Inhibitory Effects of Xanthohumol on STAT3 Activation and Cancer Development in Cholangiocarcinoma Xenograft Model

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Background and objective: STAT (Signal Transducer and Activator of Transcription) is a family of protein kinase and compose of seven members which play crucial roles in inflammation, immune response and cell development. However, constitutive activation of STATs is implicated in several cancers including cholangiocarcinoma (CCA). Our preliminary results revealed the implication of STAT3 in inflammation associated CCA and using Xanthohumol (XN), a chemopreventive agent extract from hops (*Humulus lupulus* L.), could inhibit STAT3 activation, CCA cell proliferation and induced CCA cell apoptosis. In this study, we aim to explore inhibitory effects of XN on STAT3 activation as well as CCA development in mouse xenograft model.

Methods: Six- week- old female BALB/cAJ cl- nu/nu mice were subcutaneously injected with $2x10^6$ cells of KKU-M214 at both flank sides. One week after tumors were visible, animals were divided into two groups; the control group was provided with a vehicle (0.5% ethanol) whereas treatment groups were administrated 50 µM and 100 µM of XN in drinking water for 30 days.Then, tumor volume, STAT3 activation as well as CCA development were identified.

Results: *In vivo* oral administration of XN (50 µM and 100 µM in drinking water) for 30 days, significantly attenuated tumor growth in CCA inoculated mice ($p < 0.01$) without noticeable side effects. Molecular analyses showed that XN also inhibits STAT3 activation and tumor cell proliferation in animal model.

Conclusions: Our findings reveal that XN exert therapeutic potential against CCA through inhibiting STAT3 both *in vitro* and *in vivo*, suggesting STAT3 as a promising target of XN for CCA treatment.

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