Myocardial miR-30 down-regulation caused by doxorubicin alters the beta-adrenergic system and mitochondrial death pathways

L. Roca-Alonso1; L. Castellano2; A. Mills1; S. Harding1; AR. Lyon1; J. Stebbing2
1Imperial College London, National Heart and Lung Institute (NHLI), London, United Kingdom; 2Imperial College London, London, United Kingdom

Rationale: The use of anthracyclines such as doxorubicin (DOX) has improved mortality and morbidity in cancer patients, yet associated risks of cardiomyopathy have limited their clinical application. DOX-associated cardiotoxicity is frequently irreversible and typically progresses to heart failure (HF). However, our understanding of molecular mechanisms essential for development of cardioprotective strategies and to predict HF remains largely obscure.

Objective: As microRNAs (miRNAs) have been shown to play potent regulatory roles in both cardiovascular disease and cancer, we investigated miRNA changes in chemotherapy-induced HF and the alteration of cellular processes downstream.

Methods and results: Myocardial miRNA profiling was performed after DOX-induced injury, either via acute application to isolated cardiomyocytes in vitro or chronic exposure in vivo, and also compared with miRNA profiles from remodeled hearts following myocardial infarction; the miR-30 family was down-regulated in all three models. We confirmed β1- and β2-adrenoceptors (β1AR, β2AR), Gi alpha 2 (Giα2) and the pro-apoptotic gene BNIP3L/NIX as miR-30 targets. We describe regulation of the β-adrenergic pathway by miR-30, where a preferential βAR inhibition results in a β-blocker like effect. We demonstrate that high miR-30 levels are protective against DOX insult and correlate with lower reactive oxygen species (ROS) generation. Moreover, we identify GATA-6 as a mediator of the DOX-associated reduction in miR-30 expression.

Conclusion: DOX causes acute and sustained miR-30 down-regulation in cardiomyocytes via GATA-6. miR-30 overexpression protected cardiac cells from DOX-induced apoptosis, and its maintenance represents a potential cardioprotective strategy for anthracycline cardiomyopathy. Additionally, intriguing synergic anti-cancer effects were observed for miR-30.