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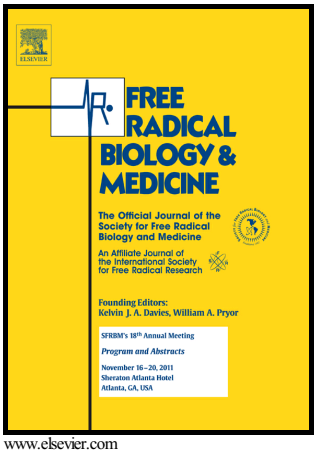

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SIGNIFICANCE OF THE MITOCHONDRIAL THIOREDOXIN REDUCTASE IN CANCER CELLS: AN UPDATE ON ROLE, TARGETS AND INHIBITORS

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Abstract

Thioredoxin reductase 2 (TrxR2) is a key component of the mitochondrial thioredoxin system able to transfer electrons to peroxiredoxin 3 (Prx3) in a reaction mediated by thioredoxin 2 (Trx2). In this way, both the level of hydrogen peroxide and thiol redox state are modulated. TrxR2 is often overexpressed in cancer cells conferring apoptosis resistance. Due to their exposed flexible arm containing selenocysteine, both cytosolic and mitochondrial TrxRs are inhibited by a large number of molecules. The various classes of inhibitors are listed and the molecules acting specifically on TrxR2 are extensively described. Particular emphasis is given to gold(I/III) complexes with phosphine, carbene or other ligands and to tamoxifen-like metallocifens. Also chemically unrelated organic molecules, including natural compounds and their derivatives, are taken into account. An important feature of many TrxR2 inhibitors is provided by their nature of delocalized lipophilic cations that allows their accumulation in mitochondria exploiting the organelle membrane potential. The consequences of TrxR2 inhibition are presented focusing especially on the impact on mitochondrial pathophysiology. Inhibition of TrxR2, by hindering the activity of Trx2 and Prx3, increases the mitochondrial concentration of reactive oxygen species and shifts the thiol redox state toward a more oxidized condition. This is reflected by alterations of specific targets involved in the release of pro-apoptotic factors such as cyclophilin D which acts as a regulator of the mitochondrial permeability transition pore. Therefore, the selective inhibition of TrxR2 could be utilized to induce cancer cell apoptosis.