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Alternative Mammalian Target of Rapamycin (mTOR) Signal Activation in Sorafenib-resistant Hepatocellular Carcinoma Cells Revealed by Array-based Pathway Profiling

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Abstract

Sorafenib is a multi-kinase inhibitor that has been proven effective for the treatment of unresectable hepatocellular carcinoma (HCC). However, its precise mechanisms of action and resistance have not been well established. We have developed high-density fluorescence reverse-phase protein arrays and used them to determine the status of 180 phosphorylation sites of signaling molecules in the 120 pathways registered in the NCI-Nature curated database in 23 HCC cell lines. Among the 180 signaling nodes, we found that the level of ribosomal protein S6 phosphorylated at serine residue 235/236 (p-RPS6 S235/236) was most significantly correlated with the resistance of HCC cells to sorafenib. The high expression of p-RPS6 S235/236 was confirmed immunohistochemically in biopsy samples obtained from HCC patients who responded poorly to sorafenib. Sorafenib-resistant HCC cells showed constitutive activation of the mammalian target of rapamycin (mTOR) pathway, but whole-exon sequencing of kinase genes revealed no evident alteration in the pathway. p-RPS6 S235/236 is a potential biomarker that predicts unresponsiveness of HCC to sorafenib. The use of mTOR inhibitors may be considered for the treatment of such tumors.

Full text:

http://www.mcponline.org/content/13/6/1429.abstract?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&fulltext=innopsys&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=date&resourcetype=HWCIT