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Mini-Review:

Role of cytoplasmic lncRNAs in regulating cancer signaling pathways*

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Abstract: Cancer remains a serious healthcare problem despite significant improvements in early detection and treatment approaches in the past few decades. Novel biomarkers for diagnosis and therapeutic strategies are urgently needed. In recent years, long noncoding RNAs (lncRNAs) have been reported to be aberrantly expressed in tumors and show crosstalk with key cancer-related signaling pathways. In this review, we summarized the current progress of research on cytoplasmic lncRNAs and their roles in regulating cancer signaling and tumor progression, further characterization of which may lead to effective approaches for cancer prevention and therapy.

Key words: Long noncoding RNA (lncRNA); Cancer signaling; Cancer therapy; Biomarker
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1 Introduction

Long noncoding RNAs (lncRNAs) are noncoding RNAs with transcript lengths over 200 nucleotides (Gibb et al., 2011; Ma et al., 2018). LncRNAs are involved in various human diseases, including inflammatory pathologies, neurological diseases, and various types of cancers (Ponting et al., 2009; Tano and Akimitsu, 2012; Zheng et al., 2017; Guo et al., 2018; Sang et al., 2018). Moreover, they are abnormally expressed in tumors and play regulatory roles in cell physiological processes, including cell proliferation, migration, metastasis, and invasion in cancers (Lin et al., 2014a, 2017; Xing et al., 2014). Signaling pathways regulate a variety of cellular biological processes, which determine the traits of an organism (Gutschner and Diederichs, 2012; Zheng et al., 2017; Ma et al., 2018; Sang et al., 2018). In addition, it has been reported that almost all tumors exhibit dysfunctional signaling pathways (Pawson and Warner, 2007). Aberrant activation of signaling pathways, including that of phosphoinositide 3-kinase (PI3K)/serine-threonine-protein kinase (AKT) (Lin et al., 2014a, 2014b), Wnt (Angers and Moon, 2009), Notch (Ntziachristos et al., 2014), and Hippo/YAP (Li et al., 2017), contributes to cancer cell proliferation, activation of angiogenesis, invasion, and metastasis.

Increasing evidence has shown that lncRNAs are located in the cytosol and are involved in multiple signaling pathways (Prensner and Chinnaiyan, 2011; Cheetham et al., 2013). The crosstalk between the signaling pathways and lncRNAs greatly impacts disease progression (Wang et al., 2015; Lin et al., 2017; Yan et al., 2017). There are many well-characterized lncRNAs that remodel signal transduction by various approaches, ranging from modulating components of signaling pathways to regulating

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the expression of targeted genes (Gutschner and Diederichs, 2012; Yang et al., 2014; Liu et al., 2015). The regulatory roles of lncRNAs enable them to function as oncogenes or tumor-suppressor genes, regulating cancer signaling pathways positively or negatively, respectively, and thus, affecting disease progression. In this review, we provide an overview of the regulatory functions of lncRNAs in cancer signal transduction, and provide insights into the mechanisms by which these lncRNAs-associated pathways regulate tumor progression. Further exploration of the lncRNA-based signaling pathways will provide us an in-depth understanding of the molecular mechanism underlying various diseases and lay the foundation for development of new targeted therapeutic intervention for these diseases.

2 LncRNAs-associated cancer signaling pathways

LncRNAs have been reported to be dysregulated in many types of cancers during tumor initiation, development, and progression (Batista and Chang, 2013; Atala, 2014; Sang et al., 2018). However, understanding the function of individual lncRNAs in tumorigenesis remains challenging. Recently, we have elucidated a novel lncRNA-mediated signaling pathway in breast cancer metastasis. It indicated that lncRNA *BCAR4* contributes to breast cancer metastasis via chemokine-induced binding of *BCAR4* to two transcription factors having extended regulatory consequences. Moreover, *BCAR4* wires up Hippo and Hedgehog signaling to reprogram glucose metabolism (Xing et al., 2014; Zheng et al., 2017). Besides, plasma lipid-associated lncRNA has been shown to regulate normoxic hypoxia-inducible factor 1α (HIF-1α) stabilization (Lin et al., 2016, 2017). These studies highlighted a crucial role of lncRNAs in cancer-related signaling pathways.

2.1 PI3K/AKT signaling pathway

The PI3K/AKT signaling pathway regulates many cellular processes, such as cell proliferation, survival, and migration (Luo et al., 2003; Mayer and Arteaga, 2016). This pathway is activated abnormally in many human malignancies, including breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, and endometrial cancer (Vivanco and Sawyers, 2002; Altomare and Testa, 2005; Hirai et al., 2010). Interaction between phosphatidylinositol-3,4,5-trisphosphate (PIP3) and pleckstrin homology (PH) domain facilitates AKT phosphorylation at Ser473 and Thr308 by phosphoinositide-dependent protein kinase-1 (PDK1) and mammalian target of rapamycin (mTOR), respectively (Manning and Cantley, 2007). The phosphorylated AKT is activated, which further activates its downstream substrates, thereby regulating tumor growth and metastasis (Citri and Yarden, 2006). Long intergenic noncoding RNA for kinase activation (*LINK-A*) has been found to be highly expressed in breast cancer, and is associated with prognosis in breast cancer patients. It has been found that *LINK-A* interacts with PIP3 (Lin et al., 2017). Although RNAs have been hypothesized to play essential roles during the origin of life, the role of RNAs in direct mediation of fundamental cellular processes remains largely unknown. Mechanistically, *LINK-A* directly promotes interactions between the plasma membrane phospholipid PtdIns(3,4,5)P_3 and AKT PH domain to facilitate the activation of AKT. *LINK-A*-dependent AKT hyperphosphorylation further activates its downstream substrates, resulting in tumor cell resistance to AKT inhibitors, and promoting tumorigenesis and metastasis. The deletion of the *LINK-A*-PIP3 binding motif renders breast cancer cells sensitive to AKT inhibitors. This PIP3-binding lncRNA regulates AKT activation with broad clinical significance. This study suggested an RNA molecule as a key mediator and catalyst involved in signal transduction, as well as a mediator of the related biological processes through direct association with lipids (Lin et al., 2017).

Further study also revealed gene amplification and a genetic variant (rs12095274: A>G) of *LINK-A* that significantly affects AKT activation and the outcome of breast cancer patients (Lin et al., 2017). In further single nucleotide polymorphism (SNP) analysis, GG and AA genotypes were marked as homozygotes, and the AG genotype was marked as heterozygote. Analysis of 923 breast cancer samples showed that *LINK-A* was highly expressed in individuals with GG genotype, who also showed significantly higher breast cancer incidence and poorer survival time than individuals with AA genotype. Moreover, the SNP at this location showed different distribution in African, European, and Asian populations, suggesting that this

lncRNA may have a role in physiology and pathology of human cancers. In light of the current lack of functional genetic association of lncRNAs with cancer, this study links an lncRNA-associated SNP to the regulation of AKT and its downstream oncogenic signaling.

2.2 HIF-1α signaling pathway

HIFs are transcription factors that control energy, iron metabolism, erythropoiesis, and development, which are activated under hypoxic or pseudohypoxic conditions, and mediate adaptive responses of cells against these states (Pawson and Warner, 2007; Kaelin and Ratcliffe, 2008). HIFs consist of a stably expressed β-subunit and an oxygen-sensitive α-subunit, and is classified into three types: HIF-1α, HIF-2α, and HIF-3α (Kaelin and Ratcliffe, 2008; Keith et al., 2011). HIF-1α is expressed in all types of cells, and is significantly upregulated in most human cancers (Talks et al., 2000). The expression of HIF-1α is significantly upregulated during malignancies. High level of HIF-1α promotes the transcription of genes involved in glucose and glutamine metabolism, and promotes angiogenesis and glycolysis (Denko, 2008), which contributes to tumor proliferation and progress (Zhong et al., 1999; Kuschel et al., 2012). In addition, HIF-1α functionally interacts with many other signal transduction and transcription systems, including the NOTCH, WNT, and MYC pathways (Kaelin and Ratcliffe, 2008). It has been reported that lncRNA *LINK-A* could promote triple-negative breast cancer (TNBC) tumorigenesis by regulating the HIF-1α-associated signaling pathway (Miah et al., 2012; Schwab et al., 2012). Mechanically, heparin-binding epidermal growth factor (HB-EGF)-mediated stimulation of EGF receptor (EGFR) and its consequent heterodimerization with the receptor glycoprotein nonmetastatic melanoma protein B (GPNMB) lead to the recruitment of a complex composed of *LINK-A*, breast tumor kinase (BRK), and leucine-rich repeat kinase 2 (LRRK2). *LINK-A*, a key signaling molecule, modifies the conformation of BRK and scaffolds LRRK2 kinases, which phosphorylates HIF-1α to promote its stabilization and transcriptional activity under normoxic conditions. This study revealed a novel HIF-1α regulatory mechanism functional under normoxic conditions, divergent from the classical view held in the field of cancer biology for decades (Lin et al., 2016). This lncRNA-driven machinery highlights the magnitude and diversity of cytoplasmic lncRNAs in signal transduction. Clinically, monoclonal antibodies, small molecule inhibitors, and locked nucleic acids (LNAs) that target GPNMB, BRK, *LINK-A*, HIF-1α, and LRRK2 could all serve as promising therapeutic targets for TNBC treatment. The expression level of *LINK-A*, as well as the phosphorylation status of EGFR, GPNMB, BRK, and HIF-1α, could be considered as promising prognostic markers of TNBC patients, which would be of therapeutic significance.

2.3 Hippo signaling pathway

Over the past few decades, the Hippo pathway has been established as a tumor suppressor pathway because it restricts proliferation and induces apoptosis (Pan, 2010; Zhao et al., 2010; Halder and Johnson, 2011; Zhou et al., 2015). Dysregulation of the Hippo pathway is associated with a broad spectrum of cancers (Pan, 2010; Harvey et al., 2013; Yu et al., 2015). YAP has been identified as an oncoprotein associated with breast cancer (Overholtzer et al., 2006) and is highly expressed in human breast cancer samples (Dong et al., 2007; Zhou et al., 2015). Loss of YAP suppresses oncogene-induced tumor growth in mouse mammary glands (Chen et al., 2014). In addition, YAP promotes breast cancer cell survival and mobility (Wang et al., 2012; Haskins et al., 2014; Salah et al., 2014; Song et al., 2015). Similar to an earlier study (Overholtzer et al., 2006), YAP overexpression in non-transformed mammary epithelial cells (i.e. MCF10A) led to epithelial-to-mesenchymal transition, suppression of apoptosis, growth factor-independent proliferation, and anchorage-independent growth (Wang et al., 2011, 2012). Moreover, in vivo studies have also revealed the abilities of YAP (or its analog TAZ) in promoting human breast cancer metastasis, maintaining self-renewal and tumor-initiation capacities of breast cancer stem cells (Lian et al., 2010; Cordenonsi et al., 2011; Chen et al., 2012; Beyer et al., 2013). These findings not only revealed the critical roles of the Hippo-YAP pathway in human breast cancer development and progression, but, more importantly, also proposed YAP as a therapeutic target for breast cancer treatment. However, the detailed mechanisms beyond the restriction of cell proliferation and survival are yet to be fully understood, which

could be explained by the lack of well-defined cellular functions of the downstream effector YAP. A previous study indicated that lncRNA *MAYA* mediated methylation and upstream kinase activity of MST1/2 in Hippo signaling, which consequently led to failure of LATS1 phosphorylation and activation of YAP1 target genes (Li et al., 2017). A recent study also uncovered an lncRNA *BCAR4* as a direct transcriptional target of YAP, which is involved in the YAP-dependent glycolysis. Mechanistically, long-term-activated YAP upregulated the transcription of *BCAR4*, which, in turn, promoted the transcription of two glycolysis-related enzymes HK2 and PFKFB3, through Hedgehog effector GLI2/p300 complex-mediated histone acetylation marked by H3K27ac. Intriguingly, targeting the YAP-*BCAR4*/Hedgehog-HK2/PFKFB3 axis using *BCAR4* antisense-LNA or inhibitors of HK2 and PFKFB3 dramatically suppressed the YAP-dependent glycolysis and YAP-induced cell proliferation and tumorigenesis. Pathologically, the expression level of *BCAR4* is positively correlated to YAP in breast cancer patient samples, in which low expression of both *BCAR4* and YAP favors the recurrence-free survival rate of breast cancer patients. This study revealed that lncRNA *BCAR4* is an essential downstream mediator of the Hippo-YAP pathway, involved in reprogramming glucose metabolism, which will potentially transform the prevailing dogma of cancer signaling and metabolism. Moreover, the identification of a new YAP-*BCAR4*/Hedgehog-glycolysis signaling axis in breast cancer also provides additional therapeutic targets for breast cancer patients.

3 Conclusions and perspective

There have been a number of studies reporting that dysregulation of lncRNAs and related signaling pathways are tightly associated with tumor cells or immune cells (Table 1). These lncRNAs could be considered as biomarkers for diagnosis and prognosis (Wapinski and Chang, 2011; Ling et al., 2013). For example, *lnc-DC* has been indicated to bind to STAT3 in the cytoplasm and prevent its dephosphorylation by SHP1, serving as an indicator for development of dendritic cells (DCs) (Wang et al., 2014). LncRNA *NKILA* regulates IκB kinase (IKK)-induced inhibitor of NF-κB (IκB) phosphorylation and nuclear factor-κB (NF-κB) activation, indicating its essential roles in

Table 1 Cytoplasmic lncRNAs in cancer signaling pathways

Gene	Main distribution	Related signaling pathway	Mechanism	Reference
LINK-A	Triple-negative breast tumor	HIF-1α	Mediates HB-EGF triggered, EGFR: GPNMB heterodimer-dependent HIF-1α phosphorylation, leading to HIF-1α stabilization and activation of HIF-1α transcriptional programs	Lin et al., 2016
		PI3K/AKT	Contributes to the AKT-PIP3 interaction and enhances EGF-induced AKT kinase activity	Lin et al., 2017
MAYA	Majority of human solid tumors	Hippo-YAP	HER3-LLGL2-*MAYA*-NSUN6 complex methylates MST1 to activate YAP and target genes	Li et al., 2017
Lnc-DC	Dendritic cells	STAT3	Promotes STAT3 phosphorylation	Zhong et al., 1999
NKILA	Normal breast epithelia or non-invasive breast tumors	NF-κB	Inhibits IKK-induced IκB phosphorylation to restrain NF-κB activity	Liu et al., 2015
ACOD1	Most of the cells and organs	GOT2 metabolic pathway	Binds the metabolic enzyme GOT2 and enhances its catalytic activity	Wang et al., 2017
Lnc-Lsm3b	Immune cells and organs	IFN I	Binds to RIG-I and inhibits its activation to terminate type I IFN production	Jiang et al., 2018

HIF-1α: hypoxia-inducible factor 1α; HB-EGF: heparin-binding epidermal growth factor; EGFR: EGF receptor; GPNMB: glycoprotein nonmetastatic melanoma protein B; PI3K: phosphoinositide 3-kinase; AKT: serine-threonine-protein kinase; STAT3: signal transducers and activators of transcription 3; NF-κB: nuclear factor-κB; IκB: inhibitor of NF-κB; IKK: IκB kinase; GOT2: glutamate-oxaloacetate transaminase 2; IFN: interferon; RIG-I: retinoic acid-inducible gene I

cancer metastasis (Liu et al., 2015). *H19* interacts with p53 and induces p53 inactivation, and its up-regulation promotes gastric cancer (GC) cell proliferation and GC tumor progression, suggesting that *H19* status in tumors may be a useful tool for detecting prognosis of a patient suffering from GC (Hadji et al., 2016).

The incidence and mortality of cancers, including lung cancer and breast cancer, have increased significantly recently and are expected to continue to rise in the coming decades. Thus, it will be extremely urgent to develop techniques for early diagnosis for efficient cancer treatment. Recently, lncRNAs, which are contributing to human pathogenesis, have attracted increased attention. LncRNAs have rapidly emerged as crucial regulators that interact with signaling pathways and control many cellular processes. The aberrant expression of lncRNAs has been shown to promote tumor progression in various types of cancers, including breast, liver, and kidney cancers, highlighting their therapeutic potential.

LncRNAs could interact with signaling molecules, and activate signaling pathways influencing tumor initiation and progression (Wang et al., 2014; Liu et al., 2015; Lin et al., 2016, 2017; Li et al., 2017; Zheng et al., 2017). The aberrant expression of lncRNAs in tumors and the related cancer signaling pathways have greatly impacted tumorigenesis in multiple types of cancers. Therefore, a better understanding of the function and molecular mechanism of lncRNAs will help us in not only identifying useful biomarkers for the diagnosis but also developing effective therapeutic targets for cancer treatment.

Contributors

Pei-fen FU, Xin ZHENG, and Xiao FAN wrote and edited the manuscript. Ai-fu LIN edited and checked the final version. All authors read and approved the final manuscript.

Compliance with ethics guidelines

Pei-fen FU, Xin ZHENG, Xiao FAN, and Ai-fu LIN declare that they have no conflict of interest.

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中文概要

题　目：细胞质 lncRNAs 与肿瘤信号调控

概　要：恶性肿瘤疾病长期作为危害人类健康的重要隐患，目前针对重要信号调控通路的一系列靶向抑制剂在临床后期业已出现耐药现象，迫切要求人们在肿瘤生物学研究和靶向治疗方向不断寻找新的可替代性靶点。长链非编码 RNAs（lncRNAs）作为最新关注的研究热点，其在肿瘤发生和转移中的重要调节功能不断被我们及相关学者重点报道。随着 RNA 通量深度测序等相关研究技术的推广和发展，使人们得以饱览赏析 lncRNAs 作为健康和疾病重要调节因子的宏观图谱。本综述总结了胞质 lncRNAs 在调节肿瘤重要信号通路中的研究进展及其在肿瘤发生发展中的作用，为癌症的预前预后和靶向治疗提供帮助。

关键词：长链非编码RNAs（lncRNAs）；信号转导；肿瘤标志物；肿瘤靶点

Introducing editorial board member:

Dr. Ai-fu LIN, Professor of College of Life Sciences, Zhejiang University, is a Scholar of Thousand Youth Talents-China, Scholar of Thousand Talents-Zhejiang, and Scholar of Hundred Talents-Zhejiang University. His research interests include: (1) dissecting and targeting the lncRNA-based cancer therapies for cancer treatment; (2) defining the novel regulators involved in cancer progression and stem cell development.

Dr. Ai-fu LIN dedicates his effort to perform research on lncRNAs, a new and expanding area of research that adds complexity as well as greater depth in understanding the processes of breast cancer development, metastasis, and the reprogramming of cancer metabolism (*Cell*, 2014; *Nature Cell Biology*, 2016; *Nature Cell Biology*, 2017; *The EMBO Journal*, 2017; *Cancer Letters*, 2018). Dr. Ai-fu LIN also focuses on exploring the mTOR-associated signaling pathways in cancer metabolism and stem cell maintenance (*Oncogene*, 2013; *Cancer Research*, 2014; *Nature Cell Biology*, 2016). These works represent exciting biomedical research approaches that acknowledge the importance of the study of lncRNA in cancer-related signaling, and also provide valuable clues to future therapies that could impact the treatment of many related diseases.