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Commentary

Small nucleolar RNAs (snoRNAs) as potential non-invasive biomarkers for early cancer detection

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Abstract

Small nucleolar RNAs (snoRNAs) are non-coding RNA (ncRNA) molecules, which are associated with specific proteins to form small nucleolar ribonucleoparticles. However, the function of snoRNAs in cancer still remains elusive. Recently, several independent lines of evidence have indicated that these ncRNAs might have crucial roles in controlling tumorigenesis, and snoRNAs could be potential biomarkers for cancer.

Key words Non-coding RNA, small nucleolar RNA, tumorigenesis

Very recently, a leading edge featured article "Small nucleolar RNA 42 acts as an oncogene in lung tumorigenesis" by Mei *et al*. (University of Maryland) was published in *Oncogene*[1]. In this article, the authors investigated the role of SNORA42 in the tumorigenesis of non–small cell lung cancer (NSCLC) because it is a commonly overexpressed snoRNA in lung tumors[2]. First, the functional significance of SNORA42 in lung cancer cell lines was determined through gain- and loss-of-function analyses. The authors found that SNORA42 suppression inhibited cell growth and proliferation and induced apoptosis of cancer cells, whereas forced SNORA42 expression in bronchial epithelia promoted cell growth and colony formation. Second, cancer cells transfected with SNORA42-siRNA were inoculated into mice through either the tail vein or subcutaneous injection. The results showed that SNORA42 knockdown suppressed tumorigenesis *in vivo*. Additionally, the genomic dosages and expression levels of SNORA42 and its host gene, KIAA0907, were simultaneously assessed in 10 NSCLC cell lines and a human bronchial epithelial cell line. The authors concluded that SNORA42 rather than its host gene was frequently and highly expressed in NSCLC cells. Finally, the expression level of SNORA42 in frozen, surgically resected lung tumor tissues from 64 patients with stage I NSCLC was evaluated. The results showed that gene amplification and elevated expression of SNORA42 rather than KIAA0907 were frequently observed in lung cancer cells, suggesting that SNORA42 is overexpressed in this milieu via gene amplification. Together, these results showed that the suppression of SNORA42 inhibited cell growth, proliferation, and tumorigenicity by inducing p53-dependent apoptosis and that SNORA42 expression was inversely associated with the survival of NSCLC patients. Therefore, increased SNORA42 expression could have an oncogenic role in lung tumorigenesis, participating in driving the malignant phenotype rather than simply reflecting cellular stress or a secondary effect of cancer transformation. Thus, SNORA42 activation might have an oncogenic role in lung tumorigenesis and serve as a potential diagnostic/therapeutic target for this malignancy.

Soon after this paper was published, Dr. Gwyn T. Williams and Dr. Farzin Farzaneh in the UK published a review entitled "Are snoRNAs and snoRNA host genes new players in cancer?" in *Nature Reviews Cancer*[3], which cited the work of Mei *et al*. They stated that Mei *et al*. had provided strong and clear evidence that snoRNAs and their host genes were new players in cancer, and snoRNAs activation might have an oncogenic role in tumorigenesis and served as a potential diagnostic/therapeutic target for the malignancy.

Small non-coding RNAs (ncRNAs) are important in regulating gene expression at many levels, such as chromatin architecture, transcription, mRNA stability, and translation. The functions of some small ncRNAs, including Piwi-interacting RNAs (piRNAs), short

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interfering RNAs (siRNAs), and microRNAs (miRNAs), have been shown to be perturbed in cancer and other diseases. piRNAs have been shown to control neuronal, muscle, and germline development[4-6], whereas siRNAs and miRNAs could guide the sequence-specific cleavage of target mRNAs and possibly cause splicing abnormalities in cancer[7,8]. In addition, miRNAs have been identified to function as classical oncogenes or tumor suppressor genes, which made it as potential diagnostic and prognostic markers[9-15].

Interestingly, a limited number of snoRNAs, another class of small ncRNAs, were reported to have ncRNA-like functions in gene splicing and silencing. For example, the snoRNA HBII-52 was found to regulate the alternative splicing of 5-HT2CR by binding to a silencing element in one exon[16]. As another example, small RNAs that originated from the snoRNA ACA45 could function like miRNAs in post-transcriptional gene silencing[17]. The pleiotropic nature of gene regulation by ncRNAs led us to hypothesize that certain snoRNAs might be endowed with the ability to function as crucial modulators of human cancers.

snoRNAs comprise a highly abundant group of small ncRNAs. Except for the RNase mitochondrial RNA processing enzyme (MRP), all snoRNAs fall into two major families: C/D box and H/ACA box snoRNAs. Only a small fraction of snoRNAs (e.g., snR30, U3, and RNase MPR) is required for the specific cleavage of pre-rRNAs[18]. The majority of C/D box snoRNAs functions as guides for 2'-O-ribose methylation, and most H/ACA box snoRNAs functions as guides for the pseudouridylation of rRNAs, small nuclear RNAs (snRNAs), and tRNAs[19-21]. However, the role of snoRNAs in the establishment and progression of human cancer remains unclear until function of SNORA42 is clarified.

As snoRNAs are ncRNA molecules of 60–300 nucleotides in length, they are not easily degraded in body fluids. In fact, it has been demonstrated that snoRNA signatures served as biomarkers for NSCLC. In a previous study, Liao *et al.*[22] used a GeneChip Array to successfully identified three snoRNAs that displayed altered expression in NSCLC patients. Using these three snoRNAs, they were able to distinguish NSCLC patients from health individuals and chronic obstructive pulmonary disease (COPD) patients with 81.1% and 95.8% specificity, respectively. Thus, the application of snoRNAs in clinical settings may provide a useful mean of improving early cancer detection and hence reducing cancer mortality.

As the function and importance of snoRNAs in cancer have become more clear, some interesting questions have arisen: (1) Have all snoRNAs been discovered? (2) Are there any snoRNAs regulate different gene transcripts, specifically genes with different splicing isoforms and different functions in cancer? (3) If snoRNAs can serve as non-invasive biomarkers for early detection of cancer, are they associated with clinical outcomes? Are they useful as new therapeutic targets? These questions will drive further investigations to elucidate the roles of snoRNAs in cancer.

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