Antitumor effects of OSU-2S, a nonimmunosuppressive analogue of FTY720, in hepatocellular carcinoma

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Accumulating evidence suggests the therapeutic potential of the immunosuppressive agent FTY720 (fingolimod) in hepatocellular carcinoma (HCC). Based on our previous finding that FTY720 mediates apoptosis in HCC cells by activating reactive oxygen species (ROS)-protein kinase C? (PKC?) signaling independent of effects on sphingosine-1-phosphate (S1P) receptors, we embarked on the pharmacological exploitation of FTY720 to develop a nonimmunosuppressive analogue with antitumor activity. This effort led to the development of OSU-2S, which exhibits higher potency than FTY720 in suppressing HCC cell growth through PKC? activation. In contrast to FTY720, OSU-2S was not phosphorylated by sphingosine kinase 2 (SphK2) in vitro, and did not cause S1P1 receptor internalization in HCC cells or T lymphocyte homing in immunocompetent mice. Although devoid of S1P1 receptor activity, OSU-2S exhibited higher in vitro antiproliferative efficacy relative to FTY720 against HCC cells without cytotoxicity in normal hepatocytes. Several lines of pharmacological and molecular genetic evidence indicate that ROS-PKC?-caspase-3 signaling underlies OSU-2S-mediated antitumor effects, and that differences in the antitumor activity between FTY720 and OSU-2S were attributable to SphK2-mediated phosphorylation of FTY720, which represents a metabolic inactivation of its antitumor activity. Finally, OSU-2S exhibited high in vivo potency in suppressing xenograft tumor growth in both ectopic and orthotopic models without overt toxicity. CONCLUSION: Using the molecular platform of FTY720, we developed OSU-2S, a novel PKC?-targeted antitumor agent, which is devoid of S1P1 receptor activity and is highly effective in suppressing HCC tumor growth in vivo. These findings suggest that OSU-2S has clinical value in therapeutic strategies for HCC and warrants continued investigation in this regard.
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