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Commentary

Cell-type-specific alternative polyadenylation as a therapeutic biomarker in lung cancer progression

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Lung cancer stands as the leading cause of global cancer-related mortality, resulting in an approximate annual toll of 1.6 million lives.[1] Within this context, non-small cell lung cancer (NSCLC) comprises about 85% of cases, encompassing a range of histological subtypes.[2] Given the intricate genetic modifications underlying the emergence and progression of NSCLC, extensive gene expression profiling has pinpointed a multitude of dysregulated genes.[3] These discoveries have significantly informed clinical prognostications and predictions of therapeutic responsiveness. An array of mechanisms, including exon deletion, copy-number variation, and epigenetic modification, have been linked to the disruption of gene expression profiles, as demonstrated by numerous studies.[4] Nonetheless, the comprehensive understanding of the driving forces behind gene expression dysregulation in NSCLC remains an ongoing pursuit. Alternative polyadenylation (APA) has been identified as one of the drivers of aberrant gene expression. Extensive APA events were found in multiple cancer types, which could regulate the expression of oncogenes and tumor suppressors. Accumulated evidence indicates that many APA events are cancer-type and cell-state specific. In a recent issue of *Molecular Therapy – Nucleic Acids*, Huang et al. describe the identification of heterogeneity of alternative polyadenylation events that occurs in multiple cell types by using bioinformatics pipeline and cell line experiments.[5]

In the current study, Huang et al. collected single-cell RNA sequencing data from previously published studies. Then, the authors systematically analyzed APA events in over 40,000 cells, identifying broadly dysregulated APA events across seven distinct cell types. To ascertain the potential implications of these APA events, the authors pinpointed the loss of microRNA (miRNA)-binding sites resulting from shortened 3′ UTRs, as well as the influence of APA-mediated miRNA regulation. Furthermore, the authors discerned the functional significance of APA-associated genes and validated their roles in cancer cell migration and metastasis. In a bid to explore potential interactions with APA-related genes, the authors conducted drug sensitivity tests on lung cancer cell lines using the Genomics of Drug Sensitivity in Cancer (GDSC) database (Figure 1).

According to the analyses, Huang et al. identified widespread APA events in NSCLC across various cell types. Among these events, many are specific to certain cell types and regulate the expression of oncogenes. For instance, the authors noted significant upregulation of eight genes in four distinct cell types in NSCLC samples: SPARC, RGS5, and CD59 in cancer-associated fibroblasts (CAFs), IL1RN in myeloid cells, TMBIM6 in alveolar cells, and RPL22, DERL1, and HM13 in B cells. Notably, the expression of SPARC displayed a robust correlation with patient prognosis. Subsequently, the authors explored the patterns of miRNA-binding site loss induced by APA events in these seven cell types. Prior research had already highlighted the loss of multiple miRNA-binding sites due to APA events. In line with these findings, the authors revealed the widespread occurrence of miRNA-binding site loss in genes affected by APA events. As an example, both bioinformatic analysis and experiments demonstrated the loss of the miR-203a-3p.1-binding site due to APA events in SPARC. It was also shown that miR-203a-3p.1 significantly suppressed the expression of SPARC. Furthermore, the evasion of miR-203a-3p.1 led to the inhibition of tumor-suppressor genes SOCS3 and ETS2. Additionally, the authors uncovered interactions between SPARC and genes regulated by epithelial-mesenchymal transition (EMT), such as COL1A1, TGFBR2, and VCAM1. These interactions are strongly correlated with cancer progression and metastasis. The study then confirmed the role of SPARC in lung cancer proliferation and migration through experiments involving SPARC knockdown cell lines. Drug response analysis also revealed that patients with high SPARC expression levels displayed greater sensitivity to cisplatin treatment compared with the low-SPARC-expression group. Therefore, the analysis suggested that patients with high SPARC expression might derive more benefits from cisplatin treatment.

The innovation of cell-type-specific APA represents a significant advancement in the field of NSCLC. Currently, our understanding of dynamic APA regulation in different cell types remains rudimentary. The heterogeneity of APA in distinct cell types may yield valuable insights into the mechanisms of carcinogenesis, progression, and metastasis. While SPARC has been extensively studied in various cancer cell lines, its role in tumorigenesis remains controversial due to its highly cell-type-specific functions.[6] A previous study demonstrated that the low expression of SPARC in lung cancer cells

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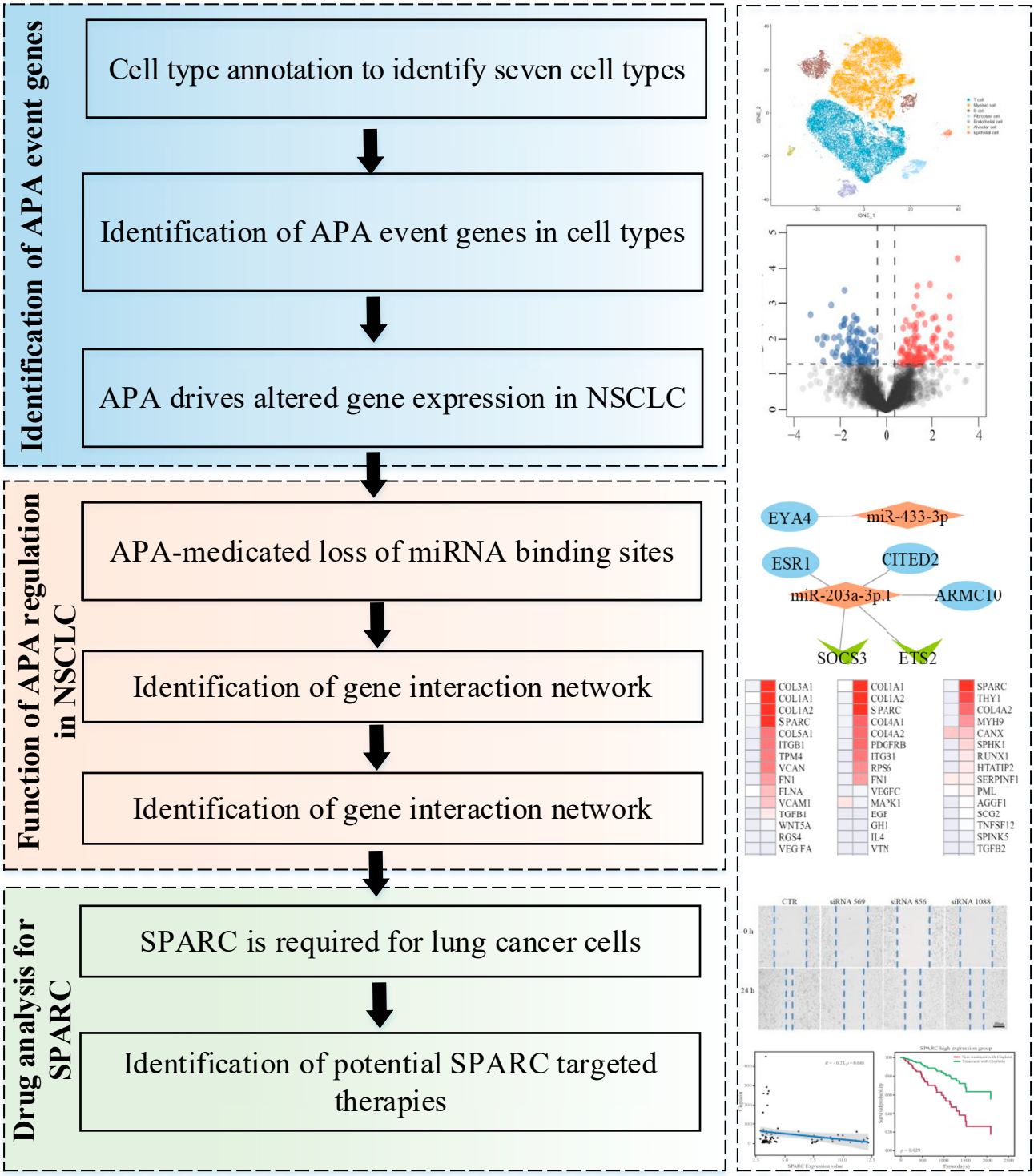

Figure 1. General representation of the Huang et al. study with key highlights and methods

After identifying the APA events in multiple cell types, the study focused on exploring the functions of cell-type-specific APA events. APA can result in the loss of miRNA-binding sites and the upregulation of mRNA expression, subsequently influencing downstream genes and signaling pathways involved in cancer progression and metastasis. Additionally, this study revealed the APA-induced upregulation of SPARC in cancer-associated fibroblasts, which can be utilized to predict the prognosis of patients with NSCLC for cisplatin treatment.

results from its aberrant methylation.[7] However, the cell-type-specific function of SPARC in NSCLC remains unknown. This study not only broadens our understanding of the underlying biological mechanisms of NSCLC but also identifies potential targets for predicting the response to cisplatin treatment in patients with NSCLC. Future research should aim to optimize the therapeutic potential of SPARC in CAFs, uncover its response to other therapies, and comprehensively assess its efficacy as a drug target in mouse models and preclinical trials. In conclusion, this study provides novel insights into the mechanisms underpinning drug resistance in patients with NSCLC.

AUTHOR CONTRIBUTIONS

All authors actively contributed to the writing of this commentary.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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