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The Roles of Ferroptosis-related Long Non-coding RNAs in Urologic Cancers

Wenchao Xie[1], Jie Gu[2], Zhenqian Qin[1], Yimin Xie[1]

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Abstract

Ferroptosis is a type of programmed cell death that has been recent topic of interest in cancer therapy. Growing evidence indicates that long noncoding RNAs (lncRNAs) are involved in ferroptosis and associated with the incidence and progression of cancer. However, the relationship between lncRNA and ferroptosis in urologic cancers has not been fully elucidated. In this review, we summarize ferroptosis-related lncRNAs (frlncRNAs) in urologic cancers. Studies indicate that frlncRNAs are associated with cancer metabolism, tumor microenvironment, and immune cell infiltration. In addition, frlncRNAs could regulate ferroptosis related genes both at the mRNA and protein level. Therefore, a deep understanding of the roles of frlncRNAs in urologic cancers occurrence and progression will provide novel information for the development of anticancer therapies.

Key words ferroptosis, lncRNA, prostate cancer, proteasome, lysosome

1. Department of Urology, Affiliated Hospital of Jiangsu University-Yixing Hospital, Yixing, Jiangsu, 214200, China.
2. School of Life Sciences, Jiangsu University, Zhenjiang, Jiangsu, 212013, China.
Correspondence: Yimin Xie (Department of Urology, Affiliated Hospital of Jiangsu University-Yixing Hospital, Yixing, Jiangsu, 214200, China; Email: 2221513084@stmail.ujs.edu.cn).

Introduction

In recent years, studies have shown that long non-coding RNA (lncRNA) regulate various cellular processes in cancer cells, such as proliferation, migration, invasion, differentiation, and apoptosis, which might be critical for the development of cancer. Ferroptosis is a type of programmed cell death that has been recent topic of interest in cancer therapy. LncRNAs are shown to be involved in the initiation and development of various cancers. Increasing evidence suggests that lncRNAs have close association with ferroptosis in cancer [1]. However, there are still some unknowns in the regulation of lncRNAs in ferroptosis in cancers [2].

Ferroptosis distinct from apoptosis and refers to iron overload-mediated excessive lipid peroxidation [3]. Interestingly, increasing research on ferroptosis and cancer play critical role in cancer initiation, progression, metastasis and therapeutic resistance. Various cancer-related signaling pathways that regulate ferroptosis demonstrate unique metabolism in cancer cells [4]. Thus, targeting ferroptosis might offer great potential in cancer therapy.

Previous studies have suggested that lncRNAs induce or inhibit ferroptosis of cancer cells in few malignancies including gastric, hepatocellular, and lung cancer [5-7]. Recently, it has been identified that few ferroptosis-related lncRNAs (frlncRNAs) regulate the incidence and progression of urologic malignancies including prostate cancer (PCa), kidney cancer, and bladder cancer (BCa). In this review, we highlight the emerging role of frlncRNAs to predict prognosis of urologic cancers. Moreover, based on current finding on various signaling pathways of the frlncRNAs in urologic cancers we summarize that frlncRNAs regulate ferroptosis-related genes through sponging miRNA, modulating transcription factors and m6A methylation, and alteration in ferroptosis-related proteins through autophagy-lysosomal and proteasome-ubiquitination pathways. We also discuss the roles of metabolism and immune related frlncRNAs in urologic cancers. This review contributes to a comprehensive understanding of the identification and regulation of frlncRNAs in urologic cancers and provide novel information for the development of precise strategies for the treatment of urologic cancers.

Identification of frlncRNAs in urologic cancer

Identification of frlncRNAs in prostate cancer

Through a ferroptosis-related gene prognostic index (FGPI) analysis combiningg four Gene Expression Omnibus (GEO) database, Feng et al. found that lncRNA PART1 was significantly associated with the prediction biochemical recurrence (BCR) of PCa [8]. Subsequently, ferroptosis-related lncRNA (frlncRNAs) signature was established to predict PCa prognosis, and 5 frlncRNAs (AP006284.1, AC132938.1, BCRP3, AL360181.4 and AL135999.1) were identified for the prediction of PCa BCR [9]. However, validation studies are further required before their progress in clinical application.

Identification of frlncRNAs in kidney cancer

The kidney renal clear cell carcinoma (KIRC) accounts for 80% of cases and the kidney renal papillary cell carcinoma (KIRP) account for 10-15% as two major types of renal cell carcinoma. Through analysis of the RNA-seq count data of KIRC (72 controls vs. 530 cancers) and KIRP (35 controls vs. 291 cancers) and the corresponding clinical information from The Cancer Genome Atlas (TCGA) open database, 5 frlncRNAs were identified as differentially expressed (DOCK8-AS1, SNHG17, RUSC1-AS1, LINC02609, and LUCAT1) and independently correlate with the overall survival (OS) in patients with renal cancer [10]. The differentially expressed frlncRNAs in KIRC have been used to predict the prognosis of KIRC [11, 12]. Based on the ferroptosis-related genes and lncRNAs obtained from the FerrDb and GENCODE databases, a risk assessment model was constructed including 3 frlncRNAs (DUXAP8, LINC02609, and LUCAT1) which significantly correlate with the overall survival of KIRC as an independent factor [13]. This was followed by employing 5 frlncRNAs LINC00460, LINC00894, VPS9D1-AS1, CYTOR, FOXD2-AS1 for construction and validation for the prognostic signature of KIRC [14].

The frlncRNAs also have been identified to predict the prognosis and overall survival of the papillary renal cell carcinoma (PRCC). Through data analysis of PRCC from TCGA, a prognostic signature consisting of 15 frlncRNAs was constructed by Dang et al. [15]. The study found that 7 different frlncRNAs had strong link to the prognosis of patients with PRCC [16]. The frlncRNAs CASC19, AC090197.1, AC099850.3, AL033397.2, LINC00462, and B3GALT1-AS1 were designated as oncogenes in PRCC, whereas LNCTAM34A and AC024022.1 are recognized as tumor suppressor genes in PRCC [17]. These studies have demonstrated that frlncRNAs are associated with the prognosis of kidney cancers, and play diverse roles in cancer progression.

Identification of frlncRNAs in bladder cancer

The frlncRNAs were identified to predict prognosis of bladder cancer (BCa) patients, and a signature composed of 9 frlncRNAs (AL031775.1, AL162586.1, AC034236.2, LINC01004, OCIAD1-AS1, AL136084.3, AP003352.1, Z84484.1, AC022150.2) was constructed [18]. Wang et al. identified 538 differentially expressed frlncRNAs from the TCGA database through co-expression method and differential expression analysis was performed in BCa [19]. In addition, Hou et al. identified 11 differentially expressed frlncRNAs were associated with poor BCa prognosis [20]. However, these two studies did not further investigate the roles of these frlncRNAs in BCa cells. Recently, Liu et al. investigated that AC006160.1 expression was lower in several BCa cell lines BIU-87, T24, RT4, RT-112, and 5637 than in the normal cell line SV-HUC-1, and the overexpression of AC006160.1 significantly inhibited cell proliferation, metastasis, and drug resistance [21]. Through single cell transcriptome sequencing (scRNA-seq), it was indicated that frlncRNAs express specifically in BCa tumor microenvironment, and AL356740.1, LINC02535 and LINC00867 were majorly expressed in tumor cells [22]. These studies showed that frlncRNAs play key roles in the progression of BCa.

Regulations of frlncRNAs targeting genes and proteins in urologic cancers

FrlncRNAs-miRNA regulates gene expression in urologic cancers

Accumulated data suggest that frlncRNAs play critical roles in targeting the regulation of miRNA associated with gene expression. Liu et al. found that the expression of 53 genes potentially interact with frlncRNAs in PCa [9]. Acyl-CoA synthetase long-chain 4 (ACSL4) and solute carrier family 7 membrane 11 (SLC7A11) are common targets that play key roles in ferroptosis. In non-small-cell lung cancer, overexpression of lncRNA NEAT1 can inhibit the expression of ACSL4 but increase the expression of SLC7A11, and decreased ferroptosis and cell apoptosis [23]. In PCa, LncRNA PART1 was speculated to modulate the mRNA expression of endothelial PAS domain containing protein-1 (EPAS1) and ACSL3 through interacting with 60 miRNAs [8]. LncRNA OIP5-AS1 was shown to inhibit ferroptosis of PCa cells after long-term cadmium exposure through miR-128-3p/SLC7A11 signaling [24]. In docetaxel-resistant PCa, lncRNA prostate cancer-associated

Table 1. Summary of regulation of ferroptosis-relative lncRNAs in urologic cancers.

Urologic Cancers	LncRNA	Pathway	Target	Associated Effects	Reference
Pca	PART1	60miRNAs	mRNA: EPAS1, ACSL3	Inhibited ferroptosis, Increased biochemical recurrence and radiation resistance	[8]
Pca	OIP5-AS1	miR-128-3p	mRNA: SLC7A11	Ferroptosis resistance, Promoted cell growth	[24]
Pca	PCAT1	c-Myc/miR-25-3p	mRNA: SLC7A11	Restrained ferroptosis, Increased docetaxel-resistant	[25]
ccRCC	SLC16A1-AS1	miR-143-3p	mRNA: SLC7A11	Induced ferroptosis, Inhibited cell viability, proliferation, and migration	[26]
Bca	RP11-89	sponging miR-129-5p	mRNA: PROM2	Ferroptosis resistance, Promotes tumorigenesis	[28]
PCa Kidney cancer	Unknown	Unknown	STAT3	Mediated ferroptosis, Regulated the progression of PCa and kidney cancer	[31, 32]
BCa	AC096921.2, LINC02762, etc.	m6A methylation	m6A methylation related gene	Induced or inhibited ferroptosis, Protective or poor BCa prognosis	[19]
BCa	AL583785.1, LINC02762, etc.	m6A methylation	m6A methylation related gene	Different between the high and low risk groups, predicting the prognosis of BCa	[20]
PCa	HOTAIR	E3 ubiquitin	MDM2	Castration-resistant	[41]
PCa	PCBP1-AS1	AR/AR-V7 deubiquitination	USP22-AR/AR-V7	Castration-resistant	[42]
Pca	NEAT1	Sponging miR-34a-5p and miR-204-5p	mRNA: ACSL4	Increased oxidation of fatty acids, docetaxel resistance	[46]
PCa	AP006284.1, AC132938.1, etc.	Unknown	Unknown	Immune cell infiltration	[8, 9]
ccRCC	AC026401.3, LINC01615, etc.	CD80, IDO1, and LAG3	Unknown	Immune cell infiltration and changed immune microenvironment	[12, 50-53]
PRCC	ZFAS1, AC010624.2, etc.	Unknown	CD80, IDO1, and LAG3	Immune cell infiltration	[15]
PRCC	CASC19, AC090197.1, etc.	Unknown	CD160, TNFSF4, CD80, BTLA, and TNFRSF9	Predicted the overall survival outcome	[17]
Bca	High risk group lncRNAs	IL-17 signaling pathway and TNF signaling pathway	PDCD-1 (PD-1), CTLA4, and LAG3	Predicted immune and tumor-related pathways	[20, 56]

transcript 1 (PCAT1) was highly expressed, which restrained ferroptosis cell death through c-Myc/miR-25-3p/SLC7A11 signaling [25]. These studies demonstrate that lncRNA promotes progression of PCa by modulating ferroptosis through miRNA and associated genes.

In addition, lncRNAs binding miRNAs also regulate ferroptosis in kidney and bladder cancers. Silencing lncRNA SLC16A1-AS1 induced ferroptosis in ccRCC through miR-143-3p/SLC7A11 signaling [26]. In PRCC, frlncRNAs have been shown to interact with sponge miRNAs and bind proteins to modulate cell proliferation and metastasis [27]. In BCa, LncRNA RP11-89 promotes tumorigenesis and ferroptosis resistance through PROM2-activated iron export by sponging miR-129-5p [28]. The frlncRNAs binding on miRNA to regulate target gene expression results in the progression of urologic cancers. However, additional studies are required.

FrlncRNAs regulates genes through transcription factors and m6A methylation in urologic cancers

As the transcription factors link the lncRNA, target genes, and miRNA, hence the transcription factors might also be involved in frlncRNAs-regulated ferroptosis in cancer cells. Previous studies have shown that the transcription factors such as stem cell factor (SOX2), BTB and CNC homology 1 (BACH1) play important roles in ferroptosis of cancer cells [29, 30]. The signal transduction and activators of transcription 3 (STAT3)-mediated ferroptosis regulate the progression of PCa and kidney cancer [31, 32]. Recently, lncRNAs have been reported to involve in heavy metals induced cancer development. LncRNA lnc-DC mediates arsenic (As)-induced programmed cell death 1 ligand (PD-L1) up-regulation by activating the STAT3 signaling to promote lung cancer [33].

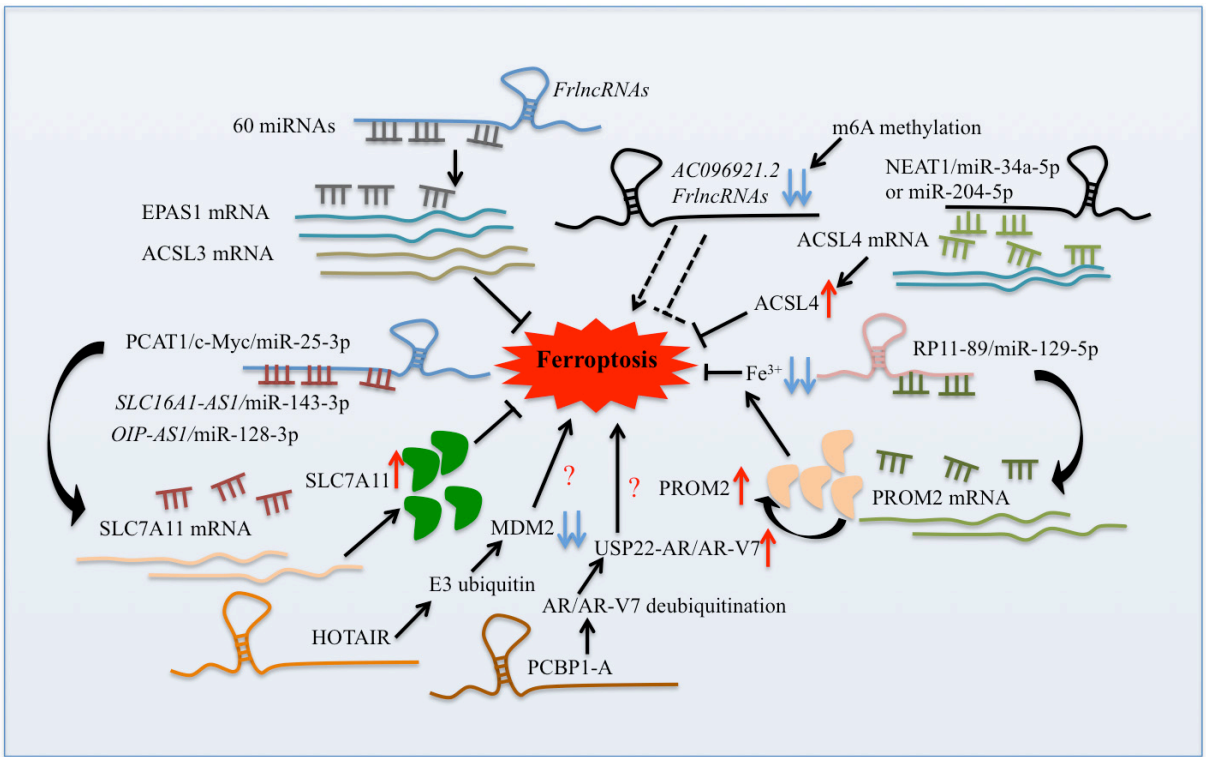

Figure 1. The mechanism of lncRNAs regulated ferroptosis urologic cancers. The lncRNAs could not only regulate ferroptosis-related genes and proteins by sponging miRNA, activating m6A methylation, and regualating ubiquitination pathway (Modified from Qu et al., 2022 [2]).

Recent studies suggest that m6A-mediated methylation regulates the expression of oncogenes or tumor suppression genes, which plays important roles in cancer progression. Wang et al. identified 538 differentially expressed frlncRNAs from the TCGA database through co-expression method and differential expression analysis, and found the upstream of 5 lncRNAs might be modified by m6A to modulate their expression in BCa [19]. In addition, Hou et al. identified 11 differentially expressed frlncRNAs were associated with poor BCa prognosis, and m6A methylation-related genes were differentially expressed between the high and low risk groups [20]. However, there is still a large gap in understanding as how frlncRNAs regulate ferroptosis related genes, sponging miRNA and the transcription factors, as well as m6A methylation in urologic cancer.

Regulation of frlncRNAs in urologic cancers by protein levels

Studies show that lncRNAs can regulate target effectors at the protein levels. The autophagy-lysosomal pathway and proteasome-mediated ubiquitination-mediated degradation are two major processes in regulating protein levels. Our previous studies have showed that lncRNA FAM66C can regulate PCa cells proliferation and metastasis through autophagy-lysosomal pathway and proteasome-ubiquitination pathways [34, 35]. In human pancreatic ductal adenocarcinoma (PDAC) cells, STAT3 mediated lysosomal cysteine protease cathepsin B expression to induce ferroptosis [36]. Therefore, ferroptosis is also proposed as a process of autophagy-lysosomal cell death. LncRNA HEPFAL was found to increase the sensitivity of erastin-induced ferroptosis in hepatocellular carcinoma, and induce ubiquitination of SLC7A11 and decrease its expression by reducing the stability of SLC7A11 protein [7]. The voltage-dependent anion channel (VDAC)-mediated mitochondria dysfunction is necessary for erastin-induced ferroptosis and VDAC3 can act as a directly target of erastin [37]. The lncRNA BDNF-AS/WDR5/FBXW7 axis mediates ferroptosis in gastric cancer peritoneal metastasis by regulating VDAC3 ubiquitination [38]. In colorectal cancer, lncRNA LINC00239 inhibits ferroptosis by binding to Keap1 to stabilize the transcription factor Nrf2 [39]. The lncRNA can also be stabilized by RNA binding protein. It is reported that high-density lipoprotein-binding protein (HDLBP)-stabilized lncRNA lncFAL reduces ferroptosis by inhibiting degradation of ferroptosis suppressor protein 1 (FSP1) in hepatocellular carcinoma [40]. It also showed that lncRNAs drive chemoresistance and metastasis by regulating ubiquitination and promote PCa cell growth [35, 41, 42]. All these studies suggested that regulations of frlncRNAs on ferroptosis-related genes and proteins may control the development of urologic cancers, but the underlying mechanism needs to be further elucidated (**Table 1**).

FrlncRNAs associated with metabolism in urologic cancer

The dysfunctions of organelles, such as mitochondria starvation, endoplasmic reticulum stress, lysosome dysfunction and golgi stress-induced lipid peroxidation all contribute to the induction of ferroptosis [37]. The network of frlncRNAs in these organelles-mediated biological processes needs to be further verified. The lipid metabolism including lipid peroxidation governs ferroptosis in cancers and lncRNAs have showed to associate with lipid metabolism. Interestingly, the EPAS1, ACSL4, and SLC7A11 play critical regulatory roles in lipid metabolism in various cells [43-45]. In PCa, lncRNA NEAT1 upregulates ACSL4 to increase oxidation of fatty acids [46]. Through enrichment analysis, the most significantly enriched gene targeted by frlncRNAs in PCa in the low-risk group were propanoate metabolism, valine leucine and isoleucine degradation, butanoate metabolism, adherens junction, peroxisome, citrate cycle (TCA cycle), fatty acid metabolism,

n-glycan biosynthesis and sphingolipid metabolism [9]. Although the information of frlncRNAs regulating metabolic pathways in cancer cells is still limited, integrated analysis of frlncRNAs with metabolism may help to find novel potential detection biomarkers and therapeutic targets.

Immune-related frlncRNAs in urologic cancer

Ferroptosis and immunity are closely linked as cells undergoing ferroptosis can interact with immune cells such as Natural Killer (NK) cells and CD8+ T cells, and the interaction plays an important role in anticancer effects [30, 47, 48]. According the studies by Feng et al. and Liu et al., frlncRNAs in PCa were involved in immune cell infiltration, such as CD4+ memory T cells, and activated NK cells [8, 9]. Three ferroptosis- and immune- related differentially expressed lncRNAs (AC124854.1, LINC02609, and ZNF503-AS2) were markedly and independently correlate with the overall survival (OS) of patients with KIRC [49]. In clear cell renal cell carcinoma (ccRCC), the change of immune microenvironment is important for survival and immunotherapy efficiency. Recent studies identified a series of frlncRNAs associated immune infiltration and immune microenvironment in ccRCC [50-52]. The frlncRNAs constructed a high level of CD8+T cells, T cell regulatory, follicular helper T cells, memory B cells and activated CD4 memory T cells infiltrations which correlate with high-risk and poor prognosis of RCC patients [14, 53]. However, underlying mechanism(s) of frlncRNAs-regulated immune cells infiltration in urological cancers are still unclear.

Based on TCGA database, it is revealed that 9 frlncRNAs signature that mediate T cell functions, such as cytolytic activity, human leukocyte antigen activity, inflammation regulation, and type II interferon response coordination are significantly different between high- and low- risk levels of ccRCC and may affect its prognosis [12]. Dong et al. analyzed the frlncRNAs signature with ccRCC prognostication, and showed that the immune checkpoint CD44, TNFRSF18, TNFSF14, TNFRSF8, CD276, and TNFRSF25 were upregulated in the high-risk group, while HAVCR2, NRP1, and HHLA2 were upregulated in the low-risk group [54]. In PRCC, 15 frlncRNAs were identified to predict the prognostic signature. Moreover, the frlncRNAs constructed high-risk group had a greater degree of immune cell infiltration than the low-risk group. A significantly higher expression level of immune checkpoints including CD80, IDO1, and LAG3 was shown in the high-risk group than in the low-risk group [15]. Wu et al. found some frlncRNAs targeting inflammation- and immune- promoting genes viz. CD160, TNFSF4, CD80, BTLA, and TNFRSF9 differentially expressed in the high- and low- risk groups with PRCC [17]. It indicates that similar and dissimilar frlncRNAs-related immune genes were found in different studies, and the accurate molecular functions still needs to further verification.

In addition, frlncRNAs also predict immune infiltration and immunotherapeutic outcomes in BCa [55]. The frlncRNAs predicted immune- and tumor- related pathways such as IL-17 signaling and TNF signaling, and the immune checkpoints such as PDCD-1 (PD-1), CTLA4, and LAG3, were differentially expressed between the high- and low- BCa risk groups [20, 56]. The high-risk BCa group was positively associated with tumor-infiltrating immune cells, including monocytes, fibroblasts, and macrophages, but negatively related to CD4+ T cells and CD8+ T cells [57]. Based on the frlncRNAs related immune landscape, developing anti-BCa mRNA vaccine facilities the individual precision treatment of BCa patients [58].

To summarize, the mechanistic relationships between ferroptosis and lncRNAs regulation in cancer progression is a recent topic of interest in cancer research. The frlncRNAs are involved in urologic cancers progression through various pathways including metabolic pathways (lipid peroxidation), and tumor microenvironment, and immune cell infiltration. Interestingly, frlncRNAs does not only regulate ferroptosis-related signaling and genes by sponging miRNA and regulating transcription factors and m6A methylation, but also control protein levels through autophagy-lysosomal and proteasome-ubiquitination degradation pathways (**Figure 1**). Certainly, there still a lot unknowns in the frlncRNAs network. Therefore, deeper understanding of how the frlncRNAs affect urologic cancer cells through integrated analysis of the network of frlncRNAs with miRNA, mRNA, targeted genes, transcription factors, metabolic pathways, and autophagy-lysosomal and proteasome-ubiquitination pathways, which will help to obtain novel discovery of anticancer therapies.

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutioalethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

WX, JG, ZQ and YX discussed the topic of this article. WX and JG wrote the draft of the manuscript. WX participated in interpretation of the literature. JG, ZQ and YX revised the review. All authors revised the draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests

All authors declare no competing interests.

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