Antroquinonol, A Natural Ubiquinone Derivative, Induces Anticancer Activity Against Human Pancreatic Carcinoma Cells Through PI3-kinase/Akt/Mtor Pathways

Chia-Chun Yu（余佳純） and Jih-Hwa Guh*

School of Pharmacy, National Taiwan University, Taipei, Taiwan

Pancreatic cancer is a malignant neoplasm of the pancreas. In recent years, the molecular mechanism of pancreatic cancer has been better understood than ever before, leading to new approaches of the treatment. Antroquinonol, a ubiquinone derivative isolated from a camphor tree mushroom *Antrodia amphorate*, induced a concentration-dependent inhibition of cell proliferation in PANC-1 and AsPC-1 pancreatic cancer cells. Flow cytometric analysis of DNA content by propidium iodide-staining showed that antroquinonol induced G1 arrest of the cell-cycle and a subsequent apoptosis. Antroquinonol inhibited Akt phosphorylation at Ser^{473}, the phosphorylation site critical for Akt kinase activity and blocked Mtor phosphorylation at Ser^{2448}, a site dependent on Mtor activity. Several signals responsible for Mtor/p70S6K/4E-BP1 signaling cascades have also been examined to validate the pathway. Moreover, antroquinonol induced the down-regulation of several cell-cycle regulators and mitochondrial anti-apoptotic proteins. In contrast, the expressions of K-ras and its phosphorylation were significantly increased. The coimmunoprecipitation assay showed that the association of K-ras and Bcl-Xl was dramatically augmented, which was indicative of apoptotic cell death. Antroquinonol also induced the crosstalk between apoptosis, autophagic cell death and accelerated senescence, which was, at least partly, explained by the up-regulation of $p21^{Waf1/Cip1}$ and K-ras. In summary, the data suggest that antroquinonol induces anticancer activity in human pancreatic cancer cells through an inhibitory effect on PI3-kinase/Akt/Mtor pathways which in turn down-regulates cyclins and Cdks. The translational inhibition causes G1 arrest of the cell cycle and an ultimate mitochondria-dependent apoptosis.

Keywords: Akt; Mtor; K-ras; pancreatic cancer; Bcl-Xl