Alejandro Español et al., J Cancer Sci Ther 2016, 8:8(Suppl)
http://dx.doi.org/10.4172/1948-5956.C1.081

Muscarinic modulation of paclitaxel actions on human breast cancer

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Cholinergic modulation of tumor progression has been described in differentexperimental models. In our laboratory, we demonstrated that long term treatment of murine mammary tumors with the non-selective agonist, carbachol (CARB) promotes cell death through the activation of muscarinic (M) receptors. We studied the effect of a combination of sub threshold doses of CARB (10-12M) with paclitaxel (PX) (10-8M) acytotoxic agent used in the treatment of breast cancer, on MDA-MB231 cells derived from a human triple negative breast tumor. The combination of CARB+PX reduced cell viability by 27±3% ($p < 0.01$ vs. control). In addition, the combination of the M2 selective agonist, arecaidine (ARE) (12.5 M) that promotes cell death in glioblastomas, with PX (10-9M) produced a similar reduction in cell viability (24±7%; $p<0.05$) effect that was not observed with drugs added separately. By Western blot we detected the expression of M receptors (M5> M1=M2). The silencing of M2 receptor with a specific siRNA increased cell viability to control values. ARE+PX also reduced by 98.7% mRNA levels of the drug transporter ABCG2 and by 97.8% the expression of the epidermal growth factor receptor ($p<0.001$ vs. control). The combination did not modify the viability of MCF-10A cells derived from human normal mammary gland that do not express M receptors. These results suggest that M receptors could be considered as therapeutic targets in breast cancer and that the combination of cholinergic agonists plus cytotoxic agents, as PX may represent a novel therapeutic tool for the treatment of this illness.

Biography

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