INDUCED PLURIPOTENT STEM (IPS) CELLS INHIBITS APOPTOSIS MEDIATED VIA AKT/PTEN PATHWAY IN DOXORUBICIN INDUCED CARDIOTOXICITY FOLLOWED BY MYOCARDIAL INFARCTION INDUCED HEART FAILURE

ACC Moderated Poster Contributions
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Background: Doxorubicin (DOXO) is an effective chemotherapeutic drug used in the treatment of various cancers. Unfortunately, cardiotoxicity has limited its clinical applications. Cell therapy is a promising option to treat cardiotoxicity. Therefore, we examined for the first time the effects of transplanted induced pluripotent stem (iPS) cells in combined model of DOXO induced cardiotoxicity followed by myocardial infarction (MI) on apoptosis, apoptotic pathway, cardiac and vascular fibrosis and cardiac function.

Methods: C57BL/6 mice were divided into five groups: Sham, DOXO-MI, DOXO-MI+cell culture (CC) media, DOXO-MI+ES cells (pluripotent cells as a control), and DOXO-MI+iPS cells. Mice were injected 3 times every other day with cumulative dose of DOXO, 12 mg/kg. Two weeks after last injection, MI was induced by coronary artery ligation. Following ligation, 5 x 10^4 ES or iPS cells or CC medium were delivered into the peri-infarct region. At day 14 post-MI, echocardiography was performed, mice were sacrificed, and hearts were harvested for further analyses.

Results: Our data reveals apoptosis was significantly inhibited in iPS cell transplanted hearts compared with DOXO-MI, DOXO-MI+CC (Sham: 0.219%±0.0435; DOXO-MI: 0.893%±0.091; DOXO-MI-CC: 0.958%±0.161; DOXO-MI-iPS: 0.325%±0.0532; p <0.05; n=7-9). Furthermore, our data suggest a significant increase in pAkt, a cell survival protein, and a decrease in levels of PTEN, a negative regulator of Akt pathway in hearts transplanted with iPS cells. Additionally, a significant (p<0.05; n=5-8) decrease in vascular and interstitial fibrosis along with improved heart function (Sham: 51.7%±2.829, DOXO-MI: 36.786%±1.548, DOXO-MI-CC: 38.2%±2.237, DOXO-MI-iPS: 45.917%±1.533; p <0.05 vs DOXO-MI and DOXO-MI-CC, n=6-8) was observed in iPS cell transplanted group. Moreover, data generated with ES cell group has similar findings as observed in iPS cells.

Conclusion: Our data suggests that transplanted iPS cells inhibit apoptosis mediated by Akt/PTEN pathway, attenuate adverse cardiac remodeling along with improved cardiac function in DOXO induced cardiotoxicity followed by MI.