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Enhancing apoptosis and overcoming resistance of gemcitabine in pancreatic cancer with bortezomib: a role of death-associated protein kinase-related apoptosis-inducing protein kinase 1

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ABSTRACT

Aims and background. To investigate the role of the apoptosis gene, DAP (death-associated protein) kinase-related apoptosis-inducing protein kinase 1 (DRAK1), which is involved in enhancing cell sensitivity and overcoming cell resistance to gemcitabine in pancreatic cancer cells by the proteasome inhibitor bortezomib.

Methods. Cultured human pancreatic cancer gemcitabine-sensitive cell lines (bxpc-3) and gemcitabine-resistant (panc-1) cell lines were divided into four groups: control, treatment with bortezomib, treatment with gemcitabine, and the two-drug combination. Expression of DRAK1 genes in each group was detected by using reverse transcription-polymerase chain reaction and western blot. Apoptosis in the pancreatic cancer cell lines was measured by flow cytometry.

Results. We found that the effects of growth inhibition and apoptosis of gemcitabine on both pancreatic cancer cell lines were enhanced by bortezomib. Treatment of panc-1 and bxpc-3 cells with bortezomib (100 nM) and gemcitabine (50 μg/ml and 0.05 μg/ml, respectively) induced an increase in the levels of DRAK1 mRNA compared with the control and single-agent treatment. Furthermore, immunblotting analysis in panc-1 but not bxpc-3 cells showed similar changes in the expression of DRAK1 protein produced by combination therapy.

Conclusions. Our results demonstrated that bortezomib enhanced cell sensitivity and overcame cell resistance to gemcitabine in pancreatic cancer cells, which may be attributed to DRAK1 induced by bortezomib and the combination with gemcitabine.

Key words: apoptosis, bortezomib, DRAK1, pancreatic cancer.

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