# 学 位 論 文 の 要 旨

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主論文の題名

Sorafenib and TRAIL have synergistic effect on hepatocellular carcinoma

主論文の要旨

A multi-kinase inhibitor, sorafenib, was recently approved and is currently recommended for the treatment of advanced hepatocellular carcinoma (HCC). However, HCC treatment outcomes are still poor and necessitate improvement. Therefore, we investigated the influence of sorafenib in combination with each of cytotoxic chemotherapy agents, hypoxia or tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), on cytotoxicity to determine which is the better adjuvant.

Additive cytotoxicity of sorafenib to chemotherapy agents, hypoxia and TRAIL, to HCC cells was assessed using cell viability assay. Intracellular levels of anti-apoptotic proteins were determined using western blot analysis. Activation of Wnt/β-catenin signaling was assessed using a luciferase reporter gene assay. Sorafenib significantly and synergistically enhanced the cytotoxicity of TRAIL to HCC cells and 4',6-diamidino-2-phenylindole (DAPI) staining showed increased apoptosis among cells treated with sorafenib and TRAIL. This augmentation in cytotoxicity was derived from sorafenib-mediated downregulation of anti-apoptotic proteins. However, sorafenib did not enhance the cytotoxicity of chemotherapy agents (cisplatin, 5-FU or doxorubicin) or hypoxic treatment to HCC. Moreover, hypoxic treatment induced Wnt/β-catenin signaling activation.

Our data showed that in combination TRAIL and sorafenib had a synergistic cytokilling effect on HCC cells and that this effect derived from sorafenib-mediated downregulation of anti-apoptotic proteins.