SUPPRESSION OF FUMARATE HYDRATASE ACTIVITY INCREASES THE EFFICACY OF CISPLATIN-MEDIATED CHEMOTHERAPY IN GASTRIC CANCER

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Background Gastric cancer (GC) is one of the most common malignancies worldwide. Due to the low rate of early detection, most GC patients were diagnosed at advanced stages and had a poor response to chemotherapy. Some studies found that Fumarate hydratase (FH) participated in the DNA damage response and its deficiency was associated with tumorigenesis in some cancers. In this study, we investigated the relationship between FH and cisplatin (CDDP) sensitivity in GC cell lines.

Methods We examined the role of FH for CDDP sensitivity in GC cells. Immunoblotting, qPCR, MTS were used to verify the relationship between FH expression and CDDP sensitivity. GC cells with FH knockdown were treated by CDDP and the apoptotic indexes were measured. Then we used FH inhibitor Miconazole Nitrate (MN) to study the role of FH on GC cell death induced by CDDP. CDDP-induced apoptosis was quantified by immunoblotting and flow cytometric analysis. The role of FH on CDDP-induced DNA damage was evaluated using electrophoresis, comet assay and immunofluorescence. The synergistic effect of MN with CDDP on GC was measured on GC cells, cell line-derived xenografts, and patient-derived xenograft (PDX) model.

Results We found that FH was the most significant gene which induced by CDDP treatment and the suppression of FH could enhance the cytotoxicity of CDDP. MN could inhibit FH activity and enhance the effect of CDDP in vitro and in vivo. We also investigated the significance of expression of FH in GC tissues. The FH expression, which was higher in GC tissues than in noncancerous tissues, was negatively associated with the prognosis of patients.

Conclusions In summary, we demonstrated that FH is a reliable indicator for response to CDDP treatment in GC and the inhibition of FH may be a potential strategy to improve the effects of CDDP-based chemotherapy.