Downregulation of m6A reader YTHDC2 promotes the proliferation and migration of lung cancer and cigarette smoke-exposed BEAS-2B cells

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Research

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Abstract

Background: Lung cancer is one of the most common carcinomas worldwide. Cigarette smoking is considered as the leading cause of lung cancer. The aberrant expression of several YTH family proteins has been reported to be closely associated with several cancers. This study aims to evaluate the expression profile and function of YTHDC2, an RNA m6A methylation reader protein, by in vitro and animal experiments and bioinformatics analysis.

Methods: The expression of YTHDC2 gene and protein was analyzed by the GEPIA online tool and Gene Expression Omnibus (GEO) database, as well as immunohistochemistry of tissue arrays. The YTHDC2 expression in cigarette smoke-exposed cells was examined by RT-qPCR and western blot assays. The TCGA datasets and proteomic analysis of YTHDC2 knockdown cells were used to predict the clinical significance and biological function of YTHDC2. Functional assays, including wound healing, transwell migration, cell cycle and cell proliferation, were used to determine the biological role of YTHDC2 in lung cancer. The xenograft animal model further validated the tumor suppressor effect of YTHDC2 in vivo. The copy number variation of YTHDC2 was analyzed by TCGA datasets and TaqMan copy number assay.

Results: YTHDC2 was significantly low-expressed in lung cancer and cigarette smoke-exposed cells. Notably, decreased YTHDC2 was found highly associated with smoking history, pathological stage, invasion depth, and lymph node metastasis, as well as poor outcomes. The YTHDC2 related genes and proteins were enriched in several cancer-related pathways, and several tumor suppressor genes were found positively correlated with YTHDC2. The in vivo and in vitro study revealed that overexpression of YTHDC2 inhibited the proliferation and migration ability of lung cancer cells, as well as the tumor growth in nude mice. Besides, a significant positive correlation between the copy number and expression level of YTHDC2 was found in lung cancer.

Conclusions: Our results indicated that the smoking-related down-regulation of YTHDC2 was associated with enhanced proliferation and migration of lung cancer cells and appeared to be regulated by DNA copy number variation. Importantly, YTHDC2 may serve as a tumor suppressor gene and a favorable prognostic indicator in lung cancer patients.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures
Figure 1

The YTHDC2 gene and protein were down-regulated in lung cancer patients from the TCGA, GEO and HPA databases, as well as in cigarette smoke-exposed cells. (A) Differential analysis of YTHDC2 mRNA expression in lung cancer tissues based on the GEPIA tool. *p < 0.05 versus normal tissues. Differential analysis of YTHDC2 mRNA expression in lung cancer tissues in GSE32665 (B) and GSE19188 (C). (D) The representative IHC images showed that the YTHDC2 staining was found in the cytoplasm of the cells...
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Identification of TSGs and MRGs in YTHDC2 related genes. Volcano plots showing the genes correlated with YTHDC2 in LUAD (A) and LUSC (B) in the TCGA database by using the LinkedOmics online tool. Scatter plots showing the KEGG enrichment results of the genes associated with LUAD (C) and LUSC (D). Scatter plots showing the biological process enrichment results of the genes associated with LUAD (E) and LUSC (F). Rich Factor is the ratio of the related genes annotated in a pathway to all the genes in this pathway.
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YTHDC2 mRNA expression was regulated by gene amplification. Distribution of LUAD (A) and LUSC (D) patients with different YTHDC2 amplification status. YTHDC2 mRNA expression in LUAD (B) and LUSC (E) tissues with different YTHDC2 amplification status. Different letters (a, b, c, and d) represent statistically significant group differences. Pearson correlation analysis showed a significant positive correlation between YTHDC2 mRNA expression and copy numbers in LUAD (C) and LUSC (F). Line represents linear regression of data (LUAD: y=1.065x+9.177, R² = 0.385; LUSC: y=0.965x+9.318, R² = 0.4444).
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