Induction of manganese superoxide dismutase (MnSOD) mediates cardioprotective effect of tamoxifen (TAM)

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Abstract
Tamoxifen (TAM), a synthetic nonsteroidal antiestrogen effectively and widely used for breast cancer treatment, is known to have antioxidant and cardioprotective effects, but whether the beneficial cardiovascular effect of TAM is linked to its antioxidant effect is unknown. In this study, we investigated the effect of TAM on the levels of manganese superoxide dismutase (MnSOD), a mitochondrial antioxidant enzyme, in cardiac tissues and cardiomyocytes. TAM treatment induced MnSOD expression in vitro and in vivo. Cardiomyocytes isolated from TAM pretreated mice also had higher MnSOD levels and fewer apoptotic cells compared to cardiomyocytes from control mice after adriamycin (ADR) treatment. To further confirm the role of MnSOD in the protection against ADR in cardiomyocytes, we used cardiomyocytes isolated from MnSOD knock-out (MnSOD+/-), wild-type (NTg) and human MnSOD transgenic (TgH) mice. TUNEL assay indicated that the percentage of cells undergoing apoptosis after ADR treatment was significantly greater in MnSOD+/- than in NTg or TgH cardiomyocytes. 3-[4,5-Dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT) assay showed that basal level of mitochondrial function was lower in MnSOD+/- cardiomyocytes than in NTg or TgH, and that MnSOD+/- was more sensitive to ADR. ADR treatment increased caspase activity, which was significantly higher in MnSOD+/- than in NTg or TgH cardiomyocytes. These results suggested that TAM-induced MnSOD expression is at least, in part, contribute to the cardioprotective effects of TAM.

Keywords: Cardiomyocytes; Manganese superoxide dismutase; Adriamycin; Tamoxifen; Apoptosis