

BLOCKING FGFR2 AND SHP2 CAN EFFECTIVELY SUPPRESS TUMOR PROGRESSION IN GASTRIC CANCERS WITH FGFR2 ALTERATION

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Background Fibroblast growth factor receptor 2 (FGFR2) alteration, including gene amplification and fusion, are closely associated with poor prognosis and low response to chemotherapy and immunotherapy in advanced gastric cancer (GC) patients. The acquired alternative activation of bypass signaling is an important cause of FGFR2 inhibitor insensitivity and resistance. Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2) is the shared downstream of all Receptor tyrosine kinases (RTKs). Meanwhile, SHP2 is also an important downstream molecule of Programmed cell death protein-1 (PD-1) signaling. Herein, blocking SHP2 and FGFR2 may be able to suppress tumor progression with both targeted intervention and immune activation in gastric cancers with FGFR2 alteration.

Methods Cell Counting Kit-8 and Annexin V-FITC Apoptosis Detection Kit were used to evaluate cell proliferation and apoptosis. Western blot was used to detect the expression levels of proteins in several FGFR2-initiated downstream signaling cascades. Primary human T cells were separated from human peripheral blood. PD-1 and IFN- γ expressions of T cells were detected by flow cytometry. Finally, drug-stimulated T cells were incubated with SNU16 cells for tumor-killing capacity assessment by CFSE-PI double staining.

Results We found that the combination administration of SHP099 and AZD4547 significantly inhibited cancer cell proliferation in vitro in FGFR2i-resistant model derived from ascites of a female GC patient with FGFR2 amplification, two FGFR2-amplified GC cell lines and GC cells transfected with one kind of FGFR2 fusion. We detected a more remarkable suppression of the downstream signals of FGFR2 in combined therapy, implying that SHP099 may be able to overcome FGFR2 inhibitor resistance by suppressing RAS/ERK and PI3K/AKT pathways. Given the immunosuppressive role of SHP2 under PD-1 signaling induction, we also proved that SHP099 treatment can significantly increase the secretion level of IFN- γ and downregulated the expression of PD-1 in human CD8+ T cells. T cells activated by SHP099 had a more potent anti-tumor ability to FGFR2-amplified gastric cell line.

Conclusions In general, SHP099 can not only boost the tumor-cytotoxicity effect and overcome the drug resistance of AZD4547, but also activate cytotoxic T lymphocytes to kill tumor cells in FGFR2-altered gastric cancers. Our results demonstrate the utility and feasibility of combining SHP2 to FGFR2 inhibitors for GC patients with FGFR2 alteration.

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