Xanthohumol

Xanthohumol (XN), a prenylated chalcone extracted from hop plant Humulus lupulus L. (Cannabaceae), has potential for cancer therapy, including gliomas.

Several miRNAs have been identified to participate in regulating glioma development. However, no studies have demonstrated whether miRNA is involved in XN cytotoxicity resulting in glioma cell death.

A study investigated the effects of XN-mediated miRNA expression in activating apoptotic pathways in glioblastoma U87 MG cells. First, Chen et al., found that XN significantly reduced cell viability and induced apoptosis via pro-caspase-3/8 cleavage and poly(ADP ribose) polymerase (PARP) degradation. They also identified that pro-caspase-9 cleavage, Bcl2 family expression changes, mitochondrial dysfunction, and intracellular ROS generation also participated in XN-induced glioma cell death. With a microarray analysis, miR 204-3p was identified as the most upregulated miRNA induced by XN cytotoxicity. The extracellular signal-regulated kinase (ERK)/c-Fos pathway was validated to participate in XN-upregulated miR-204-3p expression. With a promoter assay and ChIP analysis, we found that c-Fos dose-dependently bound to the miR-204-3p gene promoter region. Furthermore, miR-204-3p levels decreased in several glioma cell lines compared to astrocytes. Overexpression of miR-204-3p enhanced glioma cell apoptosis. IGFBP2, an upregulated regulator of glioma proliferation, was validated by a TCGA analysis as a direct target gene of miR-204-3p. XN's inhibition of the IGFBP2/AKT/Bcl2 pathway via miR-204-3p targeting played a critical role in mediating glioma cell death. These results emphasized that the XN-mediated miR-204-3p network may provide novel therapeutic strategies for future glioblastoma therapy and drug development [1)].

Stromal interacting molecule 1 (Stim1) plays important roles in regulating store operated calcium entry (SOCE), and controls invasion by cancer cells. However, the mechanisms and functions of Stim1 in glioma progression are still unclear.

Ho et al., from Taipei Medical University, Taiwan, investigated the effects of targeting Stim1 expression on glioma cell invasion. By analyzing profiles of GBM patients from RNA sequencing data in The Cancer Genome Atlas (TCGA), higher expression levels of STIM1 were correlated with the poor survival. Furthermore, signaling pathways associated with tumor malignancy, including the Epithelial-mesenchymal-transition (EMT), were activated in patients with high STIM1 expression according to gene set enrichment analyses. Higher Stim1 levels were found in glioma cells compared to human astrocytes, and these higher levels enhanced glioma cell invasion. Xanthohumol (XN), a prenylated flavonoid extracted from the hop plant Humulus lupulus L. (Cannabaceae), significantly reduced cell invasion through inhibiting Stim1 expression. From an micro RNA array analysis, miR4725-3p was upregulated by XN treatment. Overexpression of miR-4725-3p inhibited glioma cell invasion via directly targeting the 3'-untranslated region of STIM1. The extracellular signal-regulated kinase/c-Fos pathway was also validated to participate in XN-upregulated miR-4725-3p expression according to promoter and chromatin immunoprecipitation assays. These results emphasize that miR-4725-3p-inhibited STIM1 signaling is involved in XN-attenuated glioma cell invasion. These findings may provide insights into novel therapeutic strategies for future glioblastoma therapy and drug development [2)].

1)

Chen PH, Chang CK, Shih CM, Cheng CH, Lin CW, Lee CC, Liu AJ, Ho KH, Chen KC. The miR-204-3p-

targeted IGFBP2 pathway is involved in xanthohumol-induced glioma cell apoptotic death. Neuropharmacology. 2016 Nov;110(Pt A):362-375. doi: 10.1016/j.neuropharm.2016.07.038. Epub 2016 Jul 31. PubMed PMID: 27487563.

2)

Ho KH, Chang CK, Chen PH, Wang YJ, Chang WC, Chen KC. miR-4725-3p targeting Stim1 signaling is involved in xanthohumol inhibition of glioma cell invasion. J Neurochem. 2018 May 10. doi: 10.1111/jnc.14459. [Epub ahead of print] PubMed PMID: 29747239.