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Regulation of Ferroptosis by non-coding RNAs: Mechanistic insights

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List of Abbreviations:

ACSL4 (Acyl-CoA synthetase long chain family, member-4)

METTL3 (Methyltransferase-like 3)

FSP1 (ferroptosis suppressor protein 1)

DKK1 (DICKKOPF1)

GOT1 (glutamic-oxaloacetic transaminase 1)

CAFs (Cancer-associated fibroblasts)

GPX4 (glutathione peroxidase 4)

TBLR1 (TBL1-related protein 1)

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Abstract:

Discovery of ferroptosis has paradigmatically shifted our understanding about different types of cell death. Wealth of information gathered over decades of pioneering research has empowered researchers to develop a better comprehension about versatile regulators of ferroptosis. In this review we have attempted to set spotlight on the indispensable involvement of non-coding RNAs in regulation of ferroptosis. We have exclusively analyzed role of miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs in the regulation of ferroptosis and how inhibition of ferroptosis promoted carcinogenesis and metastasis.

Significance Statement

The manuscript is comprehensively written for a better mechanistic and conceptual comprehension of the recently emerging dynamics of non-coding RNAs and ferroptosis. We also analyze how this interplay shapes the complex process of carcinogenesis and metastasis.

Introduction:

Advancements in sequencing and high-throughput technologies have provided an unprecedented opportunity to mechanistically dissect human diseases on a genome-wide scale. Ground-breaking discoveries related to ferroptosis-like cell death in 1950s and 1960s spearheaded by Harry Eagle provided exciting clues that deprivation of cysteine (amino acid) can lead to cell death. Whereas, endogenously synthesized cysteine made cancer cells resistant to cell death. It is becoming gradually more understandable that cysteine has a rate-limiting role in the biosynthesis of reduced glutathione. There are different types of ferroptosis inducers: Some inducers exert effects through cystine-glutamate transporter (system XC−) and includes sulfasalazine, erastin and glutamate whereas some inducers inhibit the functionality of glutathione peroxidase (GPX) and includes RSL3 and DP17 (Dixon et al, 2012; Viswanathan et al, 2017; Chen et al, 2021; Stockwell et al, 2017). Another sizzling piece of jig-saw puzzle is related to the regulation of ferroptosis by non-coding RNAs. Discovery of non-coding RNAs has been a phenomenal accomplishment and enabled researchers to re-analyze mechanistic details of previously explored signaling pathways. There is a breakneck growth in the list of publications related to non-coding RNAs in disease and pathologies and different types of non-coding RNAs have been characterized. MicroRNA (miRNAs), long non-coding RNAs (LncRNAs) and circular RNAs have been reported to play fundamental role in regulation of various signaling cascades (Volinia et al, 2006; Lytle et al, 2007; Khraiwesh et al, 2010; Cabili et al, 2015; Iyer et al, 2015; Guttman et al, 2009; Chiu et al, 2018; Memczak et al, 2013; Hansen et al, 2013; Salzman et al, 2012). Continuously upgrading list of target genes and miRNAs has emerged at a breakneck pace (Kansakar et al, 2022; Ding et al, 2020; Sutliff et al, 2019). Interplay of lncRNAs and miRNAs is a well-studied area of research in different pathologies (Wang et al, 2020).

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This review summarizes what basic questions remain unanswered and how these answers can be obtained and how we can develop deeper and rational understanding of the functions and dysfunctions of the intricate interplay between ferroptosis and non-coding RNAs. Significant phenomenological breakthroughs have started to illuminate longstanding questions related to the role of ferroptosis, together with massive sequence and crystallographic data, have led to a deeper understanding of interplay between ferroptosis and non-coding RNAs. In thus review we have summarized exciting discoveries which have shaped the signaling landscape of ferroptosis by non-coding RNAs. At the same time, the relationships between ferroptosis and non-coding RNAs and some unresolved outstanding questions in the process of cancer metastasis were discussed, hoping to gather and present reference information for a full-fledge applied research in this field.

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Negative regulators of Ferroptosis:

In this section, we have attempted to provide an overview of the negative modulators of ferroptotic death.
ACSL4 (Acyl-CoA synthetase long chain family, member-4) is certainly a central pro-ferroptotic regulator. It catalyzes the synthesis of long-chain polyunsaturated CoAs. Moreover, lipoxygenases (ALOXs) acts as a trigger for ferroptotic death by catalyzing PUFA oxygenation.
ALOX12 (Arachidonate 12-lipoxygenase) was upregulated in miR-7-5p knockdown cells. miR-7-5p knockdown enhanced ferroptosis signaling and consequently induced cell death (Tomita, 2021).
miR-670-3p inhibitors led to significant increase in intracellular accumulation of the iron (Bao, 2021). miR-670-3p mimics reduced ferroptosis and promoted the growth and survival rates of glioblastoma cells. ACSL4 inhibition also reduced the levels of ferrous iron in miR-670-3p inhibitors-treated A172 and U87MG cells. ACSL4 silencing led to abrogation of miR-670-3p inhibitors-triggered repressive effects on the growth rate of A172 and U87MG cells. Temozolomide efficacy was noted to be more pronounced in miR-670-3p inhibitors-treated A172 and U87MG cells (Bao, 2021).
Ectopically expressed miR-4443 potently reduced the sensitivity of A549-S cells. However, miR-4443 silencing restored cisplatin sensitivity in A549-R cancer cells (Song, 2021). miR-4443 promoted cisplatin resistance by the suppression of ferroptosis. METTL3 (Methyltransferase-like 3), a methyltransferase regulates N6-methyladenosine (m6A) methylation. miR-4443 directly targeted METTL3 and enhanced drug resistance. METTL3 inhibition lowered the sensitivity of A549-S cells, but METTL3 overexpression remarkably restored cisplatin sensitivity in A549-R cells. FSP1 (ferroptosis suppressor protein 1) is a glutathione-independent suppressor of ferroptosis. Multiple m6A sites were identified in FSP1 mRNA which indicated that FSP1 expression was controlled by m6A modifications. Reduction in the methylation status of m6A in FSP1 was noticed in A549-S cells transfected with miR-4443 mimics. Contrarily, m6A methylation of FSP1 was reported to be enhanced but FSP1 mRNA levels were reduced in miR-4443

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inhibitor-treated A549-R cancer cells. Likewise, miR-4443 overexpression abrogated the inhibitory effects of cisplatin and enhanced tumor size and weight in xenografted mice. Tumor tissues from mice demonstrated higher expression of miR-4443 and FSP1 alongwith notable reduction in the levels of METTL3 (Song, 2021). Collectively, these findings indicated that miR-4443 blocked METTL3-mediated m6A modifications in FSP1 and inhibited ferroptosis (shown in fig. 1).

miR-130b-3p caused inhibition of erastin and RSL3-mediated ferroptosis in melanoma cells (Liao, 2021). miR-130b-3p prevented peroxidation of the lipids and iron overload during ferroptosis. DICKKOPF1 (DKK1) is reportedly involved in the inhibition of taurine-triggered NRF2 cascade in UMR-106 cells. miR-130b-3p negatively regulated and directly targeted DKK1 (shown in fig. 1). miR-130b-3p overexpression evidently blocked erastin-induced ferroptosis in G-361 and A375 cells however, these inhibitory effects were antagonized by DKK1 restoration. Overexpression of miR-130b-3p caused rapid increase in the weight and volume of xenografted tumors (Liao, 2021).

Uptake of Glutamine is dependent on receptors SLC1A5 and SLC38A1 (Zhang, 2018). During glutaminolysis, glutamine is deamidated to glutamate. GOT1 (glutamic-oxaloacetic transaminase 1) catalyzes the conversion of glutamate to α-KG. miR-9 considerably reduced erastin- and RSL3-mediated cell death. Whereas, these inhibitory effects were rescued by GOT1 overexpression. miR-9 overexpression led to repression of GOT1 by binding directly to 3'-UTR and suppressed erastin- and RSL3-mediated ferroptotic death (shown in fig. 1). On the contrary, miRNA-9 suppression greatly enhanced the sensitivity of erastin and RSL3 in melanoma cells (Zhang, 2018).

miR-137 has been shown to negatively regulate ferroptosis by direct targeting of SLC1A5 (glutamine transporter) in melanoma cells (Luo et al, 2018). Ectopically expressed miR-137 induced suppression of SLC1A5 and reduced malondialdehyde accumulation and glutamine uptake (shown in fig. 1). Importantly, antagomir-mediated miR-137 inactivation potently sensitized melanoma cells to erastin- and RSL3-mediated ferroptotic death. Notably, miR-137-overexpressing or miR-137-knockdown A375 cancer cells were xenografted into the subcutaneous spaces of rodent models. miR-137 inhibition induced shrinkage of the size of the tumors. Contrastingly, the size of tumors derived from miR-137-overexpressing cancer cells was reported to be markedly bigger which clearly indicated that miRNA-137 blocked erastin-mediated ferroptotic cell death in tumor-bearing mice (Luo et al, 2018).

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Physcion 8-O-β-glucopyranoside (PG) has been reported to be effective against cancer (Niu et al, 2019). PG promoted ferroptosis in MKN-45 and MGC-803 cells through blockade of miR-103a-3p-mediated inhibitory effects on the expression of glutaminase-2. miR-103a-3p overexpression remarkably abrogated PG mediated suppressive effects on the invasive and migratory properties of MKN-45 and MGC-803 cancer cells. Intraperitoneal injection of PG hampered the rapid growth of MGC-803 cancer cells in tumor-bearing mice (Niu et al, 2019).

Cancer-associated fibroblasts (CAFs) secreted miRNA-522 suppressed ferroptotic death and promoted acquired chemo-resistant phenotype in gastric cancer cells (shown in fig. 2) (Zhang et al, 2020). Cancer-associated fibroblasts (CAFs) secrete exosomes which are packed with different non-coding RNAs. Exosomally delivered-miR-522 suppressed ferroptosis in gastric cancer cells. Exosomally-delivered-miR-522 secreted by cancer-associated fibroblasts suppressed ALOX15 in GC cells (shown in fig. 2). Heterogeneous nuclear ribonucleoproteins (hnRNP) family has a contributory role in the packaging of non-coding RNAs into exosomes. Overexpression of USP7 or hnRNPA1 in CAFs promoted sophisticated miRNA-522 packaging into exosomes. Yet, knockdown induced relative reduction in exo-miR-522 levels. Paclitaxel or cisplatin enhanced USP7 and hnRNPA1 expression in CAFs. USP7 deubiquitinated hnRNPA1, which resulted in an increase in miR-522 packaging in exosomes. Knocking down of hnRNPA1, USP7 or miRNA-522 in CAFs caused tumor growth impairment and greatly improved cisplatin sensitivity (Zhang et al, 2020).

Figure 1

Figure 2:

Positive regulators of Ferroptosis:

In this section, we will summarize how different regulators positively modulate ferroptosis.

miR-302a-3p mimics induced iron overload, lipid peroxidation and ferroptosis, thus blocked the growth and colony forming abilities of NSCLCs cells (Wei, 2021). However, miR-302a-3p inhibitors caused blockade of erastin- or RSL3-mediated ferroptosis as well as tumor suppressive effects. In addition, miR-302a-3p directly targeted 3' UTR of ferroportin, whereas, overexpression of ferroportin significantly reduced miR-302a-3p mimics-mediated ferroptosis and consequent prevention of the cancer progression (Wei, 2021).

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miR-375 overexpression-mediated downregulation of $CD44^+$ sub-population with stemness was attenuated by the overexpression of SLC7A11 (Ni, 2021). miR-375 also directly targeted SLC7A11 and induced ferroptosis. Metastasizing potential of miR-375-overexpressing cancer cells was reported to be reduced as evidenced by notable decrease in metastatic nodules. SLC7A11 knockdown suppressed the tumor-initiating ability and metastatic capacity of cancer cells (Ni, 2021).

miR-214 overexpression induced an increase in the malondialdehyde and ROS levels, rise in Fe^{2+} concentrations and reduction in glutathione levels in erastin-treated cancer cells (Bai et al, 2020). ATF4 (Activating transcription factor 4) has been shown to inhibit ferroptosis. Furthermore, erastin triggered activation of ATF4 in Hep3B and HepG2 cells. ATF4 upregulation led to prevention of ferroptosis and lipid oxidation induced by erastin and miR-214. However, pre-miR-214 overexpression reduced the levels of ATF4. Erastin-mediated tumor growth inhibitory effects were reported to be greatly augmented in mice subcutaneously injected with miR-214-overexpressing Hep3B. Erastin noticeably reduced the growth of Hep3B tumor mass in vivo. Erastin-mediated ferroptosis-inducing effects were found to be more pronounced upon overexpression of miR-214 (Bai et al, 2020).

miR-324-3p overexpression led to reversal of cisplatin resistance in cancer cells (Deng et al, 2021). miR-324-3p directly targeted glutathione peroxidase 4 (GPX4), whereas overexpression of GPX4 reversed miR-324-3p-mediated re-sensitization of A549/DDP cancer cells to cisplatin. Additionally, GPX4 inhibitor RSL3 mimicked the effects of miR-324-3p upregulation and re-sensitized cisplatin-resistant cancer cells to chemotherapeutic drugs (Deng et al, 2021).

miR-101-3p directly targeted TBLR1 (TBL1-related protein 1) (Luo et al, 2021). TBLR1 has been shown to play an oncogenic role. TBLR1 inhibition significantly reduced the activity of NF-κB pathway. miR-101-3p mimics induced an increase in ROS levels. GPX4 (glutathione peroxidase 4) eliminated ROS and reduced oxidative stress. GPX4-mediated elimination of ROS was notably reduced in miR-101-3p mimics-treated cancer cells. Besides, miR-101-3p mimics caused significant decline in the level of GPX4 and simultaneously increased the expression of PTGS2. Low levels of PTGS2 and high levels of GPX4 were reported in TBLR1/miR-101-3p co-transfected cancer cells. Tail vein injections of nanocarrier containing miR-101-3p mimics induced tumor retrogression in mice transplanted with A549 cancer cells (Luo et al, 2021).

Positive regulation of Ferroptosis by anesthetic agents:

Levobupivacaine is an anesthetic drug and has been shown to trigger ferroptosis (Mao, 2021). Levels of lipid ROS and Fe^{2+}/iron were enhanced by levobupivacaine in RSL3 and erastin-treated gastric cancer cells. Importantly, levobupivacaine-mediated miRNA-489-3p augmented ferroptotic death in gastric cancer cells. Notably, SLC7A11 belongs to the family of heterodimeric Na^+-independent anionic amino acid transport system. SLC7A11 is highly specialized for transportation of glutamate and cystine. miR-

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489-3p directly targeted SLC7A11. MiRNA-489-3p played central role in levobupivacaine-mediated ferroptotic death in gastric cancer cells. Tumor growth was hampered considerably by levobupivacaine in the mice xenografted subcutaneously with SGC7901 cancer cells. Erastin suppressed the growth of SGC7901 cancer cells and enhanced the levels of Fe^{2+}, iron and lipid ROS in the experimental mice. Furthermore, combinatorial treatment with erastin and levobupivacaine further enhanced the effects of erastin (Mao, 2021).

Lidocaine is also an anesthetic drug and has been shown to enhance ferroptosis (Sun, 2021). Lidocaine promptly enhanced lipid ROS in T47D and SKOV-3 cancer cells. Likewise, levels of GPX4 and SLC7A11 were suppressed in lidocaine-treated SKOV-3 and T47D cancer cells. Colony forming abilities of T47D and SKOV-3 cells were reduced by treatment with miR-382-5p mimics. Depletion of miRNA-382-5p caused blockade of lidocaine-induced ferroptotic death in breast and ovarian cancer cells. Growth rates of SKOV-3 cancer cells were reduced by lidocaine in the nude mice. Levels of miRNA-382-5p were upregulated but simultaneously there was a marked reduction in SLC7A11 levels in the tumor tissues of mice treated with lidocaine (Sun, 2021).

In the upcoming sections, we will comprehensively analyze and discuss how long non-coding RNAs and circular RNAs regulate ferroptosis.

Role of Long non-coding RNAs in the regulation of Ferroptosis:

OIP5-AS1 expression was found to be significantly elevated in PC3 and DU145 cells chronically exposed with cadmium. OIP5-AS1 acted as a sponge of miR-128-3p and potentiated the expression of SLC7A11. Tumor growth was found to be enhanced in mice xenografted with cadmium-exposed prostate cancer cells (Zhang).

Vincristine stimulated the expression of LINC00618 and induced ferroptosis and apoptosis. Levels of LSH (lymphoid-specific helicase) and SLC7A11 were found to be reduced in LINC00618-overexpressing K562 and MV4-11 cells. LSH transcriptionally upregulated SLC7A11 and inhibited ferroptosis (Wang).

GABPB1-AS1 reduced the levels of GABPB1. Interactions between GABPB1 mRNA and eIF4A were found to be significantly enhanced in GABPB1-AS1-depleted cells. GABPB1 transcriptionally upregulated Peroxiredoxin 5 (PRDX5) (shown in fig. 3). Repression of PRDX5 led to accumulation of ROS and consequent induction of ferroptosis (Qi).

P53RRA, an lncRNA promoted the nuclear accumulation of p53. P53RRA interacted with G3BP1 through RRM interaction domain (shown in fig. 3). P53RRA-G3BP1 interactions led to displacement of p53 from a G3BP1 complex which resulted in greater nuclear accumulation of p53 (Mao).

p53 was recruited to the promoter region of ELAVL1 but LSH blocked p53 mediated transcriptional downregulation of ELAVL1 in PC9 cells (Wang). LINC00336 interacted with ELAVL1 through its RRM

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interaction domain and inhibited ferroptosis. Moreover, ELAVL1 increased post-transcriptional stability of LINC00336 (shown in fig. 3). LINC00336 overexpression potently resisted erastin-induced ferroptosis in A549 or SPC-A-1 cells. LINC00336 efficiently blocked MIR6852-mediated targeting of CBS (cystathionine-β-synthase). Injections of LINC00336-expresing-A549 and LINC00336-expressing-SPC-A-1 cells in experimental mice clearly indicated that LINC00336 overexpression led to significant formation of tumor mass. Whereas, expectedly, tumor growth was significantly reduced in experimental models injected with LINC00336-silenced PC9 cells (Wang).

RP11-89 promoted proliferation, migration and carcinogenesis via miR-129-5p/PROM2 axis. RP11-89 markedly antagonized miR-129-5p-mediated targeting of PROM2 (Luo).

TMEM161B-AS1 sequestered hsa-miR-27a-3p away and relieved inhibitory effects of hsa-miR-27a-3p on FANCD2 and CD44. TMEM161B-AS1 silencing or hsa-miR-27a-3p overexpression inhibited the growth of tumors in nude mice (Chen).

Figure 3:

Role of Circular RNAs in the regulation of Ferroptosis:

CircPVT1 has been reported to be frequently overexpressed in 5-fluorouracil-resistant ESCC cells (Yao). Knockdown of circPVT1 sensitized ESCC cells to 5-fluorouracil. CircPVT1 acted as a sponge of miRNA-30a-5p and potentiated the expression of Frizzled3 (FZD3). It was noted that increase in 5-fluorouracil drug-sensitivity by circPVT1 knockdown was reversed by miR-30a-5p inhibitors. In addition, evident increase in 5-FU drug sensitivity by miR-30a-5p mimics was reversed upon overexpression of Frizzled3. Moreover, circPVT1 knockdown enhanced ferroptosis via suppression of phosphorylated-β-catenin, glutathione peroxidase-4 and SLC7A11 whereas inhibition of miR-30a-5p or Frizzled3 overexpression reserved ferroptosis by inducing an increase in the levels of phosphorylated-β-catenin, glutathione peroxidase-4 and SLC7A11 (Yao).

Circ_0000745 knockdown efficiently inhibited the progression of cell cycle as well as glycolysis and induced ferroptosis and apoptosis (Yang). Circ_0000745 has the ability to serve as a sponge for miRNA-494-3p in acute lymphoblastic leukemia cells. Knockdown of miR-494-3p partially abolished circ_0000745 silencing-mediated tumor-suppressive effects in ALL cells. Essentially, NET1 (neuroepithelial cell transforming 1) was directly targeted by miR-494-3p. Furthermore, miR-494-3p overexpression-mediated ferroptosis induction in acute lymphoblastic leukemia cells were partially reversed because of NET1 overexpression (Yang).

CircFOXP1-silenced lung cancer cells demonstrated marked reduction in the migratory and invasive properties (Wang). Importantly, vimentin expression was reduced but E-cadherin levels were noted to be

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enhanced in circFOXP1-knockdown cancer cells. Moreover, erastin or RSL3 effectively repressed the viability of lung cancer cells but circFOXP1 overexpression rescued the phenotype. Levels of iron, malondialdehyde and lipid reactive oxygen species were found to be enhanced upon circFOXP1 silencing in both erastin and RSL3-stimulated lung cancer cells. Significantly, CircFOXP1 potentiated the expression of SLC7A11 by the blockade of miR-520a-5p-mediated targeting of SLC7A11 in lung cancer cells. Use of either miR-520a-5p inhibitors or SLC7A11 overexpression reversed circFOXP1 silencing-mediated ferroptosis in lung cancer cells (Wang).

Silencing of circGFRA1 drastically reduced the proliferation potential of HER-2-positive breast cancer cells (Bazhabayi). Intra-tumorally injected si-circGFRA1 led to notable reduction in tumor mass in mice subcutaneously administered with breast cancer cells. Suppression of circGFRA1 remarkably suppressed number of pulmonary metastatic lesions in tumor-bearing mice (shown in fig. 4). CircGFRA1 antagonized miR-1228-mediated targeting of AIFM2 (Apoptosis inducing factor mitochondria associated-2). Generally, AIFM2 is considered as a ferroptosis suppressor and CircGFRA1 silencing led to significant reduction in the levels of AIFM2. CircGFRA1-silenced cancer cells demonstrated notably decrease in the levels of GPX4. Importantly, decrease in the GSH/GSSG ratio resulted in the deactivation of GPX4, which further enhanced the accumulation of toxic lipid reactive oxygen species and ferroptosis induction (Bazhabayi).

CircFNDC3B enhanced SLC7A11 expression by interfering with miR-520d-5p-mediated targeting of SLC7A11 (Yang). However, miR-520d-5p induced ferroptosis of OSCC cells by downregulation of SLC7A11. Notably, there was a marked reduction in the tumor growth in mice injected subcutaneously with circFNDC3B-silenced CAL27 cells (Yang).

circDTL silencing led to the release of mitochondrially located proteins cytochrome c and SMAC/DIABLO into the cytosol (Shanshan). circDTL interfered with miR-1287-5p-mediated targeting of GPX4. Increase in cell death and release of mitochondrial proteins caused by circDTL knockdown were also impaired upon GPX4 overexpression. Tumor growth rates were found to be reduced in mice xenografted with circDTL-silenced NSCLC cells (Shanshan).

circ_0067934 knockdown induced apoptotic death of thyroid cancer cells and repressed proliferation of thyroid cancer cells (Wang). SLC7A11 is a negative regulator of ferroptosis. Circ_0067934 potentiated the expression of SLC7A11 by sequestering miR-545-3p in thyroid cancer cells. SLC7A11 overexpression or miR-545-3p inhibition led to reversal of circ_0067934 silencing-mediated suppression of thyroid cancer cell proliferation. Tumor growth was significantly reduced in mice subcutaneously injected with circ_0067934-silenced-FTC-133 cancer cells (Wang).

circKIF4A fueled the malignancy of papillary thyroid tumor by sponging miR-1231 and upregulation of GPX4 (Chen). Intra-tumoral injections of si-circKIF4A induced regression of the tumors in mice

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subcutaneously injected with KAT-5 and TPC-1 cancer cells. Silencing of circKIF4A also reduced pulmonary metastasis in mice injected with cancer cells through tail veins (Chen) (shown in fig. 4).

Circ0097009 acts as a competing endogenous RNA to regulate the expression of SLC7A11 by sponging miR-1261 (Lyu). Intra-tumoral injections of si-circ0097009 considerably inhibited tumor growth in mice xenografted with HepG2 cells. Pulmonary metastasis was also noted to be drastically reduced in mice intravenously injected with circ0097009-silenced-HepG2 cells into the tail veins (Lyu) (shown in fig. 4).

circEPSTI1 antagonized miRNA-375, miRNA-409-3p and miRNA-515-5p-mediated targeting of SLC7A11. Injections of si-crEPSTI1 led to evident shrinkage of tumor xenografts in mice inoculated with HeLa cells (Wu).

SLC7A11 (xCT) was frequently overexpressed at the cytoplasmic membranes and SLC7A11-induced metabolic reprogramming fueled the progression of lung cancer (Ji et al, 2018). Mice injected with circP4HB-overexpressing cells demonstrated an evident increase in growth rates of the tumors. Levels of circP4HB and SLC7A11 were increased in the tumor xenografts in mice injected with circP4HB-overexpressing cells (Pan et al, 2022).

circ-BGN, an oncogenic circular RNA is frequently overexpressed in trastuzumab resistant-breast cancer cells (Wang et al, 2022). OTUB1 is a deubiquitinating enzyme and it de-ubiquitinates SLC7A11. Importantly, circ-BGN interacted with OTUB1 and rapidly enhanced OTUB1-driven de-ubiquitination of SLC7A11. Orthotopically implanted tumor model clearly revealed that erastin and circ-BGN inhibition considerably impaired tumor growth by trastuzumab-resistant breast cancer cells (Wang et al, 2022).

circCDK14 sponged miR-3938 and upregulated PDGFRA in glioma cells (Chen et al, 2022). Levels of PDGFRA, p-PDGFRα, SLC7A11 and GPX4 were reported to be profoundly enhanced in circCDK14 overexpressing-U87 cells. However, expectedly, PDGFRA, p-PDGFRα, Vimentin, ZEB1, SLC7A11 were noted to be drastically suppressed in circCDK14-knockdown tumors (Chen et al, 2022).

Tumor suppressive roles: circLMO1 antagonized miR-4192-mediated targeting of ACSL4 in cervical cancer cells (Ou et al, 2022). circLMO1 potently hampered proliferation and invasion capacities of CaSki cells, whereas ACSL4 depletion or miR-4291 overexpression exerted inhibitory effects on circLMO1-mediated tumor suppressive effects. circLMO1-overexpressing CaSki cells were injected through tail veins for the establishment of cervical cancer lung metastasis animal model. circLMO1 overexpression remarkably impaired cancer metastases in circLMO1-overexpressing rodent models. Moreover, circLMO1-overexpressing CaSki cells formed smaller pulmonary metastatic nodules (Ou et al, 2022).

Circ_0000190 suppressed proliferation and motility and induced ferroptotic death in gastric cancer cells. circ_0000190 overexpression caused an increase in ZNRF3 levels along with concomitant reduction in the levels of MMP9 in tumor tissues. Circ_0000190 blocked miR-382-5p-mediated inhibition of ZNRF3 (Jiang et al, 2022).

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Figure 4:

Concluding remarks:

Ferroptosis activators can cause bone marrow injuries (Song et al, 2016) which is certainly a related toxicity of cytotoxic therapies. Minimizing the off-target effects or toxicity of drugs promoting ferroptotic death remains an overarching goal in clinical and molecular oncology. Keeping in view the limitations that one key cannot unlock every lock, it is imperative to decode context-specific regulatory mechanisms that drive cell type-specific or tissue-specific ferroptotic process in various cancers. Excitingly, discovery of non-coding RNAs and phenomenal advancements in characterization of non-coding RNAs have paradigmatically shifted our conceptual knowledge about regulation of ferroptosis in different cancers. Series of seminal research-works provided detailed insights about momentous contributory roles of miRNAs, lncRNAs and circRNAs in the regulation of ferroptosis. Consequently, researchers identified oncogenic and tumor suppressor non-coding RNAs which contextually regulated ferroptotic death. With growing evidence of instrumental role of non-coding RNAs in regulation of ferroptosis, scientists also analyzed pharmacologically valuable non-coding RNAs for cancer inhibition/prevention. Pharmacological targeting of RNAs has emerged as an advantageous strategy for the treatment of different diseases (Yu et al, 2020). These challenges will require well designed sophisticated preclinical models and innovative technology.

Author Contributions:

Ammad Ahmad Farooqi: Wrote or contributed to the writing of the manuscript.

Gulnara Kapanova: Performed data analysis, Wrote or contributed to the writing of the manuscript.

Sundetgali Kalmakhanov: Performed data analysis, Wrote or contributed to the writing of the manuscript.

Abay Z. Kussainov: Wrote or contributed to the writing of the manuscript, Performed data analysis

Zaure Datkhayeva: Performed data analysis

References:

Bai T, Liang R, Zhu R, Wang W, Zhou L, Sun Y. MicroRNA-214-3p enhances erastin-induced ferroptosis by targeting ATF4 in hepatoma cells. J Cell Physiol. 2020 Jul;235(7-8):5637-5648. doi: 10.1002/jcp.29496.

Bao C, Zhang J, Xian SY, Chen F. MicroRNA-670-3p suppresses ferroptosis of human glioblastoma cells through targeting ACSL4. Free Radic Res. 2021 Aug 9:1-12. doi: 10.1080/10715762.2021.1962009.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Bazhabayi M, Qiu X, Li X, Yang A, Wen W, Zhang X, Xiao X, He R, Liu P. CircGFRA1 facilitates the malignant progression of HER-2-positive breast cancer via acting as a sponge of miR-1228 and enhancing AIFM2 expression. J Cell Mol Med. 2021 Nov;25(21):10248-10256. doi: 10.1111/jcmm.16963.

Cabili MN, Dunagin MC, McClanahan PD, Biaesch A, Padovan-Merhar O, Regev A, Rinn JL, Raj A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. Genome Biol. 2015 Jan 29;16(1):20. doi: 10.1186/s13059-015-0586-4.

Chen Q, Wang W, Wu Z, Chen S, Chen X, Zhuang S, Song G, Lv Y, Lin Y. Over-expression of lncRNA TMEM161B-AS1 promotes the malignant biological behavior of glioma cells and the resistance to temozolomide via up-regulating the expression of multiple ferroptosis-related genes by sponging hsa-miR-27a-3p. Cell Death Discov. 2021 Oct 23;7(1):311. doi: 10.1038/s41420-021-00709-4.

Chen S, Zhang Z, Zhang B, Huang Q, Liu Y, Qiu Y, Long X, Wu M, Zhang Z. CircCDK14 Promotes Tumor Progression and Resists Ferroptosis in Glioma by Regulating PDGFRA. Int J Biol Sci. 2022 Jan 1;18(2):841-857. doi: 10.7150/ijbs.66114.

Chen W, Fu J, Chen Y, Li Y, Ning L, Huang D, Yan S, Zhang Q. Circular RNA circKIF4A facilitates the malignant progression and suppresses ferroptosis by sponging miR-1231 and upregulating GPX4 in papillary thyroid cancer. Aging (Albany NY). 2021 Jun 21;13(12):16500-16512. doi: 10.18632/aging.203172.

Chen X, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. Nat Rev Clin Oncol. 2021 May;18(5):280-296. doi: 10.1038/s41571-020-00462-0.

Chiu HS, Somvanshi S, Patel E, Chen TW, Singh VP, Zorman B, Patil SL, Pan Y, Chatterjee SS; Cancer Genome Atlas Research Network, Sood AK, Gunaratne PH, Sumazin P. Pan-Cancer Analysis of lncRNA Regulation Supports Their Targeting of Cancer Genes in Each Tumor Context. Cell Rep. 2018 Apr 3;23(1):297-312.e12.

Deng SH, Wu DM, Li L, Liu T, Zhang T, Li J, Yu Y, He M, Zhao YY, Han R, Xu Y. miR-324-3p reverses cisplatin resistance by inducing GPX4-mediated ferroptosis in lung adenocarcinoma cell line A549. Biochem Biophys Res Commun. 2021 Apr 16;549:54-60. doi: 10.1016/j.bbrc.2021.02.077.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Ding S, Liu D, Wang L, Wang G, Zhu Y. Inhibiting MicroRNA-29a Protects Myocardial Ischemia-Reperfusion Injury by Targeting SIRT1 and Suppressing Oxidative Stress and NLRP3-Mediated Pyroptosis Pathway. J Pharmacol Exp Ther. 2020 Jan;372(1):128-135. doi: 10.1124/jpet.119.256982.

Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B 3rd, Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012 May 25;149(5):1060-72. doi: 10.1016/j.cell.2012.03.042.

Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL, Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458(7235):223-7.

Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature. 2013 Mar 21;495(7441):384-8. doi: 10.1038/nature11993.

Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015;47(3):199-208.

Ji X, Qian J, Rahman SMJ, Siska PJ, Zou Y, Harris BK, Hoeksema MD, Trenary IA, Heidi C, Eisenberg R, Rathmell JC, Young JD, Massion PP. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. Oncogene. 2018 Sep;37(36):5007-5019. doi: 10.1038/s41388-018-0307-z.

Jiang M, Mo R, Liu C, Wu H. Circ_0000190 sponges miR-382-5p to suppress cell proliferation and motility and promote cell death by targeting ZNRF3 in gastric cancer. J Biochem. 2022 Jan 14:mvac003. doi: 10.1093/jb/mvac003.

Kansakar U, Varzideh F, Mone P, Jankauskas SS, Santulli G. Functional Role of microRNAs in Regulating Cardiomyocyte Death. Cells. 2022 Mar 12;11(6):983. doi: 10.3390/cells11060983.

Khraiwesh B, Arif MA, Seumel GI, Ossowski S, Weigel D, Reski R, Frank W. Transcriptional control of gene expression by microRNAs. Cell. 2010 Jan 8;140(1):111-22.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Liao Y, Jia X, Ren Y, Deji Z, Gesang Y, Ning N, Feng H, Yu H, Wei A. Suppressive role of microRNA-130b-3p in ferroptosis in melanoma cells correlates with DKK1 inhibition and Nrf2-HO-1 pathway activation. Hum Cell. 2021 Sep;34(5):1532-1544. doi: 10.1007/s13577-021-00557-5.

Luo M, Wu L, Zhang K, Wang H, Zhang T, Gutierrez L, O'Connell D, Zhang P, Li Y, Gao T, Ren W, Yang Y. miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ. 2018 Aug;25(8):1457-1472. doi: 10.1038/s41418-017-0053-8.

Luo W, Wang J, Xu W, Ma C, Wan F, Huang Y, Yao M, Zhang H, Qu Y, Ye D, Zhu Y. LncRNA RP11-89 facilitates tumorigenesis and ferroptosis resistance through PROM2-activated iron export by sponging miR-129-5p in bladder cancer. Cell Death Dis. 2021 Nov 2;12(11):1043. doi: 10.1038/s41419-021-04296-1.

Luo Y, Niu G, Yi H, Li Q, Wu Z, Wang J, Yang J, Li B, Peng Y, Liang Y, Wang W, Peng Z, Shuai X, Guo Y. Nanomedicine promotes ferroptosis to inhibit tumour proliferation in vivo. Redox Biol. 2021 Jun;42:101908. doi: 10.1016/j.redox.2021.101908.

Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. Proc Natl Acad Sci U S A. 2007 Jun 5;104(23):9667-72.

Lyu N, Zeng Y, Kong Y, Chen Q, Deng H, Ou S, Bai Y, Tang H, Wang X, Zhao M. Ferroptosis is involved in the progression of hepatocellular carcinoma through the circ0097009/miR-1261/SLC7A11 axis. Ann Transl Med. 2021 Apr;9(8):675. doi: 10.21037/atm-21-997.

Mao C, Wang X, Liu Y, Wang M, Yan B, Jiang Y, Shi Y, Shen Y, Liu X, Lai W, Yang R, Xiao D, Cheng Y, Liu S, Zhou H, Cao Y, Yu W, Muegge K, Yu H, Tao Y. A G3BP1-Interacting lncRNA Promotes Ferroptosis and Apoptosis in Cancer via Nuclear Sequestration of p53. Cancer Res. 2018 Jul 1;78(13):3484-3496. doi: 10.1158/0008-5472.CAN-17-3454.

Mao SH, Zhu CH, Nie Y, Yu J, Wang L. Levobupivacaine Induces Ferroptosis by miR-489-3p/SLC7A11 Signaling in Gastric Cancer. Front Pharmacol. 2021 Jun 9;12:681338. doi: 10.3389/fphar.2021.681338.

Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F,

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013 Mar 21;495(7441):333-8. doi: 10.1038/nature11928.

Ni H, Qin H, Sun C, Liu Y, Ruan G, Guo Q, Xi T, Xing Y, Zheng L. MiR-375 reduces the stemness of gastric cancer cells through triggering ferroptosis. Stem Cell Res Ther. 2021 Jun 5;12(1):325. doi: 10.1186/s13287-021-02394-7.

Niu Y, Zhang J, Tong Y, Li J, Liu B. Physcion 8-O-β-glucopyranoside induced ferroptosis via regulating miR-103a-3p/GLS2 axis in gastric cancer. Life Sci. 2019 Nov 15;237:116893. doi: 10.1016/j.lfs.2019.116893.

Ou R, Lu S, Wang L, Wang Y, Lv M, Li T, Xu Y, Lu J, Ge RS. Circular RNA circLMO1 Suppresses Cervical Cancer Growth and Metastasis by Triggering miR-4291/ACSL4-Mediated Ferroptosis. Front Oncol. 2022 Mar 7;12:858598. doi: 10.3389/fonc.2022.858598.

Pan CF, Wei K, Ma ZJ, He YZ, Huang JJ, Guo ZZ, Chen ZP, Barr MP, Shackelford RE, Xia Y, Wang J. CircP4HB regulates ferroptosis via SLC7A11-mediated glutathione synthesis in lung adenocarcinoma. Transl Lung Cancer Res. 2022 Mar;11(3):366-380. doi: 10.21037/tlcr-22-138.

Qi W, Li Z, Xia L, Dai J, Zhang Q, Wu C, Xu S. LncRNA GABPB1-AS1 and GABPB1 regulate oxidative stress during erastin-induced ferroptosis in HepG2 hepatocellular carcinoma cells. Sci Rep. 2019 Nov 7;9(1):16185. doi: 10.1038/s41598-019-52837-8.

Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 2012;7(2):e30733. doi: 10.1371/journal.pone.0030733.

Shanshan W, Hongying M, Jingjing F, Yiming Y, Yu R, Rui Y. CircDTL Functions as an Oncogene and Regulates Both Apoptosis and Ferroptosis in Non-small Cell Lung Cancer Cells. Front Genet. 2021 Sep 21;12:743505. doi: 10.3389/fgene.2021.743505.

Song X, Xie Y, Kang R, Hou W, Sun X, Epperly MW, Greenberger JS, Tang D. FANCD2 protects against bone marrow injury from ferroptosis. Biochem Biophys Res Commun. 2016 Nov 18;480(3):443-449. doi: 10.1016/j.bbrc.2016.10.068.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Song Z, Jia G, Ma P, Cang S. Exosomal miR-4443 promotes cisplatin resistance in non-small cell lung carcinoma by regulating FSP1 m6A modification-mediated ferroptosis. Life Sci. 2021 Jul 1;276:119399. doi: 10.1016/j.lfs.2021.119399.

Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, Noel K, Jiang X, Linkermann A, Murphy ME, Overholtzer M, Oyagi A, Pagnussat GC, Park J, Ran Q, Rosenfeld CS, Salnikow K, Tang D, Torti FM, Torti SV, Toyokuni S, Woerpel KA, Zhang DD. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell. 2017 Oct 5;171(2):273-285. doi: 10.1016/j.cell.2017.09.021.

Sun D, Li YC, Zhang XY. Lidocaine Promoted Ferroptosis by Targeting miR-382-5p /SLC7A11 Axis in Ovarian and Breast Cancer. Front Pharmacol. 2021 May 26;12:681223. doi: 10.3389/fphar.2021.681223.
Sutliff AK, Watson CJW, Chen G, Lazarus P. Regulation of UGT2A1 by miR-196a-5p and miR-196b-5p. J Pharmacol Exp Ther. 2019 May;369(2):234-243. doi: 10.1124/jpet.118.255935.

Tomita K, Nagasawa T, Kuwahara Y, Torii S, Igarashi K, Roudkenar MH, Roushandeh AM, Kurimasa A, Sato T. MiR-7-5p Is Involved in Ferroptosis Signaling and Radioresistance Thru the Generation of ROS in Radioresistant HeLa and SAS Cell Lines. Int J Mol Sci. 2021 Aug 2;22(15):8300. doi: 10.3390/ijms22158300.

Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, Kaffenberger SD, Eaton JK, Shimada K, Aguirre AJ, Viswanathan SR, Chattopadhyay S, Tamayo P, Yang WS, Rees MG, Chen S, Boskovic ZV, Javaid S, Huang C, Wu X, Tseng YY, Roider EM, Gao D, Cleary JM, Wolpin BM, Mesirov JP, Haber DA, Engelman JA, Boehm JS, Kotz JD, Hon CS, Chen Y, Hahn WC, Levesque MP, Doench JG, Berens ME, Shamji AF, Clemons PA, Stockwell BR, Schreiber SL. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. Nature. 2017 Jul 27;547(7664):453-457. doi: 10.1038/nature23007.

Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006 Feb 14;103(7):2257-61.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Wang HH, Ma JN, Zhan XR. Circular RNA Circ_0067934 Attenuates Ferroptosis of Thyroid Cancer Cells by miR-545-3p/SLC7A11 Signaling. Front Endocrinol (Lausanne). 2021 Jul 5;12:670031. doi: 10.3389/fendo.2021.670031.

Wang J, Xing H, Nikzad AA, Liu B, Zhang Y, Li S, Zhang E, Jia Z. Long Noncoding RNA MNX1 antisense RNA 1 Exerts Oncogenic Functions in Bladder Cancer by Regulating miR-218-5p/RAB1A Axis. J Pharmacol Exp Ther. 2020 Mar;372(3):237-247. doi: 10.1124/jpet.119.262949.

Wang M, Mao C, Ouyang L, Liu Y, Lai W, Liu N, Shi Y, Chen L, Xiao D, Yu F, Wang X, Zhou H, Cao Y, Liu S, Yan Q, Tao Y, Zhang B. Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA. Cell Death Differ. 2019 Nov;26(11):2329-2343. doi: 10.1038/s41418-019-0304-y.

Wang S, Wang Y, Li Q, Li X, Feng X. A novel circular RNA confers trastuzumab resistance in human epidermal growth factor receptor 2-positive breast cancer through regulating ferroptosis. Environ Toxicol. 2022 Mar 2. doi: 10.1002/tox.23509.

Wang W, Xie Y, Malhotra A. Potential of Curcumin and Quercetin in Modulation of Premature Mitochondrial Senescence and Related Changes during Lung Carcinogenesis. J Environ Pathol Toxicol Oncol. 2021;40(4):53-60. doi: 10.1615/JEnvironPatholToxicolOncol.2021039371.

Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, Tam S, Xiao D, Liu S, Wen F, Tao Y. A Nuclear Long Non-Coding RNA LINC00618 Accelerates Ferroptosis in a Manner Dependent upon Apoptosis. Mol Ther. 2021 Jan 6;29(1):263-274. doi: 10.1016/j.ymthe.2020.09.024.

Wei D, Ke YQ, Duan P, Zhou L, Wang CY, Cao P. MicroRNA-302a-3p induces ferroptosis of non-small cell lung cancer cells via targeting ferroportin. Free Radic Res. 2021 Aug 6:1-10. doi: 10.1080/10715762.2021.1947503.

Wu P, Li C, Ye DM, Yu K, Li Y, Tang H, Xu G, Yi S, Zhang Z. Circular RNA circEPSTI1 accelerates cervical cancer progression via miR-375/409-3P/515-5p-SLC7A11 axis. Aging (Albany NY). 2021 Feb 2;13(3):4663-4673. doi: 10.18632/aging.202518.

Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
This article has not been copyedited and formatted. The final version may differ from this version.

Yang J, Cao XH, Luan KF, Huang YD. Circular RNA FNDC3B Protects Oral Squamous Cell Carcinoma Cells From Ferroptosis and Contributes to the Malignant Progression by Regulating miR-520d-5p/SLC7A11 Axis. Front Oncol. 2021 Aug 9;11:672724. doi: 10.3389/fonc.2021.672724.

Yang X, Li Y, Zhang Y, Liu J. Circ_0000745 promotes acute lymphoblastic leukemia progression through mediating miR-494-3p/NET1 axis. Hematology. 2022 Dec;27(1):11-22. doi: 10.1080/16078454.2021.2008590.

Yao W, Wang J, Meng F, Zhu Z, Jia X, Xu L, Zhang Q, Wei L. Circular RNA CircPVT1 Inhibits 5-Fluorouracil Chemosensitivity by Regulating Ferroptosis Through MiR-30a-5p/FZD3 Axis in Esophageal Cancer Cells. Front Oncol. 2021 Dec 13;11:780938. doi: 10.3389/fonc.2021.780938.

Yu AM, Choi YH, Tu MJ. RNA Drugs and RNA Targets for Small Molecules: Principles, Progress, and Challenges. Pharmacol Rev. 2020 Oct;72(4):862-898. doi: 10.1124/pr.120.019554.

Zhang H, Deng T, Liu R, Ning T, Yang H, Liu D, Zhang Q, Lin D, Ge S, Bai M, Wang X, Zhang L, Li H, Yang Y, Ji Z, Wang H, Ying G, Ba Y. CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. Mol Cancer. 2020 Feb 27;19(1):43. doi: 10.1186/s12943-020-01168-8.

Zhang K, Wu L, Zhang P, Luo M, Du J, Gao T, O'Connell D, Wang G, Wang H, Yang Y. miR-9 regulates ferroptosis by targeting glutamic-oxaloacetic transaminase GOT1 in melanoma. Mol Carcinog. 2018 Nov;57(11):1566-1576. doi: 10.1002/mc.22878.

Zhang Y, Guo S, Wang S, Li X, Hou D, Li H, Wang L, Xu Y, Ma B, Wang H, Jiang X. LncRNA OIP5-AS1 inhibits ferroptosis in prostate cancer with long-term cadmium exposure through miR-128-3p/SLC7A11 signaling. Ecotoxicol Environ Saf. 2021 Sep 1;220:112376. doi: 10.1016/j.ecoenv.2021.112376.

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Downloaded from jpet.aspetjournals.org at ASPET Journals on April 23, 2024

JPET Fast Forward. Published on September 2, 2022 as DOI: 10.1124/jpet.121.001225
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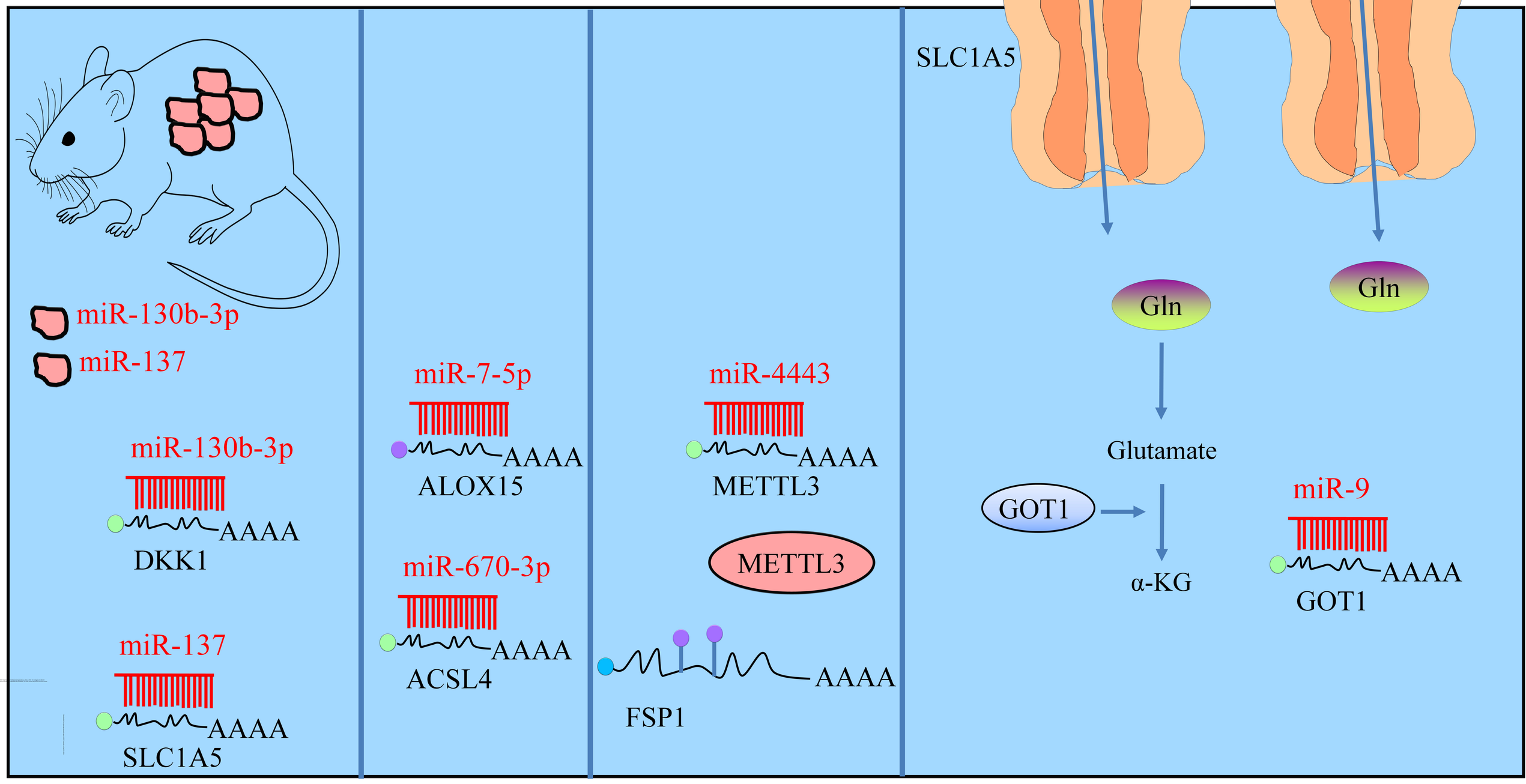
Figure 1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miR-670-3p
AAAA
ACSL4
miR-4443
AAAA
METTL3
METTL3
AAAA
FSP1
Gln
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α-KG
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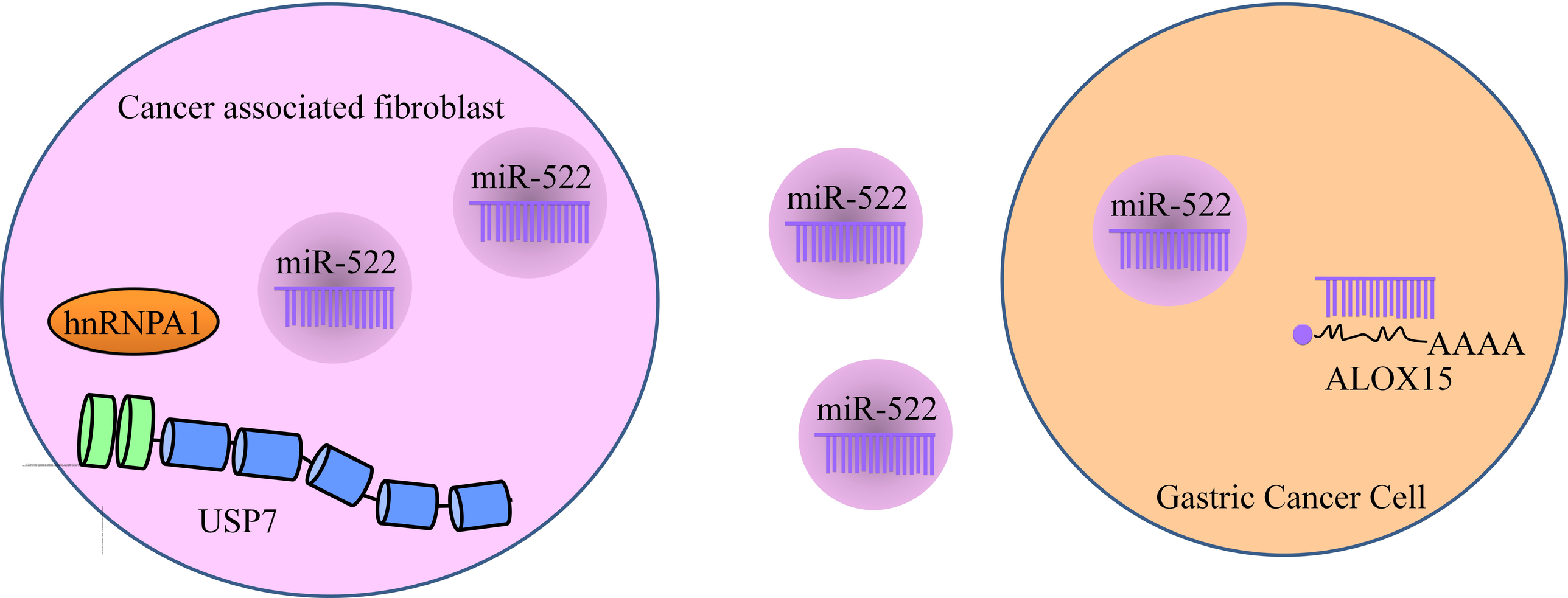
miR-9
AAAA
GOT1

Figure 2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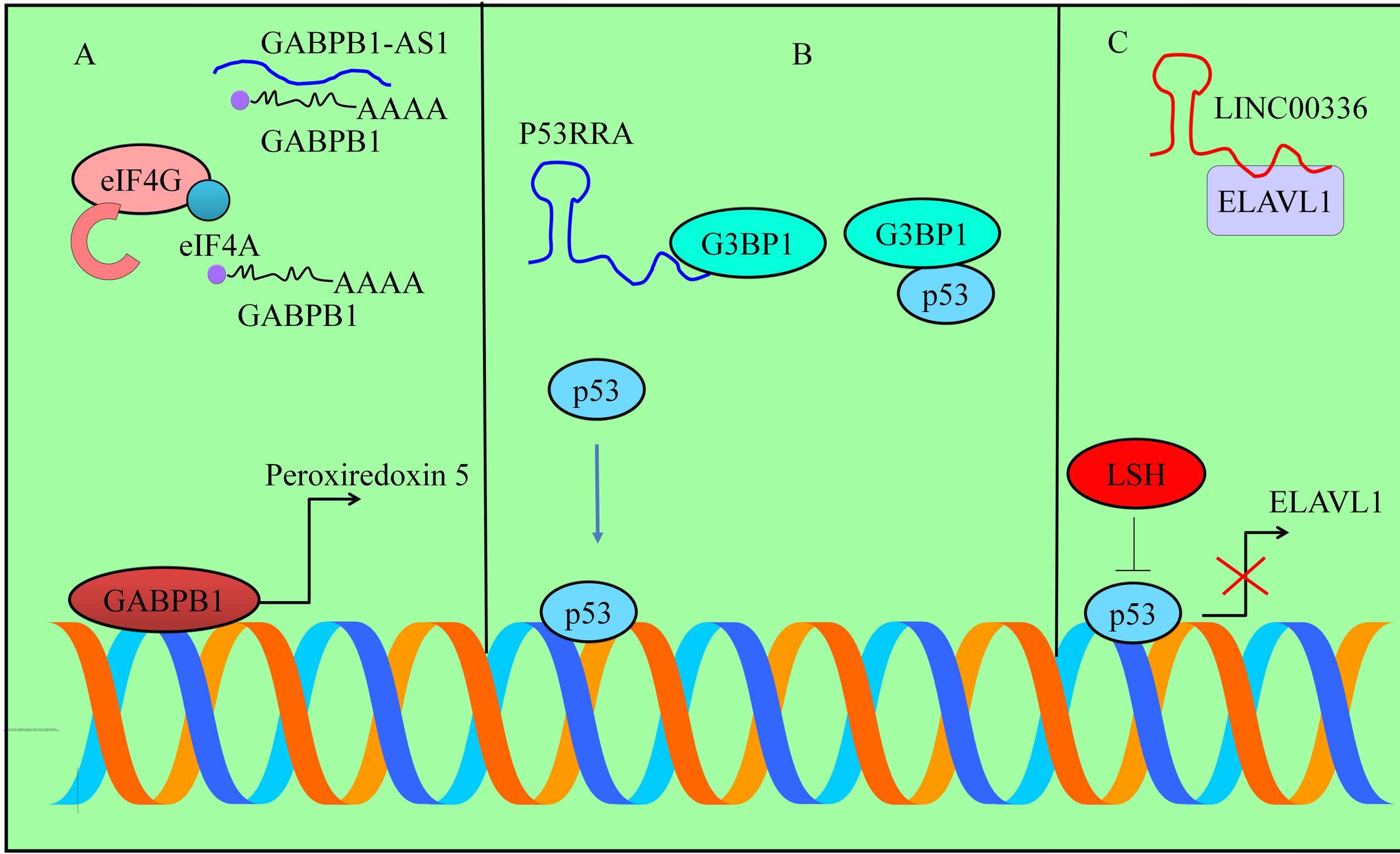
miR-522
AAAA
ALOX15
Gastric Cancer Cell

Figure 3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GABPB1
B
P53RRA
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G3BP1
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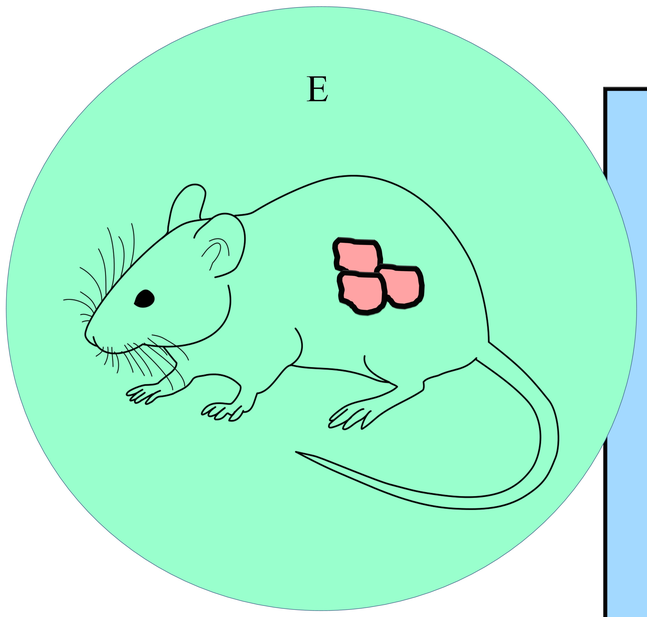
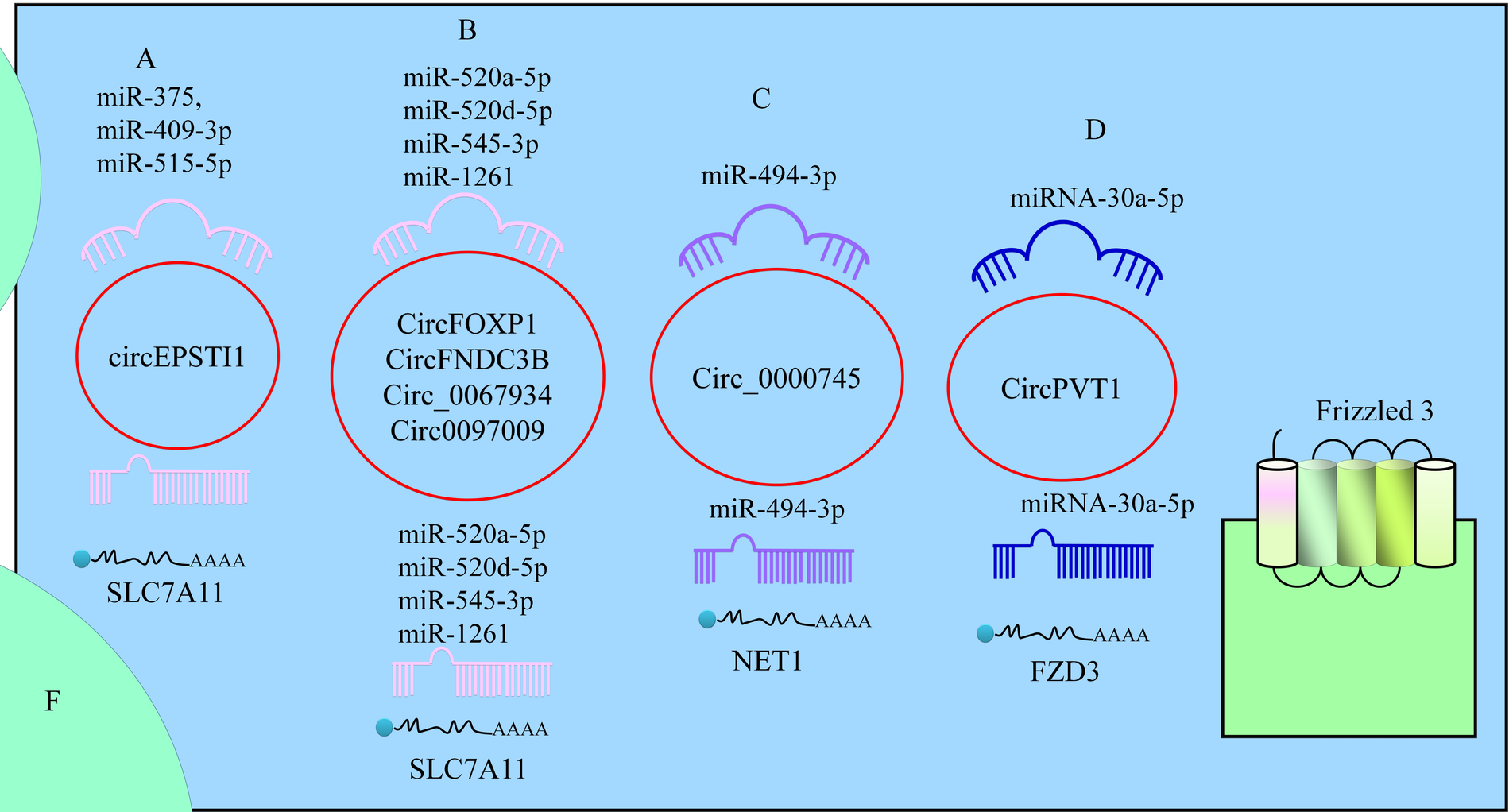
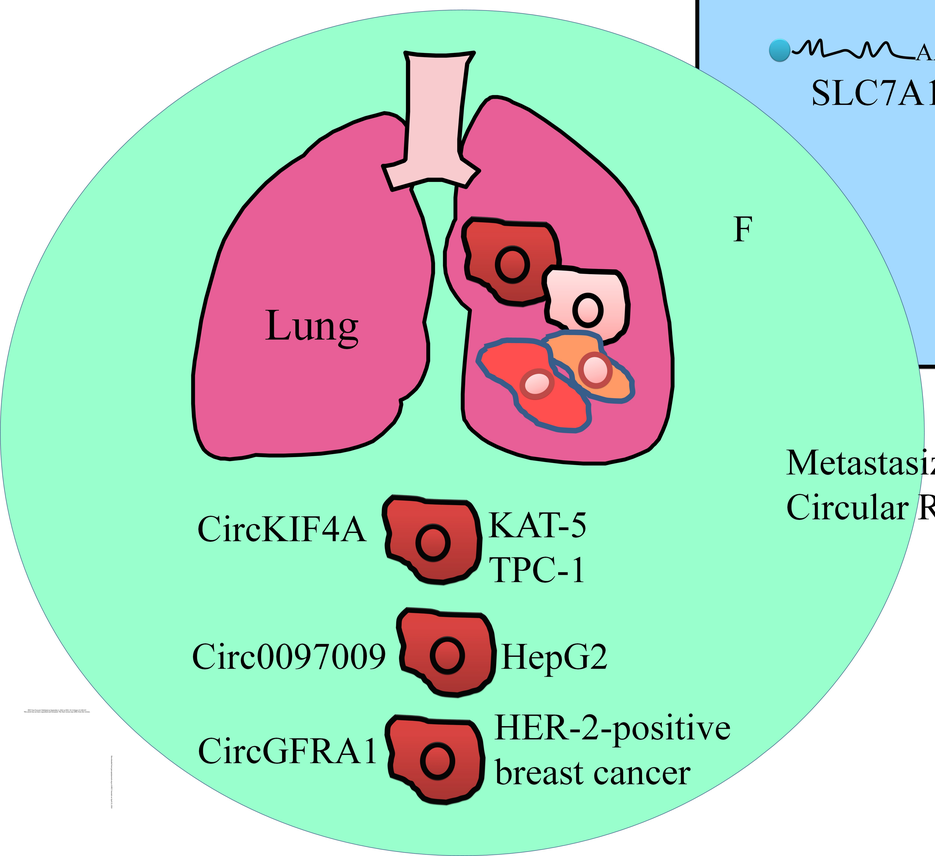
p53

Figure 4







Metastasizing potential of
Circular RNA expressing cancer cells