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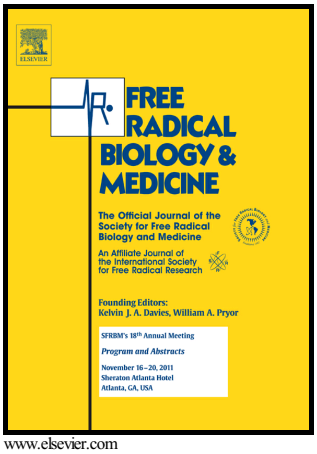

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Selenocysteine in mammalian thioredoxin reductase and application of ebselen as a therapeutic

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Abstract

Thioredoxin system is a ubiquitous disulfide reductase system evolutionarily conserved through all living organisms. It contains thioredoxin (Trx), thioredoxin reductase (TrxR) and NADPH. TrxR can use NADPH to reduce Trx which passes the reducing equivalent to its downstream substrates involved in various biomedical events, such as ribonucleotide reductase for deoxyribonucleotide and DNA synthesis, or peroxiredoxins for counteracting oxidative stress. Obviously, TrxR stays in the center of the system to maintain the electron flow. Mammalian TrxR contains a selenocysteine (Sec) in its active site, which is not present in the low molecular weight prokaryotic TrxRs. Due to the special property of Sec, mammalian TrxR employs a different catalytic mechanism from prokaryotic TrxRs and has a broader substrate-spectrum. On the other hand, Sec is easily targeted by electrophilic compounds which inhibits the TrxR activity and may turn TrxR into an NADPH oxidase. Ebselen, a synthetic seleno-compound containing selenazol, has