Oral Presentation

Metformin Enhances Cisplatin-Induced Cell Cytotoxicity and Antiproliferation in Cholangiocarcinoma Cells

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Background and objective : Cancer of the bile duct is one of the most deadly disease because of its aggressive nature and resistance to most chemotherapy. Metformin (Met) is the first-line antidiabetic drug acting on cellular energy sensor shifting the metabolic state of proliferating cells, thereby, restraining the growth of cancer cells. Recent epidemiological studies have suggested that Met could reduce risk of some cancers i.e. liver, colorectal, pancreas, stomach and esophagus. The objective of this study was to determine anticancer effect of Met in cholangiocarcinoma (CCA) cells.

Medthods : CCA cells, KKU-M156 and kidney epithelial cells (NRK-52E) were treated with Met alone or in combination with cisplatin (Cis). Cytotoxicity of the cells was analyzed by MTT assay. Induction of apoptotic and necrotic cells were examined by acridine orange-ethidium bromide staining. Cis and Met-induced reproductive death was examined by clonogenic assay. The mechanism of antiproliferation of Met with Cis was explored by Western blot analysis of proteins involving with cell growth.

Results : Met had significant higher cytotoxicity to KKU-156 cells than NRK-52E cells, whereas Cis exhibited a comparable toxicity to both cells. Combination of Met with Cis caused cytotoxicity in KKU-M156 cells in greater extent than NRK52E cells. Met also sensitized CCA cells to Cis-induced apoptotic cell death and suppressed colony forming ability. The antiproliferation and induction of cell death enhanced by Met was associated with activation of AMP-activated protein kinase (AMPK), suppression of p-mTOR with subsequent inhibition of p-Akt and cyclin D1 protein expression.

Conclusions : Met enhanced Cis-induced CCA cell cytotoxicity, with modest toxicity to non-cancer kidney cells. The mechanism of cancer cell suppression may involve with activation AMPK with subsequent suppression of Akt- mTOR pathway.

Keywords : Metformin, cisplatin, cholangiocarcinoma, AMPK, mTOR

Acknowledgement : This work was supported by Grant-in-aid from Khon Kaen University and Research funding from Faculty of Medicine, Khon Kaen University.