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MK-2206 induces cell cycle arrest and apoptosis in HepG2 cells and sensitizes TRAIL-mediated cell death

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Abstract It has become evident that AKT inhibitors have great potential in cancer treatment. In this study, we investigate the anticancer activity of MK-2206, a novel AKT inhibitor, on HepG2 hepatocellular carcinoma cell, and to show whether MK-2206 enhances the apoptosis-inducing potential of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The cell growth inhibition was evaluated by MTT assay and colony formation assay. Cell cycle distribution was assessed by propidium iodide flow cytometry. Apoptosis was determined by AnnexinV-FITC/PI double staining assay and caspase-9, casapse-7, caspase-3, and PARP cleavage. The results of present study showed that MK-2206-induced G1-phase arrest was associated with a marked decrease in the protein expression of cyclin D1 with concomitant induction of p21 and p27. MK-2206-induced apoptosis was characterized by cleavage of a pro-caspase in a concentration-dependent manner. Moreover, the MAP family kinases p38 kinase and JNK were activated by exposure to MK-2206. SB203580, an p38-specific inhibitor, partially blocked MK-2206-induced death of HepG2 cells and caspase activation. A combination of MK-2206 with TRAIL significantly inhibited growth of TRAIL resistant HepG2 cells. Taken together, our findings provide a new insight to better understand anticancer mechanisms of MK-2206, at least in HepG2 cell. Using of MK-2206 as a potent sensitizer to TRAIL-induced apoptotic cell death offers a promising means of enhancing the efficacy of TRAIL-based HCC treatments.

Keywords MK-2206 · HepG2 cell · PI3K/AKT · Cell apoptosis · TRAIL

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Introduction

Hepatocellular carcinoma (HCC) accounts for up to 70 % of cancer deaths in Eastern Asia and Central Africa, being the most common malignant hepatobiliar disease [1, 2]. Nearly 85 % of these cases occur in less developed countries, with China alone accounting for more than 50 % of the total [3]. The main cause of HCC is the cirrhotic liver, which associates with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and the consumption of alcohol. Dysregulation of cellular proliferation and apoptosis are frequent events related with malignant phenotype and poor responsiveness of HCC toward chemotherapy [4]. Therefore, developing effective pharmacological therapy to these dysregulation is a valid target for HCC clinical treatment.

The phosphatidylinositol3-kinase (PI3K)/AKT pathway is activated in the majority of human cancers [5, 6].