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The role of cardiac glycosides in influencing breast cancer cell proliferation

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Introduction

Cardiac Glycosides (CGs) are commonly used to treat congestive heart failure. CGs inhibit the Sodium Potassium ATPase (Na+/K+ ATPase) pump. Interestingly, CGs have been suggested to inhibit proliferation and migration of breast cancer cells. A pool of non-pumping Na+/K+ ATPase reportedly localizes in specific membrane organelles, caveolae, by interacting with the structural protein caveolin-1. It has been postulated that Na+/K+ ATPase forms a complex with caveolin-1 and the tyrosine kinase Src, and that binding of CGs to Na+/K+ ATPase activates Src-dependent signalling cascades. In this project we explored whether CGs reduce proliferation in breast cancer cells and whether these effects might involve Src and ERK (Extracellular-signal-Regulated Kinases).

Methods

MDA-MB 231 cells [highly-invasive breast cancer cells] were transfected with siRNA to knock down caveolin-1 expression. MDA-MB-231 cells in which caveolin-1 was knocked down and MCF 10A cells (non-invasive breast cancer cells) were treated with CGs and subjected to MTT proliferation assays. MCF 7 cells (weakly-invasive breast cancer cells) were treated with the Src inhibitor PP2 in the presence or absence of CGs and analysed by western blotting for phosphorylated Src and phosphorylated ERK.

Results

High dose CGs (Digoxin>150nM, Ouabain>10nM, Oleandrin>100nM) reduced proliferation in MCF 10A cells over 72 hrs. Caveolin-1 was successfully knocked-down in MDA-MB 231 cells, but this did not appear to abrogate the anti-proliferative effects of CGs. Early results suggest that phospho-Src and phospho-ERK expression were increased in MCF 7 cells treated with Digoxin. Interestingly, this was not abrogated by pre-treatment with the Src inhibitor PP2.

Conclusions

This project has demonstrated that CGs exert anti-proliferative effects on a range of breast cancer cell lines. Early results suggest that the effects of CGs may not be directly linked to Src and ERK signalling. Ongoing work is determining whether caveolin-1 knockdown alters the anti-proliferative response to CG treatment. We suggest that further exploration of the mechanisms whereby CGs inhibit proliferation may reveal potential uses for CGs as anti-cancer drugs in the future.

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