A NEW THERAPEUTIC APPROACH IN HEPATOCELLULAR CARCINOMA: TARGETING SIGNALING PATHWAYS

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Introduction

Hepatocellular carcinoma (HCC) is a highly prevalent and lethal neoplasia. Despite its significance, there are only limited therapeutic options, many with negligible clinical benefit. These poor results are related with diagnosis at advanced stages, being rarely amenable to radiotherapy, and with the highly resistance to currently available chemotherapeutic agents. In fact, advances in the understanding of tumor biology open new paths for HCC prevention and treatment through the development of targeted therapies.

Objectives

The aim of this study was to evaluate the therapeutic potential of mTOR (Everolimus), farnesiltransferase (L-744,832) and proteasome inhibitors (MG-262) as new targeted therapies in HCC cell lines in monotherapy and in combination with conventional chemotherapy.

Materials and methods

For this purpose, two HCC cell lines, the HepG2 andHUH-7 cells, were cultured in absence or presence of increasing concentration of Everolimus, L-744,832 and MG-262. The cytotoxic effect was assessed by the Alamar Blue assay and the mechanisms of cell death by optic microscopy (after May-Grünwald-Giemsa staining) and flow cytometry (Annexin V/ Propidium Iodide assay). The molecular mechanisms involved in drug cytotoxicity, namely the expression of ubiquitin conjugates, laminin A/C, cyclin D1 and proteins related to cell death (BAX and BCL2), were analysed by flow cytometry using monoclonal antibodies labeled with fluorescent probes. Cell cycle analysis was also performed by flow cytometry (IP/RNase).

Results

Our results showed that mTOR, farnesiltransferase and proteasome inhibitors had antiproliferative and cytotoxic effects in monotherapy in a dose and time dependent manner, inducing cell death preferentially by apoptosis. Furthermore, combination of Everolimus, L-744,832 and MG-262 in lower doses
than the IC50, with conventional chemotherapeutic drugs, demonstrated a synergistic cytotoxic effect.

Conclusions
Our study suggests that mTOR, farnesiltransferase and proteasome inhibitors may a new therapeutic approach in HCC, either in monotherapy or in association with conventional chemotherapy.

Key words
Hepatocellular carcinoma; Molecular targeted therapy; Signaling Pathways