

Doxorubicin induces trans-differentiation in cardiac fibroblasts via cell death-independent pathways

Masanari Umemura^{1,2}, Ryo Tanaka^{1,2}, Masatoshi Narikawa², Rina Nakakaji^{1,3}, Islam Rafikul¹, Kohei Osawa^{1,3}, Mayu Hikichi¹, Yoshihiro Ishikawa¹

¹Dept. CVRI., Grad. Scho. Med. Yokohama Univ., ²Medical Science and Cardiorenal Medicine., Grad. Scho. Med. Yokohama Univ., ³Dept. Oral and Maxillofacial Surgery., Grad. Scho. Med. Yokohama Univ.

Background: Doxorubicin (DOX)-induced heart failure has a poor prognosis, and effective treatments have not been established. The effect of DOX on cardiac fibroblasts at non-lethal concentrations remains unknown. The aim of this study was to investigate the direct effect of doxorubicin on the activation of cardiac fibroblasts independent of cell death pathways. **Methods:** An animal study was performed to confirm the effects of a lower dose of DOX than a toxic cumulative dose. Human cardiac fibroblasts (HCFs) were used. The effects of DOX on mRNA expression were evaluated by microarray analysis. mRNA of collagen and the other fibrotic factor were measured by RT-PCR. Protein expression was evaluated by western blot. **Results:** DOX-induced fibrosis was localized to the perivascular area in mice. Microarray analysis showed that DOX increased the expression of the immune system, inflammatory reaction and matrix metalloproteinase (MMP) genes, resulting in cardiac remodelling. DOX enhanced mRNA of alpha smooth muscle actin (α -SMA) (a marker of trans-differentiation), interleukin (IL)-1, IL-6, transforming growth factor (TGF)- β , collagen and MMP1 expression in less than 0.1 μ M which did not inhibit the cell viability in HCFs. DOX also promoted the protein expression of fibrotic markers, such as α -SMA. Furthermore, DOX induced mitochondrial damage and mitophagy. **Conclusions:** These findings suggested that doxorubicin directly induced fibrotic change of cardiac fibroblast via cell death-independent pathway. There may be potentially new mechanisms of doxorubicin induced cardiotoxicity.