

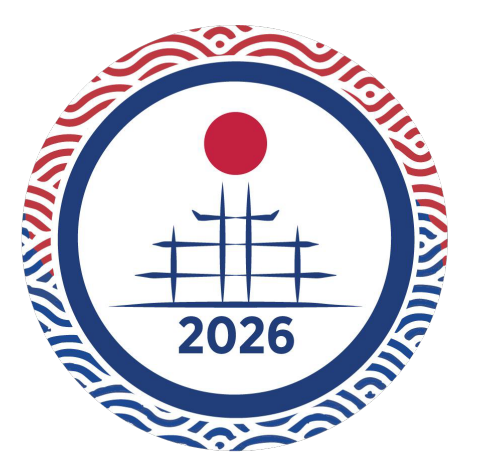


P2.035: Testosterone Promotes NSCLC Metastasis via the FGF21/AKT/mTOR Signaling Axis

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IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Metastasis remains a major determinant of poor prognosis in non-small cell lung cancer (NSCLC). Emerging evidence suggests that Testosterone contributes to tumor progression, yet its role and underlying mechanisms in NSCLC metastasis are not fully understood. This study aimed to investigate whether Testosterone promotes NSCLC metastasis through the FGF21/AKT/mTOR signaling pathway and to elucidate the associated molecular mechanisms.

DISCUSSION AND CONCLUSION

This study demonstrates that Testosterone promotes NSCLC metastasis via activation of the FGF21/AKT/mTOR signaling axis, thereby enhancing EMT and metastatic potential. Pharmacological inhibition of androgen signaling with finasteride suppresses this pathway, suggesting a potential therapeutic strategy. These findings provide mechanistic insights and support targeting androgen-related pathways in NSCLC metastasis.

METHODS

Mendelian randomization (MR) analysis was conducted to evaluate the causal relationship between Testosterone and AKT phosphorylation. NSCLC cell lines (PC9, A549, and H1299) were treated with Testosterone, and Western blot analysis was performed to assess activation of the AKT/mTOR pathway. Transcriptomic sequencing identified key downstream mediators. Lentiviral systems were used to construct stable FGF21 knockdown and overexpression cell lines to evaluate their effects on cell migration, invasion, and epithelial-mesenchymal transition (EMT). A mouse liver metastasis model was established to assess the in vivo effects of Testosterone. Immunohistochemistry (IHC) was used to examine FGF21 and EMT-related markers. Additionally, the antiandrogen finasteride was applied to validate pathway involvement.

KEYWORDS

Testosterone; NSCLC; FGF21

RESULTS

MR analysis demonstrated a significant causal association between Testosterone and AKT1/2/3 phosphorylation (OR = 1.588, p = 0.036). In vitro, Testosterone markedly increased phosphorylation of AKT and mTOR in all three NSCLC cell lines, activating the AKT/mTOR pathway and promoting EMT. Transcriptomic analysis identified FGF21 as a critical mediator, with its expression significantly upregulated following Testosterone treatment. Functional assays showed that FGF21 overexpression enhanced migration and invasion, whereas its knockdown suppressed these effects. In vivo, Testosterone significantly increased liver metastasis formation in NSCLC-bearing mice. IHC confirmed elevated FGF21 expression and EMT marker changes in metastatic lesions. Notably, finasteride treatment effectively reversed Testosterone-induced metastatic phenotypes, accompanied by reduced FGF21 expression and inhibition of AKT/mTOR signaling.

