Target P13K sensitizes FGFR inhibitor in cholangiocarcinoma

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Introducton

Intrahepatic cholangiocarcinoma (ICC) is highly malignant with limited treatment options[1-4]. FGFR inhibition (FGFRi) holds significant therapeutic value for ICC with FGFR2 fusion mutations. However, progress in clinical trials has been slow, and the occurrence of drug resistance poses a challenging problem. Effective combination targeted strategies are of significant importance for improving patient prognosis[5]. The purpose of this study is to identify FGFRi combination therapy approaches[6].

Methods and Materials

In this study, we established ICC models harboring FGFR2-fusion through high-pressure tail vein injection of NICD+AKT+FGFR2 plasmids in C57BL/6 mice. Subsequently, FGFR2 fusion-positive ICC organoids were cultured from mouse models[1-4] . Further, FGFR2 fusion stable transfectants of human ICC cell lines HuCCT1 and RBE were generated via lentivirus infection[5] . Additionally, organoids of human ICC with FGFR2 fusion mutations were cultivated[5-6] .

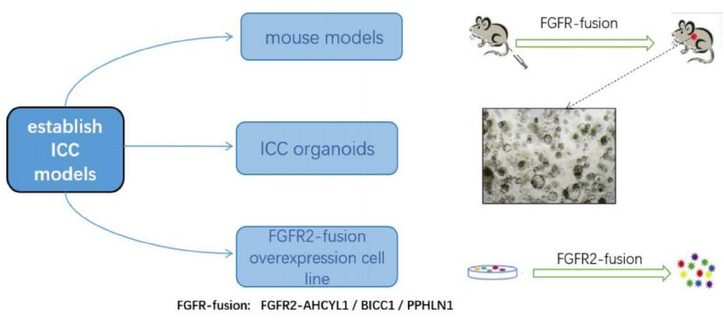

Figure 1 Schematic diagram

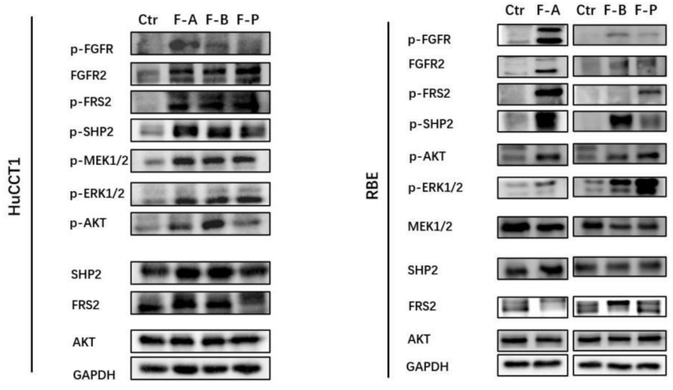

Figure 2 Hucct1/RBE：FGFR2-AHCYL1/BICC1/PPHLN1 overexpression promotes activation of downstream signaling pathways such as MEK/ERK and AKT

Result

After treating murine ICC organoids with FGFRi monotherapy using BGJ398, RNA-seq analysis revealed the activation of the MAPK signaling pathway. Subsequently, we observed a synergistic anti-tumor effect when combining MEK inhibitor, trametinib, with BGJ398 at the level of murine ICC organoids and in situ ICC in mice. Finally, consistent results were obtained using HuCCT1 and RBE cell lines with FGFR2 fusion stable transfectants, as well as human ICC organoids harboring FGFR2 fusion. Therefore, we conclude that MEK inhibition sensitizes the efficacy ofFGFRi. The combination therapy of MEKi and FGFRi represents a promising therapeutic strategy for FGFR2 fusion ICC with significant clinical implications.

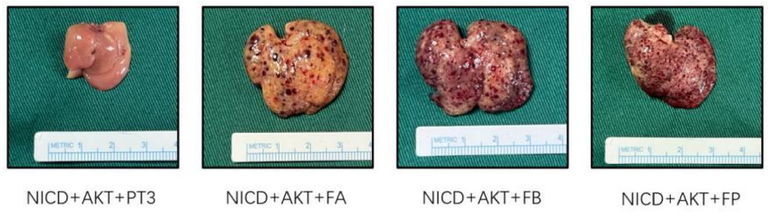

Figure 3 ICC models harboring FGFR2-fusion through high-pressure tail vein injection of NICD+AKT+FGFR2 plasmids in C57BL/6 mice：FGFR2 fusion acelerated tumor formation

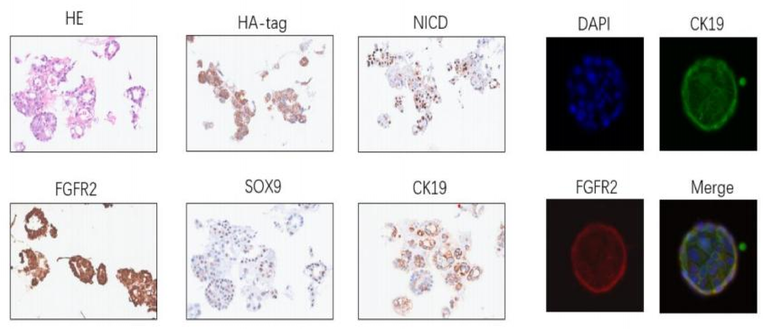

Figure 4 Mice ICC organoids :HE/ IHC/ IF

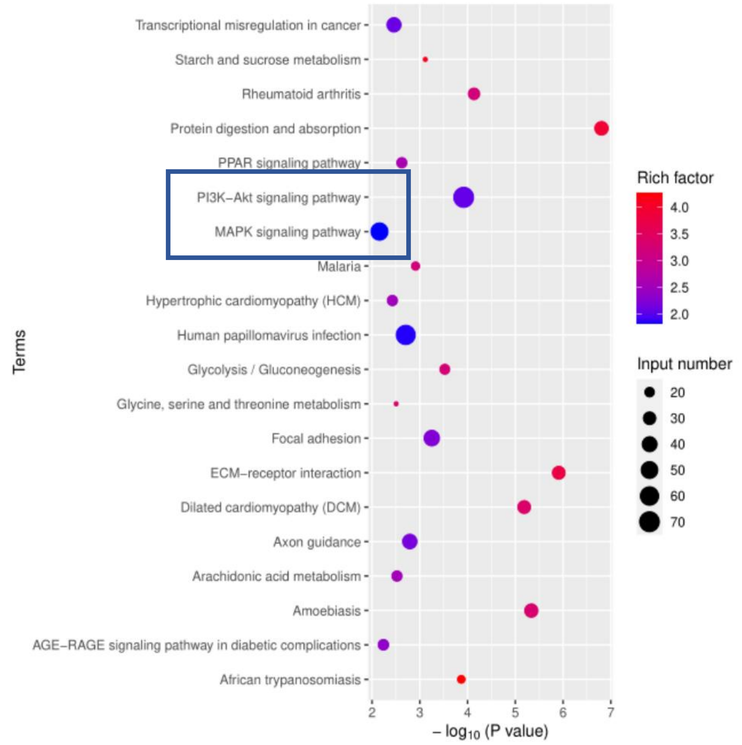

Figure 5 RNA-seq analysis revealed the activation of the MAPK signaling pathway

Conclusions

Consistent results were obtained using HuCCT1 and RBE cell lines with FGFR2 fusion stable transfectants, as well as human ICC organoids harboring FGFR2 fusion. Therefore, we conclude that MEK inhibition sensitizes the efficacy of FGFRi. The combination therapy of MEKi and FGFRi represents a promising therapeutic strategy for FGFR2 fusion ICC with significant clinical implications.

References

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