Roles of alternative splicing in the pathogenesis of lung cancer

Hongyan Liu1, Lianlian Li1, Xiaoyu Zhang1, Dayong Cui2

1Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan, 250062, Shandong, China
2School of Life Sciences, Qilu Normal University, Jinan, 250200, Shandong, China

Correspondence: Hongyan Liu or Dayong Cui
E-mail: hyliudycui@aliyun.com or cuidayong@qlnu.edu.cn
Received: August 11, 2017
Published online: September 18, 2017

Alternative splicing contributes to the vast complexity of mRNA transcripts and protein isoforms. It has been estimated that the majority of protein-coding genes are subject to alternative splicing in humans. Alternative splicing plays a critical role in physiological processes and cell development programs, and dysregulation of alternative splicing is often associated with pathologic conditions such as cancer. Indeed, the abnormal splicing is frequently found in lung cancer, which produces various protein isoforms with properties that may have different functions and therefore even diverse effects on tumor malignant development. In this highlight, we summarize the evidence supporting the functional role of alternative splicing in lung cancer, discuss the regulation of alternative splicing, and highlight the relevance of splicing variation on lung cancer therapy.

Keywords: alternative splicing; cell proliferation; migration; metastasis; lung cancer therapy

To cite this article: Hongyan Liu, et al. Roles of alternative splicing in the pathogenesis of lung cancer. Can Cell Microenviron 2017; 4: e1596. doi: 10.14800/ccm.1596.

Copyright: © 2017 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

Introduction

Alternative splicing is a mechanism for increasing protein diversity through modulating specific exon recombination during post-transcriptional processing of a transcript. Alternative splicing has essential roles in cell homeostasis and cellular processes. Growing evidence shows that deregulation of splicing is often associated with pathologic conditions such as cancer [1-3]. The abnormal splicing is frequently found in lung cancer. Consequently, the studies indicate that alternatively spliced proteins are particularly relevant in lung cancer cell growth, migration and metastasis, which will be discussed in detail below.

Roles in regulation of cell proliferation and migration

The RNA-binding protein Quaking (QKI) as a critical regulator of splicing in lung cancer is frequently down-regulated [4]. QKI-5 regulates the alternative splicing of NUMB through binding to two RNA elements of NUMB pre-mRNA, which in turn suppresses cell proliferation and blocks the activation of the Notch signaling pathway. The reduced QKI abundance is strongly associated with poorer prognosis [4], and low-level nuclear QKI in non-small cell lung cancer (NSCLC) is an independent prognostic factor for disease-free survival [5]. Another study has demonstrated that RNA binding motif protein RBM5 and its homologous RBM6/10 antagonistically regulate NUMB exon 9 alternative splicing to control tumor cell proliferation and xenograft tumor growth [6]. RBM10 mutations identified in lung cancer.
The role of SRPK1 in the maintenance of cancer stem cell-like phenotype

Splicing factors are also shown to be involved in the maintenance of cancer stem cell features. For example, the splicing factor serine-arginine protein kinase 1 (SRPK1) has been reported to stimulate a stem cell-like phenotype in human NSCLC [12]. Gong et al found that SRPK-transduced cells expressed higher levels of pluripotency-associated markers and greater self-renewal capacity [12]. Further they performed gene knockdown experiment to suppress expression of SRPK and demonstrated the converse effect. The in vivo experiments on BALB/c nude mice showed that tumors produced by SRPK1-transduced NSCLC cells were larger than those formed by control cells, suggesting that SRPK1 promotes stem cell accumulation.

EGF signaling and alternatively spliced genes

To identify oncogenesis genes in lung cancer, we performed exon array analyses of clinical specimens from adenocarcinomas and squamous cell carcinoma. We discovered many novel alternatively spliced genes such as SPAG17 (5' deletion), VAV3 (5' deletion) and BMXΔN [13, 14]. We performed 5' RACE or 3' RACE followed by Sanger sequencing to confirm these new isoforms. BMXΔN lacks the N-terminal sequence from exon 1 to exon 8. BMXΔN only expresses in lung cancer but not in paired non-cancerous tissues. Based on its function in promoting cell growth, cell migration and oncogenic transformation we suggested that BMXΔN might play important roles in lung tumorigenicity. Interestingly, BMXAN is strongly associated with EGFR mutation in these specimens [14]. Previous studies showed that EGF signaling could induce alternative splicing. In Zhou’s work [15], they demonstrated that Akt-SRPK-SR axis constitutes a major branch in transducing EGF signaling to regulate splicing program in the nucleus. A recent work reported that EGF-induced ubiquitylation of a well-known splicing regulator, hnRNP A1 together with the activation of SRPKs results in the upregulation of Rac1 splicing isoform, Rac1b, to promote cell motility [16]. We speculate that BMXΔN might be the EGF signaling pathway-induced splicing event in lung cancer. Although we found its function may be due to increased activation of ERK, the exact mechanism that drives the activation also remains to be elucidated.

Alternatively spliced genes as therapeutic targets in lung cancer

MET exon 14 skipping and MET activation have been revealed in lung cancer [17-19]. NIH3T3 cells harboring MET exon 14 splicing alterations are sensitive to MET inhibitors. Further clinical trial reported that three patients with MET exon 14 alternative spliced variant in lung or histiocytic sarcoma tumors showed durable response to MET-targeted therapies. The patients were treated with crizotinib or capmatinib for 4-5 months or 13 months with tumor reduction of 60%, 53%, and 61%, respectively [19]. The kruppel-like zinc finger transcription factor (KLF6) generates at least four alternatively spliced isoform. Kruppel-like factor splice variant 1 (KLF6-SV1) is an oncogenic splice of the KLF6 tumor suppressor gene that was found to be overexpressed in a number of human cancers including lung
cancer [20], Increased expression of KLF6-SV1 contributes to chemo-resistance in lung cancer. Targeted reduction of KLF6-SV1 by RNA interference results in the induction of spontaneous apoptosis in cell culture synergizes with chemotherapeutic agents like cisplatin, and lead to significant tumor regression in vivo [21]. These observations emphasized the importance of investigation of alternative splicing genes in lung cancer for improving targeted therapy.

Conclusions

Genome-wide analyses including microarrays and RNA-seq accelerate the identification of cancer-associated splice variants. For example, Li et al. generated alternative splicing profiles in lung adenocarcinoma and lung squamous cell carcinoma patients in TCGA by using RNA-seq data [22]. They demonstrated that a total of 3691 and 2403 alternative splicing events were significantly correlated with patient survival in lung adenocarcinoma and lung squamous cell carcinoma, respectively, including PIK3C3, RRAS2, and FGFR2. Because the isoforms are usually functionally distinct, the detailed study about a direct role of these alternatively spliced proteins as drivers of cancer development is necessary. The commonly observed transcript variants may also possess a normal physiological function, thus identification of genes with tumor-specific splicing is also needed. In conclusion, future studies in alternative splicing not only help to identify diagnostic marker may also help to develop targeted therapies.

Conflicting interests

The authors have declared that no conflict of interests exist.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81372509, 81101583), the Innovation Project of Shandong Academy of Medical Sciences, the Project for Shandong Medical and Health Science and Technology Plan Project (2014WS0067, 2015WS0193), the Foundation for Outstanding Young Scientist in Shandong Province (2014BSC03013), and the Excellent Innovation Team of Shandong Academy of Medical Sciences.

Author contributions

H.L. and D.C. wrote the manuscript, L.L. and X.Z. revised the manuscript.

Abbreviations


References


