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Review Article

Thioredoxin promotes survival signaling events under nitrosative/oxidative stress associated with cancer development

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ABSTRACT

Accumulating mutations may drive cells into the acquisition of abnormal phenotypes that are characteristic of cancer cells. Cancer cells feature profound alterations in proliferation programs that result in a new population of cells that overrides normal tissue construction and maintenance programs. To achieve this goal, cancer cells are endowed with up regulated survival signaling pathways. They also must counteract the cytotoxic effects of high levels of nitric oxide (NO) and of reactive oxygen species (ROS), which are by products of cancer cell growth. Accumulating experimental evidence associates cancer cell survival with their capacity to up-regulate antioxidant systems. Elevated expression of the antioxidant protein thioredoxin-1 (Trx1) has been correlated with cancer development. Trx1 has been characterized as a multifunctional protein, playing different roles in different cell compartments. Trx1 migrates to the nucleus in cells exposed to nitrosative/oxidative stress conditions. Trx1 nuclear migration has been related to the activation of transcription factors associated with cell survival and cell proliferation. There is a direct association between the p21Ras-ERK1/2 MAP Kinases survival signaling pathway and Trx1 nuclear migration under nitrosative stress. The expression of the cytoplasmic protein, the thioredoxin-interacting protein (Txnip), determines the change in Trx1 cellular compartmentalization. The anti-apoptotic actions of Trx1 and its denitrosylase activity occur in the cytoplasm and serve as important regulators of cell survival. Within this context, this review focuses on the participation of Trx1 in cells under nitrosative/oxidative stress in survival signaling pathways associated with cancer development.

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Thioredoxin-1 in the context of the thioredoxin system

Cytosolic thioredoxin-1 (Trx1) and mitochondrial thioredoxin-2 (Trx2) are 12 kDa multi-functional proteins with two conserved Cys residues (Cys32 and Cys35 for Trx1 and Cys31 and Cys34 for Trx2) at their redox active site. They play a major role in cellular redox balance and signaling in normal cells and tumor cells [1–5]. Thioredoxins are expressed in prokaryotic and eukaryotic cells and apparently are present in all living cells [1,6].

Trx1 and Trx2 (Trxs) are part of the Trx system, a major antioxidant system which is essential for maintenance of the intracellular redox status. The Trx system is formed by the Trxs, NADPH and the Trx reductases (TrxR). Mammalian TrxRs are selenoenzymes that operate as pyridine nucleotide disulfide oxidoreductases [5,7,8]. They maintain Trxs in their reduced state due to the presence of a selenocysteine residue in the active site of TrxRs [9], TrxRs are highly reactive proteins which consume NADPH and reduce the disulfide form of Trxs to a dithiol [Fig. 1].

TrxRs comprise a group of three isoenzymes, the cytosolic TrxR1 [10,11], the mitochondrial TrxR2 [12,13], and the testis specific Trx glutathione reductase [14] . Expression and subcellular localization of the different members of the Trx system expands the number of their targets. Direct targets such as peroxiredoxins, which are essential for reduction of H_2O_2 and organic peroxides associated with intracellular redox signaling require disulfide reduction by Trx1 or Trx2 for their function [5]. Ribonucleotide reductase activity as an indirect target of the Trx system is of major importance for the supply of DNA precursors. The enzyme which is up regulated in tumor cells uses Trx1 as an electron donor for deoxyribonucleotide and DNA synthesis [2,5,15]. Elevated expression of TrxR1 is found in human and murine tumor cell lines [2,3,16,17]. P53 mutations in glioblastomas are associated with increased expression of TrxRs and this expression is used for tumor grading in astrocytomas [18]. Inhibition of expression of TrxR1 in a mouse model of prostate cancer and in human hepatocellular carcinoma SMMC-7721 cells causes growth inhibition in both situations [19,20].

In the absence of TrxRs, alternative pathways may be operative in maintaining intracellular redox status. The methionine sulfoxide pathway may be a possible alternative pathway. After generation of null-hepatocytes for both TrxR and GSH reductase genes in transgenic mice, though they were long-term viable, these mice were dependent on methionine supplementation in their diets needed for *de novo* synthesis of cysteine and GSH [21]. There are other reductases capable of redox-regulation of the system, but the methionine sulfoxide pathway is responsible for maintaining the redox environment when NADPH does not deliver the reducing power either to Trx or to GSH [22–24].

Among the Trxs the best characterized is Trx1 [5]. It regulates the activity of various signaling proteins and antioxidant enzymes within cells. Trx1 also acts as a positive regulator of survival related signaling pathways to enhance survival of tumor cells [25,26]. Trx1 provides reducing equivalents to peroxiredoxins that in turn will reduce reactive oxygen species (ROS) [5], and directly inhibits pro apoptotic proteins such as the apoptosis signal-regulating kinase 1 (ASK-1) [27]. The intracellular location of Trx1 is a determining factor for its function as a mediator of signaling events occurring either in the cytoplasm or in the nucleus.

Trx1 plays a central role in signaling associated with the Trx system in normal and tumor cell development. This occurs in the regulation of a large number of transcription factors that are redox sensitive [28–34], the interaction with partners of components of the system, e.g. the Thioredoxin interacting protein – Txnip [35,36] and the metabolism of low molecular weight S-nitrosothiols (SNO) [37–45]. All have in common the central role played by Trx1.

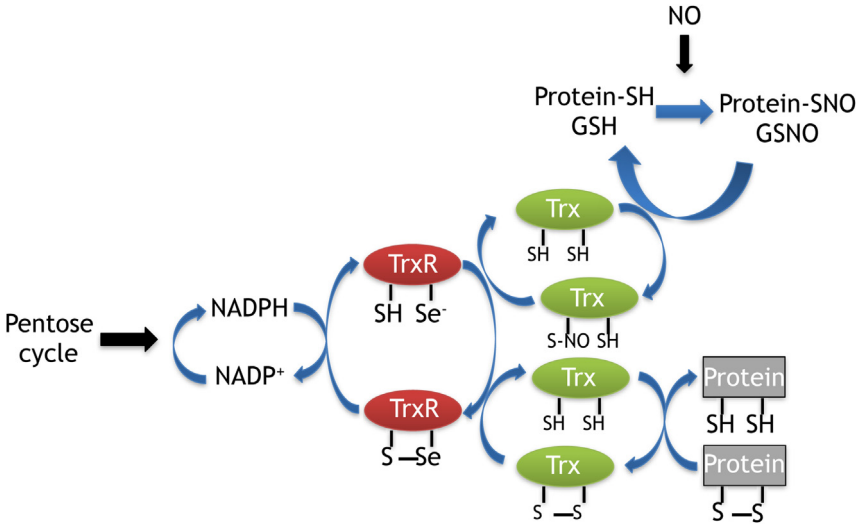

Fig. 1 The Trx system and its redox couples: *TrxRSSe/TrxR/SHSe and TrxSS/Trx(SH)2 are responsible for the delivery of reducing equivalents from NADPH and are essential for denitrosylase activities. *SHSe stands for Selenothiol and SSe stands for Selenylsulfide.