14-3-3ζ/TGFβR1 promotes tumor metastasis in Lung Squamous Cell Carcinoma

Xiaoyuan Wang, Jianqun Ma, Yanbin Zhao, Li Cai

Conclusion
- An isoform of the 14-3-3 protein family, 14-3-3ζ, has been linked with tumor cell proliferation and apoptosis. However, the role of 14-3-3ζ in the progression of lung squamous cell carcinoma (SCC) remains unknown.
- Here, we report that 14-3-3ζ plays a critical role in lung SCC metastasis and prognosis. The expression of 14-3-3ζ was markedly higher in cancer tissues compared to adjacent normal tissues.
- Overexpression of 14-3-3ζ was correlated with advanced TNM stage (p<0.05) and lymph node metastasis (p<0.05). And the expression of 14-3-3ζ protein was associated with high levels of TGFβR1 protein (p=0.005), and pSMAD3 (p=0.033).
- Lung SCC patients with high 14-3-3ζ expression had a shorter overall survival and a higher rate of recurrence. Additionally, 14-3-3ζ knockdown inhibited cell proliferation, migratory and invasive properties in vivo and vitro, which was concurrent with downregulation of epithelial mesenchymal transition (EMT).
- Thus, this study provides the evidence that 14-3-3ζ is a novel tumor promoter and may serve as a candidate prognostic biomarker and target for new therapies in lung SCC.

Introduction
- Lung cancer is the leading cause of cancer morbidity and mortality worldwide. Lung SCC is lack of effective targeted therapy compared with adenocarcinoma, in which a biomarker is utilized to select patients most likely to benefit.
- 14-3-3ζ is observed in various cancers and has been emphasized as a critical role in tumor genesis and progression such as intracellular signaling, cell cycle control, apoptosis and transcription regulation.
- Transforming growth factor β (TGFβ) superfamily plays crucial roles in cell proliferation, EMT and metastasis. Two types of cell-surface receptors, TGFβR1 and TGFβR2, are mainly involved in the transmission of TGFβ signaling to perform multiple intracellular functions.

Results
- Expression of 14-3-3ζ is significantly up-regulated in lung SCC tissues compared with adjacent normal tissues.
- The expression of 14-3-3ζ, TGFβR1 and pSMAD3 proteins in lung SCC tissues and the relationship with clinicopathological characteristics.
- Knockdown of 14-3-3ζ suppressed tumor growth and decreases the formation of metastases in vivo.

Association of 14-3-3ζ and TGFβR1 proteins with survival of lung SCC patients.
- 14-3-3ζ promotes the proliferation of in lung SCC cells in vitro.
- 14-3-3ζ induces the migration, invasion and regulates EMT marker of in lung SCC cells in vitro.
- 14-3-3ζ regulates proliferation, metastasis and EMT markers through TGFβR1.

Although great efforts have been made to understand the mechanism of adenocarcinoma, current knowledge of SCC remained limited.
- In the light of the above findings, 14-3-3ζ can be considered as a novel marker of metastasis and prognosis in lung SCC patients.