2016 RESEARCH AWARD UPDATE

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Determination of Xanthohumol inhibits Notch Signaling in vivo and Increases the Survival and Reduces Tumor Progression in HCC Liver Xenograft

Primary liver cancers have few effective treatments. Survival of patients is dependent upon detection of small tumors amenable to ablation, resection, or transplantation, and tumor response to a handful of systemic therapy options. Curcumin analogs including Xanthohumol (XN) have demonstrated hepatoprotective and antiproliferative effects in various cancers. Under the mentorship of Dr. T. Clark Gamblin and Dr. Muthusamy Kunnimalaiyaan, the AHPBA Research Grant has allowed us to examine the efficacy of curcumin analogs as novel systemic therapies for primary liver cancer.

Notch signaling and the signal transducer and activator of transcription 3 (STAT3) pathway play important roles in cellular differentiation and survival and are upregulated in many cancers, including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). In the work supported by the AHPBA Research Grant, we examine the effects of curcumin analogs Xanthohumol (XN) and HO-3867 (a STAT3 inhibitor) on liver cancer cell proliferation, cell cycle arrest, and apoptosis. We hypothesized that treatment of HCC and CCA with XN and HO-3867 would result in downregulation of Notch signaling and the STAT3 pathway, arrest the cell cycle, and promote apoptotic pathways in liver tumor cells. Our recent findings suggest that dose-dependent HO-3867 decreases expression of cell cycle proteins and upregulates pro-apoptotic factors in HCC. These findings are associated with reduced activated STAT3 protein expression, decreased expression of Notch, and an associated decrease in tumor cell proliferation in three HCC cell lines. Similarly, XN significantly reduced CCA growth through Notch signaling in two mice xenografts.

Supported by the AHPBA Research Grant, this research has the potential to develop innovative new systemic therapies for primary liver cancer which block Notch signaling and STAT3 pathways and could lead to promising anti-cancer compounds to target primary liver cancer on a molecular level.

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