Repurposing antimuscarinics to treat lethal chemoresistant prostate and lung cancers

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Abstract

Background: Advanced non-small cell lung cancer (NSCLC) and prostate cancer (PCa) remain leading causes of cancer-related deaths in the United States and worldwide. The current study investigates the ability of antimuscarinics to resensitize chemotherapy resistant NSCLC and PCa to chemotherapy-induced apoptosis.

Methods: The chemotherapy drug docetaxel (DTX) resistant human NSCLC and PCa cell cultures were established to recapitulate clinical emergence of chemoresistance. These cultures were used to harvest total RNA and protein for qPCR and Western blot analyses, respectively. DTX's ability to induce apoptosis was measured with crystal violet survival assay and TUNEL assay.

Results: DTX-resistant NSCLC ($A549^R$) and PCa ($DU145^R$) cells show increased expression of the muscarinic acetylcholine receptors 1 and 3 (CHRM1 / CHRM3). Treatment of these DTX-resistant cells with the CHRM1 antagonist dicyclomine (Dic) or the CHRM3 antagonist darifenacin (Dari) resensitize these cells to DTX-induced cell death. This treatment repurposes Dic and Dari, which are currently used in the clinic to treat irritable-bowel syndrome and overactive bladder, respectively. Decreased cell survival was observed with crystal violet survival assay, which led to increased cell death at a lower concentration of DTX compared to cells treated with DTX alone ($A549^R$ [DTX IC50]: DTX = No response, Dic + DTX = 5.2 nM, Dari + DTX = 2.2 nM / $DU145^R$ [DTX IC50]: DTX = No response, Dic + DTX = 4.2 nM, Dari + DTX = 1.4 nM). Furthermore, cells treated with Dic + DTX or Dari + DTX show increased apoptosis measured by TUNEL assay compared to cells treated with DTX alone ($A549^R$ [TUNEL positive %]: DTX = 0.9%, Dic + DTX = 22.2%, Dari + DTX = 88.2% / $DU145^R$ [TUNEL positive %]: DTX = 3.6%, Dic + DTX = 96.4%, Dari + DTX = 90.1%).

Conclusion: We show that chemoresistant NSCLC and PCa have high expression of CHRM1 and CHRM3 and that antimuscarinics effectively resensitize these lethal forms of cancer to chemotherapeutics. Our data support the rationale of repurposing these therapies to treat chemoresistant NSCLC and PCa, allowing quick entry into a Phase II clinical trial and further translation into clinical practice, in a more cost-effective and less financially risky way, to benefit cancer patients.

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