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MALAT1: An Onco-Long Noncoding RNA

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Multiple lines of evidence increasingly link mutations and dysregulations of long non coding RNAs (lncRNAs) to diverse human diseases [1,2]. The question of whether alterations in the primary structure, secondary structure, and expression levels of lncRNAs as well as their cognate RNA-binding proteins underlie cancer has occupied researchers and clinicians for decades. Recent progress suggests that lncRNAs seem to influence and/or cause cancer onset, progression, and outcome [3].

Long-non-coding RNAs

Large-scale analyses of full-length cDNA sequences have detected large numbers of lncRNAs in human, mouse and fly. These lncRNAs have been shown to play key roles in imprinting control, cell differentiation, immune responses, human diseases, tumorigenesis and other biological processes [4]. Generally, lncRNAs are as poorly conserved as the introns of coding genes and less conserved than the 5'- or 3'-untranslated regions (UTRs) of mRNAs. The low-conservation level of lncRNAs suggests they evolve more quickly than protein-coding genes, rendering functional prediction by genomic comparison very difficult. Besides, functional prediction of lncRNAs is also hampered by the lack of collateral information. It has been proposed that the functional properties of lncRNAs are mainly related to their secondary structures [5]. In spite of much effort, the number of lncRNAs with known functions remains scarce, and efficient prediction of lncRNA functions is still a considerable challenge.

Regulation Manners of lncRNAs on Gene Expression

The regulatory roles of lncRNAs in the expression, activity and localization of protein-coding genes have attracted much attention [6]. Recent studies demonstrate that lncRNAs can guide changes in gene expression either in *cis* (on neighboring genes) or in *trans* (distantly located genes) manner that is not easily predicted based on lncRNA sequence [7,8]. In principle, lncRNAs can guide chromatin change in *cis* in a cotranscriptional manner (tethered by RNA polymerase) or as a complementary target for small regulatory RNAs; guidance in *trans* can occur by lncRNA binding to target DNA as a RNA:DNA heteroduplex, as RNA:DNA:DNA triplex, or RNA recognition of complex surface of specific chromatin features [9].

Onco-lncRNA: Metastasis Associated Lung Adenocarcinoma Transcript 1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a long non-coding RNA (lncRNA) located on chromosome 11q13, is up-regulated in many solid tumors and associated with cancer metastasis and recurrence [10,11]. MALAT1 was originally identified to have over expression in the early-stages of non-small cell lung cancers that subsequently metastasize compared with those that do not. Phylogenetic analysis indicates that MALAT1 is highly conserved among mammals, up to 90% identity between human and mouse in the last 5 kb of the RNA [12].

MALAT1 lacks open reading frames of significant length, and the in vitro translation of MALAT1 yields no peptides, suggesting that MALAT1 functions as a long (7 kb) ncRNA [13]. After transcription, nascent MALAT1 is processed into a 5'-long transcript and a 3'-short tRNA-like transcript by RNase P cleavage [14]. The long form of MALAT1 is subsequently localized to nuclear speckles [15]. Several lines of evidence suggest that nuclear speckles function as storage/assembly/modification compartments that supply splicing and transcription factors to active transcription sites [16], or that they act as hubs facilitating the efficiency and integration of distinct steps in gene expression, ranging from transcription to mRNA export [17]. Nuclear MALAT1 is relatively stable compared with the short half-life of mascRNA [18].

MALAT-1 and Cancer

A focus of current research is the analysis of the role of noncoding RNAs (ncRNAs) in cancer development. Nevertheless, little is known about lncRNAs and their impact on cancerogenesis regulatory processes [19]. Because they lacked open reading frames, MALAT1 was identified to modulate the transcript repertoire as a result of post-transcriptional modifications of primary transcripts [20].

Clinical study showed that the non-small-cell lung carcinoma (NSCLC) and hepatocellular carcinoma (HCC) patients with high-level expression of MALAT1 were shown to have significantly worse prognosis compared to patients with low-level expression of these genes [21,22]. MALAT1 showed broad expression in normal human and mouse tissues and was over expressed in many human carcinomas, including metastatic non-small cell lung carcinomas [21], up-regulated in six types of human carcinomas [23], HCC [22], syngeneic murine colon carcinomas [24], endometrial stromal sarcoma [25], squamous cell carcinoma of the lung [26], neuroblastoma cell line [27] and EpH4 cells transformed with the ErbB2 oncoprotein [28]. But, Sun et al. showed markedly decreased expression in c-myc expressing mammary glands and mammary tumors [29]. Recently, MALAT1 was also reported to be overexpressed in placenta previa and supposed to regulate trophoblast invasion [30]. On genetic level, MALAT-1 contributes to some cellular events underlying metastatic transformation in many cancer cells, such as cellular growth, movement, proliferation, signaling, and immune regulation through the regulation of pre-mRNA expression [22,26,31,32].

Conclusion and Perspective

In general, it has been shown that misexpression of lncRNAs such

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as HOTAIR [33-35], Malat1, PCAT1 [36], contributes to numerous diseases. However, future studies are needed to elucidate the mechanism by which disease-causing mutations in lncRNA functional motifs can affect its regulatory domains and compromise its ability to interact with other molecules, thereby contributing to the pathogenesis of disease. With the development of array and novel sequencing technologies, further study of lncRNA motifs could yield new RNA-based targets for the prevention and treatment of human disease [36-39].

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