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INTRODUCTION TO MINIREVIEW SERIES

Thioredoxin–thioredoxin reductase – a system that has come of age

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Recent publications make it evident that the thioredoxin–thioredoxin reductase system has come of age. The four minireviews presented here attempt to put this field in perspective. The system was first recognized in the early 1960s as the reductant of methionine sulfoxide and PAPS (3′-phosphoadenosine-5′-phosphosulfate) in yeast and of ribonucleotides in *Escherichia coli* [1–3]. It became clear that fraction B in the *E. coli* system was a $M_r = 12\,000$ protein having a redox active disulfide; thioredoxin was the name assigned to this protein [4]. It was shown that thioredoxin was reduced by thioredoxin reductase in a NADPH-dependent reaction and that in its dithiol form, thioredoxin served as the reductant of ribonucleotides via a ribonucleotide reductase. It was suggested that thioredoxin was equivalent to enzyme II in the methionine sulfoxide-reducing system and to fraction C in the sulfate-reducing system [4]. Thioredoxin reductase was shown to be a dimeric flavoenzyme containing a redox active disulfide and a FAD in each subunit [3]. The intense study of the various physiological functions of thioredoxin and thioredoxin reductase is the subject of the first Minireview [5].

The thioredoxin–thioredoxin reductase system is very broadly distributed and the two proteins have been isolated from many species. Thioredoxins are similar to one another in structure and the conformation of the single domain is referred to as the thioredoxin fold with the redox-active disulfide forming a protrusion about 35 residues from the N-terminus. Thioredoxin reductases, on the other hand, fall into two classes as first noticed by Holmgren and his colleagues [6]. The low M_r type ($M_r = 35\,000$ per subunit) is typified by the *E. coli* enzyme. The high M_r type ($M_r = 55\,000$ per subunit) is found in higher eukaryotes and is related in structure and mechanism to glutathione reductase, lipoamide dehydrogenase and other members of the pyridine nucleotide–disulfide oxidoreductase enzyme family [7]. Differences between the mechanisms of the high and low M_r types are covered in the second Minireview [8].

It has become clear only recently that the two proteins comprising the thioredoxin–thioredoxin reductase system are of considerable medical interest as indicators of a wide variety of diseases including rheumatoid arthritis, HIV–AIDS and cancer. Therefore, they are prime prospective drug targets. These fascinating topics are covered in the third Minireview [9].

Several eubacteria contain a single protein that is closely related to the thioredoxin–thioredoxin reductase system. The C-terminal 60% is similar to low M_r thioredoxin reductase, including its redox-active disulfide located just in the pyridine nucleotide binding domain. The N-terminal 40% is a tandem repeat of two thioredoxin-like folds with the redox-active disulfide retained in only one of them. These proteins function as NADH-dependent reductants of peroxyredoxins that in turn reduce alkyl hydroperoxides. The final Minireview will cover this interesting system [10].

The chloroplast thioredoxins f and m, that are reduced by ferredoxin–thioredoxin reductase rather than by thioredoxin reductase are mentioned briefly in the first Minireview [11].

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