

MANF Drives Ferroptosis Resistance in Lung Adenocarcinoma Through RELA-dependent Activation of the KIF2C/AKT Signaling Axis

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INTRODUCTION

Ferroptosis resistance is increasingly recognized as a key mechanism underlying tumor progression and therapeutic failure in lung adenocarcinoma (LUAD). The upstream regulators that sustain anti-ferroptotic signaling remain incompletely defined. Mesencephalic astrocyte-derived neurotrophic factor (MANF), an endoplasmic reticulum stress-related protein, has been implicated in cellular stress responses, but its role in LUAD progression and ferroptosis regulation is unknown. This study investigated the clinical significance and molecular function of MANF in LUAD.

METHODS

Expression and prognostic analyses were performed using TCGA-LUAD and GEO datasets, with validation in lung adenocarcinoma tissue microarrays. Gain- and loss-of-function experiments were conducted in LUAD cell lines. Cell proliferation, migration, and ferroptosis-related biochemical parameters were evaluated. Protein interaction, transcriptional regulation, and signaling pathway activation were examined using co-immunoprecipitation, GST pull-down, ChIP-qPCR, and luciferase reporter assays. Xenograft models were used for in vivo validation.

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RESULTS

MANF was significantly upregulated in LUAD tissues and independently associated with poor overall survival. Functional studies showed that MANF promoted proliferation and migration of LUAD cells and suppressed ferroptosis, characterized by decreased Fe²⁺ and lipid peroxidation and increased GPX4 activity. Mechanistically, MANF directly interacted with RELA and enhanced its nuclear translocation, leading to transcriptional activation of KIF2C. KIF2C upregulation maintained AKT phosphorylation and reinforced antioxidant defense, thereby inhibiting ferroptosis. Disruption of the MANF-RELA-KIF2C-AKT axis restored ferroptotic sensitivity and suppressed tumor growth in vitro and in vivo.

CONCLUSIONS

MANF promotes ferroptosis escape in lung adenocarcinoma by facilitating RELA nuclear translocation and activating the KIF2C/AKT pathway. Targeting the MANF-RELA-KIF2C axis may represent a potential therapeutic strategy to enhance ferroptosis-based treatment in LUAD.