Digitoxina induz citotoxicidade nas células neoplásicas: inibe: epidermal growth factor receptor, Src, pKc, e mitogen-activated protein kinases

Digitoxin-Induced Cytotoxicity in Cancer Cells Is Mediated through Distinct Kinase and Interferon Signaling Networks.

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Source

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Abstract

Cardiac glycosides (e.g., digoxin, digitoxin) constitute a diverse family of plant-derived sodium pump inhibitors that have been in clinical use for the treatment of heart-related diseases (congestive heart failure, atrial arrhythmia) for many years. Recently though, accumulating in vitro and in vivo evidence highlight potential anticancer properties of these compounds. Despite the fact that members of this family have advanced to clinical trial testing in cancer therapeutics, their cytotoxic mechanism is not yet elucidated. In this study, we investigated the cytotoxic properties of cardiac glycosides against a panel of pancreatic cancer cell lines, explored their apoptotic mechanism, and characterized the kinetics of cell death induced by these drugs. Furthermore, we deployed a high-throughput kinome screening approach and identified several kinases of the Na-K-ATPase-mediated signal transduction circuitry (epidermal growth factor receptor, Src, pKc, and mitogen-activated protein kinases) as important mediators downstream of cardiac glycoside cytotoxic action. To further extend our knowledge on their mode of action, we used mass-spectrometry-based quantitative proteomics (stable isotope labeling of amino acids in cell culture) coupled with bioinformatics to capture large-scale protein perturbations induced by a physiological dose of digitoxin in BxPC-3 pancreatic cancer cells and identified members of the interferon
family as key regulators of the main protein/protein interactions downstream of digitoxin action. Hence, our findings provide more in-depth information regarding the molecular mechanisms underlying cardiac glycoside-induced cytotoxicity. Mol Cancer Ther; 10(11); 2083-93. ©2011 AACR.

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