INVolvEmEnt OF C-SRC IN ComBINED ANtIProLIFERATIVE EfFECT OF DI GOxIN AND CI SPlATIN TREATMEN T

Pereira D.G^1, Salgado M.A.R^1, Santos, H.L^1, Barbosa L.A^1, Cortes V.F^1, Fontes C.F.L^2

^1Laboratório de Bioquímica Celular, Universidade Federal de São João Del-Rei, Divinópolis/MG - Brazil
^2Departamento de Bioquímica, Universidade Federal do Rio de Janeiro, Rio de Janeiro/RJ - Brazil

The standard chemotherapy protocol for cervical cancer treatment is the utilization of platinum compounds, and the most widely used is cisplatin. However, cisplatin causes severe side effects and also has a low response rate for this type of cancer. The objective of this study was to evaluate the effect of combined treatment of digoxin and cisplatin in cervical cancer cells, check the role of Na,K-ATPase and the involvement of the possible signaling pathway on this effect. HeLa cells were treated with different concentrations of digoxin and cisplatin for 48 hours, the cytotoxic effect was observed by MTT assay and the evaluation of cell proliferation was performed by Trypan blue. Na, K-ATPase activity and the expression levels were also evaluated. The inhibitors of Src (PP2) and MAPK (PD98059) were used to investigate the involvement of signaling pathways on cell proliferation effect. The treatment with digoxin 1nM was shown to enhance the cytotoxic and antiproliferative effect of cisplatin 1μM, and these concentrations did not show effect when treated isolated. Combination treatment was shown to decrease the expression of the α1 subunit of Na,K-ATPase in total cell extracts, but was not capable to modulate the enzymatic activity. The use of PP2 (5μM) blocked the effect of combined treatment, different from that observed for PD98059 (20μM), that only causes the enhancement of digoxin effect, indicating that the effect of the combined treatment may be correlated with a pathway signal dependent of the Src activation. As digoxin and cisplatin are already clinically used drugs, this study opens the possibilities for clinical trials with the combination treatment, allowing more effective treatment with less toxicity and side effects.

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