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1631 / 18 - Targeting ER stress for treating hepatocellular carcinoma (HCC)

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Section 17

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Disclosures

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Abstract

Background: Hepatocellular carcinoma (HCC) accounts for more than 90% of instances of liver cancer, which ranks as the fifth most frequent cancer in the United States. Furthermore, Texas leads the nation in the age-adjusted incidence of HCC. Most patients are diagnosed with advanced, unresectable HCC, and their 5-year survival rate is less than 5% when using current systemic treatments. Therefore, there is an immediate unmet need for new treatment approaches for HCC. Recently, the unfolded protein response (UPR) and endoplasmic reticulum (ER) stress have been recognized as targetable vulnerabilities. From a curated screen, we have previously identified that a synthetic oligo-benzamide, ERX-315, that targets protein encoded by lysosomal acid lipase A (*LIPA*), causes ER stress and cancer cell death without affecting normal cells. This study aims to evaluate the utility of ERX-315 for treating HCC by targeting ER stress

Methods: Tissue micro arrays (TMAs) and Immunohistochemistry (IHC) were used to confirm the expression of LIPA in HCC. LIPA expression in HCC tumors was also confirmed using TNM database. The impact of ERX-315 on 6 well-established HCC cell lines was evaluated using the MTT and colony formation assays. The specificity of ERX-315 targeting activity was confirmed by CRISPR-KO of *LIPA* in one of the HCC cell lines. For mechanistic investigations, Western blotting, RT-qPCR, and splicing assays were employed. Huh7 organoids generated from xenografts were utilized to evaluate the effects of ERX-315 *ex vivo*. Huh7 cell-based xenografts and patient-derived xenograft (PDX) models were used to validate the efficacy of ERX-315 *in vivo*.

Results: TNM plot analysis revealed that HCC tumors exhibited elevated levels of LIPA expression in comparison to normal tissue. Analysis of TMA samples showed that compared to normal tissue, HCC samples exhibit increased levels of LIPA expression. ERX-315 treatment significantly decreased both colony formation and cell viability (IC₅₀ between 30-150nM) and promoted apoptosis in HCC cells. In contrast, ERX-315 did not cause apoptosis in normal liver epithelial cells. Compared to wild type cells, KO of LIPA dramatically attenuated the effect of ERX-315 on colony formation and cell viability in HCC cells. Mechanistic studies using splicing assay, RT-qPCR, and Western blotting demonstrated elevated levels of ER stress indicators upon treatment with ERX-315 in a dose dependent manner. Xenograft-derived Huh7 organoids' cell viability was considerably reduced by ERX-315. ERX-315 therapy

dramatically decreased the tumor volume in Huh7 xenograft and PDX models in both male and female mice. Conclusion: Collectively, our results suggest that ERX-315 promotes ER stress and cell death in HCC *in vitro*, *ex vivo*, and *in vivo*. ERX-315 represents a promising novel therapeutic option for HCC. Since ERX-315 is in clinical trials, these data strongly support evaluation of ERX-315 in patients with liver cancer.