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Role of thioredoxin system in cell death caused by toxic compounds

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ABSTRACT

Thioredoxin systems, comprising Trx, TrxR and NADPH, are one of the major disulfide reductase systems, which is crucial in maintaining cellular redox balance in mammalian cells. TrxR is a selenoprotein with a Sec residue in its C-terminal active site. The low pK_a value and the easily accessible property of the Sec residue make TrxR a target of many electrophilic compounds, including some clinically approved drugs. TrxR exert most of its cellular function by reducing Trx. Through the substrates of Trx, or its interacting proteins, Trx plays important roles in DNA synthesis, cellular defense against oxidative stress, regulation of transcription factors and cell death pathways.

There are two distinct Trx systems in mammalian cells, Trx1 system located in cytosol and Trx2 system located in mitochondria. In Paper I we found that treatment with brilliant green (BG) can cause a dramatic decrease of Trx2 in the mitochondria and subsequent cell death. The natural amount of Trx2 in Hela cells are much higher compared to that in fibroblast cells. Down-regulation of the amount of Trx2 by using an siRNA method in both cell lines can greatly sensitize Hela cells towards BG toxicity, but not fibroblast cells, suggesting the importance of Trx2 for some cancer cells.

Different from Trx2, which only have two Cys residues in the active site; Trx1 has three additional Cys residues, Cys62, Cys69 and Cys73. Previous studies about the function of Trx1 are mainly focused on the active site cysteines. However, accumulating evidence showed that the three so called structural Cys residues also play important roles in regulating Trx1´s activities and functions. In paper II and IV, we focused on studying the impact of the second disulfide (Cys62-Cys69) on Trx1 activity. We show that Trx1 with two disulfides can be found in cells under high oxidative stress, and although it is not a substrate of TrxR, but it can be reduced by the glutaredoxin (Grx) system at the expense of GSH. In addition the formation of the second disulfide or only the disulfide between Cys62 and Cys69 disturbed the ability of Trx1 to reduce oxidized Prx1, and sensitized SH-SH5Y cells towards arsenic compounds inducing cell death. In Paper III we characterized that GSH plus Grx2 can be a backup of TrxR and can reduce both Trx1 and Trx2 when TrxR was inhibited. Overexpression of Grx2 in Hela cells can protect cells from cell death induced by the inhibitors of TrxR.

Apart from Trxs, we also explored the role of TrxR as a target of the clinically applied anti-cancer drug mitomycin C and mercury. In paper V, we proposed that targeting TrxR as a new mechanism of mitomycin C´s action. In Paper VI, TrxR was shown to be a target of mercury, and selenium can reactivated the TrxR treated with mercury by a substitution mechanism.

In summary, in the thesis we stressed the role of Trx and TrxR in the cell death induced by the toxic compounds which are targeting the Trx system.

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