B1

Xanthohumol Reduces Notch and Induces Apoptosis in Neuroblastoma

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Background: Neuroblastoma (NB) is a highly malignant neuroendocrine cancer accounting for 15% of childhood cancer-related deaths. At diagnosis, more than 40% of patients present with aggressive disease and distant metastases, and 5 year disease-free survival remains below 50%. Recent studies have revealed deregulated expression of Notch signaling in NB; however, therapeutic targeting of Notch represents a significant challenge. Xanthohumol (XN), a prenylated chalcone, exerts anti-proliferative activity against various cancers. We have reported that growth suppression by XN in primary liver and pancreatic cancer is due to reduced Notch signaling. However, the effect of XN in NB has not yet been studied. We therefore hypothesized that XN could also reduce NB growth via downregulation of Notch.

Methods: The proliferation of several XN-treated human NB cell lines (SK-NA-S, NGP, and SH-5Y-SY) was assessed by MTT assay as well as real-time cellular proliferation assay using IncuCyte Live-Cell Imaging system. Expression levels of pro- and anti-apoptotic proteins were analyzed by Western blotting after XN treatment. The effects of XN treatment on Notch pathway proteins were studied via Western blotting and quantitative RT-PCR.

Results: NB cells treated with increasing concentrations of XN (0-30 µM) showed dose-dependent reduction in growth. Significant growth reduction was noted at or above 10 µM of XN in all three cell lines tested. This growth suppression appeared to be apoptotic as evidenced by increased expression of c-PARP and cleaved caspase-3 in addition to decreased levels of Bcl2 and survivin. Furthermore, XN treatment reduced levels of Notch3 and associated downstream targets Hes1 and ASCL1.

Conclusions: We report for the first time that XN targets Notch3 signaling in NB cells. Our data collectively establish that XN could potentially be used therapeutically.