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Activation of invariant natural killer T cells by alpha-galactosylceramide ameliorates doxorubicin-induced cardiotoxicity in mice

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Objective: Doxorubicin (DOX) is an effective antineoplastic agent commonly used to treat many types of cancer but its clinical use is limited because of cardiotoxicity, which might proceed to irreversible cardiac dysfunction in a dose-dependent manner. The precise mechanism of DOX-induced cardiotoxicity is still not fully elucidated but it has been reported that cardiac inflammation is involved in the cardiotoxicity. Invariant natural killer T (iNKT) cells, a unique subset of T lymphocytes that recognize glycolipid antigens and secrete a large amount of Th1 and Th2 cytokines on activation, have been shown to play crucial roles in the regulation of immune responses. However, it remains unclear whether iNKT cells are involved in DOX-induced cardiotoxicity.

Methods and results: Male C57BL/6J mice were administered DOX (20mg/kg body weight single intraperitoneal injection; n=28) or vehicle (Vehicle; n=6). DOX-administered mice were further divided into 2 groups; α-galactosylceramide (αGC, 0.1μg/g body weight twice intraperitoneal injection; DOX-αGC; n=14), which specifically activates iNKT cells, or phosphate-buffered saline alone (PBS; DOX-PBS; n=14) 4 days before and 3 days after DOX administration. Survival rate at 14 days after DOX/Vehicle administration was significantly lower in DOX-PBS than in Vehicle (71% vs. 100%, $P<0.05$), and this decrease was completely attenuated in DOX-αGC (100%, $P<0.05$ vs. DOX-PBS). Echocardiography at 14 days after DOX/Vehicle administration revealed that left ventricular (LV) fractional shortening was significantly reduced in DOX-PBS compared to Vehicle (49.3±0.8% vs. 59.2±1.7%, $P<0.05$), and this decrease was completely attenuated in DOX-αGC (57.7±1.3%, $P<0.05$ vs. DOX-PBS) without affecting LV end-diastolic diameter. Picro-sirius red staining revealed that the ratio of fibrosis area to the cardiac tissue was markedly higher in DOX-PBS than in Vehicle (4.3±0.5% vs. 2.2±0.1%, $P<0.05$), and this increase was completely attenuated in DOX-αGC (2.8±0.1%, $P<0.05$ vs. DOX-PBS). Real-time PCR analysis revealed that mRNA expression of anti-inflammatory Th2 cytokine IL-4 was enhanced by 7.9-folds in DOX-αGC compared to DOX-PBS, though the difference did not reach statistically significance ($P=0.09$).

Conclusions: Activation of iNKT cells by αGC ameliorates DOX-induced cardiotoxicity in mice via up-regulation of anti-inflammatory IL-4 and reducing cardiac fibrosis. iNKT cell activation may be a novel therapeutic strategy against DOX-induced cardiotoxicity.