Abstract: 792

**Doxorubicin-induced cardiomyopathy: gene variant TRPC6 as therapeutic target**

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**Background:** Doxorubicin is an anthracycline used as a chemotherapeutic drug for the treatment of a wide range of adult and pediatric cancers. Doxorubicin use is limited due to its association with an increased risk of cardiomyopathy and heart failure. It is estimated that up to 10% of patients treated with doxorubicin will develop cardiac complications. The cardiotoxic effect of doxorubicin is dose-dependent with an increased percentage of patients developing heart failure at cumulative doses higher than 300-400mg/m2. A GWAS conducted of 1,191 patients from the N9831 clinical trial identified that cardiac gene expression and genetic variants of TRPC6 were associated with a decline in left ventricular ejection fraction (LVEF) (p=0.005 and p=1.62x10^-6 respectively). TRPC6 is a non-selective cation channel expressed in heart and vascular tissue. TRPC6 participates in the pathogenesis of cardiac hypertrophy as a pathological response to chronic mechanical stress. Chronic activation has been found to promote cardiac fibrosis leading to heart failure. Overall these data suggest that TRPC6 variants could be associated with increased risk of doxorubicin-induced cardiotoxicity.

**Purpose:** Tests to determine which patients may progress to cardiomyopathy and heart failure are currently lacking and there are no targeted treatments to prevent cardiomyopathy in these patients.

**Methods:** In preliminary in vivo data, B6.129 wild-type mice (10 females, 10 males) were treated with either 6x intraperitoneal saline or 4mg/kg doxorubicin injections (cumulative dose of 24mg/kg).

**Results:** Our in vitro preliminary data show that inhibition of TRPC6 using the TRPC6 inhibitor GsMTx-4 in human iPSC-derived cardiomyocytes significantly reduced doxorubicin-induced apoptosis (p<0.0001). In vivo we found doxorubicin decreased HW/BW (p=0.008) and HW/TL (p=0.0004) ratios and increased cardiac vacuolation (p<=0.001) in male mice treated with doxorubicin compared to controls. Higher HW/BW ratio were also observed in TRPC6 knock out mice treated with doxorubicin compared to wild-type mice (p=0.005). Additionally, we found that doxorubicin-induced injury was significantly reduced in TRPC6 knock-out mice compared to wild-type mice based on reduced vacuolation (p=0.0004 males, p=0.03 females). Furthermore, a significant decrease in stroke volume (p=0.007), diastolic volume (p=0.01) and cardiac output (p=0.004) were found at day 21 post treatment in wild-type male mice treated with doxorubicin in comparison to control and TRPC6 knock-out mice.

**Conclusions:** Our results suggest that TRPC6 could be a novel therapeutic target in the prevention of chemotherapy-induced cardiomyopathy and heart failure. Genetic mapping of TRCP6 functional variants may provide a new screening tool to determine which cancer patients are at increased risk of developing heart failure and may benefit from increased cardiac monitoring and TRPC6-specific therapies.