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Evaluation of the Potential Antitumor Effect of Sulfasalazine Alone or in Combination with Sorafenib on Hepatocellular Carcinoma Cell Line

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common and lethal human malignancies. Lack of efficient therapy for advanced HCC is a pressing problem worldwide. Sorafenib is the only approved therapy. NFκB is now widely recognized as a key positive regulator of cancer cell proliferation. Therefore, it is reasonable to combine multikinase inhibitor with NFκB inhibitor. So, more than one anticarcinogenic agent may affect several signaling pathways and lead to much more effective killing of the tumor cells. This study aimed to evaluate the potential anti-carcinogenic effects of either sorafenib or sulfasalazine on HCC cell line and to find synergistic effect using sorafenib and sulfasalazine. HEPG2 cells were maintained in a complete medium and treated with sorafenib and/or sulfasalazine for 3 days. Sorafenib and sulfasalazine have improved PI3K/AKT (p-AKT), RAF/ERK (p-ERK, p38-MAPK) and NFκB pathways. Additionally, sulfasalazine confirmed its anticarcinogenic effects by lowering cyclin-D1 and p-eIF4E, HIF-1α, HGF, p-STAT-3, its apoptotic effect by improving the level of caspase-3, and its antiangiogenic effect by lowering VEGF level in a pattern similar to that of sorafenib. On the molecular level, sorafenib and sulfasalazine downregulated the gene expression levels of both *HIF-1α* and *c-MET*. On almost all the parameters, the sulfasalazine effects surpassed that of sorafenib, while the combination regimen showed the best effects. Our present study showed for the first time the additive effect of the coadministration of sorafenib and sulfasalazine on proliferation and apoptosis of HCC cells. This indicates an improvement in HCC therapy with sorafenib by coadministration of sulfasalazine.

(Keywords: Hepatocellular Carcinoma; PI3K/AKT pathway; Caspase-3; sulfasalazine; sorafenib; elF4E; HIF-1α; multikinase inhibitor; NFκB)