Long non-coding RNA and Notch regulation in non-small cell lung cancer

Pancewicz J.^A-F

Department of Histology and Embryology, Medical University of Białystok, Poland

ABSTRACT

Non-small cell lung cancer is one of the most commonly diagnosed cancer with a very high mortality rate. Trying to understand the mechanisms underlying the progression of this type of cancer, it is necessary to evaluate the changes occurring at molecular level in cancer cells. Besides the widely studied signaling pathways and genes which are dysregulated in NSCLC, there is a large group of non-coding RNAs involved in cancer pathogenesis. Those RNAs are tissue specific heterogeneous class of RNAs that play many functions in physiological condition in cells, nevertheless current data has shown that lncRNAs are also functional in different types of cancer. Moreover, it has been suggest that lncRNAs are involved in cancer progression by controlling key signaling pathways involved in diverse types of tumors. Notch signaling is one of those pathways, very often deregulated in NSCLC. Therefore in this review I summarized recent outcomes according the importance of lncRNAs in regulation of Notch pathway in the pathogenesis of NSCLC. Keywords: Notch, non-small cell lung cancer, lncRNAs

DOI:

*Corresponding author:*
Department of Histology and Embryology, Medical University of Białystok, Waszyngtona 13, 15-269 Białystok, Poland
E-mail: jpancewicz@ymail.com

Received: 31.04.2020
Accepted: 22.05.2020

Progress in Health Sciences
Vol. 10(1) 2020 pp 108-112
© Medical University of Białystok, Poland
INTRODUCTION

It has been estimated that the human genome contains around 20,000 protein-coding genes, which is nearby 2% of the total genome [1], while at least 50% of the genome is transcribed into RNA [2]. In general, non-coding RNAs (ncRNAs) consist of many classes of small ncRNAs including tRNAs, small nuclear RNAs, small nucleolar RNAs, microRNAs, short interfering RNAs, piwi-interacting RNAs, or small RNAs. However, non-coding RNAs that have more than 200 nucleotides are named long non-coding RNAs (lncRNAs). Those RNAs are tissue specific heterogeneous class of RNAs involved in many biological processes, however recent experiments has shown that lncRNAs are also deregulated in different types of cancer [3,4]. Furthermore, it has been suggest that lncRNAs are involved in cancer progression by controlling key signaling pathways involved in different types of tumor cells, including lung cancer [5].

Lung cancer is a heterogeneous malignancy that has the highest mortality rate among all types of cancers [6]. In 2018, lung cancer affected 11.6% of all newly diagnosed cancer cases and caused 18.4% of all cancer deaths [7].

Non-small cell lung cancer (NSCLC) is one of the types of lung cancer and is composed of three subtypes. Nonetheless of therapeutic developments, mortality of patients with NSCLC has not improved. Chemotherapy is still the standard treatment for advanced non-small cell lung cancer (NSCLC); however, chemoresistance and metastasis are huge clinical problems and possible mechanisms causing chemoresistance of NSCLC are of great attention in clinical oncology. Therefore, recent studies are focused on different options helpful in understanding pathomechanism of NSCLC, and exploring of lncRNAs is one of them. Therefore, it has been already acknowledged that lncRNAs maintain many functions in cells, including x-chromosome silencing, stem cell pluripotency rearrangement, myocyte differentiation, and regulation of apoptosis and invasion. Moreover, researchers already have discovered, that deregulated expression of lncRNA can be engaged in the progression of many human diseases including tumors over different mechanisms, such as: DNA or histone modification, chromatin remodeling, and as a sponge for microRNAs [8]. Furthermore, it has been acknowledged that unusual expression of lncRNA is associated with the development of NSCLC and the metastasis. Consequently, I decided to evaluate its role in non-small cell lung cancer (NSCLC).

Keeping in mind, that lncRNAs are involved in cancer progression by controlling key signaling pathways involved in different types of tumor cells, including lung cancer [5].

According to literature, lncRNAs regulate the expression of Notch receptors on a transcriptional level by interacting with transcription factors (TFs) and the promoter region of Notch receptors and on a posttranscriptional level by acting as miRNA sponges. Besides, lncRNAs also moderate the expression of Notch ligands and are downstream targets of Notch signaling [11]. Taking the above, it appears that lncRNAs are a good target to evaluate in order to understand the mechanisms leading to NSCLC progression (Figure1).

Figure 1. Scheme of the possible impact of lncRNAs on Notch signaling in NSCLC; lincRNAs could regulate the expression of : Notch receptors on a transcriptional and the promoter region of Notch receptor and on downstream targets of Notch signaling.
Overview of long non-coding RNA involved in NSCLC through Notch regulation

RNA NBR2

Analysis of long non-coding RNA (lncRNA) neighbor of BRCA1 gene 2 (NBR2) let the authors to assume that it is functional in preventing tumor progression process in non-small-cell lung cancer (NSCLC). The results presented in above mentioned studies indicate that the expression of lncRNA NBR2 was reduced in NSCLC patients tissues. Moreover, the results from lncRNA NBR2 analysis were correlated with overall poor prognosis. Furthermore, the expression of NBR2 in patients with NSCLC was associated with tumor size. Other experiments conducted by the same group indicated that overexpression of NBR2 inhibited the viability and migration of NSCLC cells and the expression of Notch1. Rendering the authors, synchronized overexpression of NBR2 and Notch1 possibly could reverse the inhibitory effect of NBR2 on proliferation and migration of NSCLC cells [12]. Taking the above, the authors presented a new insight into the role of lncRNA NBR2 in NSCLC pathogenesis involving Notch signaling.

RNA lbx2-as1

In the study presented by Tang Lx et al. it has been proposed that long non-coding RNA LBX2 antisense RNA 1 (LBX2-AS1) acts as a significant regulator in non-small cell lung cancer development. The authors examined the expressions of LBX2-AS1 in 165 paired NSCLC tissues and adjacent non-cancerous tissues taken from NSCLC patients by quantitative real-time PCR (qRT-PCR) method. Moreover, many cellular functions important in cancerogenesis have been tested after LBX2-AS1 knockdown in NSCLC cells. Therefore, the researchers evaluated cell proliferation, migration, and invasion in cancer cells. As results, it has been obtained that LBX2-AS1 was greatly expressed in NSCLC tissues and cell lines. Furthermore, the increased levels of LBX2-AS1 were detected to be positively correlated with TNM stage, histological grade, and lymph node metastasis. Additionally, it has been revealed that patients with higher expressions of LBX2-AS1 had worse overall survival. Other experiments indicated that the reduced of LBX2-AS1 in some NSCLC cell lines repressed cell proliferation, migration, and invasion. If it comes to connection of above mention lncRNA to Notch pathway, the suppression of LBX2-AS1 resulted in the reduced expressions of Notch1, p21, and Notch target gene Hes1. These results according to the authors suggest that LBX2-AS1 might promote the activation of the Notch pathway in NSCLC [13].

RNA xist

The purpose of the next presented study was to explore the biologic function and potential mechanism of long ncRNA (lncRNA)-X-inactive specific transcript (XIST) in NSCLC progression. According to the authors, XIST was abnormally upregulated in NSCLC tissues and cell lines. XIST reduction inhibited cell proliferation and TGF-β1-induced EMT in NSCLC A549 and H1299 cell lines. Further analysis showed an contrary correlation between miR-137 and XIST in NSCLC tissues. Moreover, miR-137 levels were found to be reduced in A549 and H1299 cells. Additionally, XIST could act as an endogenous sponge by directly binding to miR-137, negatively regulating its expression. miR-137 overexpression inhibited proliferation and TGF-β1-induced EMT in A549 and H1299 cells, although XIST could reverse the inhibitory effect of miR-137 on proliferation and TGF-β1-induced EMT. In addition, Notch1 was identified as a direct target gene of miR-137, with the XIST-miR-137 axis regulating activation of the Notch-1 pathway [14].

RNA let

Other studies conducted on lncRNA-low expression in tumor (LET) in non-small cell lung cancer indicated that RNA LET was downregulated in this type of cancer, either in lung tissues and in cell lines. According to the authors, decreased lncRNA-LET expression was strongly associated with advanced tumor stages and worse overall survival of NSCLC patients. Moreover, overexpression of LncRNA-LET in one of the NSCLC cell line significantly inhibited mechanisms which are the most important in cancer progression, which means: cell proliferation, migration and invasion. On the other hand, knockdown of lncRNA-LET in different NSCLC cell line showed contrary result, which according to the authors suggest a tumor-suppressive role for lncRNA-LET in NSCLC. As to the role of above mentioned lncRNA-LET in the Notch signaling regulation, it has been demonstrated that its overexpression significantly reduced the expression of Notch1 intracellular domain (NICD1) in NSCLC H292 cells while knockdown of lncRNA-LET increased NICD1 expression in other NSCLC H1975 cells. Similarly, NSCLC lung tissues with high levels of lncRNA-LET had lower NICD1 expression. Taking the above, it has been suggested that lncRNA-LET could serve as a prognostic indicator and a potent therapeutic target for NSCLC patients, and highlight a novel lncRNA-LET/Notch axis in regulating NSCLC cell fate and tumor progression [15].
CONCLUSION

Analysis of the recent literature shows that numerous lncRNAs are dysregulated in non-small cell lung cancer [16-21]. It is also known that lncRNAs can employ their functions through collaborations with other transcripts and proteins. Although there are not many results on the role of lncRNAs through Notch signaling pathway in NSCLC (Table 1). Nevertheless, the already available results show importance of the key regulatory pathway in the NSCLC pathogenesis and regulation of lncRNAs.

Table 1. The list of lncRNAs important in pathogenesis of NSCLC acting through regulation of Notch signaling

<table>
<thead>
<tr>
<th>Type of lncRNA acting through Notch regulation</th>
<th>Biological effect in NSCLC</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>lncRNA NBR2</td>
<td>inhibits EMT progression</td>
<td>[12]</td>
</tr>
<tr>
<td>lncRNA LBX2-AS1</td>
<td>promotes cell proliferation and metastasis-poor prognosis</td>
<td>[13]</td>
</tr>
<tr>
<td>lncRNA-XIST</td>
<td>suppresses Proliferation and TGF-β1-Induced EMT</td>
<td>[14]</td>
</tr>
<tr>
<td>lncRNA-LET</td>
<td>promotes cell proliferation and metastasis-poor prognosis</td>
<td>[15]</td>
</tr>
</tbody>
</table>

Conflicts of interest
None declared.

REFERENCES