TARGETING RAS IN HCC

Only about 30% of patients with hepatocellular carcinoma (HCC) are eligible to receive curative therapies and, even in these patients, recurrence rates are still high. Consequently, new therapeutic strategies are required. Pippa Newell and colleagues found that molecular alterations of the Ras pathway are common in HCC and that the multikinase inhibitor sorafenib, given alone or in combination with the mTOR inhibitor rapamycin, had antineoplastic effects in experimental models.

A comprehensive and integrative genomic analysis of 351 samples taken from patients with HCC during liver resection or transplantation showed that overexpression of H-RAS, DNA copy number gains in *B-RAF*, and aberrant methylation of the Ras-binding tumor suppressor proteins RASSF1A or NORE1A were common and varied according to the stage of hepatocarcinogenesis. Activation of the Ras pathway was assessed by measuring the phosphorylation of ERK, a downstream target of Ras, and was seen in 10.3% of the tumor tissue and 60.3% of the endothelial cells in the samples studied.

Treatment of human HCC cell lines with sorafenib or rapamycin alone reduced cell proliferation and induced apoptosis, and treatment with sorafenib plus rapamycin enhanced these effects. In xenograft models, tumor growth was inhibited in both the monotherapy and combination groups, and the extent of tumor necrosis was greater in the animals treated with combination therapy.

By demonstrating the synergistic effect of inhibiting the Ras and mTOR signaling pathways, these data provide a clear rationale for testing sorafenib and an mTOR inhibitor, such as rapamycin or rapamycin analogs, in early phase clinical trials in patients with HCC.

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