Editorial

# Metastasis-associated lung adenocarcinoma transcript 1 regulates tumor progression: old wine in a new bottle

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In the post-genomic era, non-coding RNAs (ncRNAs) have aroused great attention in chemistry and life sciences (1-3). Generally, ncRNAs are divided into two categories depended on the length of a transcript. Small ncRNAs, which are less than 200 nucleotides (nt) in length, include microRNA (miRNA), PIWI-interacting RNA (piRNA), promoter-associated RNA (paRNA), and small nucleolar RNA (snoRNA). Long ncRNAs (lncRNAs), which exceed 200 nucleotides, include pseudogene RNA (4,5). lncRNAs are the most numerous of the ncRNAs. lncRNAs have been comprehensively studied concerning structure and functions. lncRNAs have a transcribing length of 200–100,000 nt and lack a complete functional open reading frame (ORF). As an RNA or functional short peptide, lncRNAs play essential roles in maintaining cell differentiation, proliferation and apoptosis, as well as other functions. The disrupted expression of lncRNAs has been associated with human diseases that include diabetes mellitus (6), nervous system diseases (7), coronary artery disease (8), and cancer (1). Recent studies have implicated lncRNAs as being very important in cancer, with correlations demonstrated with cancer progression and development due to the regulation of a series of cellular signalling pathways, including the nuclear factor-kappa B pathway (9), Hippo pathway (10), and Wnt pathway (11). A series of cancer-associated lncRNAs include *PVT1* (12), ANRIL (13), and *TUG1* (14). lncRNAs exhibit strong tissue- and cell-specific expression patterns in humans (15), and thus are often used as tumour biomarkers for the early diagnosis and monitoring of cancer progression.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also known as nuclear-enriched abundant transcript 2 (NEAT2), has been the subject of many disease-associated studies. Exemplifying this, a literature searches of the PubMed database using the search term "MALAT1" returned 450 research papers (excluding editorials, meta-analyses, reviews, letters, comments, and case reports) through February 25, 2018. The numbers of research articles have increased markedly since 2013, attesting to the burgeoning focus on lncRNAs. MALAT1 has a length of approximately 8,000 nt. It was first identified as a prognostic marker for the early stage of lung adenocarcinoma (16). Studies have associated MALAT1 with tumour progression and metastasis (17,18). As research continues, increasing numbers of studies have reported the elevated expression of MALAT1 in a wide variety of cancers, including oral squamous cell carcinoma (19), breast cancer (20), and hepatocellular carcinoma (21). MALAT1 has been implicated with radio- or chemotherapy resistance and poor prognoses in patients (22-24). Altered levels of MALAT1 in animal tumour models or multiple cancer cell lines have been demonstrated to affect tumour growth, differentiation, invasion, and metastasis via a series of regulatory steps. One example is the recruitment and interaction with

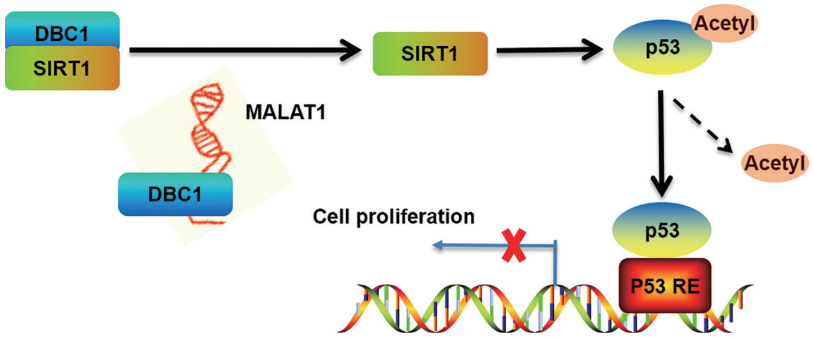


**Figure 1** Schematic representation of a model for the "MALAT1-DBC1-SIRT1-P53" axis.

proteins (25), where MALAT1 acts as a co-regulator or a co-repressor (26) and interacts with miRNA (27). Moreover, MALAT1 may have potential value as a therapeutic target in cancer treatment. Arun *et al.* demonstrated in a mouse mammary tumour virus (MMTV)-PyMT mouse mammary carcinoma model that MALAT1 antisense oligonucleotides slow tumour growth accompanied by significant differentiation into cystic tumours and a reduction in metastasis (28).

Chen *et al.* (29) recently reported that MALAT1 as an epigenetic regulator via its interaction with a protein termed depleted in breast cancer 1 (DBC1). The interaction regulates p53 activity and reduces the transcription of a series of its downstream target genes, which promote cell proliferation and inhibit cell apoptosis. The authors employed a high-throughput strategy, including RNA pull-down and quantitative proteomics, to screen the interacting proteins of MALAT1, and identified 127 potential MALAT1-interacting proteins. In a series of bioinformatics analyses and experimental validations, the authors verified the physical interaction between MALAT1 and amino acids 120–180 of DBC1. The same authors used mechanistic experiments to reveal that MALAT1 binding competes with the interaction between sirtuin1 (SIRT1) and DBC1, sequentially regulating the deacetylation of p53, which forms a regulatory axis designated "MALAT1-DBC1-SIRT1-P53" to affect a spectrum of p53 downstream biological functions (*Figure 1*). The study and the observations are compelling and important. However, the conclusion drawn by Chen *et al.* should be further verified for the following reasons. Firstly, although MALAT1 is almost always retained in the nucleus (30) where it is localized within nuclear speckles (31,32), studies have reported MALAT1 interaction with miRNA in the cytoplasm (21,27,33). Therefore, the subcellular localization of MALAT1 should be verified in HepG2 cells. Secondly, the conclusion of this article was relied on the use of HepG2 cells. Thus, it is not known whether the MALAT1-DBC1-SIRT1-P53 regulatory axis is relevant in other cancer cell lines or animal models. Finally, the article lays the foundation for the biological motif of MALAT1 that is located at the 3' end of MALAT1 (nt 6,918–8,441) (34). However, it is unknown whether the nuclear retention signals of MALAT1 are also located in this region. If so, the nuclear retention signals may be affected in a competitive manner by the binding of MALAT1 with the aa120–280 region of DBC1.

In summary, the findings of Chen *et al.* have expanded our knowledge of the MALAT1 protein interactome and have clearly established the novel regulatory network between MALAT1 and p53 in tumorigenesis, which may provide a potential strategy for the targeting therapy of MALAT1 in specific cancer patients (29). However, validation of the *in vitro* findings using *in vivo* models is necessary before clinical applications can be contemplated. With the development of next-generation sequencing technologies, more lncRNAs are being discovered and identified. Because of their unique structure, lncRNAs are very stable in disease-related tissues, cells, and serum. Furthermore, compared with protein detection, the extraction and detection of lncRNAs is being done with greater specificity, sensitivity, and stability (35). However, lncRNAs are expressed at low levels relative to miRNAs, which is a challenge to the potentially use of lncRNAs as the biomarkers for cancer diagnosis. Identification and verification of novel functional lncRNAs *in vivo* and *in vitro* is a pressing priority for the exploration of the underlying molecular mechanisms of diseases. Even though the weight of evidence clearly supports the potential value of lncRNAs for cancer diagnosis and therapeutics, these

 

clinical applications remain elusive (36,37). We believe that novel approaches and techniques will ultimately shed light on these processes and provide a new strategy for the early screening and therapy of cancers.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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