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The expanding roles of long non-coding RNAs in the regulation of cancer stem cells

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a novel class of gene regulators playing multifaceted roles in physiological processes as well as pathological conditions such as cancer. Cancer stem cells (CSCs) are a small subset of tumor cells that constitute the origin and development of various malignant tumors. CSCs have been identified in a wide spectrum of human tumors and could act as a critical link underlying the processes of tumor metastasis and recurrence. Mounting evidence indicates that lncRNAs are aberrantly expressed in diverse CSCs and regulate CSC properties at different molecular levels. Here, we very briefly summarize the recent findings on the potential roles of lncRNAs in regulating various functions of CSCs, and elaborate on how can lncRNAs impact CSC properties via interacting with other macromolecules at the epigenetic, transcriptional, and post-transcriptional levels. This mini-review also highlights the understanding of the modular regulatory principles of lncRNA interactions in CSCs.

1. Introduction

Long non-coding RNAs (lncRNAs) are longer than 200 nucleotides and have no potential to code proteins, with poor conservation across species (Morris and Mattick, 2014). Current studies indicate that lncRNAs play versatile roles in various cellular processes via interacting with different molecules including DNA, RNA, and protein. Growing evidence indicates that lncRNAs manipulate epigenetic modification, transcriptional regulation, and post-transcriptional regulation in the eukaryotic genome (Marchese et al., 2017). During the latest decade, accumulating research indicates that lncRNAs play an expanding role in physiologic and pathologic processes including cancer cell biology (Chew et al., 2018; Li et al., 2018a; Liu et al., 2018). To date, numerous studies have discovered that dysregulation of lncRNAs plays vital roles in tumorigenesis and metastasis by regulating cancer stem cells.

Cancer stem cells (CSCs), also known as tumor-initiating cells or CSC-like cells, possess exclusive properties of self-renewal and the ability to differentiate into heterogeneous lineages of cancer cells (Clarke et al., 2006; Visvader and Lindeman, 2012). CSCs play critical roles in the initiation, progression, metastasis, recurrence, and drug resistance of malignant tumors (Amaya and Bryan, 2015). Therefore, it is extremely valuable to understand the biology of CSCs to improve diagnosis and therapeutics in various ailments (Rosen and Jordan, 2009). Here we summarize recent findings that highlight the expanding role of lncRNAs in CSC biology. We also characterize the functions and mechanisms of lncRNAs interacting with different molecules in CSCs.

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Furthermore, we examine how lncRNAs contribute to CSC properties and could be utilized for assessing cancer progression and metastasis.

2. LncRNAs are a novel class of gene regulators in cancer stem cells

With the advent of next-generation sequencing, massive RNA transcripts have been identified with similar properties to mRNAs in a variety of tissues. LncRNAs are a class of linear transcripts and function as versatile molecules that regulate diverse biological processes via nucleotide base pairing or specific structures generated by RNA folding. To date, lncRNAs function mainly as a signal, decoy, guide, and scaffold for their interacting partners, such as DNA, RNA or proteins (Liu et al., 2017; Wang and Chang, 2011). Uncovering the roles of lncRNAs has revealed and established a new scheme of diagnostic and therapeutic opportunities in human diseases.

Under normal cases, lncRNAs are widely expressed in all humans and could be related to maintaining cellular function (Jiang et al., 2016). Similar to protein-coding cancer genes, an increasing number of lncRNAs have been found to be targets of cancer signaling pathways. However, most lncRNAs are dysregulated and highly tissue-specific, with more versatile modes of action than mRNA genes in malignant tumors (Iyer et al., 2015). Current studies indicate that the dysregulation of lncRNAs is associated with the initiation and progression of diverse tumors, including liver cancer, breast cancer, lung cancer, gastric cancer, and colon cancer (Huarte, 2015; Schmitt and Chang, 2016). Recent research has demonstrated that certain dysregulated lncRNAs in malignant tumors associate with a variety of CSC characteristics. For example, a well-known lncRNA termed HOTAIR, is significantly upregulated and promotes CSC properties in breast and colon CSCs (Deng et al., 2017; Padua Alves et al., 2013). Therefore, a better understanding of lncRNA regulation of CSCs will provide novel targets for the development of effective therapeutic and prognostic strategies in malignant tumors.

3. The role of lncRNAs at the epigenetic and transcriptional level in CSCs

3.1. Chromatin modification and regulation

An accumulation of findings has indicated that lncRNAs regulate gene expression as epigenetic modifiers in CSCs via interacting with chromatin remodeling complexes. In colon CSC asymmetric division, lnc34a promotes self-renewal and tumorigenesis by epigenetically silencing miR-34a expression via recruiting PHB2/Dnmt3a and histone deacetylase inhibitor 1 (HDAC1) to methylate and deacetylate the promoter (Fig. 1A) (Wang et al., 2016a). Similarly, lncCAMTA1 facilitates proliferation and CSC-like properties via inhibiting tumor suppressor CAMTA1 by altering the chromatin structure at its promoter (Ding et al., 2016). LncRNA CUDR promotes another lncRNA HULC or β-catenin dysregulation via restraining HULC promoter methylation, and thereby acting as a positive potential role to govern malignant differentiation in human liver stem cells (Gui et al., 2015). lnc-β-Catm maintains CSC self-renewal and tumor propagation by facilitating the stability of β-catenin. Therefore, lnc-β-Catm acts as a scaffold for activation of Wnt/β-catenin signaling by regulating β-catenin methylation, which then suppresses the ubiquitination of β-catenin (Zhu et al., 2016a). Studies identifying additional lncRNA partners of epigenetic modification will broaden our understanding of CSCs to enable therapeutic interventions.

3.2. Transcriptional activators or repressors

lncRNAs have also been confirmed as a novel group of transcriptional activators or repressors in a wide range of malignant tumors. As mentioned above, CUDR functions not only as an epigenetic modifier but also has an oncogenic effect to promote the proliferation of liver CSCs and malignant transformation by activating c-Myc and TERT via interacting with Cyclin D1 and forming a transcriptional complex at the promoters of c-Myc and H19 (Pu et al., 2015). In human glioma stem cells (GSCs), decreasing the expression of HOTAIR inhibits their proliferation, invasion, and tumorigenicity, and activates the expression of tumor suppressor PDCD4 by repressing the recruitment of EZH2 and LSD1 (Fang et al., 2016). Conversely, increasing HOTAIR expression contributes to epithelial mesenchymal transition (EMT) and to the development of lung CSCs induced by cigarette smoke extract, which establishes a novel modulation for cigarette smoke extract-induced lung carcinogenesis (Liu et al., 2015). HOTAIR promotes tumorigenesis via repressing SETD2 in liver CSCs and reducing the recruitment of the CREB/P300/RNA polII complex to the SETD2 promoter (Li et al., 2015). In liver tumor-initiating cells (TICs), lncSox4 facilitates liver TIC self-renewal by activating Sox4 expression by acting as a scaffold for recruiting Stat3 to the Sox4 promoter (Fig. 1B) (Chen et al., 2016). Another similar study has indicated that lncTCF7 activates TCF7 gene transcription and maintains liver CSC self-renewal by recruiting the SWI/SNF complex to the TCF7 promoter (Wang et al., 2015). LncBRM interacts with BRM to activate YAP1 signaling, thereby promoting self-renewal of liver CSCs and initiating tumor propagation (Zhu et al., 2016b).

Recent research has indicated lncGata6 promotes tumor initiation and progression in colorectal CSCs. LncGata6 interacts with Bptf and recruits the NURF complex to activate Ehf transcription, which forms the lncGATA6-Bptf-Ehf axis to initiate Lgr4/5 expression and activate the Wnt signaling pathway (Zhu et al., 2018). Recent research demonstrates that lncRNA is also a key transcriptional repressor of liver CSCs. lnc-DILC suppressed liver CSC expansion via competitively binding the IL-6 promoter and suppressing IL-6 transcription to block NF-κB mediated transcription, thereby inhibiting autocrine IL-6/STAT3

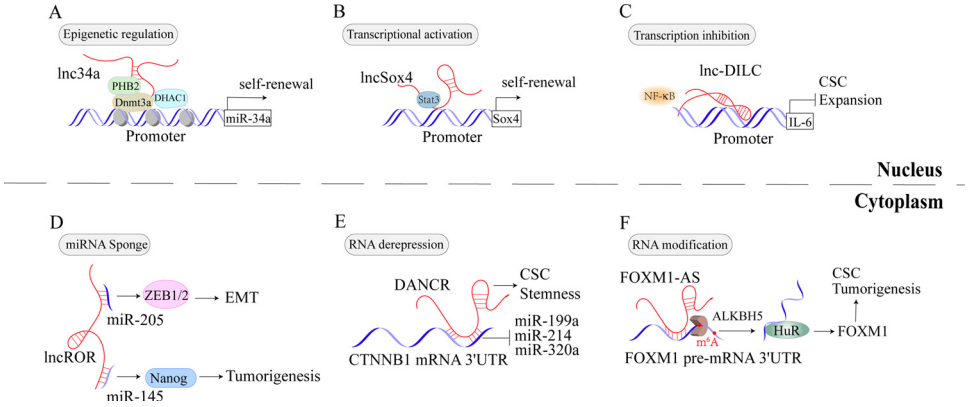

Fig. 1. lncRNAs regulate CSC properties at different molecular levels. Currently, lncRNAs interact with their molecules through a multitude of mechanisms in epigenetic and transcriptional (up) and post-transcriptional regulation (down). Specifically, lncRNAs function as epigenetic modifiers (A), transcriptional regulators (B. C), and post-transcriptional regulators (D. E. F) in various CSCs. lncRNAs display versatile roles in gene regulation of CSCs via RNA-protein (e.g., Lnc34a and lncSox4) or RNA-DNA (e.g., lnc-DILC) and RNA-RNA (e.g., lncROR and DANCR) interactions.

signaling (Fig. 1C) (Wang et al., 2016b). Taken together, mounting studies demonstrate that lncRNAs manipulate a transcriptional switch through interacting with CSC related molecules.

4. The role of lncRNA at the post-transcriptional level in CSCs

4.1. Interactions with miRNAs and mRNAs

Interestingly, lncRNAs function as a miRNA sponge to sustain the expression of stemness related transcription factors and proteins through binding to miRNAs, while miRNAs negatively regulate expression of these proteins. To date, studies have indicated that lncRNAs act as miRNA sponges and RNA binding partners to affect CSC fate (Huang et al., 2013, 2017).

Recent research has uncovered that the lncRNA–miRNA–mRNA regulatory circuitry can modulate post-transcriptional gene expression in breast and glioma CSCs. LncRNA H19, let-7, and LIN28 form a dual-feedback loop, promoting breast CSC clonogenicity, migration, and mammosphere-forming ability (Peng et al., 2017). Another tumor suppressive lncRNA, GAS5, acts as a sponge for miR-196a-5p to rescue FOXO1 generation, thus promoting PID1 and MIIP expression in GSCs. Furthermore, FOXO1 facilitates GAS5 transcription, forming a positive feedback loop to suppress malignancy of human GSCs (Zhao et al., 2017).

Studies have also indicated that an increasing number of lncRNAs are associated with stem cell properties of CSCs. lncRNA ROR is up-regulated in most tumor tissues and acts as a sponge for many miRNAs to modulate EMT, stemness, tumorigenesis, and metastasis. ROR acts as a competitive endogenous RNA (ceRNA) by sponging the let-7 family and miR-145 to promote stem cell properties in pancreatic CSCs (Fig. 1D) (Fu et al., 2017; Gao et al., 2016). Another study found that ROR functions as a miRNA sponge to regulate the EMT program by blocking degradation of mir-205 targets (ZEB1/ZEB2) in breast cancer tumorigenesis and metastasis (Fig. 1D) (Hou et al., 2014). RoR functions as a miR-145 sponge to decrease miR-145-induced tumor sphere differentiation in endometrial CSCs. In a similar mechanism to ROR, NEAT1 and CRNDE are abundantly expressed and upregulated in GSCs, promoting GSC proliferation, migration, and invasion by absorbing let-7e and miR-186 (Gong et al., 2016; Zheng et al., 2015). LncRNA Sox2ot functions as a ceRNA to promote EMT with the miR-200 family in pancreatic ductal adenocarcinoma by absorbing miR-194-5p and miR-122 in GSCs (Li et al., 2018b; Su et al., 2017). In addition, lncRNA TUG1 facilitates self-renewal by sponging miR-145 and recruiting polycomb via YY1-binding activity to inhibit the expression of differentiation genes (Katsushima et al., 2016). Taken together, lncRNAs act as ceRNAs to compete with stemness-related genes by binding to these molecules with miRNA sponges.

Although numerous studies have focused on a ceRNA mechanism by which lncRNAs sponge miRNAs to manipulate stem cell properties in the cytoplasm, recent studies have identified that lncRNAs exert their effects via binding to messenger RNAs. As an example, a novel miRNA-blocking lncRNA, DANCR, can interact with CTNNB1 mRNA and significantly promote stemness features of hepatocellular carcinoma cells. Mechanistically, DANCR competitively binds to the 3′UTR of CTNNB1 to block the repressing effect of microRNAs (miR-214, miR-320a, and miR-199a) on CTNNB1 (Fig. 1E) (Yuan et al., 2016). This study uncovered a novel mechanism of CSC properties involving lncRNAs, messenger RNAs, and miRNAs.

4.2. RNA and protein modifications

LncRNAs have also been recognized as novel post-translational modifiers that may influence many aspects of CSCs. The lncRNA PVT1 is located with the well-known oncogene c-Myc. The stability of MYC protein modulated by phosphorylation is regulated by PVT1 (Tseng et al., 2014). LncRNA-hPVT1 facilitates cell proliferation and cell cycling by stabilizing NOP2 protein, thereby contributing to stem cell-like properties of hepatocellular carcinoma (Wang et al., 2014). An X-inactive specific transcript lncRNA (termed Xist) could be used to predict tumor response to treatment with the HDACi abexinostat; thus, suggesting modulation of histone acetylation could alter the breast CSC proportion (Salvador et al., 2013). Additionally, a feed-forward loop between lncRNA and YAP activity was uncovered in TICs. lncARSR-YAP interaction facilitates the viability of renal TICs, preventing the phosphorylation of YAP by LATS1 and facilitating YAP nuclear translocation (Qu et al., 2016). Taken together, studies have indicated that lncRNAs exert functional roles in the generation and regulation of CSCs by regulating the modification of stemness-related molecules.

Non-coding RNAs are emerging as fundamental regulators of RNA modification and post-transcriptional regulation. Increasing modifications have been identified in different cellular processes; N6-methyladenosine (m6A) is the most abundant RNA modification on mammalian lncRNA and mRNA (Chen et al., 2017). Recently, the m6A modification has been identified in many CSCs. FOXM1-AS can also promote the interaction of ALKBH5 with FOXM1 nascent transcripts to maintain glioblastoma stem-like cell tumorigenesis (Fig. 1F) (Zhang et al., 2017). Mechanistically, the m6A demethylation activity of ALKBH5 critically impacts mRNA nuclear export. While the functional investigation of lncRNAs has shed light on protein post-translational modifications, many intriguing questions remain regarding how lncRNAs are interfering with the RNA modifications of massive tumor molecules.

5. Concluding remarks

LncRNAs, lacking significant protein-coding capacity, can regulate a wide range of biological processes through diverse molecular mechanisms. An increasing number of studies has indicated that dysregulation of lncRNAs alters gene expression via a broad spectrum of mechanisms, including chromatin modification, transcriptional and post-transcriptional regulation of CSCs (Table 1). Currently, research regarding the impact of lncRNAs on CSCs has mainly concentrated on familiar molecules. In epigenetic and transcriptional regulation, the role of lncRNA interacting molecules has mainly concentrated on chromatin modification factors and transcription factors, such as EZH2, SUZ12, TP53, and MYC. In post-transcriptional regulation, numerous studies have focused on a ceRNA mechanism through which lncRNAs can regulate miRNAs-mediated cellular processes by sponging up miRNAs in most CSCs. In summary, we have briefly emphasized here

Table 1
Examples of lncRNAs interacting with various molecules in CSCs.

Category	Examples	Interaction Class	Functions	Reference
lncRNA:chromatin regulators	CUDR: H3K27me3	DNA-protein	malignant transformation	Gui et al. (2015)
lncRNA:TFs	LncSox4: Stat3	RNA-protein	TIC self-renewal and tumor initiation,	Chen et al. (2016)
lncRNA:RNA binding protein	lncBRM: BRM	RNA-protein	activate YAP1 signaling, promoting self-renewal of CSCs	Zhu et al. (2016b)
lncRNA:promoter region	lnc-DILC: IL-6	RNA-DNA	Decrease IL-6 transcription, inhibit CSC expansion	Wang et al. (2016b)
lncRNA:miRNA	ROR: miR-205	RNA-RNA	EMT, tumor progression, and metastasis	Hou et al. (2014)
lncRNA:mRNA	DANCR: CTNNB1	RNA-RNA	increase stemness features	Yuan et al. (2016)

TFs: transcription factors, TIC: tumor-initiating cell.

the multifaceted roles of lncRNAs in CSCs. With the discovery of potential molecular mechanisms for modulating lncRNAs in CSCs as well as other stem cells, lncRNA-based therapies could become promising curative treatments for numerous cancers.

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