Cancer Letters 419 (2018) 203–209

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Long non-coding RNAs in glioma progression

Jiajie Xi, Qiaoyi Sun, Li Ma, Jiuhong Kang*

Clinical and Translational Research Center of Shanghai First Maternity and Infant Health Hospital, Shanghai Key Laboratory of Signaling and Disease Research, School of Life Science and Technology, Tongji University, 1239 Siping Road, Shanghai, 200092, PR China

ARTICLE INFO

Article history:
Received 17 October 2017
Received in revised form
7 January 2018
Accepted 10 January 2018

Keywords:
Glioma
LncRNA
Diagnostic biomarker
Therapeutic target

ABSTRACT

Glioma is one of most malignant primary tumors of the brain. However, due to a lack of effective means for diagnosing and treating glioma, the prognosis of glioma patients remains poor. Therefore, understanding the molecular mechanism of glioma progression is essential for effective treatment. Long non-coding RNAs (lncRNAs) are novel regulators of gene expression at the transcriptional, post-transcriptional and epigenetic levels. Recent evidence indicates that lncRNAs may play important roles in regulating the progression of glioma. In this article, we review the expression profile of lncRNAs in glioma and discuss the functions and known mechanisms of several representative lncRNAs in detail, as well as the prospects of lncRNAs as diagnostic and prognostic biomarkers and therapeutic targets.

1. Introduction

Glioma is the most common malignant tumor of the central nervous system. Based upon cellular origin, gliomas may be sub-classified into astrocytomas, oligodendrogliomas, ependymomas, and mixed tumors (e.g., oligoastrocytomas) [1]. The World Health Organization (WHO) has divided gliomas into four grades within each subtype. Grades I and II are typically considered low-grade gliomas, while grade III and IV tumors are considered high-grade gliomas. Glioblastoma multiform (GBM, grade IV astrocytoma) is the most malignant tumor type, with a median survival time of only 12–14 months after initial diagnosis [2]. A better understanding of the precise molecular mechanisms of glioma pathogenesis could lead to improved glioma treatments.

LncRNAs are transcripts of more than 200 nucleotides without a functional protein-coding ability. Recent studies have shown that lncRNAs play key roles in a wide range of cellular physiological processes by regulating gene expression at the transcriptional, post-transcriptional and epigenetic levels [3,4]. LncRNAs may be classified into five archetypes based on their mode of action and functions in cells. 1) Signals. As lncRNA transcription responds to diverse stimuli, including combinations of transcription factors and signaling pathways during biological processes, lncRNA expression could reflect the regulation of gene sets in space and time and serve as markers of functionally significant biological events [5]. 2) Molecular decoys. LncRNAs may act as molecular decoys that bind and titrate effector proteins away from a specific location to inhibit effector proteins from executing their functions [6]. 3) Molecular guides. LncRNAs can serve as molecular guides to direct the localization of ribonucleoprotein complexes to specific targets sites on chromatin. The regulatory functions of lncRNAs in gene expression could occur either in cis (on neighboring genes) or in trans (distantly located genes) [7,8]. 4) Scaffolds. LncRNAs can serve as central platforms for protein complex assembly by binding distinct effector molecules. LncRNAs possess distinct protein-binding domains for binding multiple effector components, which may have transcriptional activating or repressing activity, together in both time and space to regulate gene transcription or repression [9]. 5) Competing endogenous RNAs (ceRNAs). Increasing experimental evidence shows that lncRNAs may be potent natural microRNA (miRNA) sponges. LncRNAs containing binding sites for a miRNA de-repress miRNA target genes though complementary binding to miRNAs [10].

Dysregulated lncRNA expression could potentially alter basic cell biological processes and contribute to tumorigenesis [11,12]. Recent evidence indicates that lncRNAs play important roles in glioma pathogenesis. In this review, we explore the expression profile, functions, and known mechanisms of lncRNAs in glioma, as well as their potential for use as diagnostic and prognostic biomarkers and therapeutic targets.

* Corresponding author.
E-mail address: jhkang@tongji.edu.cn (J. Kang).

https://doi.org/10.1016/j.canlet.2018.01.041
0304-3835/

2. LncRNA expression profiles in glioma

As dysregulated lncRNA expression may affect gene regulation in the pathogenesis and development of glioma, the gene expression profiles of lncRNAs in glioma have been widely analyzed. Han et al. compared the lncRNA and mRNA expression profiles of glioblastoma and normal brain tissues. They identified 654 lncRNAs that were up-regulated and 654 lncRNAs that were down-regulated in the GBM group. They also found 104 matched lncRNA-mRNA pairs for 91 differentially expressed lncRNAs and 84 differentially expressed genes. Furthermore, *ASLNC22381* and *ASLNC2081* were predicted by lncRNA gene network analysis to target growth factor-related *IGF-1* genes that play roles in the regulation of glioma signaling pathways [13]. Zhang et al. analyzed a series of previously published gene expression profiles for glioma from the Gene Expression Omnibus (GEO) and determined the associations of the lncRNA expression signatures with the different glioma grades and histological subtypes. They identified 129 lncRNAs that were differentially expressed between glioma and non-tumor brain tissues [14]. Murat et al. found 81 lncRNAs (37 up-regulated and 44 down-regulated) differentially expressed in glioma [15,16]. Grzmil et al. found 147 differentially expressed lncRNAs by analyzing the gene profiles of 30 glioma samples [16,17]. Li et al. compared the expression of lncRNAs and mRNAs in GBM versus normal brain tissues and found that 398 lncRNAs and 1995 mRNAs were distinctively expressed in GBM. Among these lncRNAs, 98 lncRNAs were involved in 30 pathways and 32 gene functions related to tumorigenesis, development, and metastasis [18].

The expression pattern of lncRNAs also exhibits a significant association with glioma malignancy grade. Zhang et al. identified 10 lncRNAs that were closely associated with the astrocytoma malignancy scale by comparing the expression profiles of normal and high-grade tumors. Among these lncRNAs, *CRNDE* and *HOTAIRM1* were up-regulated with ascending malignancy grades, while *PAR5*, *MEG3*, *C21orf131*, and others were similarly down-regulated [14]. Wang et al. screened a four-lncRNA signature (*AGAP2-AS1*, *TPT1-AS1*, *LINC01198* and *MIR155HG*) in anaplastic glioma patients and found that the anaplastic gliomas could be divided into grade II-like and grade IV-like groups based on the expression level of these four lncRNAs: the expression levels of *AGAP2-AS1*, *LINC01198* and *MIR155HG* increased with tumor grade, while that of *TPT1-AS1* decreased [19]. These findings suggest that lncRNA dysregulation plays an important role in gliomagenesis.

3. The functions of several representative lncRNAs in glioma

To provide an exhaustive description of the molecular mechanisms and potential functions of the lncRNAs in the pathogenesis and development of glioma, several representative lncRNAs will be discussed in the following sections (Table 1).

3.1. HOTAIR

HOTAIR, which arises from transcription of the antisense strand of the *HOXC* gene, flanked by *HOXC12* and *HOXC11* in chromosome 12, regulates chromatin dynamics and induces transcriptional gene silencing by interacting with polycomb repressive complex 2 (PRC2) and LSD1 [20,21]. *HOTAIR* also serves as a platform for ubiquitin-mediated protein degradation. *HOTAIR* helps in assembling both E3 ubiquitin ligases and their substrates, acts as a platform for ATAXIN-1 ubiquitination by interacting with the E3 ubiquitin ligase DZIP3, and facilitates the ubiquitination of SNURPORTIN-1 by MEX3b [22]. A recent study has shown that *HOTAIR* acts as a ceRNA for *miRNA-130a* to regulate the proliferation and invasion of endometrial carcinoma cells and interacts with *miR-331-3p* in regulating tumorigenesis [23].

HOTAIR has been characterized as a negative prognostic factor in breast and colon cancer patients [20,24]. *HOTAIR* was found to be up-regulated in glioma and preferentially expressed in the classical and mesenchymal subtypes compared with the neural and proneural subtypes. *HOTAIR* expression is closely associated with glioma grade and poor prognosis [25]. As such, *HOTAIR* primarily serves as a prognostic factor for glioma patient survival, as well as a biomarker for identifying glioma molecular subtypes [26]. *HOTAIR* also serves as a critical regulator of cell cycle progression and positively regulates a cell cycle-related mRNA network in glioma [27]. *HOTAIR* down-regulation inhibits cell proliferation, promotes cell apoptosis, and suppresses cell invasion and migration in glioma progression. *HOTAIR* might regulate cell cycle progression through EZH2, the predominant PRC2 complex component, as overexpression of the PRC2-binding domain of *HOTAIR* (5′ domain), but not of the LSD1-binding domain of *HOTAIR* (3′ domain), accelerates cell cycle progression [28]. *HOTAIR* can increase the density of histone 3 lysine 27 trimethylation on the promoter of *PDCD4* to promote the proliferation and invasion of glioma cells [29].

Bromodomain and extraterminal (BET) domain proteins are epigenetic modulators that have been identified as up-regulated in GBM and are known to regulate GBM cell proliferation. BET bromodomain inhibitors reduce GBM progression. *HOTAIR* has been reported to mediate the effect of BET proteins on regulating GBM cell proliferation. The BET protein BRD4 directly binds to the promoter of *HOTAIR* to regulate its expression. The treatment of GBM cells with a BET protein inhibitor reduced the *HOTAIR* expression level, and *HOTAIR* overexpression could abrogate the anti-proliferative activity of the BET protein inhibitor. As *HOTAIR* could modulate the expression of the cyclin-dependent kinase inhibitor p21/Cip1, the anti-proliferative activity of the BET protein inhibitor may occur via the induction of p21/Cip1 by reducing *HOTAIR*. Therefore, *HOTAIR* may account for much of the antitumor effect of BET bromodomain inhibitors [30].

Moreover, *HOTAIR* plays an important role in glioma initiation and malignant progression by interacting with miRNAs. *HOTAIR* is a target of *miR-326*, and the knockdown of *HOTAIR* can be used to evaluate the expression level of *miR-326*. Further studies have shown that *miR-326* plays a glioma-suppressive role by down-regulating the oncogene FGF1. The PI3K/AKT and MEK1/2 signaling pathways are also involved in this process [31]. As *HOTAIR* is one target of *miR-148b-3p*, the effect of *HOTAIR* on the malignant biological behaviors of glioma cells can be suppressed by *miR-148b-3p* [32]. *HOTAIR* can regulate blood-tumor barrier permeability via binding to *miR-148b-3p*, which further reduces tight junction-related protein expression in glioma-microvascular endothelial cells by targeting *USF1* [33]. *HOTAIR* had been reported to be an endogenous 'sponge' of *miR-141*, thereby regulating the expression of the *miR-141* target gene SKA2. The knockdown of *HOTAIR* could markedly down-regulate the expression levels of SKA2. SKA2 functions to promote glioma cell proliferation and invasion. Either the knockdown of *HOTAIR* or the overexpression of *miR-141* could result in a significant reduction of tumor growth through reduced SKA2 expression [34]. *HOTAIR* can also interact with *miR-125a* to regulate glioma cell proliferation and migration through the mTOR signaling pathway [35]. Collectively, these results suggest that *HOTAIR* may potentiate glioma development in many ways, and the detailed molecular mechanisms of *HOTAIR* regulation remain to be elucidated.

3.2. H19

LncRNA H19, which is located on human chromosome 11p15.5, is transcribed from the imprinted gene complex *IGF2/H19* [36]. *H19* is