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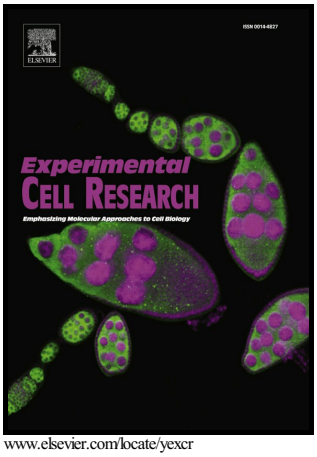

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MicroRNA-30e-5p suppresses non-small cell lung cancer tumorigenesis by regulating USP22-mediated Sirt1/JAK/STAT3 signaling

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Abstract

MicroRNA-30e-5p (miR-30e-5p) is a tumor suppressor that is known to be downregulated in non-small cell lung cancer (NSCLC). However, how miR-30e-5p inhibits NSCLC tumorigenesis is not known. Ubiquitin-specific peptidase 22 (USP22) is upregulated in NSCLC and promotes tumorigenesis via a Sirt1-JAK-STAT3 pathway. In this study, we investigated whether miR-30e-5p inhibits tumor growth by targeting USP22 in NSCLC. Our results reveal that miR-30e-5p expression was correlated negatively with USP22 in NSCLC tissues. Luciferase reporter assays showed that miR-30e-5p negatively regulated USP22 expression by binding to a specific sequence in the 3′UTR. MiR-30e-5p overexpression and *USP22* knockdown significantly inhibited tumor growth *in vivo* and induced cell cycle arrest and apoptosis in NSCLC cells *in vitro*. The effects of miR-30e-5p inhibition were prevented by *USP22* knockdown. MiR-30e-5p inhibited SIRT1 expression and increased expression of p53 and the phosphorylated form of STAT3 (pSTAT3). Furthermore, miR-30e-5p prevented USP22-mediated regulation of SIRT1, pSTAT3, and p53 expression. Taken together, these findings suggest that miR-30e-5p suppresses NSCLC tumorigenesis by downregulatingUSP22-mediated Sirt1/JAK/STAT3 signaling. Our study has identified miR-30e-5p as a potential therapeutic target for the treatment of NSCLC.

Keywords Non-small cell lung cancer; microRNA-30e-5p; ubiquitin-specific peptidase 22; tumorigenesis; tumor suppressor; oncogene.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1] and the majority of cases are diagnosed as non-small cell lung cancer (NSCLC). NSCLC is usually diagnosed in advanced stages and cannot be treated with curative surgery. Although progress has been made in developing new treatments, the prognosis of advanced NSCLC remains poor. Therefore, it is necessary to identify novel therapeutic targets to improve the treatment of NSCLC patients.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding directly to the 3′UTR of target genes. MiRNAs play critical roles in the pathogenesis of different cancers [2]. MiR-30e-5p functions as a tumor suppressor by targeting the oncogenic Wnt/β-catenin/BCL9 pathway in multiple myeloma [3]. Furthermore, miR-30e-5p