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# FGF19 Is Coamplified With CCND1 to Promote Proliferation in Lung Squamous Cell Carcinoma and Their Combined Inhibition Shows Improved Efficacy

*Yanshuang Zhang*[1], *Tingyu Wu*[1], *Fan Li*[1], *Yirui Cheng*[1], *Qing Han*[1], *Xin Lu*[1], *Shun Lu*[2] *and Weiliang Xia*[1]*

[1] State Key Laboratory of Oncogenes and Related Genes, Ren Ji Hospital, School of Medicine and School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China, [2] Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Lung squamous cell carcinoma (LUSC) remains as a major cause of cancer-associated mortality with few therapeutic options. Continued research on new driver genes is particularly important. FGF19, a fibroblast growth factor, is frequently observed as amplified in human LUSC, which is also associated with multiple genomic gains and losses. However, the importance of these associated changes is largely unknown. In this study, we aimed to clarify a novel mechanism that link neighboring oncogene co-amplification in the development of LUSC. We found that FGF19 was co-amplified and co-expressed with its neighboring gene CCND1 in a subset of LUSC patients and associated with poor prognosis. Moreover, FGF19 combined with CCND1 promoted the cell cycle progression of LUSC cells. Mechanistically, FGF19 also enhanced CCND1 expression by activating FGFR4-ERK1/2 signaling and strengthening CCND1-induced phosphorylation and inactivation of retinoblastoma (RB). In a murine model of lung orthotopic cancer, knockdown of CCND1 was found to prolong survival by attenuating FGF19-induced cell proliferation. Furthermore, the combination treatment of the FGFR4 inhibitor BLU9931 and the CDK4/6 inhibitor palbociclib potentiated the growth inhibition and arrested cells in G1 phase. *In vivo*, co-targeting FGFR4 and CDK4/6 also showed marked inhibition of tumor growth than single agent treatment. These findings further elucidate the oncogenic role of FGF19 in LUSC and provide insights into how the co-amplification of neighboring genes synergistically function to promote cancer growth, and combined inhibition against both FGF19 and CCND1 is more effective.

**Keywords: LUSC, FGF19, FGFR4, CCND1, CDK4/6, amplification, combined inhibition**

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***Correspondence:**
*Weiliang Xia*
*wlxia@sjtu.edu.cn*

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