REVIEW

Long non-coding RNA SPRY4-IT1: a new player in different diseases

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Long non-coding RNAs (lncRNAs) refer to a class of RNA molecules with poor protein coding potential and are usually larger than 200 nucleotides. SPRY4-IT1, a member of lncRNA, is derived from an intronic region within the SPRY4 gene. And accumulating evidence demonstrates that aberrant expression of SPRY4-IT1 is involved in the development of various diseases such as melanoma, esophageal squamous cell carcinoma (ESCC), renal cancer, gastric cancer, breast cancer, bladder cancer, Non-small-cell lung cancer (NSCLC), and preeclampsia. SPRY4-IT1 is significantly related to not only progression and prognosis of diseases but also cell proliferation, migration, invasion. SPRY4-IT1 contributes to various diseases via different molecular mechanism such as regulating the expression of proteins related to cell growth and migration, involving in epithelial–mesenchymal transition (EMT), affecting lipid metabolism, and regulating downstream gene expression. Moreover, SPRY4-IT1 can also be regulated by some epigenetic factors including Zeste homolog 2 (EZH2). Therefore, SPRY4-IT1 may be a novel prognostic biomarker and a potential therapeutic candidate for different diseases including various solid cancers and preeclampsia.

Keywords: lncRNA; SPRY4-IT1; diseases

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Introduction

While only 1.5% of the human genome has been reported as protein-coding regions [1], a large part of the genome gives rise to noncoding RNAs (ncRNAs), which have little or no protein-coding capability. The ncRNAs can be categorized into several groups, long non-coding RNAs (lncRNAs), such as microRNAs (miRNAs), small interfering RNAS (siRNAs), small nuclear (snRNAs), small nucleolar RNAs (snoRNAs), and piwi-interacting RNAs (piRNAs), etc. NcRNA may play a crucial role in cellular proliferation, physiology and pathologies although initially considered to be transcriptional noise or artifacts [2, 3].

NcRNAs can also be grouped into two major groups according to their size. Small ncRNAs are transcribed RNA molecules shorter than 200 nucleotides, which include miRNA, siRNA, piRNA, etc, and lncRNA, which are usually longer than 200 nucleotides and are mostly transcribed by RNA pol II from different regions across the genome. LncRNAs are classified by their position relative to coding genes, therefore, they are usually defined as sense, antisense, or bidirectional when their transcription is initiated in close proximity and opposite orientation to a neighboring coding transcript, intronic if it is derived wholly from within an intron of a second transcript, and intergenic or intervening when it lies within the genomic interval between two genes [4]. They play diverse structural and regulatory roles in cells such as chromatin modification, transcription, and

posttranscriptional processing. Except for diverse biological processes, different studies have already shown that aberrant lncRNA expression may result in the progression of human diseases, including cancers [3].

In this review, we describe the roles of long-non coding RNA SPRY4-IT1 as one of the most important regulatory RNAs in human cells, and discuss the implication of SPRY4-IT1 for diagnosis, assessment and treatment of different diseases.

Long non-coding RNA SPRY4-IT1

SPRY4, a member of Sprouty family of genes, is an inhibitor of the receptor-transduced mitogen-activated protein kinase (MAPK) signaling pathway through inhibit the Rat Sarcoma/Extracellular regulated protein kinases (Ras/Erk) encoding. It could activate the RAS gene, an oncogene, and impairs the formation of active GTP-RAS [5]. Studies have identified SPRY4 as a tumor suppressor in acute myeloid leukemia [6], non-small cell lung cancer [7], etc. *Khaitan et al* originally reported that SPRY4-IT1 (708 bp) was derived from an intronic region within the SPRY4 gene and was predicted to contain several long hairpins in its secondary structure, and may play an important role in melanoma pathogenesis in humans [8]. SPRY4-IT1 transcript size is approximately 1.8 kb, and it is proposed to carry both intronic and exonic sequences and can be considered as a noncoding splice variant of the SPRY4 gene [9]. Additionally, studies show that the transcription and function of SPRY4-IT1 is independent from its host gene SPRY4 although they may be regulated by the same transcriptional machinery [9]. Studies show that SPRY4 expression levels were not significantly changed after SPRY4-IT1 knockdown, suggesting that SPRY4-IT1 directly rather than SPRY4 indirectly induced the phenotypic changes following the knockdown of SPRY4-IT1 [10].

SPRY4-IT1 as a novel biomarker in various diseases

Recently, an increasing number of studies have shown that aberrant expression of lncRNA SPRY4-IT1 occurs in various diseases more than tumors, and SPRY4-IT1 appears different phenotype and function according to different diseases, indicating SPRY4-IT1 may be a potential diagnostic and prognostic biomarker.

SPRY4-IT1 and different Solid Tumors

In 2011, researchers initially reported that expression of the lncRNA SPRY4-IT1 in melanoma cells is higher than in normal human melanocytes [8]. Knockdown of SPRY4-IT1 blocked melanoma cell invasion and proliferation, and increases apoptosis, indicating that the abnormal upregulation of SPRY4-IT1 expression may have an important role in the molecular etiology of human melanoma [8]. Moreover, In esophageal squamous cell carcinoma (ESCC) patients, studies showed that SPRY4-IT1 levels were significantly higher not only in ESCC tissues and cells [10], but also in patients plasm samples [11], and the ESCC patients with higher SPRY4-IT1 expression had an advanced clinical stage and poor prognosis than those with lower SPRY4-IT1 expression. Moreover,studies also found that SPRY4-IT1 is up-regulated and associated with aggressive progression and poor prognosis in renal cancer [12], gastric cancer [13], breast cancer [14] and bladder cancer [15], indicating that SPRY4-IT1 may become a novel potential prognostic biomarker for these malignant solid tumors.

In contrast to the over-expression of SPRY4-IT1 in the cancers previously mentioned, SPRY4-IT1 was downregulated in Non-small-cell lung cancer (NSCLC), and correlated with a poor prognosis of NSCLC. The high level of SPRY4-IT1 expression led to the significant inhibition of cell proliferation, migration, invasion, and the promotion of apoptosis, while knockdown of SPRY4-IT1 expression promoted cell migration and invasion [16]. These studies suggest SPRY4-IT1 may play complex roles and involves in various molecular mechanism in different cancers.

SPRY4-IT1 and preeclampsia

Zou et al found a higher expression level of SPRY4-IT1 in preeclampsic placental tissues as compared with the normal pregnancies [17]. In Trophoblast Cells (HTR-8/SVneo cells), the inhibition of SPRY4-IT1 led to the increase of migration rate and proliferation and the decrease of their apoptosis rate, while reverse results were observed in vitro when SPRY4-IT1 was overexpressed [17]. These phenomenon is contrary to most of malignant tumors above, indicating LncRNAs SPRY4-IT1 may show various phenotypes in different tissues and different stages of disease process. Moreover, this study found lncRNA SPRY4-IT1 might also partly taken part in the process of spiral artery remodeling in preeclampsia.

SPRY4-IT1 functions through various molecular mechanism

The molecular mechanism of lncRNA SPRY4-IT1 functions in different diseases is complicated, and to further explore the molecular mechanism could contribute to fully understand diseases including cancer conversely.

Up-regulate the expression of cyclin D1, MMP2, and MMP9

Cyclin D1 is a member of highly conserved cyclin family [18]. Overexpression of cyclin D1 could alter cell cycle progression. MMP2 andMMP9 belong to the matrix metalloproteinases (MMP) gene family, and they are involved in cell motility, and matrix invasion [19]. Studies showed that the inhibition of SPRY4-IT1 significantly lead to the downregulation of cyclin D1, MMP2 and MMP9 expression level, which means SPRY4-IT1 was positively correlated with cyclin D1, MMP2, and MMP9 expression [13, 14]. These findings indicate that SPRY4-IT1 may affect tumor cells proliferation, migration, and invasion partly via regulating cyclin D1, MMP2, and MMP9 expression.

Involvement in epithelial–mesenchymal transition (EMT)

The epithelial–mesenchymal transition (EMT) is the process of cells conversing from a differentiated epithelial state into a dedifferentiated migratory mesenchymal phenotype, which plays a pivotal role in remodeling embryogenesis and is implicated in the promotion of tumor cell invasion and metastasis [20]. Recently, studies found decreased SPRY4-IT1 expression inhibited E-cadherin expression and promoted vimentin expression, while increased SPRY4-IT1 expression levels could induce E-cadherin expression and decrease that of vimentin [16]. This study indicate that SPRY4-IT1 affects NSCLC cell proliferation and metastasis partly via the epithelial–mesenchymal transition (EMT), which advances our understanding of the role of SPRY4-IT1 as regulators of different tumors such as NSCLC pathogenesis.

Coordination with lipin 2

Mazar et al purified SPRY4-IT1 from melanoma cells and used mass spectrometry to identify the protein lipin 2 as a major binding partner, which is an enzyme that could convert phosphatidate to diacylglycerol (DAG) [21]. Inhibition of SPRY4-IT1 rises theaccumulation of lipin2 protein and upregulate the expression of diacylglycerol O-acyltransferase 2 (DGAT2), an enzyme that could catalyze DAG to triacylglycerol (TAG), and induces significant changes in a number of lipid species, including increased acyl carnitine, fatty acyl chains, and triacylglycerol (TAG) [21]. These results suggest SPRY4-IT1 may regulate cell proliferation by lipin 2-mediated alterations in lipid metabolism in melanoma.

Regulate ZNF703 gene

ZNF703, a member of zinc finger transcription factors, is located on chromosomes 8 (8p11.23), contributes to aspects of growth and patterning across evolutionarily diverse species [22]. ZNF703 has been identified as a novel oncogene in human breast cancer [23], colorectal cancer [24], gastric cancer [22], etc. ZNF703 has been demonstrated promotes ER(−) breast carcinoma cell proliferation and suppresses apoptosis in vivo, and recently studies showed that ZNF703 could be regulated by SPRY4-IT1 as a downstream target gene of SPRY4-IT1 [14]. Nevertheless, it still remains unclear and requires further investigation about the precise molecular mechanism regulating how SPRY4-IT1 controls ZNF703.

Regulation of SPRY4-IT1

Zeste homolog 2 (EZH2) is a methyltransferase and the core catalytic subunit of polycomb repressive complex 2. It plays an essential role in the epigenetic maintenance of the histone H3 trimethylation (H3K27me3) repressive chromatin mark [25]. *Sun et al* found that the expression of SPRY4-IT1significantly upregulated after knockdown of EZH2 expression, while chromatin immunoprecipitation assays showed that inhibition of EZH2 expression prevented its binding to the SPRY4-IT1 promoter region and reduced H3K27me3 modification, which upregulated SPRY4-IT1 expression, suggesting that the epigenetic factor EZH2 could regulate the transcript levels of SPRY4-IT1 via H3K27me3 modification [16]. However, the understanding about cellular molecular mechanism that may regulate SPRY4-IT1 expression at multiple levels is extremely limited so far.

Prospect

Accumulating evidence demonstrates the crucial roles of SPRY4-IT1 in the initiation and progression of various diseases. Exploring the biological roles of SPRY4-IT1 in different types of diseases including cancer may help us to determine the efficiency of SPRY4-IT1 as a diagnostic or predictive biomarker. However, further understading of the complex molecular mechanism of long non-coding RNA SPRY4-IT1 in the pathogenesis and progressing of different diseases is still needed with conduction of clinical trials in the future to find this RNA as a suitable biomarker or therapeutic target in cancer or other diseases. Besides, SPRY4-IT1 can also be further considered as a therapeutic target to improve the sensitivity of therapy for different diseases. Moreover, the efficacy of these therapeutic approaches can be further expanded via identification of exact molecular pathways underlying the regulation of SPRY4-IT1 expression.

Conflict of interest

We declare that we have no conflict of interest.

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