Activation of invariant natural killer T cells ameliorates doxorubicin-induced cardiomyopathy

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Background: Invariant natural killer T (iNKT) cells orchestrate tissue inflammation via regulating various cytokine productions, especially strongly upregulating interferon (IFN)-γ. Activation of iNKT cells have been previously reported to exert protective effects against post-infarcted cardiac remodeling and cardiac ischemia/reperfusion injury. However, the role of iNKT cells has not been determined in doxorubicin (DOX)-induced cardiomyopathy.

Purpose: The purpose of this study was to examine whether the activation of iNKT cells by α-galactosylceramide (αGC), which specifically activates iNKT cells, could affect DOX-induced cardiomyopathy, and if so, to elucidate its downstream target.

Methods: C57BL/6J mice were received the intraperitoneal injection of either αGC (0.1µg/g, n=11) or vehicle (n=13). After 1 week, these mice were treated with a low dose of DOX (18mg/kg via intravenous 3 injections over 1 week), and were followed during 14 days.

Results: DOX mice (DOX+vehicle) showed left ventricular (LV) dysfunction and dilatation, which were significantly ameliorated in DOX mice receiving αGC (DOX+αGC) (LV fractional shortening: 27.4±4.31 vs. 31.5±4.62%, p<0.05, LV end-diastolic diameter: 3.70±0.16 vs. 3.32±0.23mm, p<0.05), with no significant changes in arterial pressure, body weight, and food consumption, 14 days after DOX injection. DOX+vehicle demonstrated a significant decrease in myocardial gene expression of Va14Jα18, a specific marker of iNKT cells, and IFN-γ compared with control mice. Va14Jα18 expression levels were higher in DOX+αGC than DOX+vehicle by 9.2 folds (p<0.05). Consistent with this change, IFN-γ was higher in DOX+αGC than DOX+vehicle by 4.4 folds (p<0.05), whereas interleukin (IL)-1, IL-4, IL-6, IL-10, IL-17, IL-23, and tumor necrosis factor (TNF)-α were not altered in both groups. Phosphorylation of Akt, its active form, in the heart was significantly increased in DOX+αGC compared with DOX+vehicle by 1.8 folds (p<0.05).

Conclusions: Activation of iNKT cells by αGC play a protective role against DOX-induced cardiac dysfunction, which was associated with enhancing expression of IFN-γ and activating Akt. Therapies designed to activate iNKT cells might be beneficial to protect the heart from DOX injury.