Gastroenterología y Hepatología 46 (2023):S210

Gastroenterología y Hepatología

https://www.elsevier.es/gastroenterologia

178 - THERAPEUTIC POTENTIAL OF TARGETING PROTEIN HYPER-SUMOYLATION IN CHOLANGIOCARCINOMA

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Resumen

Introduction and objectives: cholangiocarcinoma (CCA) comprises a heterogeneous group of malignant tumors with dismal prognosis. Alterations in post-translational modifications (PTMs), including SUMOylation, result in abnormal protein dynamics, cell disturbances and disease. Here, we investigate the role of SUMOylation in CCA development and progression.

Methods: Levels and function of SUMOylation, together with response to S-adenosylmethionine (SAMe) and ML792 (SUMOylation inhibitors) or CRISPR/Cas9 against UBE 2I were evaluated *in vitro*, in vivo and/or in patients with CCA. The impact of SUMOylation in CCA cells on tumor-stroma crosstalk was assessed performing co-culture experiments with CCA-derived cancer-associated fibroblasts (CAFs), human endothelial cells and monocytes. Proteomic analyses were carried out by mass spectrometry.

Results: The SUMOylation machinery was found overexpressed and overactivated in human CCA cells and tumors, correlating with poor prognosis. Most SUMOylated proteins found upregulated in CCA cells, after SUMO1-immunoprecipitation and further proteomics, participate in cell proliferation, survival or cell homeostasis. Genetic (CRISPR/Cas9-UBE2I) and pharmacological (SAMe and ML792) inhibition of SUMOylation reduced CCA cell proliferation and impeded colony formation *in vitro*. Moreover, both SAMe and ML792 induced apoptotic cell death in CCA cells *in vitro*. SUMOylation depletion (SAMe, ML792 or CRISPR/Cas9-UBE2I) halted tumorigenesis in subcutaneous models of CCA in vivo. Furthermore, SUMOylation deficiency in CCA cells reduced cancer-associated fibroblast and endothelial cell proliferation and impaired macrophage polarization towards an anti-inflammatory M2-like phenotype.

Conclusions: Aberrant protein SUMOylation contributes to cholangiocarcinogenesis by promoting cell survival and proliferation. Moreover, SUMOylation impacts the CCA-stroma crosstalk. Impaired SUMOylation halts CCA growth and, thus, may represent a potential new therapeutic strategy for patients with CCA.