ-glutamylcysteine synthetase promoters, and transcriptionally activates these genes to help cancer cells resist oxidative stress through a pathway that promotes glutathione synthesis, which also renders cancer cells resistant to chemo- and radiotherapy (22,25-27). c-Myc activates lymphoid specific helicase gene transcription, which promotes WD40-repeat protein 76 enrichment at the SCD1/fatty acid desaturase 2 promoter and inhibits ferroptosis through a pathway that affects lipid metabolism (28). Furthermore, c-Myc can bind to the E-box on the nuclear factor E2-related factor 2 (*NRF2*) promoter to activate NRF2 transcription, thereby maintaining intracellular redox homeostasis (29). The non-transcription factor activities of c-Myc have also been identified; for example, c-Myc has been found to be able to directly inhibit the expression of miR-23b, which regulates cellular ferroptosis by targeting glutaminase expression at the 3'-untranslated region (3'-UTR) (30,31). c-Myc was also demonstrated to directly bind and inhibit nuclear receptor coactivator 4 (*NCOA4*) mRNA expression, suppressing ferroptosis by inhibiting ferritinophagy (32).

ADP-ribosylation factor 6 (ARF6), a small GTPase belonging to the Ras superfamily, is mainly localised in the plasma membrane and endosomal compartments, and plays a crucial role in plasma membrane endocytosis, cytokinesis, endosomal recycling, cytokinesis and actin cytoskeletal reorganisation (33). ARF6 is located downstream of the ERK/MAPK signalling pathway and ERK1/2 activates ARF6 transcription via c-Myc (34). Notably, ARF6 continuously activates the ERK/MAPK pathway by interacting

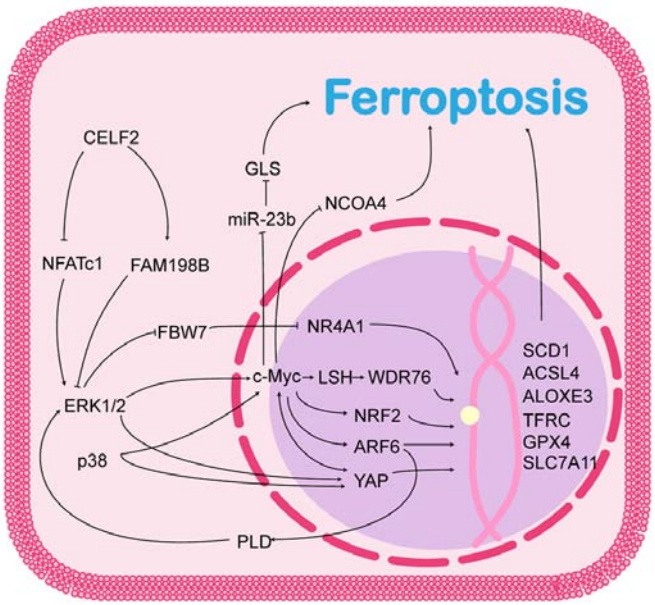

Figure 1. CELF2 affects ferroptosis through the MAPK signalling pathway. CELF2, CUGBP, ELAV-like family number 2; MAPK, mitogen-activated protein kinase; NFATc1, nuclear factor of activated T-cell c1; ERK, extracellular signal-regulated kinase; FAM198B, family with sequence similarity 198, member B; FBW7, F-box and WD repeat domain-containing 7; PLD, phospholipase D; GLS, glutaminase; NR4A1, nuclear receptor subfamily 4 group A member 1; LSH, lymphoid specific helicase; WDR76, WD40-repeat protein 76; NRF2, nuclear factor E2-related factor 2; ARF6, ADP-ribosylation factor 6; YAP, yes-associated protein; SCD1, stearoyl-CoA desaturase 1; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOXE3, arachidonate lipoxygenase 3; TFRC, transferrin receptor protein; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11.

with phospholipase D (35). This forms a positive feedback mechanism that maintains high levels of c-Myc in cancer cells (34). Recent studies have revealed that although ARF6 does not directly regulate lipid peroxidation, it can alter the sensitivity of cancer cells to oxidative stress, rendering them less sensitive to ferroptosis induced by RSL3 and erastin, and thereby participating in the development of drug resistance in cancer cells (36,37). ARF6 has been reported to inhibit the expression of acyl-CoA synthetase long-chain family member 4 (ACSL4) (36) and GPX4 (37) at the transcriptional level, allowing pancreatic and gastric cancer cells to develop tolerance to tabine analogues.

Yes-associated protein (YAP) can be activated by the ERK/MAPK pathway and plays a dual role in ferroptosis. YAP is a key effector of the Hippo pathway and is frequently dysregulated in human cancers. Aberrantly activated YAP has emerged as a key driver of tumorigenesis, chemoresistance and tumour metastasis (38). YAP is a co-transcription factor that interacts with DNA-binding transcription factors to regulate diverse cellular behaviours (39). Recent studies have revealed that YAP is located downstream of the MAPK pathway and that ERK1/2/5 (40-42), p38 (41), mechanistic target of rapamycin (mTOR)C2 (43) and c-Myc (44) can activate YAP in a non-Hippo pathway-dependent manner. Notably, the reciprocal upregulation of c-Myc and YAP has been observed in hepatocellular carcinoma. In hepatocellular carcinoma cells, c-Myc activates YAP transcription by interacting with hepatitis B X-interacting protein (44), while YAP promotes c-Myc transcription by binding to c-Abl (45). Taken together, YAP and c-Myc promote the development of hepatocellular carcinoma. However, its role in ferroptosis remains unclear. YAP enhances the binding of transcriptional enhanced associate domain (TEAD)4 to transferrin receptor protein (*TFRC*), *ACSL4*, and arachidonate lipoxygenase (*ALOX*)E3 (46-48), thereby enhancing the sensitivity of cancer cells to ferroptosis, whereas the YAP-TEAD complex inhibits the expression of threonine tyrosine kinase and TFRC via s-phase kinase-associated protein 2 (49), thereby protecting cancer cells from ferroptosis. Moreover, the YAP-activating transcription factor (ATF)4 complex can bind to the *SLC7A11* promoter and promote its transcription, thereby promoting the resistance of hepatocellular carcinoma cells to sorafenib (50). These studies suggest that the role of YAP in ferroptosis is complex and may be related to the cancer cell type and genetic background, and that the role of YAP in ferroptosis requires further exploration.

CELF2 is a regulator of the MAPK signalling pathway. Based on the data from available studies, CELF2 may affect the MAPK pathway through both the human family with sequence similarity 198, member B (FAM198B) and nuclear factor of activated T-cell c1 (NFATc1) pathways. FAM198B is an *N*-linked glycoprotein with unknown functions that is localised to the Golgi membrane (51). CELF2 stabilises FAM198B mRNAs by binding to its AREs (AU/U-rich elements) within the 3'-UTR and then upregulates the expression of FAM198B (52). FAM198B is downregulated in lung and ovarian adenocarcinomas and is associated with a poor patient prognosis (51,52). FAM198B also functions in the tumour microenvironment. For example, Zheng *et al* (53) observed that the expression level of FAM198B in macrophages of colon cancer tissues correlated with patient prognosis. FAM198B regulates M2 polarisation in macrophages and promotes colon cancer progression by targeting SMAD2 (53). Existing research demonstrates that FAM198B exerts its tumour-suppressive effects mainly by inhibiting the ERK/MAPK pathway (51,52); however, the exact mechanisms involved remain elusive. The only factor that can be determined is that the inhibitory effect of FAM198B on the ERK/MAPK pathway depends on its three major glycosylation sites, namely, Asn98, Asn289 and Asn322, and that defects in the glycosylation sites would result in FAM198B being unable to inhibit the ERK/MAPK signalling pathway (51).

NFATc1 is a major transcription factor involved in osteoblast differentiation. Recent studies have demonstrated that it is upregulated in a variety of cancer types and mediates the malignant behaviour of cancer cells. The cancer-promoting function of NFATc1 is largely dependent on c-Myc expression. In addition to directly binding to the TGFβ inhibitory element of the *c-Myc* promoter (54), NFATc1 upregulates c-Myc expression by activating the ERK1/2/p38 MAPK signalling pathway (55), thereby promoting the progression of ovarian (55), lung (56) and pancreatic (54) cancers. The knockdown of NFATc1 reduces ERK1/2 phosphorylation, whereas the pharmacological inhibition of ERK1/2 similarly impairs NFATc1 expression (57). NFATc1 and the ERK1/2 MAPK signalling pathway appear to have a mutually reinforcing

relationship. The mechanisms through which NFATc1 regulates the MAPK signalling pathway remain unclear. One possible explanation is that NFATc1 maintains the activation of the MAPK signalling pathway by interacting with STAT3 and promoting the transcription of proteins upstream of the MAPK signalling pathway (58). CELF2 exerts tumour-suppressive effects by regulating NFATc1 expression. A previous animal study discovered that tumour size and weight were substantially reduced in mice overexpressing CELF2, and that the overexpression of CELF2 was associated with reduced NFATc1 levels in tumour tissue (59). Furthermore, NFATc1 overexpression significantly reversed the CELF2-mediated reduction in the viability and invasive capacity of MCF-7 cells (59). Taken together, these results suggest that CELF2 affects tumour progression via the NFATc1/MAPK pathway.

2. The PI3K/AKT signalling pathway is critical for the regulation of ferroptosis by CELF2

The PI3K/AKT signalling pathway inhibits the ferroptosis process through multiple mechanisms. PI3K is a lipid kinase that phosphorylates the 3-OH moiety of phosphatidylinositol in the plasma and cell membranes. There are several PI3K classes, among which, the most extensively studied is class I PI3K, whose activation is involved in a variety of biological behaviours in cancer cells. The main focus of the present review was PI3K signalling pathway. Class I PI3K converts phosphatidylinositol-3,4-bisphosphate (PIP2) on the plasma membrane to phosphatidylinositol 3,4,5-triphosphate (PIP3), which binds AKT and pyruvate dehydrogenase lipoamide kinase isozyme 1 to PH domains and facilitates their interaction to phosphorylate and activate AKT (60,61). Activated AKT phosphorylates several downstream effectors, ultimately leading to cell growth, survival, and proliferation. The PI3K/AKT signalling pathway has been shown to promote tumour progression and drug resistance development by inhibiting ferroptosis (62,63). The role of CELF2 in the PI3K/AKT signalling pathway and its possible role in ferroptosis is illustrated in Fig. 2.

NRF2, a key antioxidant gene, is upregulated by the PI3K/AKT signalling pathway and confers ferroptosis resistance to cancer cells. NRF2 is a critical transcription factor that regulates antioxidant responses and plays a key role in preventing ferroptosis. In response to oxidative stress, the nuclear translocation of NRF2 is caused by the suppressed inhibitory effect of kelch-like ECH-associated protein 1 (Keap1) on NRF2. In the nucleus, NRF2 interacts with antioxidant response elements located in the mRNA promoter region, which encodes a subset of antioxidant genes, such as metallothionein-1G, *HO-1*, NAD(P)H:quinone oxidoreductase 1, ferritin heavy chain (*FTH*)1 and *SLC7A11*, ultimately activating and targeting gene transcription, thereby enhancing resistance to ferroptosis and promoting the development of drug resistance in cancer cells. The activation of the PI3K/AKT pathway induces the development of sorafenib resistance in cancer cells by upregulating NRF2 (64-66). Indeed, the PI3K/AKT pathway can phosphorylate and inhibit glycogen synthase kinase-3β (GSK3β), which attenuates the inhibitory effect of GSK3β on Fyn, which can phosphorylate the Tyr568 site of NRF2, leading to the nuclear export, ubiquitination and degradation of NRF2 (67-69).

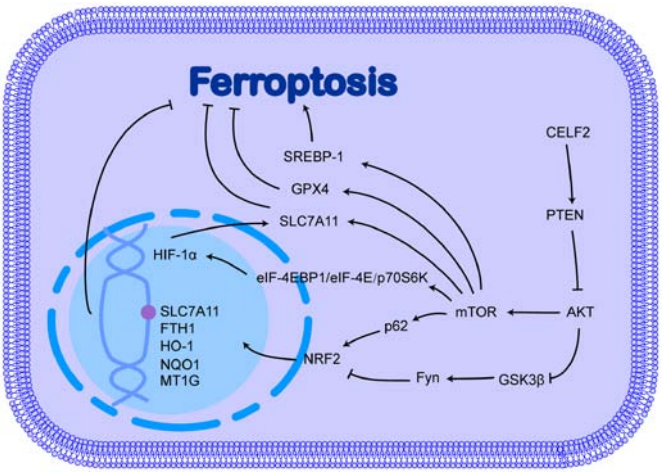

Figure 2. CELF2 affects ferroptosis through the PI3K/AKT signalling pathway. CELF2, CUGBP, ELAV-like family number 2; HIF-1α, hypoxia inducible factor-1α; SLC7A11, solute carrier family 7 member 11; FTH1, ferritin heavy chain 1; HO-1, heme oxygenase 1; NQO1, NAD(P)H:quinone oxidoreductase 1; MT1G, metallothionein 1G; SREBP-1, sterol regulatory element binding protein-1; GPX4, glutathione peroxidase 4; eIF-4, eukaryotic initiation factor-4E; EBP1, eIF4E-binding protein 1; p70S6K, TRPV1-ribosomal protein 70 S6 kinase; mTOR, mechanistic target of rapamycin; GSK3β, glycogen synthase kinase 3β; PTEN, phosphatase and tensin homolog.

mTOR is a major effector of the PI3K/AKT signalling pathway in the inhibition of ferroptosis. mTOR is a protein kinase that regulates cell growth, survival, metabolism and immunity, and is a major effector of the PI3K/AKT signalling pathway. Although mTOR can phosphorylate and activate p62, promoting the binding of p62 to Keap1 and upregulating NRF2 expression (70), its inhibitory effect on ferroptosis is not largely dependent on NRF2 (71). mTOR inhibits ferroptosis by directly upregulating GPX4 and SLC7A11 expression (72,73). In addition, mTOR upregulates sterol regulatory element binding protein-1 (*SREBP-1*) at both the transcriptional and post-translational levels (74,75), and the overexpression of SREBP-1 promotes resistance to ferroptosis through a pathway that affects lipid metabolism in cancer cells (71).

The PI3K/AKT pathway promotes hypoxia inducible factor-1α (HIF-1α) expression under normoxic conditions and consequently inhibits the onset of ferroptosis. HIF-1α is another gene downstream of the PI3K/AKT/mTOR signalling pathway. The PI3K/AKT/mTOR pathway promotes the translation of *HIF-1α* by regulating eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (eIF-4EBP1), eIF-4E and TRPV1-ribosomal protein 70 S6 kinase (p70S6K) via phosphorylation (76,77). However, the regulation of HIF-1α by the PI3K/AKT signalling pathway is cell-specific and is influenced by environmental oxygenation. The inhibition of the PI3K/AKT pathway significantly inhibits HIF-1α accumulation under normoxic conditions, but not under hypoxic conditions (78,79). Under hypoxic conditions, the PI3K/AKT pathway plays a minimal role in regulating HIF-1α. Additionally, the overexpression of HIF-1α can promote AKT phosphorylation, which is dependent on the activation of autocrine growth factor genes, such as *IGF-II* and *TGF-α* by HIF-1α (80). The positive feedback effects of the PI3K/AKT

pathway and HIF-1α combine to promote cancer progression (80). HIF-1α has also been found to play an inhibitory role in ferroptosis. For example, under hypoxic conditions, HIF-1α, which is highly expressed in gliomas and gastric cancer, promotes SLC7A11 expression by increasing the stability of SLC7A11 mRNA via the poly (methacrylic acid-niclosamide) polymer/ELAV-like RNA binding protein 1 pathway, thereby promoting resistance to ferroptosis and sulfasalazine (81,82). Moreover, HIF-1α can also promote the production of NADPH from glucose into the pentose phosphate pathway to maintain intracellular redox homeostasis (83).

CELF2 inhibits PI3K/AKT pathway activation via phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2 (PREX2)/phosphatase and tensin homolog (PTEN). CELF2 influences tumour progression by affecting the PI3K/AKT signalling pathway (84,85). Indeed, the ability of CELF2 to bind to PREX2 and reduce the interaction of PREX2 with PTEN increases the activity of PTEN phosphatase, which reverses the conversion of PIP2 to PIP3, thereby inhibiting activation of the PI3K/AKT signalling pathway (86,87). However, whether CELF2 influences ferroptosis through the PI3K/AKT signalling pathway requires further investigation.

3. CELF2 affects ferroptosis in cancer cells by promoting autophagy

The ferroptosis-promoting effect of autophagy is dependent on a severe imbalance in the intracellular redox state. Ferroptosis is a form of autophagy-dependent cell death (88,89). Autophagy was originally discovered as a cellular self-defence mechanism capable of targeting damaged organelles or various harmful biomolecules, as well as invading pathogens, thereby enabling cells to survive a variety of stimuli in many cases (88,90). Excessive or uncontrolled autophagy can trigger autophagy-dependent cell death (88,90).

NCOA4 mediates ferritinophagy and triggers mitochondrial autophagy. Recent studies have revealed that autophagy plays a crucial role in ferroptosis; for example, ferritinophagy, the degradation of ferritin by autophagy, is a main cause of cellular ferroptosis (91-93). During ferritinophagy, FTH binds specifically to NCOA4 to form a complex and forms cohesions in response to interactions between NCOA4 protein molecules (94,95), which are then degraded by lysosomes via the macroautophagic (92,96) or macroautophagic (97-99) pathways, releasing Fe^{2+} and causing ferroptosis. During this process, NCOA4 functions as an autophagic cargo receptor and is essential for ferritinophagy. Therefore, NCOA4 is a key target of ferritinophagy. In addition, NCOA4 has been reported to mediate mitochondrial autophagy in the context of iron homeostasis imbalance. For example, deferiprone, an iron chelator, causes cellular iron depletion that increases mitochondrial ferritin (FTMT) expression through the HIF-1α/transcription factor specificity protein 1 axis and localises its precursor form to the outer mitochondrial membrane, whereas NCOA4 interacts with the precursor form of FTMT and triggers mitochondrial autophagy to inhibit hepatocellular carcinoma cell growth (100,101).

The role of mitochondrial autophagy in ferroptosis is dependent on intracellular iron homeostasis and the redox status. The mitochondria play a critical role in ferroptosis. Ferroptosis is accompanied by mitochondrial dysfunction and the accumulation of mitochondrial ROS (mtROS). Mitochondria release mtROS into the cytoplasm to exacerbate their accumulation in the cytoplasm via several mechanisms (102), among which, mitochondrial autophagy may be a key mechanism (103-105). The excessive accumulation of mtROS and its resultant mitochondrial dysfunction, manifested as mitochondrial depolarisation, has been well documented as a cause of mitochondrial autophagy (105-107). Indeed, the excessive accumulation of mtROS and mitochondrial dysfunction can induce the activation of mitochondrial PTEN-induced kinase 1 (PINK1) (108) and its localisation to the outer mitochondrial membrane (109,110), leading to PINK1-mediated ubiquitin-dependent mitochondrial autophagy. Moreover, mitochondrial DNA damage caused by the excessive accumulation of mtROS leads to an increase in intracytoplasmic mitochondrial DNA, which can trigger mitochondrial autophagy via the GCAS (cyclic GMP-AMP synthase)-STING1 (stimulator of interferon response cGAMP interactor 1) signalling pathway (111). Damaged mitochondria are enzymatically cleaved in endolysosomes, which is a cellular defence mechanism that removes dysfunctional mitochondria, thereby preventing excessive ROS from damaging the cell. This also obscures the role of mitochondrial autophagy in tumour development. The analyses of public databases (112,113) have demonstrated that PINK1 expression is decreased in a variety of tumours and plays contradictory roles in various tumours and even in different cells. For example, in hepatocellular carcinoma, some studies have demonstrated a tumour-suppressive effect of PINK1-mediated mitochondrial autophagy (114,115), whereas other studies have revealed opposing results (113,116). These conflicting results indicate that mitochondrial autophagy may be influenced by certain factors that determine the ultimate effect of mitochondrial autophagy on the cell, whether facilitated or inhibited.

Endolysosomes are key sites for removing damaged organelles and abnormal proteins from cells. Endolysosomes contain significant amounts of iron and play a crucial role in maintaining cellular iron homeostasis (117,118). In acidic endolysosomes, iron is mainly present in the ferrous form and excessive iron content renders the endolysosomal membrane more susceptible to oxidative damage by ROS (117,119). It has been reported that in erastin- or RSL3-induced ferroptosis, the ROS content of the endolysosome increases rapidly and leads to endolysosomal membrane permeabilization, resulting in the release of ROS into the cytoplasm, producing a cytoplasmic ROS burst and triggering ferroptosis (120,121). Moreover, excess levels of Fe^{2+} can also lead to changes in the endolysosomal function and structure. For example, FAC, an iron agent, can significantly increase the number and surface area of endolysosomes and can lead to their dephosphorylation, which drives Fe^{2+} within endolysosomes into the cytoplasm via divalent metal transporter 1 and the related non-selective two-pore cation channels, thereby exacerbating cytoplasmic iron overload and promoting ferroptosis (122,123). In summary, these findings illustrate that endolysosomes play a role in promoting ferroptosis in the context of iron and ROS overload. During

ferroptosis, ferritinophagy and mitochondrial autophagy provide large amounts of Fe^{2+} and ROS to endolysosomes, which causes endolysosomal dysfunction and exacerbates the ferroptosis-promoting function of the endolysosome, which partially explains the conflicting roles of mitochondrial autophagy.

Therefore, the following conclusions can be inferred about autophagy and ferroptosis: During ferroptosis, autophagy is activated to eliminate excess Fe^{2+} and ROS from the cell; however, dysfunctional endolysosomes do not assist the cell to deal with the excess ROS and even leak iron and ROS from the lysosome, causing a burst of intracytoplasmic ROS and allowing ferroptosis to occur in cancer cells.

CELF2 can regulate the biological process of autophagy. CELF2, an RNA-binding protein, can directly bind to the mRNA of autophagy-related factors, allowing CELF2 to be directly associated with cellular autophagy. In colorectal cancer, the overexpression of CELF2 induced by radiotherapy is able to bind to *Beclin1* and autophagy related gene (*ATG*)5/12 mRNAs, increasing their half-life and promoting the onset of autophagic cell death (124).

In addition to directly regulating autophagy-related factors, CELF2 may indirectly regulate cellular autophagy via the MAPK and PI3K/AKT pathways. The p38/MAPK signalling pathway plays a dual role in autophagy. p38 can inhibit the activity of unc-51 like autophagy activating kinase 1 (ULK1) (125,126), ATG5 (127), ATG8 (128) and mATG9 (129), thereby reducing autophagic flux; by contrast, p38 can also promote autophagy in some cases. For example, p38 has been found to promote autophagy through the heat shock protein 27/CREB pathway, which activates the transcription of *ATG7* (130); the proteasome inhibitor MG231 is also able to induce LC3II production via the p38/GSK3β pathway, thereby activating autophagy (131). p38 also inhibits TP53 ubiquitinated degradation via phosphorylation modifications, the latter activating the downstream DNA damage-regulated autophagy modulator 1 gene, mediating autophagy induced by ROS accumulation (132). In the JNK/MAPK signalling pathway, activated JNK can enter the nucleus and promote the transcription of various autophagy regulators, such as LC3, Beclin1, Sestrin2 and ATG5/7 (133-137). Simultaneously, JNK can also promote autophagy through non-transcriptional mechanisms in some cases, such as through phosphorylation of BCL2. In addition, ERK1/2 and JNK, but not p38, can localise to the mitochondria, increasing the stability of PINK1 and promoting mitochondrial autophagy (138,139). In recent years, researchers have found that the MAPK and PI3K/AKT pathways activate p62 via the NRF2-Keap1 axis, which functions as an autophagic cargo receptor that binds to LC3 and promotes autophagosome formation (140).

mTORC1, located downstream of the MAPK and PI3K/AKT pathways, is a key junction in the regulation of autophagy. mTORC1 is a critical inhibitor of autophagy, and available studies have shown that mTORC1 affects autophagy through several mechanisms. First, ULK1 is the primary downstream target of mTORC1 that can affect ULK1 activity through phosphorylation modifications and post-translational pathways. Activated mTORC1 interacts with ULK1 and joins the ULK1-ATG13-FAK-family interacting protein of 200 kDa complex, whereas mTORC1 directly phosphorylates the Ser757 site in ULK1 (141,142). Ser757 is a key regulatory site of ULK1. The phosphorylation of ULK1 Ser757 not only prevents the activation of ULK1 by AMPK, which inhibits the phosphatase kinase activity of ULK1 (143), but also disrupts the interaction of ULK1 with ATG13, which helps localise ULK1 to the detached membrane, thereby inhibiting the initiation of autophagy (125). Moreover, mTORC1 promotes the ubiquitination of ULK1 by tumour necrosis factor receptor-associated factor 6 by phosphorylating the Ser52 site of the activating molecule in Beclin1-regulated autophagy protein 1, thereby reducing the stability of ULK1 (144). Second, activated mTORC1 phosphorylates the Ser113 and Ser120 (nuclear receptor binding factor 2 (NRBF2) sites. When mTORC1 is inhibited, the dephosphorylated form of NRBF2 binds ATG14-BECN1, facilitating the assembly of the Ptdlns3K complex and stimulating the production of Ptdlns3P on the isolated membrane, which can link to ULK1 and activate autophagy (145). Third, mTORC1 binds and phosphorylates the Ser498 site of the UV radiation resistance-associated gene (UVRAG). Phosphorylated UVRAG is able to inhibit the activity of Vps34 via RUN domain Beclin 1-interacting and cysteine-rich containing protein, whereas its function to activate homotypic fusion and vacuole protein sorting is diminished, resulting in a decrease in ras-like small GTPase superfamily member 7 activity, thereby inhibiting the initiation of autophagy and the maturation of autophagosomes and endosomes (146). Finally, mTORC1 can also reduce autophagic flux by phosphorylating autophagy regulators, such as death-associated protein 1 (147) and p70S6K (148).

The Wnt/β-catenin signalling pathway has beeb found to be a negative regulator of autophagy. This pathway inhibits autophagosome maturation mainly by suppressing p62/SQSTM1 expression (149,150). Fan *et al* (151) found that miR-363-3p led to the activation of the Wnt/β-catenin signalling pathway by targeting CELF2 and induced epithelial-mesenchymal transition (EMT) in glioma cells. That study demonstrated for the first time that CELF2 may be located upstream of the Wnt/β-catenin signalling pathway; however, it did not explain the specific regulatory mechanisms. The mechanisms through which CELF2 affects autophagy through the Wnt/β-catenin signalling pathway require further investigation. The association between CELF2 and autophagy and its possible role in ferroptosis is illustrated in Fig. 3.

4. CELF2 may influence ferroptosis through the ERAD pathway

ER stress and ferroptosis. The ER is a crucial site for protein synthesis and processing, and its function is vulnerable to external factors. A variety of conditions, such as nutritional deprivation, hypoxia, viral infection, oxidative stress and calcium depletion can cause an imbalance in cellular compartment homeostasis and lead to ER stress, which is characterised by the accumulation of misfolded proteins within the ER lumen.

ER stress is also involved in ferroptosis. Increased acidity and viscosity within the ER have been reported in erastin-induced ferroptosis, and the combination of erastin and dithiothreitol, an ER stress inducer, caused significant

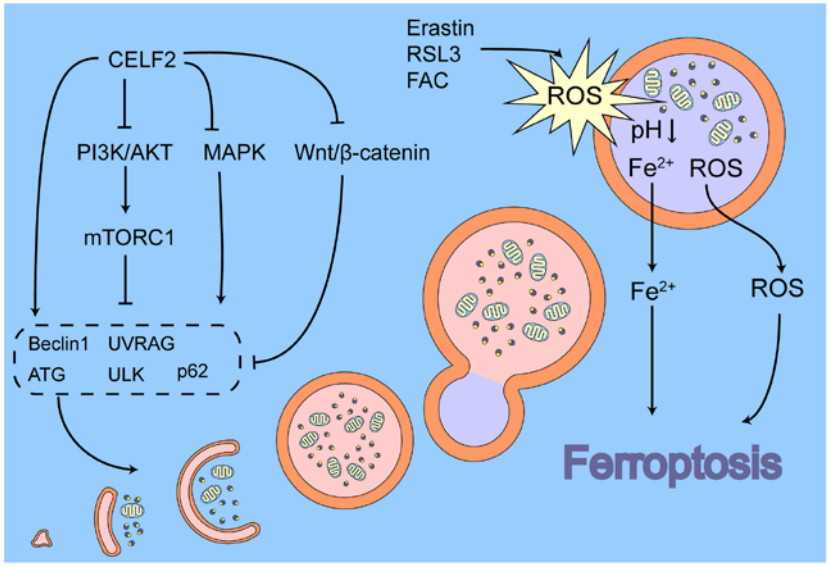

Figure 3. Possible association between CELF2 and autophagy and the promotion of ferroptosis. CELF2, CUGBP, ELAV-like family number 2; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; ATG, autophagy related gene; UVRAG, UV radiation resistance-associated gene; ULK, unc-51 like autophagy activating kinase; ROS, reactive oxygen species.

increases in acidification and viscosity in the ER over a short period, suggesting the involvement of ER stress in the ferroptosis process (152,153). However, the contribution of ER stress to ferroptosis is so complex that it cannot be explained merely by changes in ER content. ER stress exerts varying, or even contrasting, effects on ferroptosis under different conditions. For example, in renal tubular epithelial cells (154) and hepatocytes (155), ER stress induced by cadmium exposure leads to ferritinophagy, whereas in lung cancer, ER stress caused by Ca^{2+} bursts can lead to the reprogramming of Ca^{2+} distribution and mitochondrial dysfunction, facilitating the ferroptosis process through ROS production (156). Moreover, another study reported that the pharmacological inhibition or siRNA knockdown of zrt-like, and Irt-like protein family member 7 induced ER stress by affecting zinc metabolism, which promoted the transcription of homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like domain member 1 and protected MDA-MB-231, RCC1 and HT1080 cells from ferroptosis damage through an unknown mechanism (157). The unfolded protein response (UPR), a signalling mechanism induced by ER stress aimed at resolving misfolded ER proteins and restoring ER homeostasis, is one of the most critical downstream pathways of ER stress and plays an unknown role in ferroptosis. Protein kinase R-like endoplasmic reticulum kinase) and ATF6α, two major UPR effectors, have been found to play opposing roles in ferroptosis (158-161). In summary, these studies collectively suggest that ER stress is involved in ferroptosis and that its function is influenced by a variety of factors.

The ERAD pathway may be involved in the process of ferroptosis. Similar to the UPR, ERAD is a key quality control mechanism in cells capable of degrading natural or misfolded proteins within the ER and maintaining ER homeostasis (162). The ERAD process is broadly divided into three stages. First, ERAD substrates are recognised by chaperone proteins or chaperone-like lectins and are retained within the ER. Depending on their nature or sorting mechanisms within the ER, ERAD substrates are ubiquitinated by various E3 ubiquitin-linked enzymes and transported to the cytoplasm by p97/VCP proteins in an ATP-dependent manner. Finally, the substrate proteins are degraded by the proteasome (163,164). This involves complex molecular mechanisms that will not be described herein, as they exceed the scope of the present review. During ER stress, both the UPR and ERAD are activated and both mechanisms play a crucial role in restoring ER homeostasis. For example, the activation of the UPR promotes protein folding, while also increasing the expression of ERAD-related proteins and promoting the role of ERAD in degrading misfolded proteins; by contrast, defects in ERAD can also lead to the accumulation of misfolded proteins within the ER, resulting in sustained ER stress, subsequently leading to cell death (165). Therefore, these two mechanisms have complementary, synergistic and irreplaceable functions. The ER and mitochondria are highly functionally associated; therefore, the status of the ERAD pathway also appears to be associated with mitochondrial function. Eeyarestatin I, an ERAD inhibitor, reportedly reorganises the overall mitochondrial activity in HepG2 cells, resulting in mitochondrial dysfunction by elevating the intramitochondrial Ca^{2+} and ROS levels (166). In addition, the inhibition of the ERAD pathway leads to the accumulation of various substrate proteins on the ER membrane, such as sigma non-opioid intracellular receptor 1 (SigmaR1) (167) and diacylglycerol o-acyltransferase 2 (168), and the excessive accumulation of these proteins can affect mitochondrial function through various pathways and may therefore be involved in the ferroptosis process (169).

In addition to resisting ER stress, ERAD maintains a basal state of activation under normal conditions and is involved in the degradation of normal proteins within the ER. A previous study identified SigmaR1 as an ERAD substrate in brown adipocytes (167). That study demonstrated that the knockdown of the Sel1L-Hrd1 complex, the most conserved form of ERAD from yeast to humans, resulted in SigmaR1

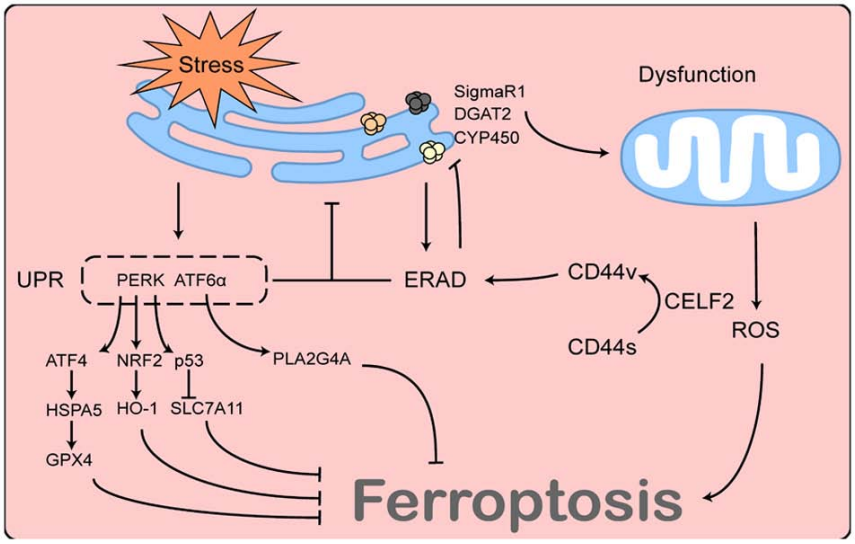

Figure 4. CELF2 affects ferroptosis via ERAD. CELF2, CUGBP, ELAV-like family number 2; ERAD, endoplasmic-reticulum-associated protein degradation; UPR, unfolded protein response; ATF4, activating transcription factor 4; HSPA5, heat shock protein family A (Hsp70) member 5; GPX4, glutathione peroxidase 4; PERK, protein kinase R-like endoplasmic reticulum kinase; ATF6α, activating transcription factor 6α; NRF2, nuclear factor E2-related factor 2; HO-1, heme oxygenase 1; SLC7A11, solute carrier family 7 member 11; DGAT2, diacylglycerol o-acyltransferase 2; SigmaR1, sigma non-opioid intracellular receptor 1; CYP450, cytochrome P450; ROS, reactive oxygen species.

accumulation on ER membranes, which allowed the mitochondria to fuse in response to cold stimulation and reduced the mitochondrial utilisation of lipid droplets. This phenomenon was independent of ER stress (167). Of note, SigmaR1 has also been found in various cancer cells (170-172) and has been shown to function as an inhibitor of ferroptosis in hepatocellular carcinoma cells (173,174). Furthermore, cytochrome P450, an upstream regulator of ferroptosis (175), can be degraded as a substrate for ERAD (176). Therefore, the ERAD pathway may function as an upstream regulator of ferroptosis.

CELF2 affects the ERAD pathway by mediating the alternative splicing of CD44. CD44 is a hyaluronan-binding cell surface signal transduction receptor that plays a crucial role in the genesis, invasion and metastasis of a number of tumours, and is widely considered a marker of cancer stem cells. CD44 contains two variable regions encoded by variable exons; therefore, there are multiple isoforms of CD44, including standard CD44 (CD44s) and variant CD44 (CD44v). The dysregulation of alternative splicing frequently occurs in cancer, resulting in a shift from CD44s to CD44v, which can profoundly affect tumour biology (177). Lai *et al* (178) observed that CELF2, an important factor for mRNA alternative splicing, was involved in the alternative splicing of CD44 and led to a transition from CD44s to CD44v. Lai *et al* (178) also found that the role of CD44v in promoting pancreatic cancer development was dependent on the ERAD pathway, and that an inhibitor of the ERAD pathway was effective in reversing the effects of CD44 on cancer cells. Although the exact mechanisms of ERAD regulation by CD44 have not yet been elucidated, it is suggested that CELF2 functions as an upstream regulator of the ERAD pathway. The association between CELF2 and ERAD and their possible role in ferroptosis are illustrated in Fig. 4.

5. CELF2 activates the Wnt/β-catenin pathway and promotes cancer cell resistance to ferroptosis

Activation of the Wnt/β-catenin signalling pathway inhibits ferroptosis. In the classical Wnt/β-catenin signalling pathway, the Wnt protein binds to the Frizzled and low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors, thereby activating Dishevelled protein (DVL). This prevents adenomatous polyposis coli, axis inhibition protein (AXIN) and GSK3β from forming a destructive complex that prevents the phosphorylation and subsequent degradation of β-catenin. The accumulated β-catenin then translocates to the nucleus and activates downstream genes by binding to different co-transcription factors to form transcriptional complexes. The Wnt/β-catenin signalling pathway plays an inhibitory role in ferroptosis. β-catenin translocated to the nucleus promotes the activation of ferroptosis regulatory genes, such as GPX4 (179), COX2 (182), SCD1 (181), peroxisome proliferator-activated receptor-γ coactivator 1-α (181), matrix metalloproteinases (182) and c-Myc (182,183), and promotes tolerance to platinum-based chemotherapeutic agents through ferroptosis resistance in gastric (184) and ovarian (179) cancers and brain metastases from lung adenocarcinoma (185).

CELF2 affects the activation state of the Wnt/β-catenin signalling pathway through multiple pathways. Fan *et al* (150) first identified an association between CELF2 and the Wnt/β-catenin signalling pathway; however, its specific regulatory mechanisms require further exploration. Based on previous studies, it is suggested that several potential mechanisms may be involved in the regulation of the Wnt/β-catenin pathway by CELF2.

The MAPK cascade, and PI3K/AKT and Wnt/β-catenin signalling pathways crosstalk in a variety of tumours, and all three pathways play synergistic or alternative roles in

promoting tumour progression. The pro-tumorigenic effects of the MAPK and PI3K/AKT pathways are partly dependent on the activation of the Wnt/β-catenin signalling pathway. Thus, the MAPK and PI3K/AKT pathways may play regulatory roles upstream of the Wnt/β-catenin signalling pathway. As previously reported, p38, JNK and ERK1/2 are all able to phosphorylate the Ser1490 and Thr1572 sites of LRP6, which allows LRP6 to provide more AXIN1 and GSK3β binding sites, while isolating these two proteins from the β-catenin destruction complex and thereby reducing the degradation of β-catenin (186,187). Therefore, GSK3β is a critical regulatory target. AKT directly phosphorylates the Ser9 site of GSK3β to negatively regulate GSK3β activity, inhibit β-catenin degradation and promote Wnt/β-catenin pathway activation (188). In addition, β-catenin is a direct target of the MAPK and PI3K/AKT pathways. (p21-Activated kinase 1, located downstream of the PI3K/AKT and ERK/MAPK signalling pathways, activates the Wnt/β-catenin pathway by directly phosphorylating β-catenin and promoting its nuclear localization (189); ERK2 also promotes the nuclear translocation of β-catenin by inhibiting the linkage of α-catenin and β-catenin through the phosphorylation of casein kinase 2α (190).

As previously mentioned (149,150), the Wnt/β-catenin pathway negatively regulates autophagy. In fact, the Wnt/β-catenin pathway has a profound interaction with autophagy. The present review demonstrated that both DVL and β-catenin can function as substrates for autophagy. For example, DVL can be ubiquitinated by Von Hippel-Lindau protein and then degraded by autophagy through a p62-mediated interaction with LC3 (191); β-catenin is degraded by autophagy through interactions with LC3 under both nutrient-dense and starvation conditions (150). Moreover, the inhibition of autophagy can alter the activation of the Wnt/β-catenin signalling pathway (150,191).

Taken together, these results suggest that CELF2 may affect the Wnt/β-catenin signalling pathway via MAPK, PI3K/AKT and autophagy. The association between CELF2 and the Wnt/β-catenin pathway and its possible role in ferroptosis are illustrated in Fig. 5.

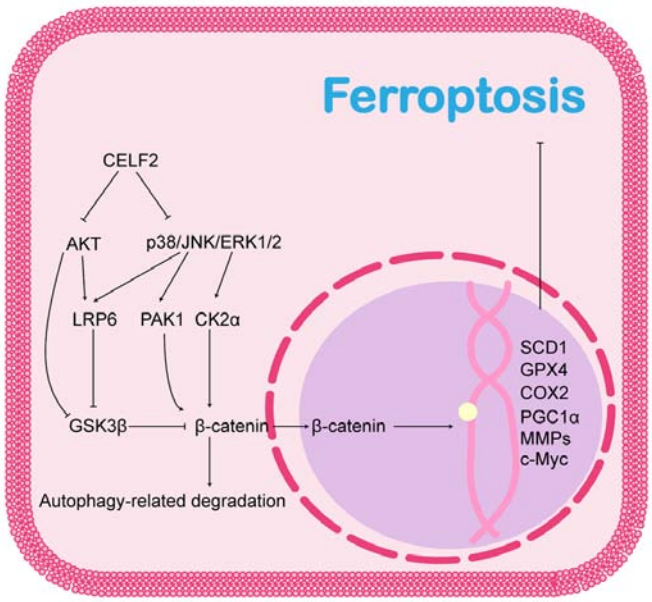

Figure 5. CELF2 affects ferroptosis via the Wnt/β-catenin pathway. CELF2, CUGBP, ELAV-like family number 2; LRP6, low-density lipoprotein receptor-related protein 6; GSK3β, glycogen synthase kinase 3β; PAK1, p21-activated kinase 1; CK2α, casein kinase 2α; SCD1, stearoyl-CoA desaturase 1; GPX4, glutathione peroxidase 4; COX2, cyclooxygenase 2; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1-α; MMPs, matrix metalloproteinases.

6. Conclusions and future perspectives

Ferroptosis is a novel form of cell death characterised by the excessive accumulation of intracellular lipid peroxide, which is dependent on an increase in intracellular iron-dependent ROS. Ferroptosis involves a variety of factors, such as the GPX4 antioxidant system, the ALOX and Ca^{2+}-independent phospholipase $A_2\beta$ pathways, DHODH and FSP1, and occurs under the combined regulatory effect of these factors. Moreover, the pro-tumour effects of signalling pathways, such as MAPK, PI3K/AKT and Wnt/β-catenin, are partly dependent on the resistance of cancer cells to ferroptosis. Ferroptosis plays a crucial role in the development of cancer cells and may serve as a mechanism for tumour therapy.

CELF2 contains three RNA recognition motifs, two at the N-terminus and one at the C-terminus, and a segment of a divergent structural domain that may mediate interactions with RNA (192). This determines the RNA-binding properties of CELF2 (192). Indeed, CELF2 expression is reduced in a variety of cancers and is significantly associated with tumour stage and a poor prognosis of patient patients with various types of cancer, including in non-small cell lung (87), colorectal (5,193), glioblastoma (151), nasopharyngeal (194), gastric (195), breast (4), ovarian (52) and pancreatic cancers (178), and CELF2 may be a key locus for the action of various dysregulated miRNAs or lncRNAs (84,86,151,193-195). The overexpression of CELF2 in these tumour cell lines has been reported to inhibit their biological behaviours, including proliferation, invasion, migration, EMT, and resistance to radio- and chemotherapy (7,85,124,193-199), although the exact mechanisms involved remain unclear. The activation of MAPK or PI3K/AKT signalling pathways owing to the downregulation of CELF2 has been found to be sufficient for inducing proliferation, invasion and migration of cancer cells in a variety of tumours (84,86,87), but CELF2 may act through multiple mechanisms throughout tumour development. For example, in gliomas, the migration and invasion of cancer cells caused by CELF2 downregulation may be associated with the activation of EMT and Wnt/β-catenin signalling pathways (151). In pancreatic cancer, the CELF2-mediated CD44 alternative splicing affects apoptosis and cell stemness by regulating the ERAD signalling pathway (178). Furthermore, the downregulation of CELF2 confers chemoresistance to cancer cells through HO-1- and COX-2-mediated cytoprotective effects (6,7). Thus, CELF2 appears to function as a key target in tumour development. The anticancer potential of CELF2 was initially demonstrated in several *in vitro* studies (7,52,200). Curcumin, a natural polyphenolic compound derived from turmeric, enhances the sensitivity of pancreatic and ovarian cancer cell lines to gemcitabine and cisplatin, respectively, by upregulating CELF2 (7,52,200). Although previous studies have identified the effects of CELF2 on the genes that regulate ferroptosis (6,7), the specific role it plays in ferroptosis remains unclear.

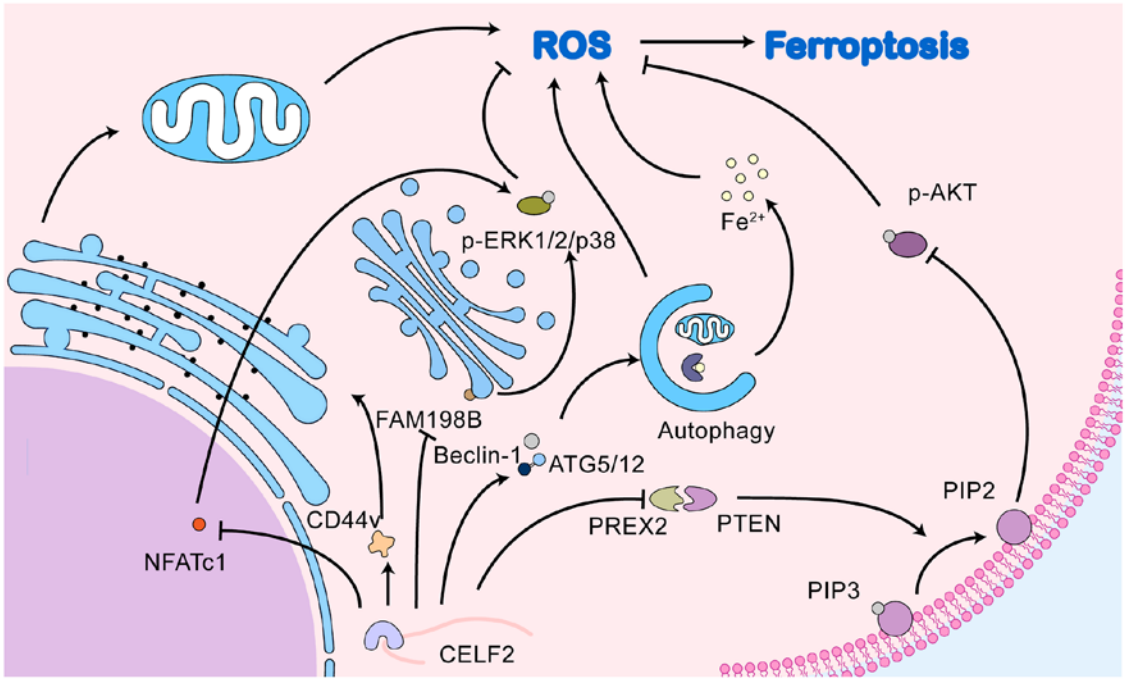

Figure 6. CELF2 is the upstream regulation factor of MAPK signalling pathway, PI3K/AKT signalling pathway, autophagy and ERAD pathway, which can promote cancer cell ferroptosis through these pathways. CELF2, CUGBP, ELAV-like family number 2; ERAD, endoplasmic-reticulum-associated protein degradation; NFATc1, nuclear factor of activated T-cell c1; FAM198B, family with sequence similarity 198, member B; ATG, autophagy related gene; PTEN, phosphatase and tensin homolog; PIP2, phosphatidylinositol-3,4-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate.

The present review summarised the downstream targets of CELF2 in detail and speculated on their role in ferroptosis in a continuous context, which also poses as a limitation of the present review. The present review identified several avenues for further research to improve the understanding of ferroptosis. Fig. 6 broadly illustrates that CELF2 affects ferroptosis through a variety of mechanisms. Overall, CELF2 can exert its oncogenic effects through multiple pathways that may be partly dependent on ferroptosis.

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Availability of data and materials

Not applicable.

Authors' contributions

JiahaoL and LX conceived the study. ZZ was involved in the search methods for relevant literature, as well as the structure of the review. JiahaoL provided the software used to prepare the figures (Adobe Illustrator CC 2018), and was also involved in determining the novelty and innovation of the direction of the topic, and in the writing and preparation of the original draft. WZ, RZ, WX and JiahaoL were involved in reading and evaluating the retrieved literature to determine whether it could be included in the review. YW was involved in the evaluation of the retrieved literature for inclusion in the review. LX, WX and JiaruiL were involved in the writing, reviewing and editing of the manuscript. ZZ and WX were involved in visualization. JiaruiL supervised the study. JiaruiL was involved in project administration. JiaruiL was involved in funding acquisition. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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