Role of SIRT1 in the development of cardiac fibrosis in a model of doxorubicin-induced cardiomyopathy

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Rationale: Doxorubicin (DOXO) is a highly effective anti-neoplastic drug used to treat several cancers but its clinical benefits have been hampered by cardiotoxicity with a high risk to develop heart failure. Several mechanisms, such as oxidative stress, apoptosis and myocardial fibrosis, have been proposed to account for the cardiomyopathy caused by DOXO (1).ROS production is partly responsible for cardiomyocytes loss as a result of a necrotic and/or apoptotic cell death by triggering TGF-β, the major fibroblast-activated cytokine. The activation of cardiac fibroblasts into myofibroblasts participate in matrix formation through their ongoing production of signalling molecules that promote fibrogenesis. Consequently, tissue architecture is disrupted by altered deposition of fibrotic tissue which leads to cardiac stiffness and dysfunction (2). Recent report showed that sirtuins may be of value in the prevention against DOXO-induced cardiotoxicity by interfering with ROS production (3). Additionally, resveratrol (RES), a direct activator of SIRT1, suppressed fibroblast transformation via inhibition of the TGF-β/Smad3 pathway and ameliorated collagen deposition improving cardiac function (4).

Objective: Considering the role of SIRT1 in oxidative stress response and its effects on the regulation of metalloproteinases, we hypothesised that RES might interfere with the development of cardiac fibrosis in a model of DOXO-induced cardiomyopathy.

Methods: F344 rats were randomly divided into two groups: 1) DOXO: injected i.p. with DOXO (15 mg/kg); 2) DOXO+RES: received RES (2.5mg/kg, by gavage) and DOXO concomitantly and then they were maintained on the intervention with RES for the following 4 weeks. Age-matched untreated animals were used as control (CTRL). Before sacrifice, rats were anesthetized, echocardiography and hemodynamics were performed and heart tissue was collected for molecular biology and histologic studies. To test the possibility that beneficial effects of RES on cardiac function is associated with a protective action at the level of fibroblasts compartment, the status of cardiac fibroblasts was evaluated both *in vivo* and *in vitro*. In particular, fibroblasts isolated from each experimental group were cultured for *in vitro* study.

Results: With respect to DOXO only, DOXO+RES co-treatment markedly improved EF, while LVPW thickness and LV diameter were only partially restored. Hemodynamically, in DOXO+RES animals, ±dP/dt were significantly improved. Importantly, the mortality rate of 67% observed in DOXO animals was reduced to 33% in DOXO+RES group. In comparison with DOXO only, RES produced a decreased number of myocyte undergoing oxidative stress and apoptosis. Moreover, RES, by influencing fibroblast compartment activation, led to a reduction of fibrosis tissue accumulation. To better assess the effects of RES on fibroblasts, we evaluated the expression of several mediators of profibrotic pathway. Fibroblasts isolated from DOXO-treated rats showed an increasing in TGF-β, p-Smad3/Smad3 ratio and MMP-2 expression, whereas RES determined a reduction of these proteins to physiologic levels. Finally, the diminished expression of α-SMA in DOXO+RES fibroblasts confirmed the beneficial effects of RES on interfering with DOXO-induced fibrosis by preventing fibroblast activation.

Conclusion: The search for compounds able to counteract chemotherapy-induced heart failure is extremely important at the age of global cancer epidemic. Our data showed that animal survival, functional and anatomical parameters compromised by DOXO were improved after the administration of RES suggesting that SIRT1 activation can attenuate myocardium injury.

References:

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