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Review

Long non-coding RNAs in glioma: Functional roles and clinical perspectives

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a new class of non-coding gene regulators. But unlike their smaller counterparts, microRNAs, relatively less is known about the roles and functions of lncRNAs. Current evidence suggests that lncRNAs may play important roles in a wide range of biological processes in human cancers, including glioma. By acting as oncogenes or tumor suppressors, lncRNAs may contribute to glioma initiation, progression and other malignant phenotypes. Their expression profiles may also have important clinical implications in glioma subclassification and patients' prognostication. Here, we review current evidence related to the functional roles of lncRNAs in glioma. We will discuss the aberrant lncRNA expression signatures associated with glioma initiation and progression, as well as the potential mechanisms underlying lncRNA dysregulation. We also discuss the functional roles of lncRNAs in glioma biological behavior. Finally, the potentials and prospects of employing lncRNAs as novel biomarkers and therapeutic targets for glioma clinical practice will also be addressed.

1. Introduction

The emerging significance of long non-coding RNAs (lncRNAs) in cancer has attracted considerable interests in recent years (Niland et al., 2012; Prensner and Chinnaiyan, 2011). While initially thought to be spurious transcriptional noise, increasing evidence began to suggest that lncRNAs indeed play critical regulatory roles in the development of many human diseases, including cancer (Gibb et al., 2011; Wapinski and Chang, 2011). Functional studies for a handful of lncRNAs revealed that the latter could regulate gene expressions at transcriptional, post-transcriptional and epigenetic levels (Mercer et al., 2009). Aberrant expressions of lncRNAs may potentially alter basic cellular biological processes and contribute to tumorigenesis (Gibb et al., 2011; Gutschner and Diederichs, 2012). Moreover, differential expressions of specific lncRNAs may correlate with disease processes, staging or other malignant phenotypes, and thus could potentially act as therapeutic targets, as well as biomarkers for diagnosis and prognosis (Qi and Du, 2013; Spizzo et al., 2012; Wahlestedt, 2013). LncRNAs are emerging as new players in cancer biology paradigm.

Gliomas account for the great majority of primary tumors in the brain (Wen and Kesari, 2008). Based on their likely cellular origins, gliomas may broadly be subclassified into astrocytomas, oligodendrogliomas, ependymomas and mixed tumors (e.g. oligoastrocytomas) (Louis et al., 2007). Within each histological subtype, they could be further categorized into grades I–IV lesions based on the degree of malignancy (Louis et al., 2007). The clinical outcomes of glioma patients depend heavily on histopathological features (Wen and Kesari, 2008). The most malignant tumor type, glioblastoma multiform (GBM, grade IV astrocytoma), is almost invariably fatal with an overall survival of just over one year only (Wen and Kesari, 2008). Despite the development of multimodal and aggressive treatments that include surgical resection, local radiotherapy and systemic chemotherapy in the past decades, patient outcomes remain unsatisfactory (Omuro and DeAngelis, 2013; Taylor, 2010). To improve treatment efficacy, a better understanding of glioma pathogenesis at the genetic and molecular levels is urgently needed (Chen et al., 2012; Jansen et al., 2010).

Recent evidence indicates that lncRNAs play important roles in glioma pathogenesis (Bian et al., 2014; Sun et al., 2013). It has been reported that lncRNAs may regulate certain tumorigenic processes in glioma such as cellular proliferation and apoptosis (Wang et al., 2012). Aberrant expressions of lncRNAs may not only reflect clinical phenotypes (Zhang et al., 2012) and patient prognosis (Zhang et al., 2013), but also can be exploited as potential therapeutic targets (Amit et al., 2012). In this review, we summarize the recent

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progress of lncRNA studies in glioma. We will first provide an overview on the dysregulated expressions of lncRNAs associated with glioma initiation and progression, and the potential underlying mechanisms. We will then discuss the functional roles of lncRNAs in regulating glioma biological behavior. Finally, we will discuss the potentials of lncRNAs as biomarkers for glioma diagnosis, prognostication and targeted therapy.

2. Dysregulation of lncRNA expression in glioma

Genome-wide profiling studies have demonstrated that lncRNAs are aberrantly expressed in gliomas as compared with non-tumoral brain tissues. Differential expressions also occur across gliomas with different malignancy grades, suggesting the potential role of lncRNAs in glioma initiation as well as progression. The lncRNA profiling studies in glioma reported so far are summarized in Table 1.

For each study reviewed here, and also in the following sections of this manuscript, the significantly differentially expressed lncRNA genes were defined by using the following consensus criteria: (1) For the lncRNAs that have featured in public journals, we totally followed their cutoff values in the original publication; (2) For the lncRNAs identified by data-mining approach here (detailed below), we used the most commonly used threshold 2-fold as the cutoff; (3) One exception was the cell motility study from Viapiano et al. (2011) (detailed in Section 4.2). We broadened the cutoff to 1.5-fold for this specific study, since there was only one gene identified to be differentially expressed by using the 2-fold threshold. The fold change cutoff adopted for individual study was also clarified where it was mentioned in the following reviewing.

2.1. Dysregulation of lncRNAs in glioma initiation

Using a commercial microarray platform, Han et al. (2012) analyzed lncRNA expression profiles in glioblastoma multiforme (GBM) and normal brain tissues. They identified 1308 lncRNAs (654 up-regulated and 654 down-regulated) that were differentially expressed between tumors and normal brain tissues (fold change $\geqslant$ 4.0). Among these, ASLNC22381 and ASLNC2081 were particularly interesting, since they may potentially target insulin-like growth factor 1 (IGF-1) signaling and contribute to GBM recurrence and malignant progression. Using a microarray-mining approach, our group has previously demonstrated the aberrant lncRNA expression patterns in two large public cohorts of glioma patients profiled on Affymetrix HG-U133 Plus 2.0 array (n = 268 and 157, respectively) (Gravendeel et al., 2009; Sun et al., 2006). We identified 127 lncRNAs that were differentially expressed between gliomas and non-tumoral brain tissues (fold change $\geqslant$ 2.0) (Zhang et al., 2012). Moreover, further hierarchical clustering analysis showed that lncRNA signatures could enable the further subclassification of the cohort. Of these, lncRNA CRNDE and HOTAIRM1 were found to be highly up-regulated in tumors (fold change = 32.0 and 7.6, respectively), while MEG3 was down-regulated (fold change = 6.7).

By using this mining approach (from Affymetrix HG-U133 Plus 2.0 platform), the aberrant expressions of lncRNAs in glioma were also observed in several other independent microarray studies (Table 1). For example, in a study of 80 glioblastoma specimens obtained from patients enrolled in clinical trials, Murat et al. (2008) found a set of 81 differentially expressed lncRNAs (out of 2448 screened). Of these, 37 were up-regulated and 44 were down-regulated in tumors as compared to non-tumoral brain tissues (fold change $\geqslant$ 2.0). Similarly, Grzmil et al. (2011) performed profiling analysis on 30 glioma samples (12 primary GBM, 3 secondary GBM, 8 astrocytomas and 7 oligodendrogliomas) and 5 GBM cell lines (LN018, LN215, LN229, LN319 and BS149). They found that 147 out of 2448 lncRNAs were differentially expressed in tumor tissues when compared with normal brain controls, and 213 lncRNAs were differentially expressed in tumor cell lines when compared with normal astrocytes. Both studies confirmed the overexpressions of CRNDE and HOTAIRM1. These findings suggest that dysregulated lncRNA expression may be an early event during tumorigenesis, and that it may play potentially important roles in glioma initiation.

2.2. Dysregulation of lncRNA in glioma progression

Differential lncRNA expressions in gliomas of different malignancy grades indicate their involvements in glioma progression. By comparing the expression profiles between low-grade and high-grade astrocytic tumors, we have previously identified a set of 45 differentially expressed lncRNAs (Zhang et al., 2012). Among these, there was a subset of 12 lncRNAs which were closely associated with astrocytoma malignancy progression, since their expression levels showed either a step-wise increase or decrease from normal to high-grade tumors. Of these, CRNDE and HOTAIRM1-

Table 1
LncRNA profiling studies in glioma.

Reference	Samples	Comparison group	Datasets GEO accession no.
Profiling studies revealing the dysregulation of lncRNAs in glioma initiation			
Han et al. (2012)	1 tumor sample; 1 control sample	Tumor vs. Control	NA
Gravendeel et al. (2009)	276 tumor samples of all histology; 8 control samples	Tumor vs. control	GSE16011
Sun et al. (2006)	157 tumor samples of all histology; 23 control samples	Tumor vs. control	GSE4290
Murat et al. (2008)	80 GBM samples; 4 control samples	Tumor vs. control	GSE7696
Grzmil et al. (2011)	30 tumor samples; 5 GBM cell lines; 5 controls	Tumor tissue vs. control tissue Tumor cell line vs. control cell line	GSE15824
Profiling studies revealing the dysregulation of lncRNAs in glioma progression			
Gravendeel et al. (2009)	Same to above	LG-AG/Control; HG-AG/LG-AG LG-AG/Control; HG-OG/LG-OG	GSE16011
Sun et al. (2006)	Same to above	LG-AG/Control; HG-AG/LG-AG LG-AG/Control; HG-OG/LG-OG	GSE4290
Vital et al. (2010)	5 LG-AGs; 30 HG-AGs	HG-AG vs. LG-AG	GSE43289
Zhou et al. (2013)	6 LG-AGs; 7 HG-AGs	HG-AG vs. LG-AG	GSE45921

Abbreviations: GEO, gene expression omnibus; LG-AG, low grade astrocytic glioma; HG-AG, high grade astrocytic glioma; LG-OG, low grade oligodendroglial glioma; HG-OG, high grade oligodendroglial glioma.
Note: 1. Profiling studies searching was performed in public GEO database (Dec, 2013).
2. Only the datasets profiled on Affymetrix HG-U133 Plus 2.0 platform were enrolled in our review analysis.
3. With regard to how to process raw Affymetrix HG-U133 Plus 2.0 data and how to mine lncRNA profiles from it, please refer to our previous paper for the details (Zhang et al., 2012).