

ESTROGEN RECEPTOR β SELECTIVE AGONISTS HAVE ANTI-CANCER EFFICACY ON EXPERIMENTAL INTRA-HEPATIC CHOLANGIOCARCINOMA: AN IN VITRO AND IN VIVO STUDY.

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Background: Cholangiocarcinoma (CCA) is a devastating disease with increasing incidence and very poor prognosis. Therapeutic options are limited: radical surgery is applicable in less than 40% of the patients, and the response to current chemotherapy is virtually absent. Recently, it has been shown that CCA cells over-express both estrogen receptor (ER) α and β . **Aim:** To investigate the in vitro and in vivo effects of selective ER modulators on CCA growth and progression. **Methods:** Changes in cell proliferation ($[^3\text{H}]$ -thymidine incorporation) and apoptosis (caspase 3 activity) were evaluated in HuH-28 cells in vitro, in the presence of various ER subtype-selective compounds. In vivo, the effect of a novel ER β selective agonist on experimental intra-hepatic CCA in rats, induced by thioacetamide (TAA), was investigated. **Results:** In contrast to the ER α selective agonist (PTT), both the ER α -selective antagonist (MPP) and the ER β selective agonist (DPN) inhibited proliferation and induced apoptosis in HuH-28 cells in vitro. In vivo, the novel ER β selective agonist (Comp A) resulted in a 50% reduction in both the number and size of liver tumors and of liver parenchyma infiltrated by CK-19/c-neu positive cells. In Comp A treated animals tumoral areas showed reduced proliferation indexes (PCNA) and increased indices of apoptosis (TUNEL and caspase-3 staining) as compared to vehicle controls. No differences in hepatic inflammatory infiltration were observed. The in vivo effects of Comp A were abolished by co-administration of the antagonist ICI 182,780 confirming that the anti-tumor effect of Comp A was ER β mediated. **Summary/conclusion:** ER β subtype exerts anti-proliferative and pro-apoptotic effects on CCA cells in vitro, while an opposite effect was observed with ER α . In vivo, an ER β selective agonist inhibited proliferation and induced apoptosis of experimental intra-hepatic CCA, resulting in a significant decrease of tumor mass and liver neoplastic invasion. These findings suggest that the pharmacological modulation of ER activity could open novel avenues for the medical treatment of intra-hepatic CCA.