Long Non-coding RNAs as Regulators of the Mitogen-activated Protein Kinase (MAPK) Pathway in Cancer

Dlouhé nekódující molekuly RNA jako regulátory mitogenem aktivované proteinkinázové dráhy (MAPK) v nádorech

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Summary

Background: The mitogen-activated protein kinase (MAPK) pathway contributes to regulation of many cellular functions, such as cell proliferation and differentiation, mobility and apoptosis. Extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK)/p38 and ERK5 construct the three main modules in this pathway. The Raf-ERK1/2 and JNK cascades contribute in cell proliferation, migration, and survival and are principal regulators of malignant phenotype. This pathway is itself regulated by several outside signals as well as lateral signals from other pathways, which construct a complex network. Long non-coding RNAs (lncRNAs) as principal modulators of gene expression at transcriptional and post-transcriptional levels also regulate this pathway. In addition, lncRNA signature can be used as biomarker and target of novel treatment strategies in cancer patients. ***Aim:*** To explore the role of lncRNAs in regulation of MAPK pathway. ***Conclusion:*** Considering the role of this pathway in the pathogenesis of several cancers, alterations in lncRNA expression lead to changes in MAPK pathway resulting in inhibition of apoptosis and induction of cell proliferation and migration. Moreover, some lncRNAs participate in cross-talk between MAPK and other cancer-related pathways, such as PI3K/Akt pathway through regulation of certain shared proteins between these pathways. Based on the availability of certain anticancer drugs that modulate this pathway, identification of lncRNAs that affect this pathway would help in establishment of effective therapies.

Key words

RNA – long noncoding – mitogen-activated protein kinases – signal transduction

Souhrn

Úvod: Mitogenem aktivovaná proteinkinázová dráha (MAPK) přispívá k regulaci mnoha buněčných funkcí, jako je proliferace a diferenciace buněk, mobilita a apoptóza. Extracelulární signálně regulovaná kináza 1/2 (ERK1/2), c-Jun N-terminální kináza (JNK)/p38 a ERK5 jsou tři hlavní moduly v této dráze. Kaskády Raf-ERK1/2 a JNK přispívají k proliferaci buněk, migraci a přežití a jsou hlavními regulátory maligního fenotypu. Tato dráha je sama regulována několika vnějšími signály, stejně jako bočními signály z jiných signálních drah, které vytvářejí komplexní síť. Dlouhé nekódující RNA (lncRNA) jako hlavní modulátory genové exprese na transkripční a posttranskripční úrovni a také regulují tuto dráhu. Kromě toho můžou lncRNA sloužit jako biomarker a cíl nových léčebných strategií u pacientů s nádory. ***Cíl:*** Prozkoumat roli lncRNA v regulaci dráhy MAPK. ***Závěr:*** Vzhledem k úloze této dráhy v patogenezi několika typů nádorů dochází ke změnám exprese lncRNA, které vedou ke změnám v dráze MAPK, což vede k inhibici apoptózy a indukci buněčné proliferace a migrace. Některé lncRNA se navíc podílejí na spojení mezi MAPK a jinými drahami souvisejícími s nádory, jako je dráha PI3K/Akt prostřednictvím regulace určitých sdílených proteinů mezi těmito drahami. Na základě dostupnosti některých protinádorových léčiv, modulujících tuto dráhu, by identifikace lncRNA, ovlivňující tuto dráhu pomohla při vytváření účinných terapií.

Klíčová slova

RNA – dlouhé nekódování – mitogenem aktivované proteinové kinázy – signální transdukce

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Introduction

The mitogen-activated protein kinase (MAPK) pathway contributes to a wide range of cellular functions, such as cell proliferation and differentiation, mobility and apoptosis. Several lines of evidence suggest that this pathway does not work as a linear signaling pathway that directly conveys certain signals to a definite cellular response. Instead, several outside signals as well as lateral signals from other pathways contribute to construction of a complex network through which MAPK pathway operates [1]. Abnormal regulation of this pathway participates in the pathogenesis of several malignancies [2]. Extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK)/p38 and ERK5 construct the three main modules in this pathway [2]. The Raf-ERK1/2 and JNK cascades contribute to cell proliferation, migration, and survival and are principal regulators of malignant phenotype [3].

Among putative regulators of this pathway are long non-coding RNAs (lncRNAs). LncRNAs make a high proportion of human transcripts, which are not translated to proteins [4,5]. With sizes more than 200 base pairs, they regulate expression of protein coding genes a well as microRNAs (miRNAs) [6]. Subsequently, they affect telomere biology, chromatin dynamics, genome structure organization [7], DNA repair [8] and tissue homeostasis [9]. They also participate in tumorigenesis process via different mechanisms, such as transcription repression [10], induction of epithelial-mesenchymal transition (EMT) [11], inhibition of tumor suppressors expression [12,13], over-expression of certain oncogenes [14,15], regulation of tumor-associated signaling pathways [16] as well as modulation of tumor microenvironment [17]. Recently, a handful of lncRNAs have been shown to regulate the MAPK pathway through modulation of the expression of different proteins within this pathway. We discuss specific roles of these lncRNAs in the following sections. Special site of their action in the MAPK pathway has been demonstrated in Fig. 1. In addition, their characteristics, such as their genomic location and their expression pattern in cancers have been summarized in Tab. 1.

Antisense RNA in the INK4 locus (*ANRIL*)

Aberrant expression of *ANRIL* has been detected in a variety of cancers including glioma in which its expression has been associated with tumor grade and patients survival. In vitro studies have shown that *ANRIL* silencing results in suppression of cell proliferation as well as induction of cell cycle arrest and apoptosis in glioma cells by modulation of expression of ERK, JNK and p38 from MAPK signaling pathway [18].

BMP/OP-Responsive Gene (*BORG*)

The expression levels of this lncRNA have been associated with invasive and metastatic potential of breast tumors. Its role in breast cancer pathogenesis is exerted through binding with Tripartite Motif Containing 28 (TRIM28) protein and subsequent enhancement of its localization and transcriptional repressive activity. *BORG*-expressing breast cancer cells attain metastatic

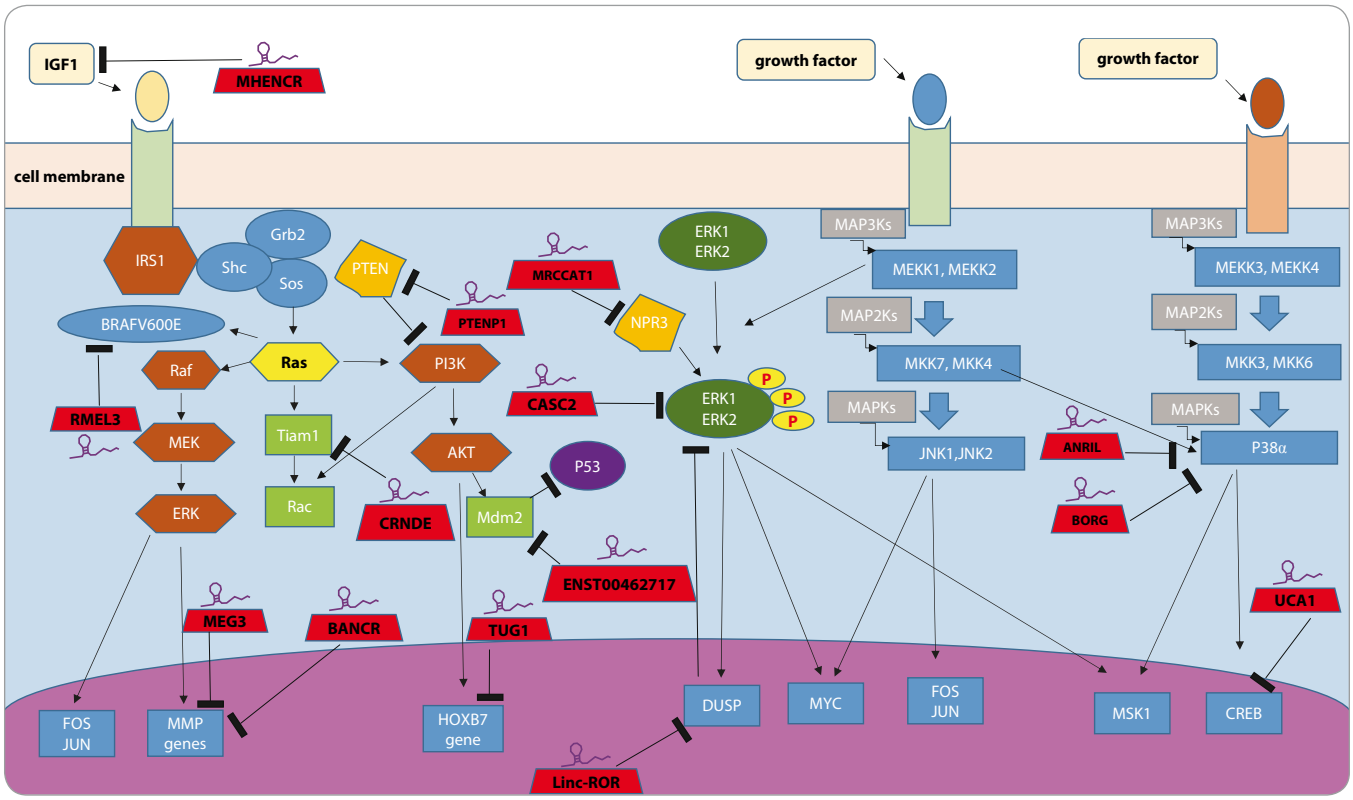

Fig. 1. Schema of mitogen-activated protein kinase (MAPK) pathway with several proteins involved in it. Long non-coding RNAs (demonstrated in red terapeziuses) regulate this pathway at several points.

Tab. 1. Detailed characteristics of long non-coding RNAs that regulate MAPK pathway.

LncRNAs	Location	Expression pattern	Cancer	Role
UCA1	19p13.12	up	bladder	regulation of expression and phosphorylation of AKT and CREB
Linc-ROR	18q21.31	up	breast	decreasing the stability of negative regulator of ERK (phosphatase DUSP7)
PTENP1	9p21	down	breast	regulation of the expression of PTEN, inhibition of cell proliferation and growth, cell cycle and migration
CYTOR	2p11.2	up	breast	cell proliferation, cell migration, cytoskeletal organization
BORG	-	up	breast	regulation of p38 MAPK activity
CRNDE	16q12.2	up	colorectal	regulation of Tiam1, GRB2 and RIN1 expression
BANCR	9q21	up	endometria	regulation of cancer cell proliferation andinvasion by regulating MMP2 and MMP1
MALAT1	11q13.1	up	gallbladder carcinoma, neuroblastoma	regulation of proliferation and metastasis, growth rate and invasion
CASC2	10q26.11	down	gastric	regulation of proliferation via ERK1/2 and JNK inactivation
ANRIL	9p21.3	up	glioma	regulation of proliferation via p38, ERK1/2 and JNK activation
MALAT1	11q13.1	down	glioblastoma	regulation of phosphorylated ERK1/2 levels
HULC	6p24.3	up	glioma	important role in angiogenesis and tumor aggravation
MALAT1	11q13.1	up	several cancers	regulation of cell proliferation and invasion by changing MMP2 expression
CASC2	10q26.11	down	hepatocellular carcinoma	regulation of cell proliferation, migration, invasion and apoptosis via p38, ERK1/2 and JNK activation
Igf2as	11p15.5	up	hepatocellular carcinoma	regulation of cell proliferation, apoptosis and invasion
BANCR	9q21	up	melanoma	regulation of cell proliferation and migration via ERK1/2 and JNK activation
RMEL3		up	melanoma	increase cell survival and proliferation
LncRNA-LET		down	nasopharyngeal carcinoma	induction of cell cycle arrest in G0/G1 phase by phosphorylation of ERK1/2
TUG1	22q12.2	down	non-small cell lung cancer	control of cell proliferation through control of HOXB7
MEG3	14q32.2	down	breast	regulation of cell proliferation, invasion, and angiogenesis by downregulating PCNA, MMP-9 and VEGFA
MHENCR	20q13.33	up	melanoma	regulation of cell proliferation, cell cycle arrest, apoptosis and migration by bounding to miR-425 and miR-489, upregulation of their target genes IGF1 and SPIN1 expression
MRCCAT1	5q15	up	clear cell renal cell carcinoma	regulation of metastasis, proliferation and migration via inhibiting NPR3 by recruiting PRC2 to NPR3 promoter
ENST00462717		down	glioma	regulation of cell proliferation, survival and migration by inhibiting MDM2
AWPPH		up	hepatocellular carcinoma	regulation of YBX1-mediated activation of SNAIL1 translation
URHC	2q31	up	hepatocellular carcinoma	regulation of proliferation and apoptosis via ZAK
lncARSR		up	hepatocellular carcinoma	regulation of drug response via decreasing PTEN expression
CCHE1	10q21.1	up	hepatocellular carcinoma	regulation of cell growth and apoptosis
CCAT1	8q24.21	up	medulloblastoma	regulation of cell proliferation and metastasis

characteristics through inhibition of p38 MAPK activity and enhancement of ERK1/2 function. This *BORG*-mediated alteration in MAPK function was TRIM28 dependent as demonstrated by high p38 MAPK : ERK1/2 activity ratios in TRIM28 silenced cells [19].

BRAF-activated non-coding RNA (*BANCR*)

Elevated expression of *BANCR* has been detected in human malignant melanoma cell lines and tissues. *BANCR* silencing has suppressed proliferation of tumor cells and inhibited MAPK pathway through down-regulation of ERK1/2 and JNK [3]. In addition, *BANCR* silencing in endometrial cancer cells inhibited their proliferation and arrested the cell cycle at G0/G1. *BANCR* anti-apoptotic role is possibly exerted through up-regulation of Cyclin D1 and Bcl-2. Besides, *BANCR* activates ERK/MAPK pathway and then induces expression of matrix metalloproteinases 1 and 2 (MMP1 and MMP2) in endometrial cancer cells leading to enhancement in proliferation, migration, and invasion of these cells [20]. In colorectal cancer (CRC) and lung cancer, *BANCR* activates mitogen-activated protein kinase (MEK)/ERK and JNK/MAPK pathways, resp. [21,22].

Cancer susceptibility candidate 2 (*CASC2*)

Its role as a tumor suppressor gene was first demonstrated in endometrial cancer in which its down-regulation has been detected [23,24]. Subsequently, its down-regulation has been confirmed in glioma and renal cell carcinoma tissues and cell lines where *CASC2* exerts its tumor suppressive role through down-regulation of miR-21 [25,26]. In lung cancer, its down-regulation was significantly correlated with advanced tumor, node and metastasis (TNM) stage and tumor size indicating its role as an independent predictor for overall survival (OS) of these patients [27]. Furthermore, lower expression of this lncRNA in CRC patients was associated with advanced TNM stage. *In vitro* studies have shown that it functions as a competing endogenous RNA (ceRNA) for miR-18 leading to up-regulation of expression of PIAS3 and STAT3 downstream genes and subsequent suppression of CRC cell proliferation [28]. More recently, its aberrant expression has been demonstrated in hepatocellular carcinoma (HCC) and gastric cancer where it has been shown to exert its role via inhibition of MAPK pathway [29,30]. In *CASC2* overexpressed CRC cells, phosphorylation of ERK and JNK was decreased showing the role of *CASC2* in inhibition of the MAPK pathway [29].

Colon cancer-associated transcript-1 (*CCAT1*)

The expression levels of *CCAT1* increase in a variety of tumors including medulloblastoma. Its silencing has remarkably suppressed cell proliferation, induced cell cycle arrest in medulloblastoma cells and decreased phosphorylated levels of MAPK, ERK and MEK. So the oncogenic roles of *CCAT1* in medulloblastoma is possibly exerted via regulating the MAPK pathway [31].

Colorectal neoplasia differentially expressed (*CRNDE*)

The elevated expression of this lncRNA has been detected in colorectal adenomas and cancers compared with normal colon epithelia [32]. In addition, high plasma levels of a certain splice variant of *CRNDE* is a putative plasma biomarker for CRC with a sensitivity of 87% and specificity of 93% [32]. Up-regulation of this lncRNA has been demonstrated in lymphocytic leukemias as well as various solid tumors [33]. Notably, in addition to anti-apoptotic effects, *CRNDE* has a role in enhancement of proliferation, migration and invasion of glioma stem cells [34]. Its over-expression has been associated with poor patients' outcome in ovarian cancer [35] and CRC patients [36]. More recently, over-expression of this lncRNA has been demonstrated in a large cohort of CRC patients with remarkable associations between its high expression and advanced cancer stages as well as poor prognosis [37]. Notably, the mRNA expression profile of *CRNDE*-knocked out CRC cells shows its regulatory function on the Ras and MAPK pathways. In addition, many of *CRNDE*-induced Ras/MAPK signaling genes participate in CRC development [37].

Cytoskeleton regulator RNA (*CYTOR*)

This intergenic lncRNA has a crucial role in cell proliferation, cell migration, and cytoskeletal organization. Its expression has been increased in all subtypes of breast cancer as well as a variety of other malignancies including thyroid, stomach, lung, renal, and liver cancers. Using an innovative method based on the recognition of correlations between the expression of lncRNA and protein-coding genes which participate in certain functions, *CYTOR* has been shown to be associated with the epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR), and MAPK pathways [38].

Insulin-like growth factor 2 antisense 1 (*Igf2as*)

The expression of this lncRNA has been increased in HCC cells and tissues. Its silencing inhibited cell proliferation and migration and induced apoptosis through inactivation of ERK/MAPK signaling pathway [39].

LincRNA regulator of reprogramming (*linc-RoR*)

This lncRNA was initially recognized to alter reprogramming of induced pluripotent stem cells [40]. Subsequently, it has been demonstrated to act as a miRNA sponge which changes the expression of the principal transcription factors in human embryonic stem cells [41]. Besides, it both inhibits p53 translation [42] and enhances c-Myc expression through interaction with heterogeneous nuclear ribonucleoprotein I (hnRNP I) [43]. While in triple negative breast cancer, linc-RoR increases cell invasion via miR-145/ARF6 pathway [44], in estrogen receptor positive breast tumors it activates MAPK/ERK pathway through diminishing the stability of dual specificity phosphatase 7 (DUSP7) which down-regulates ERK [45].

LncRNA-AWPPH

This lncRNA has been firstly identified as an over-expressed lncRNA in HCC

whose expression was correlated with invasion, advanced TNM stage as well as poor recurrence-free and OS. *In vitro* studies have shown its interaction with Y-Box Binding Protein 1 (YBX1) which leads to up-regulation of SNAIL1 and PIK3CA expressions and activation of the PI3K/AKT pathway [46].

Lnc00462717

In glioma tissues, its low expression was associated with the malignant status. *In vitro* studies have shown its suppressive effect on glioma cell proliferation, survival and migration, which is possibly due to its negative effect on MDM2 expression. In addition, it has a regulatory role on MAPK pathway through decreasing the phosphorylation of p38, ERK1/2, and JNK [47].

LncRNA-low expression in tumor (*LET*)

It is a tumor suppressor lncRNA, which is down-regulated in a variety of malignancies including nasopharyngeal carcinoma (NPC). *In vitro* studies have demonstrated its role in regulation of cell proliferation, adhesion and invasion of NPC through modulation of MAPK/ERK pathway genes. p-ERK1/2 and p-MEK were considerably down-regulated in LET over-expressed cells with no change in total-ERK1/2 and total-MEK levels. So *LET* inhibits the cell growth and invasion of NPC cells via suppression of ERK signaling pathway [48].

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*)

This lncRNA has been known as an oncogene associated with metastasis potential of several cancers. *MALAT1* enhances cancer cell migration and the EMT by modulation of the expression of several genes [49]. *MALAT1* silencing in gall bladder cancer (GBC) cell lines has led to suppression of the proliferation and metastasis of these cell in addition to down-regulation of the expression of phosphorylated MEK1/2, ERK 1/2, MAPK, and JNK 1/2/3 leading to inhibition of MAPK pathway [50]. Moreover, knockout of *MALAT1* in lung cancer cells has resulted in down-regulation of numerous metastasis related genes including Glypican 6 (GPC6) and C-X-C motif chemokine 5 (CXCL5) [51] both of which participate in regulation of MAPK pathway [52,53]. Notably, *MALAT1* has been one of the most considerably up-regulated lncRNAs during neuroblastoma-derived Neuro-2a (N2a) cell differentiation whose silencing has impaired neurite outgrowth and induced cell death possibly via inactivation of MAPK signaling pathway as well as aberrant activation of Peroxisome proliferator-activated receptor (PPAR) and P53 signaling pathway [54].

Metastatic renal cell carcinoma--associated transcript 1 (*MRCCAT1*)

This lncRNA is over-expressed in metastatic clear cell renal cell carcinoma (ccRCC) tissues. Its expression is associated with the metastatic phenotype of these cells as well as patients' outcome. *MRCCAT1* inhibits Natriuretic Peptide Receptor 3 (NPR3) transcription by recruiting polycomb repressive complex 2 (PRC2) to NPR3 promoter leading to activation of p38-MAPK signaling pathway. Forced over-expression of this lncRNA has resulted in elevation of phosphorylated p38 levels while the phosphorylation levels of ERK and JNK have not been altered [55].

Maternally expressed gene 3 (*MEG3*)

This imprinted gene is expressed in a variety of normal tissues [56]. On the other hand, its expression has been decreased or lost in several tumors including glioma [57], meningiomas [58], hepatoma [59], gastric cancer [60] and breast cancer [61]. Its tumor suppressive effects have been demonstrated by several *in vitro* studies [57,60]. In breast cancer cells, it has a fundamental role in regulation of cell proliferation and invasion as well as expression of angiogenesis-related factors which is at least partially exerted through AKT signaling pathway [61].

Melanoma highly expressed noncoding RNA (*MHENCR*)

Its expression has been increased in melanoma tissues and metastatic melanoma in association with poor survival of melanoma patients. Its silencing has resulted in inhibition of cells proliferation and migration as well as enhancement of cell cycle arrest and apoptosis. It acts as a ceRNA for miR-425 and miR-489 leading to over-expression of their target genes *IGF1* and *SPIN1* and subsequent activation of PI3K-Akt pathway [62]. Considering the role of miR-489 in regulation of MAPK signaling [63], *MHENCR* might be involved in regulation of this pathway as well.

PTEN pseudogene-1 (PTENP1)

Its over-expression in MCF7 breast cancer cells has resulted in inhibition of cell proliferation and migration as well as down-regulation of cyclin A2, CDK2, p-AKT, p-p44/42 MAPK and p-p38 MAPK, so this lncRNA can impede the proliferation and migration of breast cancer cells through modulation of AKT and MAPK signaling pathways [64].

RMEL3 (ENSG00000250961)

Elevated expression of *RMEL3* in melanoma is significantly linked with the existence of $BRAF^{V600E}$ mutation. Its knock-down has considerably decreased colony formation in melanoma cell lines that harbor this mutation. Its expression levels have been correlated with the expression of several MAPK and PI3K pathways genes. Besides, its silencing has diminished expression of pAKT and BRAF in addition to several activators or effectors of MAPK and PI3K pathways such as FGF2, FGF3, DUSP6, ITGB3 and GNG2. Consequently, both *in silico* analysis and experimental data confirmed its role in MAPK and PI3K signaling [65].

Taurine-upregulated gene 1 (*TUG1*)

This lncRNA has a role in regulation of gene expression through engagement of PRC2. Its down-regulation has been demonstrated in a variety of cancers including non-small cell lung carcinoma (NSCLC) tissues in which its down-expression has been associated with higher TNM stage and tumor size, as well as poor patients' outcome. It has been shown to be a direct transcriptional target of p53 whose silencing leads to enhancement of cell proliferation and

up-regulation of homeobox B7 (HOXB7) expression. As the levels of p-ERK, p-AKT and p-GSK3b were increased following *TUG1* silencing, it has been hypothesized that *TUG1* contributes in AKT/MAPK pathway through modulation of HOXB7 expression [66].

Urothelial carcinoma associated 1 (*UCA1*)

This lncRNA has an oncogenic role in human bladder cancer pathogenesis. Its silencing has resulted in down-regulation of p300 (encoded by EP300) and its coactivator cAMP response element-binding protein (CREB). In addition, UCA1 modulates AKT activity and cell cycle progression through CREB [67]. CREB is also been phosphorylated through activation of MAPK-interacting kinase (MNK) in MAPK cascade [68].

Up-regulated in hepatocellular carcinoma (*URHC*)

Up-regulation of this lncRNA in HCC cell lines has been demonstrated through using lncRNA microarray. In addition, its over-expression in HCC tissues has been correlated with poor OS. *In vitro* studies have shown its role in modulation of cell proliferation and apoptosis through down-regulation of leucine zipper containing kinase AZK (ZAK). ERK, JNK and p38 kinase phosphorylation has been altered in *URHC* knocked-down cells, which implies that the role of *URHC* in modulation of cell growth and apoptosis might be exerted through inactivation of the MAPK signaling pathway. Consequently, *URHC* regulates cell proliferation and apoptosis via ERK/MAPK inhibition by targeting ZAK [69].

Discussion

Recent studies have demonstrated that lncRNA signature can be used as biomarker and target of novel treatment strategies in cancer patients [70,71]. LncRNAs participate in principal cancer-related processes, such as cell proliferation, cell migration, and EMT through the modulation of important signaling pathways including mTOR and MAPK pathways [38]. A comprehensive genome-wide transcriptional investigation of lncRNA signature in breast cancer samples has led to identification of lncRNA specific profile in breast cancer subtypes. Of note, among the nine lncRNAs that constitute the luminal B signature, one chief lncRNA category was linked to the MAPK pathway [38]. Considering the prominent role of MAPK pathway in the pathogenesis of melanoma and existence of MAPK targeting therapeutic modalities in melanoma [72], expression analysis of MAPK-related lncRNAs in this kind of cancer is of special significance.

LncRNAs regulatory roles in fundamental cellular pathways are exerted through modulation of gene expression at the transcriptional or posttranscriptional level. Some of their functions have been elaborated, while others need to be clarified. For instance, the regulatory role of *CRNDE* in regulation of MAPK pathway in CRC [37] and in the maintenance of glioma stem cells [34] have been demonstrated. Considering the role of MAPK in glioma stem cells [73], future studies are needed to elucidate the functional link between the MAPK pathway, *CRNDE* and stem cell maintenance in glioma. Besides, consistent with the existence of a complex interaction network between lncRNAs, miRNAs and protein coding genes especially in the context of cancer, *CASC2* has been shown to exert its tumor suppressive role via modulation of both miRNAs and protein coding genes including those located in MAPK pathway [25,26,29]. Additionally, as revealed by independent studies, a certain lncRNA might regulate expression of different pathways in distinct types of cancers. For instance, while *MALAT1* activates MAPK pathway in GBC [50], it induces the phosphoinositide 3-kinase (PI3K/Akt) pathway in osteosarcoma cells without any significant alteration in MAPK pathway in these cells [74].

Notably, *lncRNA-AWPPH* and *UCA1* possibly participate in cross-talk between MAPK and PI3K/Akt pathways through regulation of certain shared proteins between these pathways. Previous reports have demonstrated that these two signaling pathways interact with each other at multiple levels. However, as revealed by both *in silico* and experimental studies, such interactions are context-dependent [75] which is in line with the proposed background-reliant role of lncRNAs in regulation of these pathways.

Considering the advent of pathway-based therapeutic modalities for cancer especially in the context of precision medicine [76], expression analysis of lncRNAs that modulate certain cancer related pathways is of clinical importance. Future studies are needed to elaborate function of lncRNAs in these pathways in each cancer type.

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