Editorial

Long non-coding RNA TUG1: a novel therapeutic target in small cell lung cancer

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Lung cancer is the leading cause of cancer deaths worldwide (1), and its development and progression is a multi-stage and multi-gene process. Small cell lung cancer (SCLC) accounts for 10–15% of cases (2) and has the following characteristics: a high growth fraction, a rapid doubling time, and early development of widespread metastases (3). Although significant progress has been made toward understanding the causal mechanisms, the 5-year survival rate of SCLC is still lower than 10% (4). Chemotherapy is a common treatment for SCLC, which is highly sensitive to initial chemotherapy. However, many patients eventually die owing to the failure of clinical treatment due to the development of chemotherapy resistance (5). Therefore, further research to identify molecular biomarkers and drug targets is needed to provide a new strategy for SCLC prevention, early diagnosis, and therapy.

Long non-coding RNAs (lncRNAs) are a class of endogenous RNA molecules; they have a transcript length of over 200 nt, lack a complete functional open reading frame (ORF), and rarely encode a functional short peptide (6,7). Although lncRNAs do not encode functional proteins, they are involved in many physiological processes, playing essential roles in maintaining cell proliferation, differentiation, apoptosis, etc. (8). Recent studies have revealed that the disruption of lncRNA levels is associated with cancer and is involved in cancer cell growth, proliferation, and apoptosis, invasion, metastasis, and chemoresistance (9). Moreover, lncRNAs can induce the dysregulation of multiple targets and pathways, resulting in the development of chemoresistance (10). Several lncRNAs associated with cancer chemoresistance have been identified, such as PVT1 (11), ANRIL (12), and HOTTIP (13). However, few studies have demonstrated the relationship between lncRNAs and chemoresistance in SCLC and the mechanism by which lncRNAs affect SCLC chemoresistance is unclear.

In a recently published study, Niu *et al.* (14) searched for novel targets for chemotherapy drug resistance in SCLC. The authors found that taurine up-regulated gene 1 (TUG1), a 7.1-kb lncRNA on chromosome 22q12, is overexpressed in SCLC tissues, and its expression is associated with the stage and survival of SCLC patients. TUG1 was also overexpressed in SCLC cell lines, and the expression of TUG1 in chemoresistant SCLC cell lines (H69AR and H446DDP) was higher than expression in H69 and H446 cell lines. Furthermore, the authors demonstrated that TUG1 knockdown via siRNA or shRNA inhibits SCLC cell proliferation, invasion, and metastasis, and increases prognosis and sensitivity to anticancer drugs [e.g., cisplatin (DDP), Adriamycin (ADM), and etoposide (VP-16)], both *in vitro* and *in vivo*. The regulatory mechanism may involve the binding of TUG1 to the enhancer of zeste homolog 2 (EZH2) to epigenetically regulate the expression of LIMK2b (a splice variant of LIM-kinase 2), thereby promoting cell growth, metastasis, and chemoresistance of SCLC. Taken together, these findings provide critical insight, indicating that TUG1 may be a novel molecular target for the treatment of SCLC.

In summary, Niu *et al.* clearly established that TUG1 could act not only as a clinical biomarker for SCLC patients, but also as a therapeutic target for chemotherapy drug resistance, enhancing the clinical benefits of chemotherapy in SCLC patients. With the application of next-generation sequencing and RNA-seq technology, an increasing number of lncRNAs have been discovered and characterised. Owing to their unique structure, lncRNAs are highly stable in disease-related serum, tissues, and cells. Further, lncRNAs are easy to extract and detect with higher specificity compared with that of protein detection, and can be screened with higher sensitivity and stability compared with miRNAs. Therefore, lncRNAs have served as novel diagnostic biomarkers and therapeutic targets for cancer. However, lncRNA research faces two recent challenges. First, it is necessary to sequentially validate lncRNAs derived from RNA sequencing data for human tissues or cells to demonstrate whether they are functional. Second, it is necessary to explore functional lncRNAs to establish whether they are specifically associated with one or more diseases and to determine the molecular mechanisms underlying these associations. Accordingly, further research is urgently needed to enable clinical applications. Although our current knowledge of lncRNAs is only the tip of the iceberg, novel methods and technologies will eventually clarify these processes, thereby providing a novel strategy for the prevention, early diagnosis, and treatment of cancer.

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Footnote

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

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