Zinc play a key role in adriamycin-induced cardiomyopathy

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Background Adriamycin (ADR) is a potent anticancer drug that causes severe cardiomyopathy as an adverse reaction. Previous reports have demonstrated that zinc accumulation is shown in rat myocardial cells after ADR treatment. However, the mechanism and role of zinc accumulation in ADR-induced cardiomyopathy have not yet been elucidated.

Methods We examined the zinc cytotoxicity on various types of cells including H9c2 cardiomyoblast cells and primary rat cardiomyocytes.

Results ADR induced significant cell death of the H9c2 and primary rat cardiomyocytes in a dose-dependent manner. Apparent chromatin condensation was observed in ZnCl₂-treated cardiomyocytic cells whereas nuclear fragmentation was not detected. ZnCl₂ induced a decrease in intracellular glutathione (GSH) as well as an increase in production of H₂O₂. ADR also induced a decrease of intracellular GSH. The exogenous treatment of reduced GSH prevented ZnCl₂-induced cytotoxicity as well as production of H₂O₂ via the increase of intracellular GSH level. In contrast, ADR-induced cytotoxicity was not prevented by exogenous GSH, although the intracellular GSH recovered up to the control level. Poly (ADP-ribose) polymerase (PARP) in ZnCl₂-treated H9c2 cells was cleaved as approximately 60 kDa in a caspase-independent mechanism. In addition, immunoprecipitation and reverse transcriptase-polymerase chain reaction (RT-PCR) showed the induction of metallothionein-2 (MT-2) in primary cardiomyocytes exposed by ADR. For a while, zinc accumulation in an in vivo experiment was observed in the same myocardium regions with structural alterations after treatment of ADR (cumulative dose: 16 mg/kg).

Conclusions Taken together, we suggest that ADR-induced cardiomyopathy may be caused by zinc accumulation via the upregulation of MT in specific regions of myocardium.