Abstract: **P5434**

**P300-mediated inactivation of p53 protects against doxorubicin-induced cardiotoxicity**

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Introduction: Doxorubicin is amongst the most widely prescribed chemotherapy drugs due to its effectiveness in cancer treatment. However, progressive treatment using doxorubicin severely increases the risk of congestive heart failure. Mechanistically, researchers have shown that doxorubicin (i) intercalates into DNA and disrupts topoisomerase-II-mediated DNA repair and (ii) generates free radicals which then causes damage to cellular membranes, DNA, and proteins. Ultimately these cellular insults induce cardiomyocyte (CM) death mediated by the tumour suppressor, p53. Currently, there are no clinically applicable preventative treatments for doxorubicin-induced cardiotoxicity and so, extensive research is being done in discovering a potential therapy. One such candidate is curcumin – a natural polyphenol compound non-toxic to humans. We have previously demonstrated that curcumin inhibits lysine acetyltransferase activity of p300, therefore reducing both histone and non-histone protein acetylation. To induce CM death, p53 requires acetylation by p300. Therefore, we hypothesize that curcumin protects against doxorubicin-induced CM death and cardiotoxicity via p300-mediated inactivation of p53.

**Methods:** Rat H9c2 cardiomyoblast cells were cultured and treated with a 2.5 µM dose of doxorubicin for 16 hours. One group of cells were pre-treated with curcumin (15µM) 4 hours prior to doxorubicin treatment, and controls were cultured with only diluent added. Following treatment, the cells were harvested for total protein. At end point, we performed immunoblotting to measure protein expression of key proteins involved in DNA damage (γ-H2A.X, p53), and apoptosis (cleaved-Caspase 3).

**Results:** Our findings show that following doxorubicin treatment, p53 expression was significantly increased (p < 0.001), confirming its role in doxorubicin-associated cardiotoxicity. Furthermore, doxorubicin was associated with increased DNA-damage as evidenced by increased expression and activation of DNA double-stranded breaks (DSBs) marker, γ-H2A.X (p < 0.001). Elevated levels of DNA-damage were further associated with significantly increased doxorubicin-induced apoptosis as measured by immunoblotting for cleaved-Caspase 3 (p < 0.001). However, DNA-damage and apoptosis were attenuated by pre-treatment of cells with curcumin. Curcumin treatment led to a significant decrease in both γ-H2A.X (p < 0.01) and cleaved-Caspase 3 (p < 0.01) expression compared to cells treated with only doxorubicin.

**Conclusions:** Our data provides the first evidence that curcumin protects against doxorubicin-induced apoptosis in rat cardiomyoblast cells in vitro. Further studies are warranted in vivo to confirm the potential of curcumin as a cardio-protective drug. Curcumin is a natural compound with little to no side-effects in humans, therefore our finding may provide a novel therapeutic target and treatment approach for doxorubicin-associated cardiotoxicity.