REVIEW

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INTERPLAY OF LNCRNAS, METABOLIC CELL DEATH, AND IMMUNE MICROENVIRONMENT IN GENITOURINARY MALIGNANCIES

Genitourinary cancers, including prostate, bladder, and renal cancers, represent a significant global health burden due to their high prevalence and resistance to conventional therapies. A critical aspect of cancer progression is metabolic reprogramming, which not only fuels uncontrolled growth but also profoundly influences programmed cell death pathways and the tumor immune microenvironment. This review synthesizes current research on the intricate roles of long non-coding RNAs (lncRNAs) in modulating three emerging forms of regulated cell death — cuproptosis, ferroptosis, and disulfidptosis — within the context of genitourinary malignancies. We discuss how specific lncRNA signatures are implicated in the regulation of these metabolic cell death pathways, affecting cancer cell proliferation, migration, and invasion. Furthermore, we explore the compelling association between these lncRNA expression patterns and the characteristics of the tumor immune microenvironment, highlighting their potential as prognostic biomarkers and indicators for stratifying patient responses to immunotherapy. The evidence presented underscores the multifaceted functions of lncRNAs in cancer metabolism and immunity, positioning them as promising therapeutic targets and informative biomarkers for precision oncology in genitourinary cancers.

Keywords: cuproptosis, ferroptosis, disulfidptosis, lncRNAs, prostate cancer, bladder cancers, renal cancer, immune microenvironment.

Introduction

Genitourinary cancers, including prostate, bladder, and renal cancers, are among the most prevalent malignancies worldwide. Prostate cancer (PCa) is a leading cause of cancer-related mortality in Western countries, primarily affecting men aged 45—60 [1]. Bladder cancer (BLCA) is characterized by a high rate of recurrence and progression, with a low survival rate for patients with metastasis [2]. Renal cancer, particularly clear cell renal cell carcinoma (ccRCC), often progresses to metastatic disease and demonstrates resistance to conventional therapies [3]. Despite advances in

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understanding these diseases, many aspects of their etiology and progression remain unclear. Clinically, this translates to a pressing need for improved strategies in prevention, screening, early diagnosis, and treatment.

Metabolic reprogramming is not only a hallmark of cancer but also facilitates other traits that enable cancer progression [4]. Metabolic changes in cancer cells are critical for their survival. Under conditions of hypoxia and nutrient deprivation, cancer cells reprogram their metabolism to support rapid growth and resist cell death [4, 5]. However, these changes do not always guarantee cell survival. Various metabolic pathways are intricately linked to cellular fate regulation and interact with controlled cell death pathways, which scientists are already leveraging in their search for antitumor therapies [6]. For instance, GLUT1, a glucose transporter, influences the PI3K/AKT signaling pathways, thereby regulating cell survival and apoptosis. Alterations in lipid metabolism affect ferroptosis. For example, inhibiting stearoyl-CoA desaturase activates ferroptosis in ovarian cancer cells by reducing CoQ10 levels. Pyroptosis is associated with lipid metabolism changes via fatty acid-binding protein 4 and GPX4, while cuproptosis is closely linked to the tricarboxylic acid cycle. Numerous studies have established that metabolism is inextricably tied to the death of cancer cells [6, 7]. Almost all forms of programmed cell death can be associated with specific metabolic alterations in cancer cells, including apoptosis, necroptosis, pyroptosis, ferroptosis, cuproptosis, disulfidptosis, and others [8].

Metabolic reprogramming has been shown to modulate the behavior of the tumor microenvironment, influencing antitumor immunity and immune evasion as well as responses to anticancer therapies [9]. Moreover, recent studies have demonstrated a strong connection between metabolic changes in cancer cells, different types of controlled cell death and the effectiveness of the antitumor immune response. For example, inactivation of the aforementioned glucose transporter GLUT1 not only induces apoptosis but also sensitizes tumors to antitumor immunity, creating a synergistic effect with anti-PD-1 therapy and opening new possibilities for therapeutic strategies [10]. Cisplatin (DDP)-based chemoradiotherapy can inhibit tumor growth by inducing ferroptosis, a process that can be inhibited by FGF5 secreted by cancer-associated fibroblasts in the tumor microenvironment [11]. Additionally, nanoparticle-based strategies inducing cuproptosis and ferroptosis have enhanced antigen presentation in cancer cells, upregulated PD-L1 expression, and induced immunogenic cell death [12]. Furthermore, Stockwell and Jiang [13] suggested that ferroptosis may serve as a mechanism leveraged by immune cells to prevent tumorigenesis. Thus, specific molecular alterations, such as changes in enzyme levels or epigenetic regulators, related to these conditions, can be utilized as molecular signatures for predicting disease outcomes, stratifying risk groups, and consequently aiding in the selection of optimal therapeutic strategies, particularly in immunotherapy.

Research on long non-coding RNAs (lncRNAs) highlights their significant roles in cancer, in particular genitourinary cancers [14]. LncRNAs are a class of non-coding RNAs of approximately 200 nucleotides in length, with diverse cellular functions and mechanisms of action, including guide-type and sponging mechanisms (e.g., sponging microRNAs) [15]. Some lncRNAs have already been discovered as diagnostic markers of genitourinary cancers. For example, *PCA3* is the most well-known and investigated lncRNA in PCa. It is commonly overexpressed in PCa and is highly tissue- and cancer-specific. Therefore, its expression level serves as a diagnostic biomarker for PCa, not only in tissues but also in urine, as part of FDA-approved diagnostic tests [16]. Differential expression of several lncRNAs has been observed in urological cancers. For instance, p53-induced lncRNA *PANDAR* is implicated in bladder cancer, while *HOTAIR* is associated with PCa and various other malignancies [17—19].

Multiple lines of evidence demonstrate the involvement of lncRNAs in the regulation of programmed cell death. In genitourinary cancers, previous studies have shown the role of several lncRNAs in apoptosis. In PCa, lncRNA *LNC-565686* was found to be upregulated, promoting cell proliferation and inhibiting apoptosis by stabilizing the SND1 protein, indicating its potential as a therapeutic target [20]. Conversely, lncRNA *GAS5* exhibited an opposing effect, where its overexpression led to increased apoptosis and reduced survival in the PCa cell lines, suggesting its potential as a tumor suppressor [21]. Other lncRNAs, such as *HCP5* and *SNHG7*, have been implicated

in promoting tumor proliferation and invasion by sponging miRNAs [22, 23]. In BLCA, *BANCR* was identified as a tumor suppressor, enhancing apoptosis upon overexpression [24]. Furthermore, *HNF1A-AS1* has been shown to promote proliferation and inhibit apoptosis in BLCA cells through interaction with *miR-30b-5p* [25]. The lncRNA *FILNC1* has also been studied, revealing its role in regulating energy metabolism in renal cancer cells by modulating c-MYC levels [26].

Several studies suggest a connection between long non-coding RNAs' expression patterns and pyroptosis [27—29], as well as necroptosis [30, 31]. However, this review will focus on three specific forms: ferroptosis, cuproptosis, and disulfidptosis, aiming to summarize the current state of research in this field and evaluate their perspectives and connections with other cancer hallmarks, particularly the evasion of immune responses.

Cuproptosis-Associated LncRNAs in Urological Malignancies

Cuproptosis is a form of regulated cell death that is dependent on copper [32]. LncRNAs may play crucial roles in controlling the pathways involved in cuproptosis. They can influence the expression of copper transporters such as CTR1 and ATP7A/B [33]. These proteins are essential for normal copper transport, and their dysregulation often leads to copper accumulation, which adversely affects mitochondria and stimulates cell death [32]. Therefore, identifying functional molecules that regulate this pathway is vital, as lncRNAs could serve as key regulators due to their ability to modulate gene expression at the post-transcriptional level or interact with proteins, thereby affecting their function and stability.

Zhou et al. [34] revealed that lncRNA *AP000842.3* is involved in regulating the transcription factor NFAT5, which controls gene expression related to osmoregulation and inflammation and is associated with cuproptosis in PCa. According to their experiments, lncRNA *AP000842.3* may regulate NFAT5 by sponging *miR-206*, which represses *NFAT5* gene expression.

Several genes involved in cuproptosis have been identified, including *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, *PDHA1*, *PDHB*, *MTF1*, *GLS*, and *CDKN2A* [35]. In recent years, numerous studies have focused on identifying lncRNAs associated with these genes, proposing several lncRNA signatures for characterizing and stratifying different genitourinary tumors. A prevalent approach involves bioinformatics to search for cuproptosis-related lncRNA signatures for stratifying cancers into high- and low-risk groups. For instance, in PCa, three lncRNAs (*AC010896.1*, *AC016394.2*, and *SNHG9*) associated with prognosis were identified by Lu et al. [36]. After functional validation, the authors discovered that *SNHG9* was involved in the migration, proliferation, and enhanced invasiveness of prostate cancer cells.

In the study of BLCA, Shen et al. [37] constructed an eight-gene cuproptosis-associated lncRNA prognostic signature, including lncRNA *UBE2Q1-AS1*. They validated the function of *UBE2Q1-AS1* and found its involvement in RNA degradation and ubiquitin-mediated proteolysis in BLCA. Interestingly, although *UBE2Q1-AS1* was the most differentially expressed cuproptosis-related lncRNA in BLCA between high- and low-risk groups, another study by Duan et al. [38] reported no significant differences between normal and tumor samples from BLCA patients. They identified six lncRNAs (*FAM13A-AS1*, *GHRLOS*, *LINC00456*, *OPA1-AS1*, *RAP2C-AS1*, and *UBE2Q1-AS1*) with independent prognostic values for muscle-invasive bladder cancer.

In their work, Hong et al. [39] demonstrated the potential of novel cuproptosis-related lncRNAs as biomarkers for risk assessment in ccRCC. They showed that *MINCR*, along with *FOXD2-AS1* and *LINC02154*, was detectable in the blood of patients with metastatic ccRCC undergoing immune checkpoint inhibitor-based treatments, highlighting whether these changes could distinguish patients with clinical benefit from those with progressive disease. The tested lncRNAs showed increased levels in peripheral blood, with the most notable upregulation in *FOXD2-AS1* and *LINC02154* (fold changes of 3.7 and 3.8, respectively), followed by *MINCR* (fold change of 2.6) in patients with progressive disease [40]. Additionally, panels of prognostic biomarkers composed of different lncRNAs have been proposed by Xie et al. [41]. Their panel categorizes lncRNAs as high-risk, including *AC234031.1*, *AC011921.1*, *AC005332.5*, *RNF32-AS1*, and *CKMT2-AS1*, and low-risk, including *TNFRSF14-AS1*, *AL031275.1*, *NINJ2-AS1*, *EMX2OS*, *AC092140.2*, and *AC015922.3*. In another study, Zhang et al. [42]

demonstrated that cuproptosis-related lncRNAs *FOXD2-AS1*, *LINC00460*, *AC091212.1*, *AC007365.1*, and *AC026401.3* could accurately predict prognosis in patients with ccRCC. Interestingly, in renal cancer, *FOXD2-AS1* exerts its oncogenic impact particularly via binding with transcription factor MYC [43].

Ferroptosis-Associated LncRNAs in Urological Malignancies

Ferroptosis is an iron-dependent cell death pathway characterized by lipid peroxidation and damage to cell membranes. This process is significant in cancer progression and could be utilized for risk scoring across various cancers. In PCa, biochemical recurrence (BCR) is a common event associated with unfavorable prognostic outcomes. Liu et al. [44] identified a five-lncRNA signature (*AP006284.1*, *AC132938.1*, *BCRP3*, *AL360181.4*, and *AL135999.1*) that can be used to evaluate the risk of BCR. The downregulation of *BCRP3* and *AP006284.1* in the PCa cell line 22RV1 inhibited cell proliferation, suggesting the oncogenic roles of these lncRNAs. This hypothesis was further supported by the study conducted by Zue et al. [45], which demonstrated that downregulation of *BCRP3* effectively inhibited the proliferation, migration, and invasion of PC3 cells. The authors discovered that *BCRP3* can regulate 7 microRNAs (*miR-1306-5p*, *miR-1307-3p*, *miR-132-5p*, *miR-3184-5p*, *miR-423-5p*, *miR-5581-3p*, and *miR-558*). These microRNAs target ferroptosis-related genes such as *AIFM2*, *SLC2A6*, and *TAZ*, outlining a potential mechanism through which *BCRP3* contributes to PCa progression. The authors also proposed their own BCR risk model, which consists of 9 ferroptosis-related lncRNAs (*ZNF649.AS1*, *U73166.1*, *SNHG4*, *PGM5.AS1*, *BCRP3*, *AP001412.1*, *AL807752.4*, *AC005901.1*, and *AC004066.1*).

Another lncRNA, *OIP5-AS1*, was found to stimulate cell proliferation and inhibit ferroptosis under chronic cadmium (Cd) exposure in PCa cells. Zhang et al. [46] proposed that it acts by targeting the *miR-128-3p*/SLC7A11 signaling pathway, resulting in the upregulation of solute carrier family 7 member 11 (SLC7A11). In this study, serum levels of *OIP5-AS1* were evaluated, revealing elevated transcript levels in PCa patients with higher serum Cd concentrations compared to those with lower levels. Therefore, *OIP5-AS1* could serve as a potential non-invasive biomarker for monitoring PCa. Additionally, another lncRNA activated by transcription factor AP-2 gamma (TFAP2C), *PCAT1*, also inhibits ferroptosis and increases docetaxel resistance in PCa by activating *SLC7A11* expression. *PCAT1* employs a distinct mechanism of action by interacting with and stabilizing c-MYC, which promotes the transcription of *SLC7A11*. Furthermore, *PCAT1* can enhance *SLC7A11* expression by sponging its targeting *miR-25-3p* [47].

In bladder cancer, a ferroptosis-related lncRNA signature demonstrated higher diagnostic efficiency for prognosticating patient outcomes compared to the traditional clinicopathological characteristics. Chen et al. [48] created a set of 9 ferroptosis-related lncRNAs (*AL031775.1*, *AL162586.1*, *AC034236.2*, *LINC01004*, *OCIAD1-AS1*, *AL136084.3*, *AP003352.1*, *Z84484.1*, and *AC022150.2*), which could stratify patients into high- and low-risk groups and predict their potential therapy responses. Among these, lncRNA *AL136084.3* was identified as an independent risk factor for BLCA, as demonstrated by Zhou et al. [49]. They revealed the reciprocal binding between the repressor of ferroptosis NUPR1 [49] and *AL136084.3* in BLCA cells. Conversely, another lncRNA, *AL355353.2*, was found to promote apoptosis and impair the proliferation of BLCA cells [50]. Investigating the behavior of lncRNA *RP11-89* in BLCA, Lou et al. [51] hypothesized that its influence on tumors is linked to the suppression of ferroptosis. Using transmission electron microscopy (TEM), they observed that *RP11-89* depletion in BLCA affects mitochondrial morphology, which is a critical event for ferroptosis and increases iron accumulation in the BLCA cell lines. The regulatory effect of *RP11-89* may occur through a microRNA-dependent pathway, specifically by sponging *miR-129-5p*. The downstream targets of this microRNA include *ACSL4* and *PROM2*, which are the critical regulators of ferroptosis.

Several prognostic signatures of ferroptosis-related lncRNAs have been discovered in renal cancer. Shu et al. [52] identified 5 lncRNAs (*DOCK8-AS1*, *SNHG17*, *RUSC1-AS1*, *LINC02609*, and *LUCAT1*) that are independently correlated with the overall survival of patients with renal cancer. *SNHG17*, *RUSC1-AS1*, *LINC02609*, and *LUCAT1* were significantly increased, while the expression of *DOCK8-AS1* was significantly decreased in re-

nal cancer patients with high-risk values. A seven-ferroptosis-related lncRNA prognostic signature for ccRCC (*AC006129.2*, *CTB-41I6.2*, *CTD-2510F5.4*, *RP5-994D16.9*, *RP11-298J20.4*, *CTD-2396E7.11*, and *TUG1*) was developed to distinguish patients into high-risk and low-risk groups, showing significant survival differences. Patients with ccRCC and high expression of *CTD-2396E7.11*, *RP11-298J20.4*, *RP5-994D16.9*, and *CTB-41I6.2* had better prognoses, while those with high expression of *AC006129.2*, *CTD-2510F5.4*, and *TUG1* had worse prognoses [53]. For instance, *TUG1* was shown to promote ccRCC cell proliferation while inhibiting apoptosis and autophagy by regulating the *miR-31-5p*/FLOT1 axis [54]. Additional ferroptosis-related lncRNA biomarker panels are listed in Table 1.

Disulfidptosis-Associated LncRNAs in Urological Malignancies

Disulfidptosis is a recently discovered form of controlled cell death associated with the accumulation of disulfides that cannot be reduced, inducing disulfide stress and ultimately leading to disulfidptosis. This condition is closely linked to the cysteine transporter SLC7A11 [55], which is also critically involved in ferroptosis, making it a potential therapeutic target. LncRNAs have been reported to regulate this process, and several models for risk evaluation have been developed for different genitourinary cancers. Mulati et al. [56] investigated disulfidptosis-related lncRNAs (DRLRs) associated with biochemical recurrence-free survival (BRFS) in PCa. Their model consists of 4 lncRNAs (*AC026401.3*, *SNHG4*, *SNHG25*, and *U73166.1*), which demonstrated a strong correlation with BRFS in PCa. The authors also investigated the cellular function of *AC026401.3* in the PC3 and DU145 cell lines. Depletion of this lncRNA affected the proliferation, migration, and invasiveness of PCa cells. They proposed lncRNA *AC026401.3* as a potential therapeutic target, hypothesizing that its effects might be due to its influence on intracellular glycolysis. Feng et al. [57] also included this lncRNA in their DRLRs risk model for kidney renal clear cell carcinoma, which also consists of *FAM83C.AS1*, *AC136475.2*, *AC121338.2*, *AC254562.3*, and *AC000050.2*, indicating the critical role of *AC026401.3* in disulfidptosis.

Another set of 9 DRLRs associated with BLCA prognosis was identified. Their work demonstrated that the signature comprising *AL590428.1*, *LSAMP-AS1*, *LINC01184*, *LINC-PINT*, *AC023825.2*, *AC010331.1*, *AC009716.1*, *AC104785.1*, and *AC008764.6* can be used to stratify BLCA patients into high- and low-risk groups. The proposed models were validated in clinical samples of paired tumor and adjacent normal tissues, indicating that the expression levels of lncRNAs were higher in tumor samples [58]

Chen et al. [59] demonstrated association between cuproptosis and disulfidptosis-related genes. They identified 21 cuproptosis- and disulfidptosis-related genes and created a risk model that included lncRNAs associated with these genes. This risk model divided patients with RCC into high-risk and low-risk groups, where *ACVR2B-AS1*, *AC095055.1*, and *AL161782.1* showed higher expression in the low-risk group, while lncRNA *MANEA-DT* expression was elevated in the high-risk group.

The metabolic death-related LncRNAs risk models for genitourinary cancers are usmmarized in the Table.

LncRNA Risk Models and the Immune Microenvironment

The majority of these research results demonstrate the association of lncRNA signatures with the immune characteristics of tumors. This was discovered using functional enrichment (e.g., GSEA) and/or specific tools and algorithms for immune microenvironment analysis like ESTIMATE, TIDE, IOBR, etc. For example, in the study by Cheng et al. [60], after analyzing the immune characteristics of high- and low-risk groups stratified by a cuproptosis-related lncRNA signature, the authors concluded that the high-risk group tends to have an immunosuppressive microenvironment, which further leads to a poorer prognosis. In the study performed by Lu et al. [36], who also created a cuproptosis-related lncRNA signature for PCa, they reported lower levels of proinflammatory cytokines, interferon type II, antigen-presenting cells, and co-stimulatory chemokine receptors in the high-risk group, while the low-risk group demonstrated a more robust immune microenvironment. The correlation of-ferroptosis-related lncRNAs and tumor immune

Metabolic death-related LncRNAs risk models for genitourinary cancers

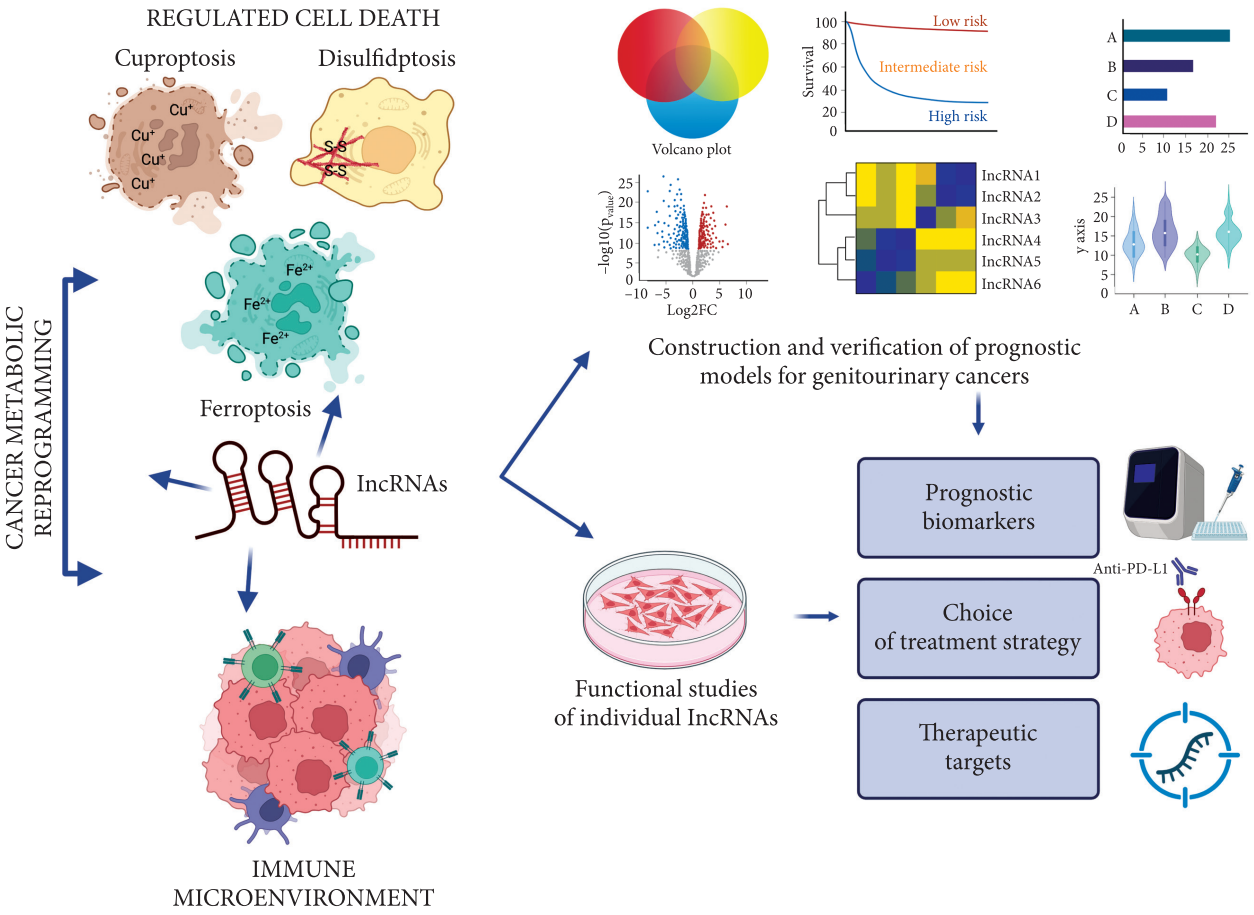
LncRNAs	Type of regulated cell death	Localization	Reference
APCDD1L-DT, *AL161782.1*, *AC026401.3*, MINCR	Cuproptosis-related lncRNAs	Renal	[39]
AC234031.1, *AC011921.1*, *AC005332.5*, *RNF32-AS1* and *CKMT2-AS1* *TNFRSF14-AS1*, *AL031275.1*, *NINJ2-AS1*, *EMX2OS*, *AC092140.2*, *AC015922.3*	Cuproptosis-related lncRNAs high-risk lncRNAs low-risk lncRNAs	Renal	[41]
FOXD2-AS1, *MINCR*, *LINC02154*	Cuproptosis-related lncRNAs	Renal	[40]
FOXD2-AS1, *LINC00460*, *AC091212.1*, *AC007365.1*, *AC026401.3*	Cuproptosis-related lncRNAs	Renal	[42]
OVCH1-AS1, *SBF2-AS1*, and *AC002451.1* *CDK6-AS1*, *LINC02154*, *AC103706.1*, and *AC034236.3*	Cuproptosis-related lncRNAs	Renal	[62]
AC010896.1, *AC016394.2*, and *SNHG9*	Cuproptosis-related lncRNAs	Prostate	[36]
↑*AC099791.2* and ↑*STPG3-AS1* ↓*AC005790.1*, ↓*AC011472.4*, ↓*AC144450.1*, and↓*LIPE-AS1*	Cuproptosis-related lncRNAs high-risk group	Prostate	[60]
AC004637.1, *AC011503.2*, *AC012065.2*, *AC099850.3*, *AL078587.1*, *MIR181A2HG*, *U47924.1*, and *UBE2Q1-AS1*	Cuproptosis-related lncRNAs	Bladder	[37]
BDNF–AS, *WDFY3-AS2*, *FBXO30-DT*, *EDRF1-DT*, *AC106820.5*, *AC011477.2*, *SGMS1-AS1*, *CKMT2-AS1*, *AC015849.3 AL031670.1*, *AC096992.2*, *AL158212.3*	Cuproptosis-related lncRNAs	Bladder	[70]
FAM13A-AS1, *GHRLOS*, *LINC00456*, *OPA1-AS1*, *RAP2C-AS1*, and *UBE2Q1-AS1*	Cuproptosis-related lncRNAs	Bladder	[38]
AC073534.2, *AC021321.1*, *HYI-AS1*, *PPP1R26-AS1*, *AC010328.1*, *AC012568.1* and *MIR4435-2HG*	Cuproptosis-related lncRNAs	Bladder	[71]
AC073534.2, *LINC01648*, *AC108449.2*, *TRG-AS1*, *LINC02886*, *AL590428.1*, *SH3RF3-AS1*, and *AL117344.2*	Cuproptosis-related lncRNAs	Bladder	[72]
AC005261.1, *AC008074.2*, *AC021321.1*, *AL024508.2*, *AL354919.2*, *ARHGAP5-AS1*, *LINC01106*, and *LINC02446*	Cuproptosis-related lncRNAs	Bladder	[73]
AC124069.1, *AC092794.1*, *GRK5-IT1*, *AC253576.2*, *AC021321.1*, *AC103746.1*, and *AL031429.2*	Cuproptosis-related lncRNAs	Bladder	[74]
high expression: *AC099850.3*, *LINC02535*, *LINC00462*, *FOXD2-AS1* low expression:	Ferroptosis-related lncRNAs	Renal	[75]
LNCTAM34A high expression: *CTD-2396E7.11*, *RP11-298J20.4*, *RP5-994D16.9*, and *CTB-41I6.2;* high expression: *AC006129.2*, *CTD-2510F5.4*, and *TUG1*	Ferroptosis-related lncRNAs better prognosis worse prognosis	Renal	[53]
↓*DOCK8-AS1*, ↑*SNHG17*, ↑*RUSC1-AS1*, ↑*LINC02609*, and ↑*LUCAT1*	Ferroptosis-related lncRNAs	Renal	[52]
CASC19, *AC090197.1*, *AC099850.3*, *AL033397.2*, *LINC00462*, and *B3GALT1-AS1*	Ferroptosis-related lncRNAs	Renal	[76]
↓*AP006284.1*, ↑*AC132938.1*, ↑*BCRP3*, ↑*AL360181.4* and ↑*AL135999.1*	Ferroptosis-related lncRNAs	Prostate	[44]

End of Table

LncRNAs	Type of regulated cell death	Localization	Reference
ZNF649.AS1, *U73166.1*, *SNHG4*, *PGM5.AS1*, *BCRP3*, *AP001412.1*, *AL807752.4*, *AC005901.1*, and *AC004066.1*	Ferroptosis-related lncRNAs	Prostate	[45]
AL031775.1, *AL162586.1*, *AC034236.2*, *LINC01004*, *OCIAD1-AS1*, *AL136084.3*, *AP003352.1*, *Z84484.1*, *AC022150.2*	Ferroptosis-related lncRNAs	Bladder	[48]
20 LncRNA: *AC005785.1*, *AL731567.1*, *AC010618.2*, *AL136084.3*, *AC006160.1*, etc.	Ferroptosis-related lncRNAs	Bladder	[61]
36 LncRNA*: AC010973.2*, *ZFHX2-AS1*, *PTOV1-AS2*, *AC020765.2*, *AC008105.1*, etc.	Ferroptosis-related lncRNAs	Bladder	[77]
AL031775.1, *AC024060.2*, *AC018653.3*, *AC011468.1*, *AL583785.1*, *AC021321.1*, *AP003352.1*, *`ETV7-AS1`*, *U47924.1*, *AC010326.3*, and *LINC02762*	Ferroptosis-related lncRNAs	Bladder	[78]
AC099850.4, *AL731567.1*, *AL133415.1*, *AC021321.1*, *SPAG5-AS1*, *HMGA2-AS1*, *RBMS3-AS3*, *AC006160.1*, *AL583785.1*, and *AL662844.4*	Ferroptosis-related lncRNAs	Bladder	[79]
FAM225B, *ZNF503-AS1*, *SPINT1-AS1*, *WWC2-AS2*, *LINC01338*	Disulfideptosis-associated lncRNAs	Renal	[80]
SPINT1-AS1, *AL161782.1*, *OVCH1-AS1*, *AC131009.3*, and *AC108673.3*	Disulfideptosis-associated lncRNAs	Renal	[81]
FAM83C.AS1, *AC136475.2*, *AC121338.2*, *AC026401.3*, *AC254562.3*, and *AC000050.2*	Disulfideptosis-associated lncRNAs	Renal	[57]
AC026401.3, *SNHG4*, *SNHG25*, and *U73166.1*	Disulfideptosis-associated lncRNAs	Prostate	[56]
AP000439.3, *RP11-417E7.1*, *RP11-119D9.1*, *LINC01510*, *SNHG3*, *AC156455.1*, *RP11-291B21.2*, *EMX2OS*, *AC093850.2*, *HAGLR* and *RP11-389C8.2*	Disulfideptosis-associated lncRNAs	Bladder	[82]
AL590428.1, *LSAMP-AS1*, *LINC01184*, *LINC-PINT*, *AC023825.2*, *AC010331.1*, *AC009716.1*, *AC104785.1*, and *AC008764.6*	Disulfideptosis-associated lncRNAs	Bladder	[58]
ACVR2B-AS1, *AC095055.1*, and *AL161782.1*, and *MANEA-DT*	Cuproptosis and disulfideptosis-related lncRNAs benefcial prognostic factors poor prognostic factor	Renal	[59]

infiltration was also observed in PCa by Liu et al. [44], who discovered significant differences in immune characteristics between the high- and low-risk groups, which can be further used for the prediction of therapy response.

For BLCA patients, the high-risk and low-risk groups, identified using metabolism-related cell death lncRNAs, also demonstrated distinct immune patterns. In the work of Shen et al. [37], the high-risk group was characterized by a more aggressive and inflammatory immune landscape, and patients from this group responded better to anti-PD1 and anti-CTLA4 immunotherapeutics. Mutations of *RB1* and *ERBB* genes were also more abundant in the high-risk group. Immunotherapy, neoadjuvant chemotherapy, radiotherapy, and anti-angiogenic therapy tended to be more beneficial for the high-risk group of BLCA in this study. A similar distribution of immune microenvironment patterns was shown by Chen and co-authors when they analyzed ferroptosis-related lncRNAs for estimation of the risk-score in BLCA. They used ssGSEA for their analysis and found that tumors of high-risk patients were highly infiltrated



LncRNAs as mediators of the interplay between metabolic reprogramming, immune microenvironment, and metabolic cell death (Created in https://BioRender.com)

by CD8+ T cells, macrophages, mast cells, neutrophils, and Tregs. Such an immune pattern was suggested to be associated with poor prognosis. Moreover, Chen et al. [48] and Liu et al. [61] in two independent studies on ferroptosis-related lncRNAs demonstrated the higher expression of immune checkpoint molecules in the high-risk groups. Chen et al. [48] concluded that the patients from such a group may be more sensitive to anti-PD-1/L1 immunotherapy. Liu et al. [61] hypothesized that ferroptosis-related lncRNAs may play not only a crucial role in BLCA cells' phenotype but also could be involved in remodeling the tumor immune microenvironment in BLCA.

The immune microenvironment in renal cancer also correlated with metabolic death-related lncRNAs expression patterns. For instance, in RCC, high-risk and low-risk patients, divided using the cuproptosis-related lncRNA signature, demonstrated distinct immune landscapes according to the ssGSEA results. The authors applied the TIDE algorithm to evaluate the immune escape ability in either of these groups and discovered that the high-risk group has the higher immune escape ability and, therefore, anti-immune-checkpoint therapy will be more beneficial to the low-risk group [62]. Similar results were obtained by Zhang et al. [63] in their study on lncRNA signatures associated with cuproptosis. The low-risk group also seemed to have more benefits from immunotherapy than the high-risk group.

This tremendous association between lncRNA signatures and the immune microenvironment and their possible prognostic ability for immunotherapy may be explained by the function of lncRNAs included in these panels and the abovementioned impact of metabolic changes in tumors on the tumor microenvironment [64]. Some of the lncRNAs associated with cuproptosis, ferroptosis, or disulfidptosis in genitourinary cancers were also reported to be immune-associated in different cancer types or directly connected with immune cells. For example, ferroptosis-related lncRNAs in BLCA, *Z84484.1*, and *OCIAD1-AS1*, together with

cuproptosis-related lncRNA *TNFRSF14-AS1* in RCC, appeared among seven immune-related lncRNAs for prognosis of bladder cancer, discovered by Wang et al. [65]. Patients in the low-risk group had a better prognosis than those in the high-risk group. *AL161782.1* lncRNA appeared among immune-associated lncRNA signatures in melanoma [66]. In experimental research using the colorectal cancer cell line CACO2, it was demonstrated that lncRNA *SNHG4,* via sponging *miR-144-3p,* can induce interaction between cancer cells and $CD4^+$ T cells and stimulate their apoptosis by the PD-1/PD-L1 immune checkpoint mechanism [67]. Also, there are long non-coding RNAs that were previously reported to regulate inflammatory responses. For example, *LUCAT1* was described as a negative regulator of type I interferon and inflammatory cytokines expression through regulation of stability and splicing of *NR4A2* in myeloid cells [68].

Conclusion

All these findings add more reasons to the importance of further investigation of the role of individual lncRNAs in genitourinary cancers. The results of current research highlight their potential to be involved in cancer metabolic reprogramming, controlled cell death pathways, and anticancer immunity (Figure). Moreover, they could probably be transported between cancer cells and the tumor microenvironment [69] and serve as essential molecules for cell-to-cell communication during cancer development and progression. According to their multiple functions and association with numerous aspects of tumor development and progression, they could become good therapeutic targets and informative biomarkers.

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ВЗАЄМОДІЯ ДНРНК, МЕТАБОЛІЧНОЇ ЗАГИБЕЛІ КЛІТИН
ТА ІМУННОГО МІКРООТОЧЕННЯ ПРИ ЗЛОЯКІСНИХ
НОВОУТВОРЕННЯХ СЕЧОСТАТЕВОЇ СИСТЕМИ

Онкологічні захворювання сечостатевої системи, зокрема рак передміхурової залози, сечового міхура та нирки, становлять значне навантаження на глобальну систему охорони здоров'я через високу поширеність і резистентність до стандартних терапевтичних підходів. Важливим аспектом прогресування раку є метаболічне перепрограмування, яке не лише сприяє неконтрольованому росту клітин, а й суттєво впливає на шляхи запрограмованої загибелі клітин та імунне мікрооточення пухлини. У цій статті розглянуто та проаналізовано сучасні дослідження щодо складної ролі довгих некодуючих РНК (днРНК) в модуляції трьох форм регульованої клітинної смерті — купроптозу, фероптозу та дисульфідптозу — в контексті злоякісних новоутворень сечостатевого тракту. Обговорюється, яким чином специфічні експресійні сигнатури днРНК беруть участь у регуляції цих метаболічних шляхів клітинної смерті, впливаючи на проліферацію, міграцію та інвазію ракових клітин. Окрему увагу приділено взаємозв'язку між профілями експресії днРНК та характеристиками імунного мікрооточення, що підкреслює їхній потенціал як прогностичних біомаркерів і стратифікаційних маркерів відповіді на імунотерапію. Представлені дані акцентують увагу на багатогранних функціях днРНК у метаболізмі пухлинних клітин та протипухлинному імунітеті, позиціонуючи їх як перспективних терапевтичних мішеней та інформативних біомаркерів для прецизійної онкології при ракових пухлинах сечостатевого тракту.

Ключові слова: купроптоз, фероптоз, дисульфідптоз, днРНК, рак передміхурової залози, рак сечового міхура, рак нирки, імунне мікрооточення.