Gene 575 (2016) 1–8

Contents lists available at ScienceDirect

Gene

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

Review

Hypoxia-regulated lncRNAs in cancer

Ya-Nan Chang, Kun Zhang, Zhi-Mei Hu, Hai-Xia Qi, Zhe-Min Shi, Xiao-Hui Han, Ya-Wei Han, Wei Hong *

Department of Histology and Embryology, School of Basic Medical Sciences, Tianjin Medical University, 300070 Tianjin, China

ARTICLE INFO

Article history:
Received 13 June 2015
Received in revised form 23 August 2015
Accepted 24 August 2015
Available online 2 September 2015

Keywords:
Long non-coding RNA
Hypoxia
Cancer
Mechanism

ABSTRACT

Hypoxic regions are common in solid tumors and have an impact on tumor progression and on the therapeutic response. However, the underlying mechanism for hypoxic tumor microenvironment has not been entirely elucidated. Recently, long noncoding RNAs (lncRNAs) are being increasingly recognized to contribute to carcinogenesis through diverse mechanisms. To date, several lncRNAs have been described in hypoxia-associated cancer process, implying a potential role in maintaining cellular homeostasis and enabling an adaptive survival under hypoxic stress conditions. While it has been widely accepted that a complex cellular network of gene products, such as protein and miRNA, take part in hypoxic cancer progression, it remains largely elusive how lncRNAs participate in it. In this review, we introduce an update view of lncRNAs, focusing on hypoxia-related lncRNAs. We hereby summarize the cause and consequence of hypoxia-modulated lncRNAs in cancer as well as their functional mechanisms, highlighting the specific roles of lncRNAs in hypoxia response in cancer.

Contents

Abbreviations: lncRNAs, long noncoding RNAs; miRNAs, microRNAs; mRNAs, messenger RNAs; siRNA, small interfering RNA; HIF-1, hypoxia-inducible factor-1; linc-RoR, long intergenic noncoding RNA, regulator of reprogramming; NEAT1, Nuclear Enriched Abundant Transcript 1; UCA1, Urothelial cancer associated 1; CUDR, cancer up-regulated drug resistant; HINCUT-1, hypoxia-induced noncoding ultraconserved transcript 1; lncRNA-LET, Long noncoding RNA Low Expression in Tumor; RNA pol 2, RNA polymerase 2; HOTAIR, HOX Antisense Intergenic RNA; MALAT1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; GC, gastric cancer; HCC, Hepatocellular cancer; HNSCC, head and neck squamous cell carcinoma; bHLH, basic helix-loop-helix; VHL, von Hippel–Lindau; HREs, hypoxia response elements; Glut1, glucose transporter 1; ALDA, aldolase A; PGK1, phosphoglycerate kinase 1; OGT, O-linked N-acetylglucosamine transferase; IGF2, insulin-like growth factor 2; DNMT1, DNA methyltransferase 1; HDAC3, Histone deacetylases 3; TET2, the Ten-Eleven-Translocation Protein 2; ceRNAs, competing endogenous RNAs; H3K4me3, trimethylation of lysine4 of histone H3; H3K9me3, trimethylation of lysine9 of histone H3; WT, wild type.

* Corresponding author.

http://dx.doi.org/10.1016/j.gene.2015.08.049
0378-1119/

1. Introduction

Tumor hypoxia was first described in the 1950s by radiation oncologists as a frequent cause of failure to radiotherapy in solid tumors. Today, it is evident that tumor hypoxia is a common feature of many cancers and the master regulator of hypoxia, hypoxia-inducible factor-1 (HIF-1), regulates multiple aspects of tumorigenesis, including angiogenesis, proliferation, metabolism and metastasis. Activation of hypoxia pathways, in particular HIF, is associated with an aggressive tumor phenotype and poor clinical outcome in many types of cancer.

The human transcriptome comprises not only large numbers of protein-coding messenger RNAs (mRNAs), but also a large set of non-protein-coding transcripts that have structural, regulatory, or unknown functions (Wilusz et al. 2009). LncRNAs have been found to be dysregulated in a wide range of human diseases and disorders, including various types of cancer (Qiu et al. 2013), such as hepatocellular carcinoma (Huang et al. 2013), colorectal cancer (Kogo et al. 2011), prostate cancer (Prensner et al. 2011), gastric cancer (Gan et al. 2015). Although many HIF-dependent protein-coding genes contribute to adaption to hypoxia, whether lncRNAs could response to hypoxia and their regulatory roles in hypoxia-associated cancer is far from clear and a question worth thinking about.

Recently, accumulating evidences suggest the involvement of hypoxia-regulated lncRNAs in cancer cells, including NEAT1, linc-ROR, HINCUT1, UCA1, H19, WT1 lncRNA, AK058003, linc-p21, lncRNA LET and EFNA3 lncRNAs (Choudhry et al. 2014a; Choudhry et al. 2014b; Ferdin et al. 2013; Gomez-Maldonado et al. 2015; Matouk et al., 2010; McCarty and Loeb 2015; Takahashi et al. 2014; Wang et al. 2014; Xue et al. 2014; Yang et al. 2013a; Yang et al. 2013b; Yang et al. 2014) (Table 1). In this review, we focus on hypoxia-related lncRNAs identified or validated in human cancer tissues, and briefly outline the mechanism of them. We also make a summary on the functional roles of several hypoxia-regulated lncRNAs in tumor and suggest reasonable strategies for future research.

2. Long noncoding RNA

2.1. A view of lncRNA

Long noncoding RNA is commonly defined as a RNA molecular which is greater than 200 nucleotides. The overwhelming majority of lncRNAs is polyadenylated and transcribed by RNA polymerase2 (RNA pol2). LncRNAs can function in different ways according to their cellular locations (Zhang et al. 2014a; Zhang et al. 2014b). The genomic locations of lncRNA can be described in terms of their relationship to nearby protein coding genes: (i) intergenic, (ii) intronic, (iii) bidirectional, (iv) antisense and (v) sense (Ponting et al. 2009). Intergenic lncRNA (lincRNA) refers to distinct transcriptional unit that does not overlap its protein-coding gene. Other types of lncRNAs include enhancer RNA, transcribed ultraconserved gene, antisense RNA, and many others. The diversity of genomic locations and types of lncRNAs highlight the high complexity of the genetic information encoded within the human genome.

Recent studies have demonstrated that lncRNAs regulated several biological processes such as chromatin modification, gene transcription, posttranscriptional mRNA processing and nuclear-cytoplasmic trafficking. Moreover, lncRNA can also participate in other regulatory processes, for example, NEAT1 is a nuclear lncRNA that is an essential structural component of paraspeckles (Choudhry et al. 2014a; Choudhry et al. 2014b).

Similar to protein-coding genes, aberrant expression of lncRNAs can also be modulated by several mechanisms, such as epigenetic alteration and transcriptional regulation including p53 (Zhang et al. 2014a; Zhang et al. 2014b), MYC (Deng et al. 2014), etc.

2.2. Cancer-related lncRNA

A number of lncRNAs, such as HULC (Panzitt et al. 2007), HOTAIR (Gupta et al. 2010), MEG3 (He et al. 2014) and H19 (Tsang and Kwok 2007), are found to be aberrantly expressed in a number of cancers and extensively characterized as important players affecting the

Table 1
List of hypoxia-regulated lncRNAs in cancers.

Lnc RNA	Localization	Expression	Cancer types	Cellular function	Refs.
NEAT1	Nucleus	Up	Breast cancer	Induces paraspeckle formation and improves cancer cell survival in hypoxia	Choudhry et al. (2014a), Choudhry et al. (2014b)
linc-ROR	Cytoplasm	Up	Hepatic carcinoma	Extracellular transfer in intercellular signaling to promote cell survival in hypoxia	Takahashi et al. (2014)
HINCUT1	Nucleus	Up	Colorectal carcinoma, breast cancer	Supports cell proliferation specifically under hypoxia and is critical for optimal O-GlcNAcylation of proteins	Ferdin et al. (2013)
UCA1	Cytoplasm	Up	Bladder cancer	Enhances hypoxic bladder cancer cell proliferation, migration, and invasion	Xue et al. (2014))
H19	Nucleus& Cytoplasm	Up/Down	$P53^{null}$/$P53^{wt}$ cancer cells	Carcinogenicity/tumor growth retardation	Matouk et al. (2010)
WT1 lncRNA	Nucleus& Cytoplasm	Up	Myeloid leukemia	Regulates the expression of WT1	McCarty and Loeb (2015)
AK058003	–	Up	Gastric cancer	Promotes gastric cancer metastasis	Wang et al. (2014)
linc-p21	Nucleus& Cytoplasm	Up	Cervial cancer	Modulates the Warburg effect	Yang et al. (2014)
lncRNA LET	Nucleus	Down	Hepatic carcinoma	Contributes to hypoxia-mediated metastasis	Yang et al. (2013a), Yang et al. (2013b)
*EFNA3*lncRNAs	Cytoplasm	Up	Breast cancer	Promotes the dissemination of tumor cells	Gomez-Maldonado et al. (2015)