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Review

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Long Non-coding RNAs Expression in Renal Cell Carcinoma

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ABSTRACT

Renal cell carcinoma (RCC) is among common cancers of the urogenital system. Several cancer-related pathways have been shown to be implicated in its pathogenesis. More recently, dysregulation of a group of non-coding RNAs named long non-coding RNAs (lncRNAs) have been demonstrated in many cancer types such as RCC. LncRNAs have been classified to oncogenic and tumor suppressor lncRNAs based on the pattern of expression in RCC samples as well as functional *in vitro* studies. Expression of several oncogenic lncRNAs such as *CCAT2*, *HOTAIR*, *UCA1*, *TUG1* and *FTX* in RCC samples has been shown to be associated with tumor size and tumor stage. In addition, expression levels of numerous lncRNAs have been demonstrated to be independent prognostic factors in RCC patients. Consequently, lncRNA signature would be applied as diagnostic or prognostic biomarker as well as target for treatment modalities.

Key words: lncRNA, Renal cell carcinoma, Biomarker.

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1. INTRODUCTION

Renal cell carcinoma (RCC) is among malignancies whose frequency has an increasing trend in developing countries. The same as other cancers, early diagnosis is associated with better patient outcome and possibility of application of curative treatments (1). This malignancy has been recognized to have extensive heterogeneity and a genetically complex background. Several cancer-related pathways such as von Hippel-Lindau/ Hypoxia-inducible factor (VHL/HIF) pathway, chromatin remodeling/histone methylation pathway and Phosphatidylinositol-3-Kinase and Protein Kinase B (PI3K/AKT) pathway have been implicated in the pathogenesis of RCC (2). Clear cell renal cell carcinoma (ccRCC) is the most frequent type of this malignancy with both sporadic and familial forms in which *VHL* gene mutations play causative roles (2). In spite of extensive efforts to find appropriate biomarkers for this malignancy, no ideal diagnostic or prognostic biomarker has been identified until recently (3). However, recent studies have introduced serum tissue factor (4) and blood expression level of *Chemokine (C-X-C motif) ligand 7* (*CXCL7*) (5) as diagnostic biomarkers for RCC while C-reactive protein (6) as a prognostic biomarker for this malignancy. More recently, Yen et al. have introduced a reversed phase liquid chromatographic method for simultaneous measurement of creatinine, quinolinic acid, gentisic acid and 4-hydroxybenzoic acid in urine as biomarkers for RCC. However, their method has a number of limitations due the presence of background from the urine matrix or other reagents (7). In addition, a recent publication has assessed the presence of frequently mutated genes in circulating tumor DNA (ctDNA) of RCC patients using whole-exome sequencing of ctDNA. Such somatic mutations were detected in two third of RCC patients but only two of the control patients (8). Besides, the possibility of application of myeloid cell biomarkers for the differential diagnosis, prognosis, and monitoring of RCC has been assessed (9). Another study has introduced a panel of 21 volatile organic compounds (VOCs) with the ability to differentiate RCC patients from controls. The capability of two of them for such purpose was confirmed in further studies (2-oxopropanal and 2,5,8-trimethyl-1,2,3,4-tetrahydronaphthalene-1-ol). Consequently, they have demonstrated the significance of urinary volatilome for RCC diagnosis (10). Researchers have focused on assessment of genetic and epigenetic changes during the course of RCC development to unveil the underlying

causes of this malignancy and introduce novel biomarkers for it. Long non-coding RNAs (lncRNAs) comprise a large fraction of non-protein coding transcripts of human genome with sizes larger than 200 nucleotides. They control gene expression at epigenetic, transcriptional and post-transcriptional levels (11). Such vast domain of gene expression regulation has led to participation of lncRNAs in several cancer-related pathways (12-14). Expression analyses have provided several clues indicating dysregulation of lncRNAs in malignancies (15-19). In addition, numerous single nucleotide polymorphisms (SNPs) within lncRNA coding regions or regulatory sequences have been shown to modulate cancer risk in different populations (20-23). LncRNAs exert tissue specific roles during tumorigenesis. Based on these roles they are classified to oncogenic or tumor suppressor lncRNAs. Expression analyses as well as *in vitro* functional studies have revealed participation of several lncRNAs in RCC. Table 1 presents a summary of lncRNAs implicated in RCC. Considering the high mortality and morbidity rate of RCC and the necessity for finding appropriate biomarkers for early detection of this malignancy, we aimed at evaluation of the role of lncRNAs in RCC to find the underlying genetic cause of this disorder which might facilitate identification of diagnostic or prognostic biomarkers as well as design of specific treatments for this malignancy.

Table 1. Long non-coding RNAs implicated in renal cell carcinoma.

LncRNA	*Chromosomal location*	*Expression pattern in renal cell carcinoma*	*Involvement in other cancers*	*Function / characteristics*	*References*
DANCR	4q12	Down-regulation	prostate, breast, colorectal, hepatocellular carcinoma, osteosarcoma	Suppresses proliferation, migration and invasion, and induce apoptosis	(24)
CCAT1	8q24.21	Up-regulation	breast, colorectal, gastric, lung, hepatocellular carcinoma, acute myeloid leukemia, gallbladder	Promotes metastasis via inhibiting NPR3 and activating p38-MAPK signaling	(25)
CCAT2	8q24.21	Up-regulation	breast, prostate, small cell lung cancer, hepatocellular carcinoma, ovarian, bladder, lung, gastric, colon	Promotes cell proliferation and invasion through regulating Wnt/β-catenin signaling pathway	(26)
HOTAIR	12q13.13	Up-regulation	B-cell neoplasms, breast, cervical, colorectal, ovarian, esophageal squamous cell cancer, gastric, gastrointestinal, hepatocellular carcinoma, pancreas	Coordinates with chromatin-modifying enzymes to regulate gene silencing, crucial for cell proliferation and invasion, promotes metastasis of renal cell carcinoma by up-regulating histone H3K27 demethylase JMJD3	(27)
UCA1	19p13.12	Up-regulation	bladder, oral squamous cell carcinoma, squamous carcinoma, hepatocellular carcinoma, gastric cancer	Functions as an oncogene	(28)
TUG1	22q12.2	Up-regulation	B-cell neoplasms, non-small cell lung cancer, gastric cancer, osteosarcoma colorectal cancer, esophageal squamous cell carcinoma, gastric cancer , hepatocellular carcinoma, and bladder cancer	Acts as an oncogene	(29)
FTX	Xq13.2	Up-regulation	hepatocellular carcinoma, colorectal cancer	-	(30)
SRLR	-	Up-regulation	-	Elicits intrinsic sorafenib resistance via evoking IL-6/STAT3 axis	(31)
BX357664	-	Down-regulation	-	Regulates cell proliferation and epithelial-to-mesenchymal transition via inhibition of TGF-β1/p38/HSP27 signaling	(32)
MALAT1	11q13.1	Up-regulation	B-cell neoplasms, bladder, breast, cervical, colon, endometrial, gallbladder, hepatocelluar carcinoma, lung, squamous cell carcinoma, nasopharyngeal carcinoma, non-small cell lung cancer, neuroblastoma, osteosarcoma, pancreas, prostate, uterus, glioblastoma, multiple myeloma	Promotes proliferation, migration, and invasion, promotes metastasis through sponging miR-200s	(33)
TRIM52-AS1	5q35.3	Down-regulation	-	Acts as a tumor suppressor	(34)
MEG3	14q32.2	Down-regulation	acute myeloid leukemia, bladder, chronic myeloid leukemia, colon, gastric, hepatocellular carcinoma, lung, prostate	Induces apoptosis by activating the mitochondrial pathway	(35)
NBAT-1	6p22.3	Down-regulation	breast, neuroblastoma	-	(36)
SPRY4-IT1	5q31.3	Up-regulation	esophageal squamous cell carcinoma, melanoma, gastric, cervical, colorectal, glioma, hepatocellular carcinoma, prostate, lung, bladder	Regulates cell proliferation, migration, and invasion	(37)
GAS5	1q25.1	Down-regulation	breast, lymphoma, melanoma, prostate, hepatocellular carcinoma, gastric, ovarian	Act as tumor suppressor gene	(38)
CADM1-AS1	11q23.3	Down-regulation	-	Regulates cell proliferation, apoptosis and migration via the expression pattern of "CADM1-AS1/CADM1 mRNA gene pairs"	(39)

2. Oncogenic lncRNAs in RCC

More than a decade before, aHIF has been identified as a natural antisense transcript originated from hypoxia inducible factor 1α (HIF1α) gene sequences and up-regulated in all ccRCC samples examined. Its overexpression in this specific cancer type implied an oncogenic role for it (40). More recently, *Colon cancer-associated transcript-1 (CCAT1)* expression has been demonstrated to be elevated in RCC tissues and cell lines. Its silencing has decreased cell viability and induced the

apoptosis of RCC cells *in vitro*. Notably, *CCAT1* has a physical interaction with the anti-apoptotic protein, Livin. Functional studies have shown that *CCAT1* suppresses RCC cell apoptosis and enhances cell viability through enhancing the expression of Livin (25). The effect of *CCAT1* on apoptosis has been demonstrated in Figure 1.

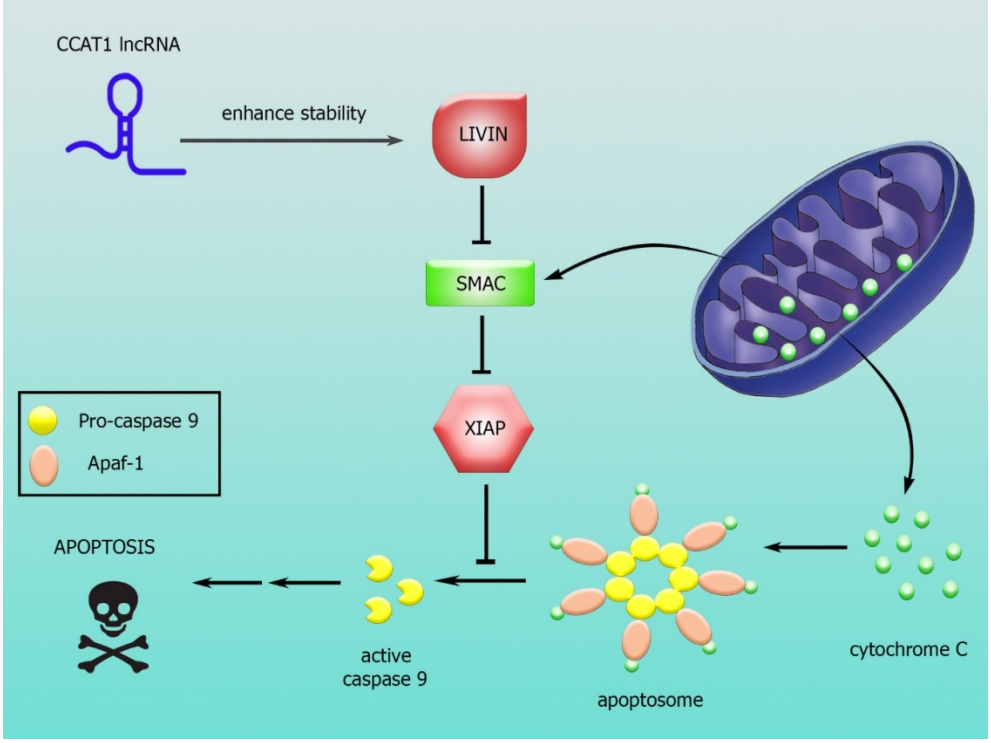

Figure 1. CCAT1 increases LIVIN protein stability and inhibits mitochondrial induced apoptosis

Colon cancer-associated transcript 2 (CCAT2) expression has been shown to be elevated in ccRCC cell lines and tissues as well. *CCAT2* silencing resulted in decreased cell proliferation, induction of apoptosis and activation of Wnt/β-catenin signaling pathway in RCC cell lines while its forced overexpression increased oncogenic characteristics of these cells. The effects of *CCAT2* knock down in inhibition of RCC tumor cells has been confirmed in mice xenograft model as well (26). *Metastatic renal cell carcinoma-associated transcript 1 (MRCCAT1)* has been identified through microarray analysis of RCC samples. The expression of this lncRNA has been shown to be elevated in metastatic ccRCC tissues and associated with the metastatic characteristics of ccRCC. Knock-in studies have shown that *MRCCAT1* enhances ccRCC cells proliferation, migration, and invasion while its silencing suppresses ccRCC cells proliferation, migration, and invasion *in vitro*, and ccRCC metastasis *in vivo*. *MRCCAT1* has a role in induction of p38-MAPK signaling pathway through inhibition of NPR3 transcription by recruiting PRC2 to its promoter (41). *HOX Transcript Antisense RNA (HOTAIR)* has enhanced RCC cell proliferation and growth *in vitro* and *in vivo*. *HOTAIR* exert an inhibitory role on expression of Salvador homolog 1 (SAV1) through increasing histone H3K27 methylation. Consequently, this lncRNA activates Hippo pathway in RCC cells (27). In addition, *HOTAIR* role in enhancing cancer cell metastasis has been shown to be exerted through reprogramming chromatin organization. Forced expression of *HOTAIR* has resulted in down-regulation of histone demethylase JMJD3 as well as its target gene Snail, while increased the level of histonemethy transferase EZH2 target gene PCDHB5. So *HOTAIR* influences both histone metylation and demethylation at various gene loci altering chromatin state in a way that facilitates metastasis program (42). *Urothelial carcinoma-associated 1 (UCA1)* has also been shown to exert oncogenic roles in RCC. UCA1 up-regulation has been demonstrated in RCC samples and cell lines (43). Its silencing has inhibited RCC proliferation and S-phase cell number *in vitro*. This lncRNA has been shown to be associated with enhancer of zeste homolog 2, which inhibited p21 expression through epigenetic mechanisms. miR-495 has also been suggested by both bioinformatics tools and functional studies to be a target of *UCA1* in RCC (28). *Taurine Up-Regulated 1 (TUG1)* expression levels have been shown to be elevated in RCC tissues compared with adjacent normal tissues (29). *TUG1* silencing has inhibited RCC cells migration, invasion and proliferation while has induced apoptosis (44). Similarly, expression level of the lncRNA *five prime to Xist (FTX)* has been higher in RCC tissues compared with normal tissues. Its silencing in RCC cells suppressed cell proliferation rate, colony formation ability, cell cycle progression as well as cell migration and invasion (30). *Long non-coding ribonucleic acid activated by transforming growth factor β (lncRNA-ATB)* silencing has resulted in suppression of cell proliferation, epithelial-to-mesenchymal transition

(EMT) program, cell migration and invasion while has induced apoptosis (45). LncRNA *metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1)* has also been implicated in RCC pathogenesis. Its knock-down has resulted in induction of cell apoptosis and reduction of RCC cell viability. *MALAT-1* has been shown to increase the stability of the anti-apoptotic protein Livin (46). Another study has shown that *MALAT-1* transcription is induced by c-Fos. It has also been demonstrated to interact with Ezh2. *MALAT-1* knock-down has also resulted in induction of E-cadherin expression and reduction of β-catenin expression through Ezh2 (47). In addition, *MALAT-1* has been regarded as a competing endogenous RNA (ceRNA) which impedes miR-200s and increases *ZEB2* expression in ccRCC (33). Figure 2 shows the mechanisms of oncogenic roles of *MALAT-1* in RCC. *RCCRT1* elevated expression has also been detected in RCC, especially in high-grade RCC tissues. Besides, its silencing has inhibited migration and invasion in RCC cell lines (48). Knockdown of *SPRY4-IT1* has similar effect in RCC cells (37).

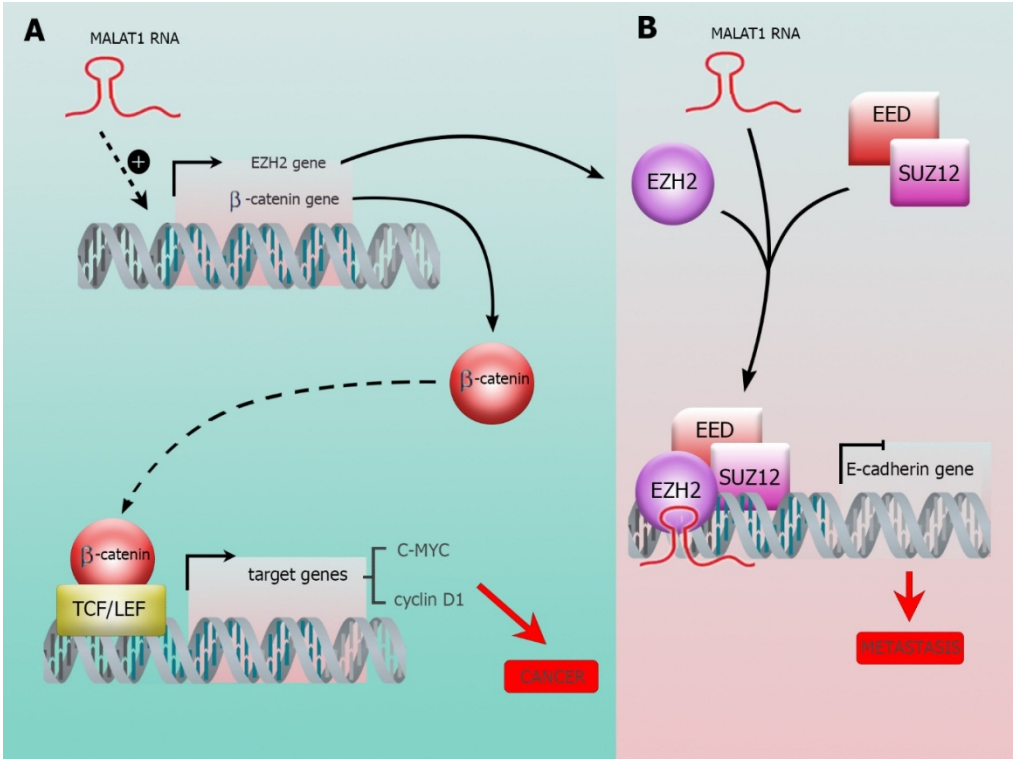

Figure 2. MALAT-1 induces expression of EZH-2 and β-catenin. β-catenin increases expression of C-myc and cyclin-D1 resulting in cell cycle progression (A). MALAT-1 cooperates with EZH2 produces PRC complex to inhibit expression of E-cadherin and promote metastasis (B)

3. Tumor suppressor lncRNAs in RCC

The expression of the lncRNA *differentiation antagonizing non-protein coding RNA (DANCR)* has been shown to be decreased in RCC tissues compared with adjacent normal tissues. Forced overexpression of this lncRNA has inhibited RCC cell proliferation, migration and invasion, and triggered apoptosis in these cells. So this lncRNA has been suggested as a tumor suppressor gene and a potential biomarker in RCC (24). Serum deprivation response antisense (SDPR-AS) in has been shown to be down-regulated in RCC tissues compared to the matched normal tissues. Overexpression of this lncRNA in RCC cells inhibited cell migration and invasion, but not cell growth (49). *BX357664* is another tumor suppressor gene in RCC whose forced overexpression has decreased migration, invasion, and proliferation of RCC cells. Such anti-tumorigenic roles are exerted through inhibition of the TGF-β1/p38/HSP27 pathway (32). The paternally imprinted non-coding *MEG3* has been also regarded as a tumor suppressor in RCC because it has been shown to be down-regulated in primary RCC tissues due to epigenetic silencing throughout the 14q32 gene cluster (50). Knock-in studies have shown the effect of *MEG3* on decreasing the viability and induction of apoptosis in RCC cells. Besides, overexpression of *MEG3* has resulted in inhibition of Bcl-2 and procaspase-9 proteins expression while increased the expression of cleaved caspase-9 protein, and enhanced the release of cytochrome c protein to cytoplasm. So *MEG3* triggers the apoptosis of RCC cells probably through activating the mitochondrial pathway (35). *LncRNA neuroblastoma associated transcript-1 (NBAT-1)* expression has been remarkably down-regulated in ccRCC tissues and renal cancer cells compared with neighboring normal tissues and normal human proximal tubule epithelial cell line. In addition, its silencing has increased renal cancer cell proliferation, migration and invasion (36). Figure 3 shows the inhibitory effect of NBAT-1 on metastasis and angiogenesis. *Growth arrest-specific transcript 5 (GAS5)* overexpression in RCC has suppressed cell proliferation, migration and invasion,

triggered cell apoptosis and arrested cell cycling. Consequently, GAS5 has been suggested as a tumor suppressor for RCC (51).

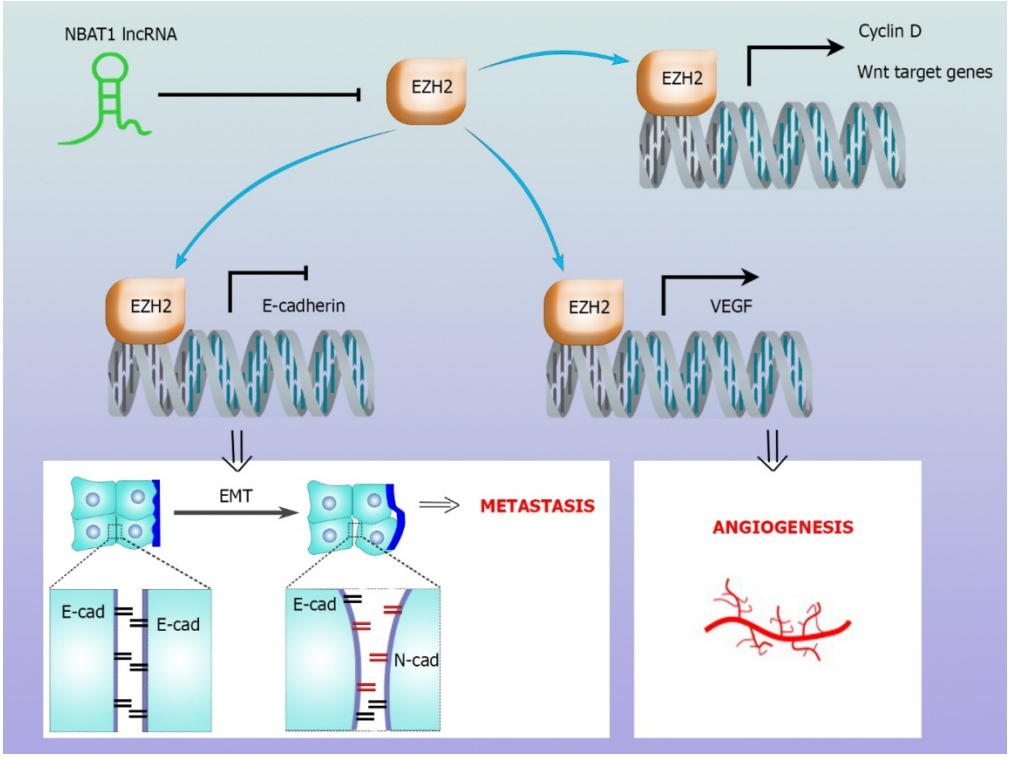

Figure 3. NBAT-1 acts as tumor suppressor gene by inhibiting EZH2 expression. EZH2 inhibits E-cadherin and induces VEGF and cyclin D expression leading to angiogenesis and metastasis

TRIM52 antisense RNA 1 (TRIM52-AS1) is another tumor suppressor lncRNA which has been down-regulated in RCC. The overexpression of *TRIM52-AS1* has inhibited cell migration and proliferation while induced apoptosis of the RCC cells (34). *CADM1-AS1* expression has also been demonstrated to be decreased in ccRCC tissues in compared with adjacent non-tumor tissues. Its silencing has increased growth and migration while decreased apoptosis of RCC cells (39).

4. The role of lncRNAs in treatment response in RCC

Sorafenib resistance-associated lncRNA (SRLR) expression has been shown to be increased in intrinsically sorafenib-resistant RCCs. *In vitro* studies have confirmed the role of this lncRNA in induction of sorafenib resistance in RCC cells. The role of *SRLR* in induction of drug resistance is exerted through its binding to NF-κB and subsequent elevation of IL-6 transcription, resulting in the activation of STAT3. Clinical data has also shown the association between SRLR expression and poor responses to sorafenib in RCC patients (31).

5. Prognostic role of lncRNAs in RCC

Expression of several oncogenic lncRNAs such as *CCAT2*, *HOTAIR*, *UCA1*, *TUG1* and *FTX* in RCC samples has been shown to be associated with tumor size and tumor stage (26-30). *CCAT2*, *MRCCAT1*, *HOTAIR*, *UCA1*, *TUG1* and *MALAT-1* expression levels have been shown to be markers of overall survival in RCC patients (26, 27, 29, 41, 47, 52). In addition, elevated expression of *HOTAIR* has been regarded as marker for poor prognosis of RCC after surgery (27). Besides, expression levels of *lncRNA-ATB* and *RCCRT1* have been associated with tumor stages, histological grade, vascular invasion, lymph node metastasis and distant metastasis in RCC patients (45, 48). Elevated levels of *SPRY4-IT1* and *H19* expressions have been associated with advanced clinical stage and poorer prognosis ccRCC patients (37, 53). In addition, multivariate analyses by Cox's proportional hazard model and Kaplan-Meier analysis demonstrated *SPRY4-IT1* and *H19* expression levels as independent prognostic factors in ccRCC, respectively (37, 53). On the other hand, higher expressions of *SDPR-AS*, *NBAT-1* and *CADM1-AS1* have been shown to be associated with better overall survival (36, 39, 49).

6. Discussion

Several oncogenic lncRNAs have been shown to participate in RCC development and progression. In addition, lots of them have been suggested as prognostic markers and putative targets for development of novel treatment options. For some lncRNAs such as MALAT-1 the prognostic implication in RCC patients have been supported by meta-analysis of data available in the literature (54). Furthermore, the high rate of mutations detected in chromatin modifier genes in ccRCC indicates

the importance of nucleosome dynamics model in its pathogenesis (2). Considering the crucial role of lncRNAs in regulation of histone modifications as well as epigenetic DNA alterations (12), lncRNAs are anticipated to participate in RCC pathogenesis as well. In addition, several lncRNAs have been shown to modulate expression of genes implicated in cancer related pathways such as *VHL/HIF*, *PI3K/AKT* and *mTOR* pathways which implies their role in RCC pathogenesis. Some other lncRNAs participate in EMT process which supports their role in metastasis. Among lncRNAs with putative role in RCC, *MALAT-1* function in RCC pathogenesis has been elucidated. Its expression is induced by c-Fos downstream of the VHL pathway and it interacts with Polycomb protein EZH2 to trigger EMT (50). Such data has been provided by functional studies in RCC cell lines. More recently, the advent of high throughput technologies such as next generation sequencing has facilitated assessment of lncRNA expression in all cancer types such as RCC. For instance, integrative analysis of RNA-sequencing profiles of primary ccRCC samples has shown association of certain lncRNA subclasses with clinicopathological and genomic characteristics of RCC (55). Such studies would facilitate lncRNA classification with the aim of recognizing tumor course and patients' outcome.

The results of *in vitro* studies as well as the limited data obtained from *in vivo* studies have provided the hope for direct targeting of oncogenic lncRNAs as a therapeutic modality for cancer. The most applied method up to now has been antisense technologies. Catalytic nucleic acids (CNAs) such as ribozymes and DNAzymes have also been suggested as tools for down-regulation of lncRNAs (50). In addition, inhibition of lncRNA interactions with their protein partners has been proposed as an alternative strategy (50). Future studies are needed to evaluate the effects of these modalities in cell lines experiments as well as animal models.

7. CONCLUSION

In conclusion, lncRNAs have been shown to be implicated in the pathogenesis of RCC in a way similar to other malignancies. This potentiates them as targets of new treatment modalities. In addition, they exert regulatory roles in well-defined pathways RCC tumorigenesis which makes them appropriate biomarkers for this malignancy.

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AUTHORS CONTRIBUTION

Mohammad Taheri contributed in electronic search and designed figures and table. Mir Davood Omrani and Soudeh Ghafouri-Fard designed the research and supervised it. Soudeh Ghafouri-Fard wrote the manuscript.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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