The Importance of the Thioredoxin System for the Development of Toxicity and Disease

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The thioredoxin system is of critical importance for the maintenance of several important functions in the cell (e.g. protein repair; cell cycle regulation). It comprises thioredoxin (Trx), thioredoxin reductase (TrxR) and NADPH. It is also one of the major antioxidants systems used by cells to maintain the reduced state in intracellular environment as well as to defend against oxidative and nitrosative stress.

Additionally, the thioredoxin system is implicated in a large number of biological functions such as DNA synthesis and cell proliferation, angiogenesis, control and activity of numerous transcription factors, protection of cells against apoptosis and cell signalling pathways by controlling the activity of transcription factors such as NF-kB, AP-1, P53 and ASK1.

Mammalian TrxR has a broad range of functions, which include reducing hydroperoxides and regenerating compounds such as dehydroascorbate, lipoate and ubiquinone. TrxR is the only enzyme able to reduce oxidized Trx. Additionally selenium-compromised forms of TrxR induce apoptosis.

Since the activity of Trx is dependent on the ability of TrxR to reduce it, factors affecting the performance of TrxR (e.g. Se depletion; electrophilic inhibitors) will compromise the metabolic pathways dependent on Trx activity. This is the basis of the treatment strategies for some pathologies related to an overexpression (e.g. cancer) or deficit (e.g. haemolytic anemia) in TrxR activity. Other pathologies that have been related to the thioredoxin system include diabetes, rheumatoid arthritis, neurodegenerative and cardiovascular diseases.

Several compounds are known to cause inhibition of both enzymes of the Trx system. TrxR is particularly prone to interaction with electrophilic agents.

Our research group has shown that mercury compounds (from seafood, amalgams, medicines, vaccines, etc.) inhibit the thioredoxin system in vitro and in vivo. The selenoenzyme thioredoxin reductase is particularly sensitive to mercury and co-exposure to selenium is only effective in protecting this enzyme from Hg^{2+} and not from MeHg. The inhibitory strength of mercurials and especially Hg^{2+} over purified TrxR is remarkable when the results among metallic compounds are compared. The results clearly show that TrxR is highly susceptible to inhibition by mercurials. Also the fact that Hg^{2+} is a stronger inhibitor of TrxR has physiological significance since it could indicate that MeHg upon demethylathion can produce an even more toxic outcome.

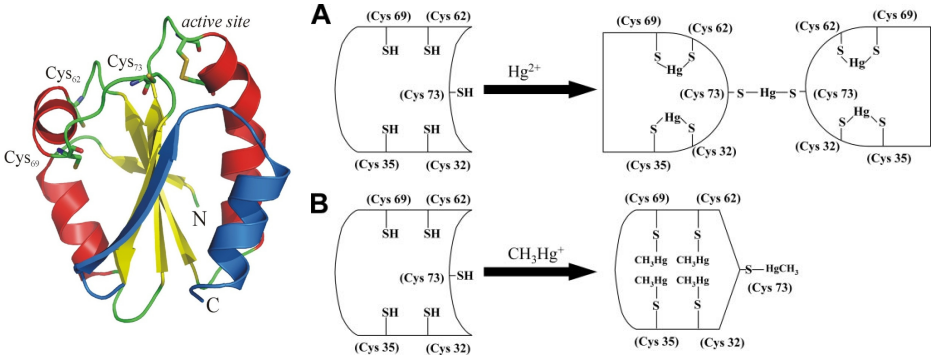

Figure 1. Structure of human thioredoxin 1 and scheme of the interaction of mercurials with Cys residues in Trx1. A – Hg^{2+}; B – MeHg (from Carvalho et al., JBC, 2008)