

Targeting MELK by OTSSP167 effectively inhibits tumor growth and hampers lung metastasis in esophageal squamous cell carcinoma

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Abstract

Background and Purpose: Esophageal squamous cell carcinoma (ESCC) is the sixth leading cause of cancer-related deaths worldwide and there is no clinically effective targeted therapeutic drugs. OTSSP167, an orally administrated inhibitor targeting maternal embryonic leucine zipper kinase (MELK), is currently in several clinical trials in patients with hematological or solid malignancies. The objective of the study is to determine the antitumor activity of OTSSP167 against ESCC and elucidate its underlying mechanism. **Experimental Approach:** Effects of OTSSP167 on ESCC cell viability, colony formation, apoptosis, migration, invasion and the related signaling molecules were determined. the anti-neoplastic activity of OTSSP167 against tumor growth and metastasis was evaluated in the ESCC xenograft model and lung metastasis mouse model, respectively. **Key Results:** OTSSP167 effectively inhibited ESCC cell proliferation and colony formation. In addition, OTSSP167 induced cell apoptosis in a mitochondrial-dependent pathway via downregulation of Survivin. OTSSP167 also exhibited strong synergism with 5-fluorouracil and cisplatin in inducing cell growth inhibition and apoptosis. Furthermore, OTSSP167 remarkably suppressed migration and invasion of ESCC cells with MMP-2 decreased. Importantly, OTSSP167 potently hampered the growth and lung metastasis of ESCC in nude mice. Mechanistically, we demonstrated that MELK/FOXM1 signaling was fundamental for the OTSSP167-mediated tumor growth inhibition as well as metastasis blockage in ESCC. **Conclusion and Implications:** OTSSP167 exhibits a strong anti-neoplastic activity against ESCC growth and metastasis through targeting MELK/FOXM1 signaling. These data suggests that OTSSP167 is a promising therapeutic agent and warrants clinical trials to further investigate its efficacy in ESCC patients.

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Figure 1

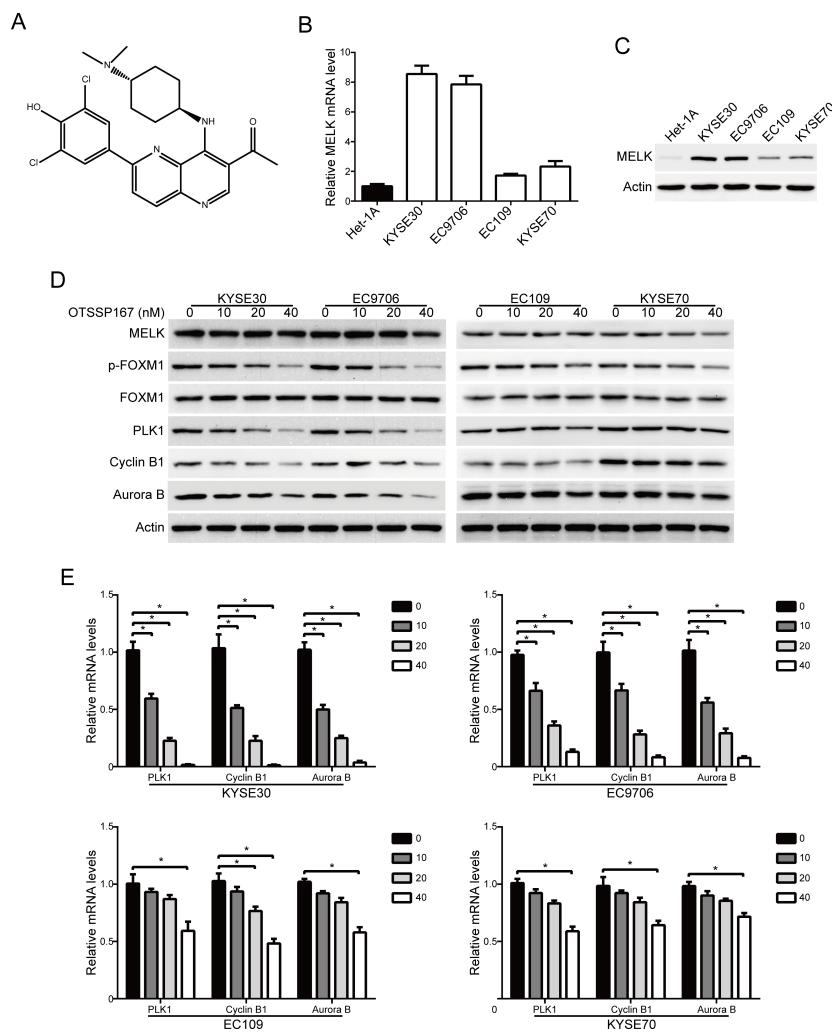


Figure 2

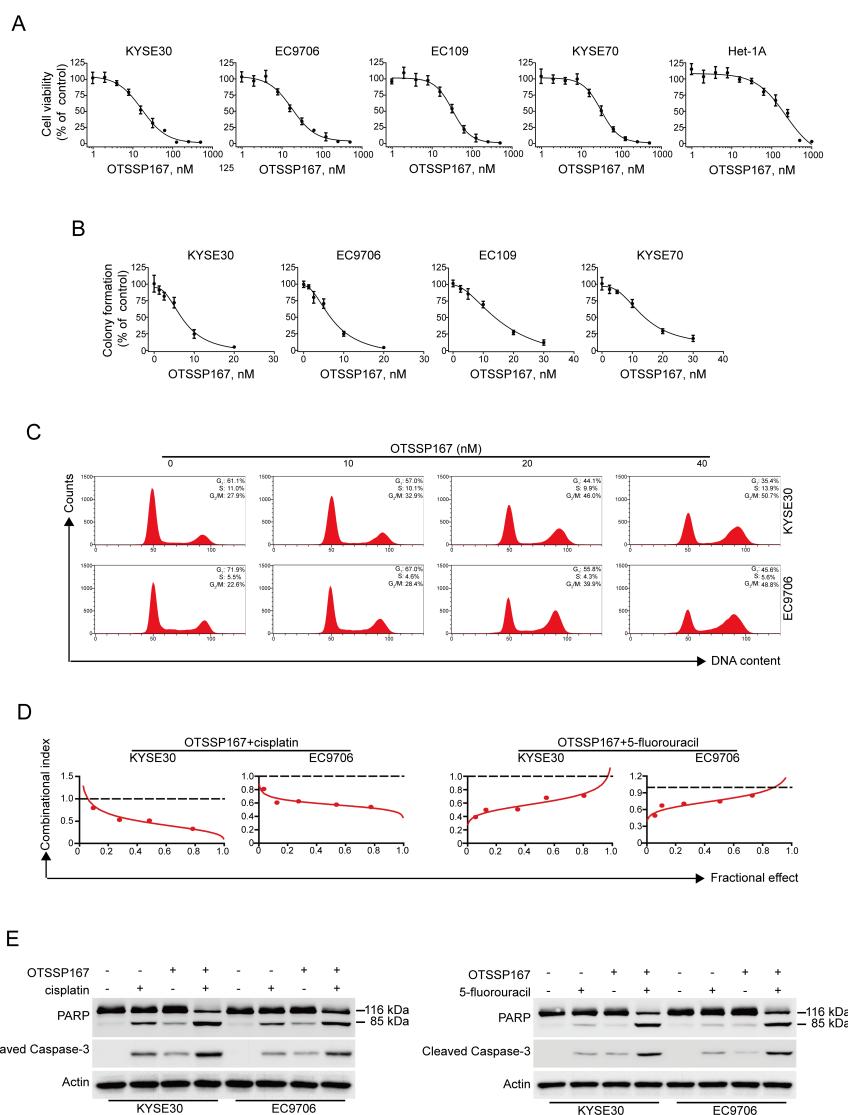


Figure 3

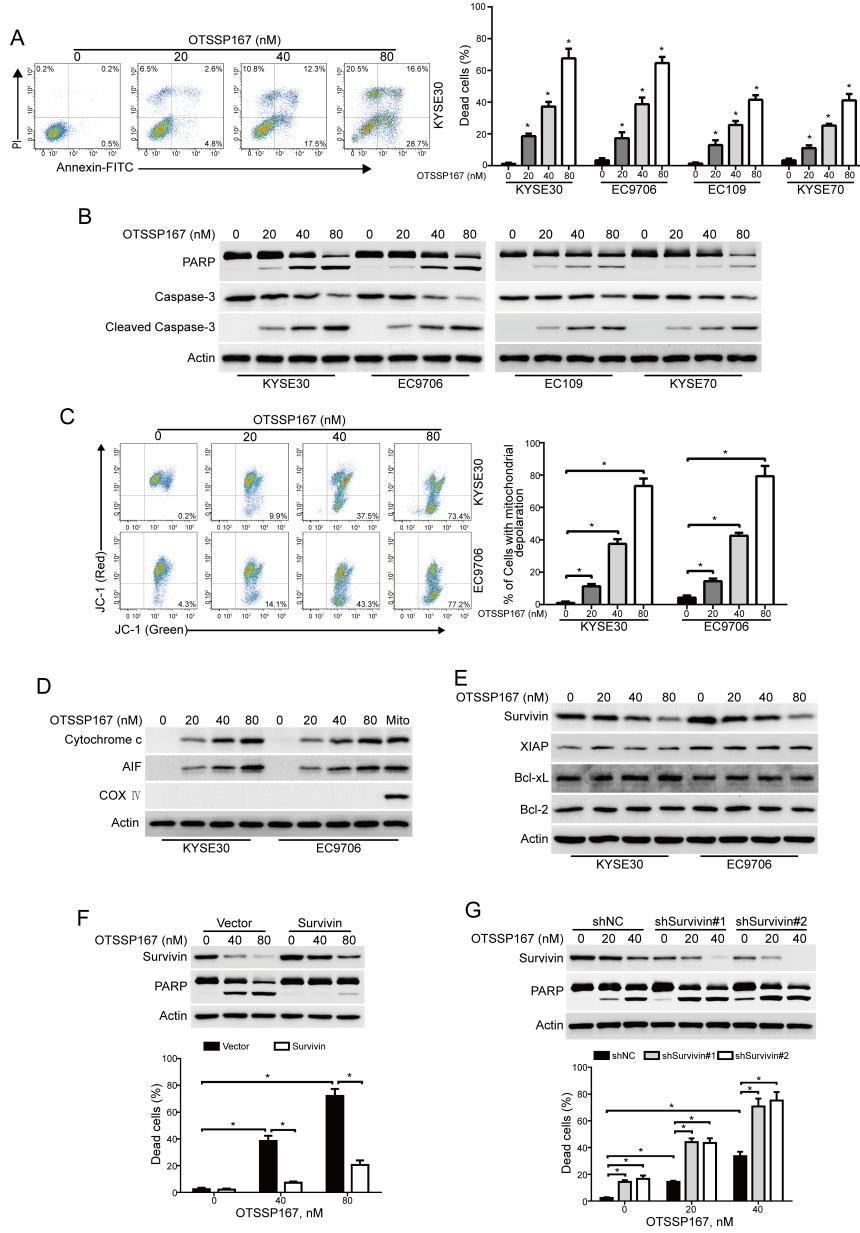


Figure 4

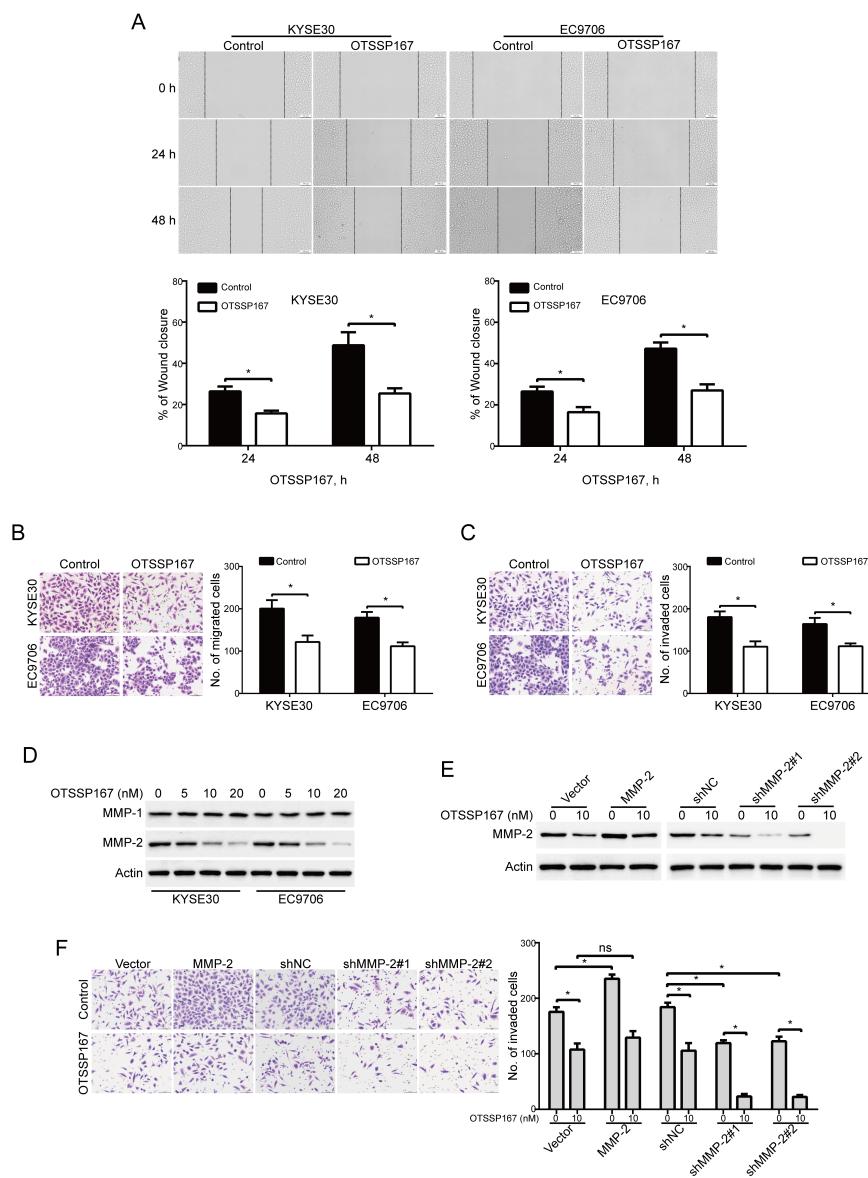


Figure 5

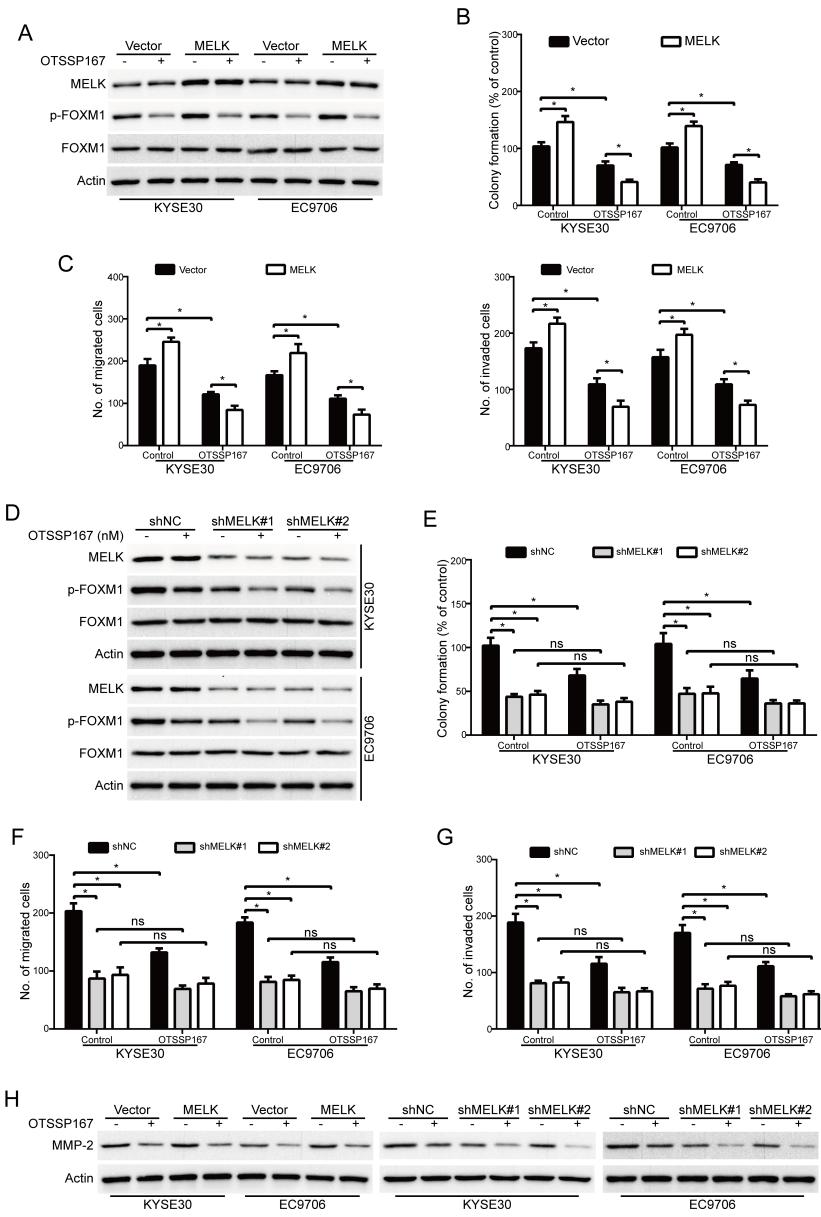


Figure 6

