The chemotherapeutic potential of isoliquiritigenin in treating pancreatic cancer involving multiple mechanistic targets

Joshua K Ko

School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

Pancreatic cancer is a leading cause of cancer-related mortality worldwide, which is characterized by its poor prognosis and limited efficacy of therapeutic options due to the aggressive invasive behavior and tendency to metastasize. It exhibits a low response rate to chemotherapy. Isoliquiritigenin (ISL) is a natural flavonoid that possesses anticancer properties in neoplasm of the cervix, breast, liver, colon and prostate. We are the first research group to report the anti-carcinogenic potential of ISL in pancreatic cancer. Effect of ISL (25, 50 or 100 microM) in the viability of human PANC-1 pancreatic adenocarcinoma cells was determined by the MTT assay. Cell migration and cell invasion had also been assessed by a wound healing assay and a BioCoat Matrigel Invasion Chamber assay, respectively. For in vivo study, subconfluent culture of Pan02 mouse adenocarcinoma cells were suspended in ice-cold Matrigel and injected into the parenchyma of pancreatic tail of C57BL/6 mice. Tumor could be detected in 3 weeks when daily ISL treatment was commenced and lasted for another 3 weeks (30 or 75 mg/kg, i.p.). Our data indicate that ISL promoted apoptosis in human PANC-1 cells, with an even stronger induction of autophagy as shown by increased conversion to LC3II and upregulation of p62. Other drug actions include modulation of STAT3 signaling, downregulation of epithelial-mesenchymal transition (EMT) and matrix metalloproteinases, leading to reduction in cancer cell migration and invasiveness. Besides, ISL also inhibited M2 polarization in the tumor microenvironment after co-culturing PANC-1 cells with RAW264.7 macrophages, which could be reversed by adding IL-4. Through orthotopic implantation of Pan01 cells into the pancreas of mice, we further demonstrate that ISL could inhibit tumor growth through promotion of apoptosis, inhibition of both angiogenesis and EMT. Based on these findings, we propose that ISL could control pancreatic cancer progression both in vitro and in vivo through diversified mechanisms of action. Our next plan is to investigate in greater detail the involvement of individual signaling pathways in autophagy and the tumor microenvironment.