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Involvement of the mitogen-activated protein kinase pathway in drug resistance in hepatocellular carcinoma cells

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Systemic treatment options for hepatocellular carcinoma are rare, since it exhibits strong intrinsic and acquired drug resistance. The overexpression of ABC transporters hampers the effects of chemotherapy and correlates with MAPK-pathway activation in HCCs. In this study, we systematically investigated the role of MAPK-pathway inhibition on mediating HCC cell proliferation and ABC transporter expression *in vitro*.

We demonstrated that Raf1 and MEK inhibitors could inhibit HCC cell growth. In particular, the combination of the MEK inhibitor with gemcitabine or doxorubicin resulted in additional growth inhibition of HCC cells. Furthermore, we detected that MEK inhibition increased the chemosensitivity of HCC cells by enhanced intracellular doxorubicin accumulation. Furthermore, MEK inhibition deactivated phosphorylated ERK and decreased the endogenous expression of the MRP1. Additionally, the treatment with MEK inhibitors reversed gemcitabine and doxorubicin-induced up-regulation of MRP1 and MRP3.

In conclusion, these results indicate that MEK inhibition increases intracellular chemo drug accumulation and reverses drug resistance through the down-regulation of MRP1 and MRP3 expression.