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Letter to the Editor

Upregulation of LINC00346 in non-small cell lung cancer cells

Dear Editor,

We read the study published by Wang et al[1] with great interest. The authors investigated expression of an intergenic long noncoding RNA (lncRNA), LINC00346, in tissues and isolated cells in patients with non-small cell lung cancer (NSCLC). The data presented in the paper showed for the first time that LINC00346 promotes NSCLC occurrence and development. The authors also demonstrated that LINC00346 partially regulates the JAK-STAT pathway.

In recent years, lung cancer has become a serious public health problem, ranking first as leading cause of death among malignant neoplasms. The incidence and mortality of lung cancer have shown an upward trend in many countries[2]. The main risk factors of lung cancer are smoking, improper diet, alcohol abuse, radiation, air pollution, pulmonary disease, and occupational complications. Although the survival rate is closely related to early diagnosis and resection, the early symptoms of NSCLC are not typical and may even be absent, with little or no discomfort reported[3].

In addition to first line chemotherapy using docetaxel, pemetrexed and erlotinib to treat patients with advanced NSCLC, several drugs have been approved, but survival rates have not improved in randomized clinical trials[4]. The efficacy of metronomic chemotherapy in metastatic NSCLC was recently shown to be a possible option[5]. A new clinical scenario includes lung cancer patients with human immunodeficiency virus (HIV), in which highly active antiretroviral therapy (HAART) has been shown to improve lung cancer prognosis[6].

Investigating the molecular mechanisms involved in NSCLC will aid in understanding pathogenesis and progression, with the ultimate goal of finding more targets for effective therapy. An interesting strategy to evaluate molecular mechanisms is the use of tissue microarray technology (TMA), an array-based high-throughput technology that can detect molecular alterations in a large number of tissues[7].

LncRNAs are more than 200 nt in length and do not have encoding capacity, but regulate gene expression at transcription, post-transcription and epigenetic levels. LncRNAs are involved in several pathways, including cellular proliferation, survival, differentiation, and apoptosis[8]. LncRNA dysregulation and/or mutation is linked to aging and onset of tumour and diseases, including diabetes, AIDS, Alzheimer's disease, and cardiovascular pathologies.

LINC00346 in particular is located on chromosome 13q34 and has a total length of 6322 bp. Zhang et al[9] recently reported LINC00346 dysregulation in human hepatocellular carcinoma, in which high expression of LINC00346 was negatively correlated with survival in hepatocellular carcinoma patients. Liu et al[10] described LINC00346 upregulation in human breast cancer, suggesting its use as biomarker for estimating prognosis. Increased expression of LINC00346 lncRNAs was also demonstrated in tumour tissues from human bladder prostate and kidney cancers, thereby promoting the malignant phenotype (Table I)[11,12].

Through accurate experimental design using *in vitro* and *in vivo* experiments, Wang et al[1] was the first to report increased expression of LINC00346 both in tissues and cells from NSCLC and investigated its biological function.

In vitro experiments in NSCLC cells transfected with short hairpin LINC00346 (sh-LINC00346) and a control (sh-NC) showed that LINC00346 promotes proliferation and inhibits apoptosis of

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Table I. Human cancers with a described upregulation in the expression of LINC00346.

Kind of human cancer	Authors
Non-small cell lung cancer (NSCLC)	Wang et al[1]
Hepatocellular carcinoma	Zhang et al[9]
Breast cancer	Liu et al[10]
Bladder cancer	Ye et al[11] and Martens-Uzunova et al[12]
Prostate cancer	Martens-Uzunova et al[12]
Kidney cancer	Martens-Uzunova et al[12]

NSCLC cells. CCK-8 assay results showed that interference in LINC00346 expression significantly inhibits the proliferation capacity of tumour cells. Flow cytometry showed that LINC00346 interference arrests the cell cycle in the G1-G0 phase and promotes apoptosis of NSCLC cells. No effects were observed on the number of cells in the M phase, and changes to the number of cells in the S phase were not significant.

In vivo experiments in nude male mice transplanted with transfected NSCLC cells demonstrated that LINC 00346 promotes the tumorigenic ability of NSCLC cells both in tumour volume and weight increase. Previous research investigating the role of lncRNAs in human cancers was mainly performed *in vitro* on tissues *ex vivo*. Previously, only Ye et al[11] showed that interference in LINC00346 expression was able to inhibit bladder cancer cell proliferation and migration *in vivo*, arresting the cell cycle and inducing apoptosis. Both groups[1,11] used a similar approach by using sh-LINC00346 to inhibit LINC00346 expression.

Wang et al[1] investigated the ratio of LINC00346 expression levels in carcinoma/para-carcinoma areas in non-treated NSCLC patients. Expression was upregulated in 50 out of 70 (71.43%) NSCLC patients. In the future, it will be important to investigate possible correlations between LINC00346 expression levels and the clinical status or survival of patients.

Regarding the biological function of LINC00346, the authors1 proved that interference in LINC00346 expression involves janus kinase (JAK) and the signal transducer and activator of transcription 3 (STAT3) pathway (Figure 1). Binding interleukins, hormones, or growth factors to their receptors can induce JAK phosphorylation and activation. Activated JAK phosphorylates STAT as a homodimer or heterodimer, which translocates to the nucleus where it binds to genes that regulate differentiation, proliferation, anti-apoptotic, immunomodulatory, angiogenesis, and hematopoietic processes. Several studies have shown that JAK/STAT3 pathway dysregulation is involved in the onset of different types of cancer, such as colorectal, lung, and ovarian tumours.

In conclusion, these data indicate that LINC00346 can be used as a biomarker for early cancer diagnosis and to improve understanding of the NSCLC malignant phenotype. These findings open to the possibility of developing new therapeutic targets for LINC00346 to treat NSCLC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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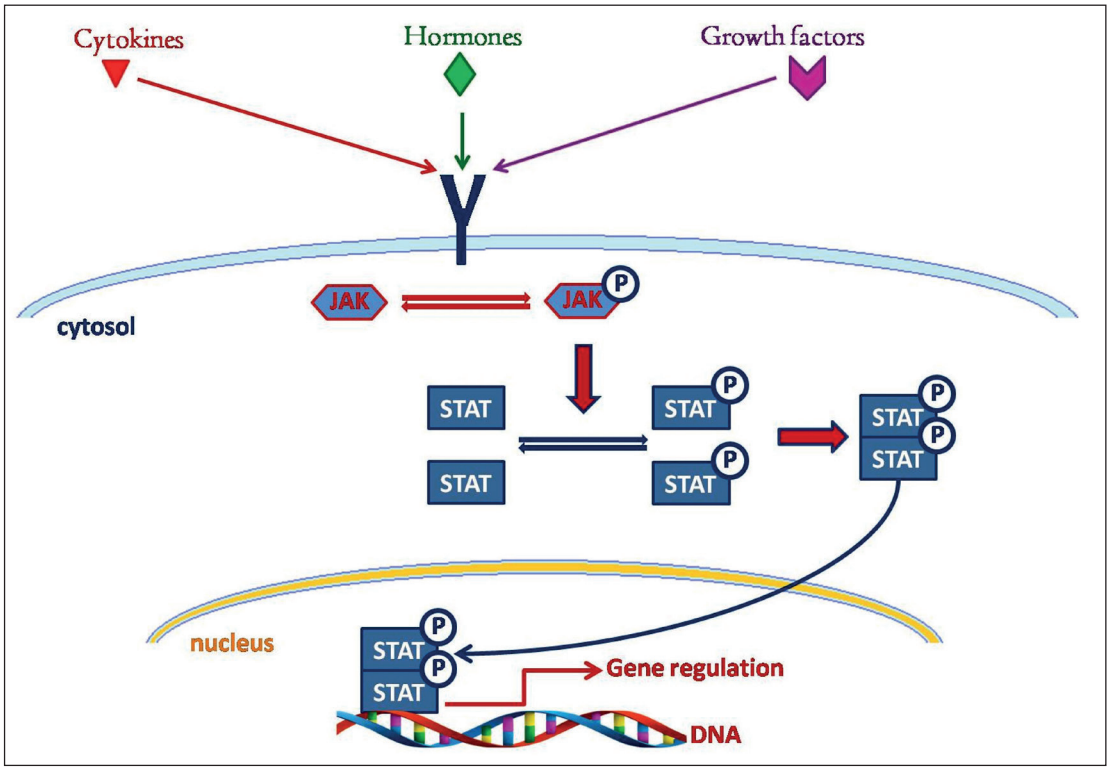

Figure 1. JAK-STAT canonical signaling pathway.

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