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REVIEW ARTICLE

Thioredoxin-related protein of 14 kDa as a modulator of redox signalling pathways

Correspondence Elias S. J. Arnér, Division of Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm SE-171 77, Sweden. E-mail: elias.arner@ki.se

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Belén Espinosa and Elias S J Arnér

Division of Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Thioredoxin-related protein of 14 kDa (TRP14; also named TXNDC17 for thioredoxin domain-containing protein 17) is a highly conserved and ubiquitously expressed oxidoreductase. It is expressed in parallel with thioredoxin 1 (Trx1, *TXN*; *TXN1*), an efficient substrate for the mammalian cytosolic selenoprotein thioredoxin reductase 1 (TrxR1; *TXNRD1*). However, TRP14, in sharp contrast to Trx1, cannot support the activities of ribonucleotide reductase, peroxiredoxins or methionine sulfoxide reductases, thus is unable to directly support cell proliferation or antioxidant defence through these pathways. However, TRP14 has been shown to efficiently reduce L-cystine, which thereby indirectly supports glutathione synthesis. TRP14 can also suppress NF-κB signalling, is functionally linked to STAT3 signalling, and can directly reactivate oxidized protein-tyrosine phosphatase PTP1B. Furthermore, TRP14 can efficiently reduce persulfidated or nitrosylated cysteine residues in many proteins, thereby having the capacity to modulate signalling through hydrogen sulfide or NO. Additional bioinformatics analyses and observations suggest further roles for TRP14; therefore, further studies of its functions are warranted. Collectively, the results available suggest that TRP14 is a member of the thioredoxin system dedicated to the control of cellular redox signalling pathways.

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Abbreviations

BECN1, beclin-1; LC8 (*DYNLL1*), dynein light chain 1 (light chain 8); PTP1B, protein-tyrosine phosphatase 1B; RRM2, ribonucleotide reductase subunit M2; SNO, S-nitrosylated cysteine residue; STRING, database of known and predicted protein–protein interactions (string-db.org); TRP14 (TXNDC17), thioredoxin-related protein of 14 kDa; Trx1 (*TXN* also named *TXN1*), thioredoxin 1; TrxR1 (*TXNRD1*), thioredoxin reductase 1

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Introduction

Redox control has a critical role in maintaining cellular functions under diverse growth conditions (Trachootham *et al.*, 2008; Holmstrom and Finkel, 2014; Navarro-Yepes *et al.*, 2014; Ye *et al.*, 2015). Physiological regulation of cellular redox status occurs mainly through the controlled oxidation of reactive cysteine residues in concert with enzymatically-controlled reduction of such cysteines. The reductive pathways are controlled by two major systems in the cytosol: the **glutathione (GSH)** and thioredoxin systems.

In the glutathione system, electrons are transferred from **NADPH** to **glutathione disulphide reductase** that reduces glutathione disulphide (GSSG). Subsequently, reduced glutathione propels those electrons to numerous enzymes, including the glutathione peroxidases, glutaredoxins and glutathione S-transferases (Lillig *et al.*, 2008; Toppo *et al.*, 2009; Deponte, 2013; Ye *et al.*, 2015).

The thioredoxin system is composed of different isoforms of thioredoxin and thioredoxin reductase, where the latter use NADPH to reduce the active site disulfide to a dithiol in their thioredoxin substrates. Cytosolic thioredoxin 1 (Trx1), reduced by TrxR1, is an oxidoreductase with a very broad substrate specificity, thus supporting many important functions in cells (Holmgren, 1995; Martin, 1995; Arner and Holmgren, 2000; Gromer *et al.*, 2004). However, it is likely to be impossible for a single protein to recognize and support all reductive pathways in a cell and, in mammals, several auxiliary Trx-like proteins complement the functions of Trx1, and are presumed to have both overlapping and specific roles in cells (Miranda-Vizuete *et al.*, 2004; Jimenez *et al.*, 2006; Funato and Miki, 2007; Su *et al.*, 2007; Dammeyer and Arner, 2011). The Trx-related protein of 14 kDa (TRP14, encoded by *TXNDC17*) is an interesting member of the Trx system that has, as yet, remained sparsely characterized.

Early on, TRP14, together with Trx1, was found to be expressed in most rat and human tissues when analysed with immunoblotting (Jeong *et al.*, 2004). If searching current databases for its expression, it indeed seems as if TRP14 (TXNDC17) is expressed in most, if not all, human cell types, cell lines and tissues (e.g. see https://www.genecards.org/cgi-bin/carddisp.pl?gene=TXNDC17&keywords=txndc17#expression, https://www.proteinatlas.org/ENSG00000129235-TXNDC17/tissue or https://www.ncbi.nlm.nih.gov/UniGene/ESTProfileViewer.cgi?uglist=Hs.408236). At present, it is unclear what role(s) TRP14 carries out in the cells where it is expressed. Recent insights regarding the potential roles of TRP14 in the control of redox signalling events are the main focus of this review.

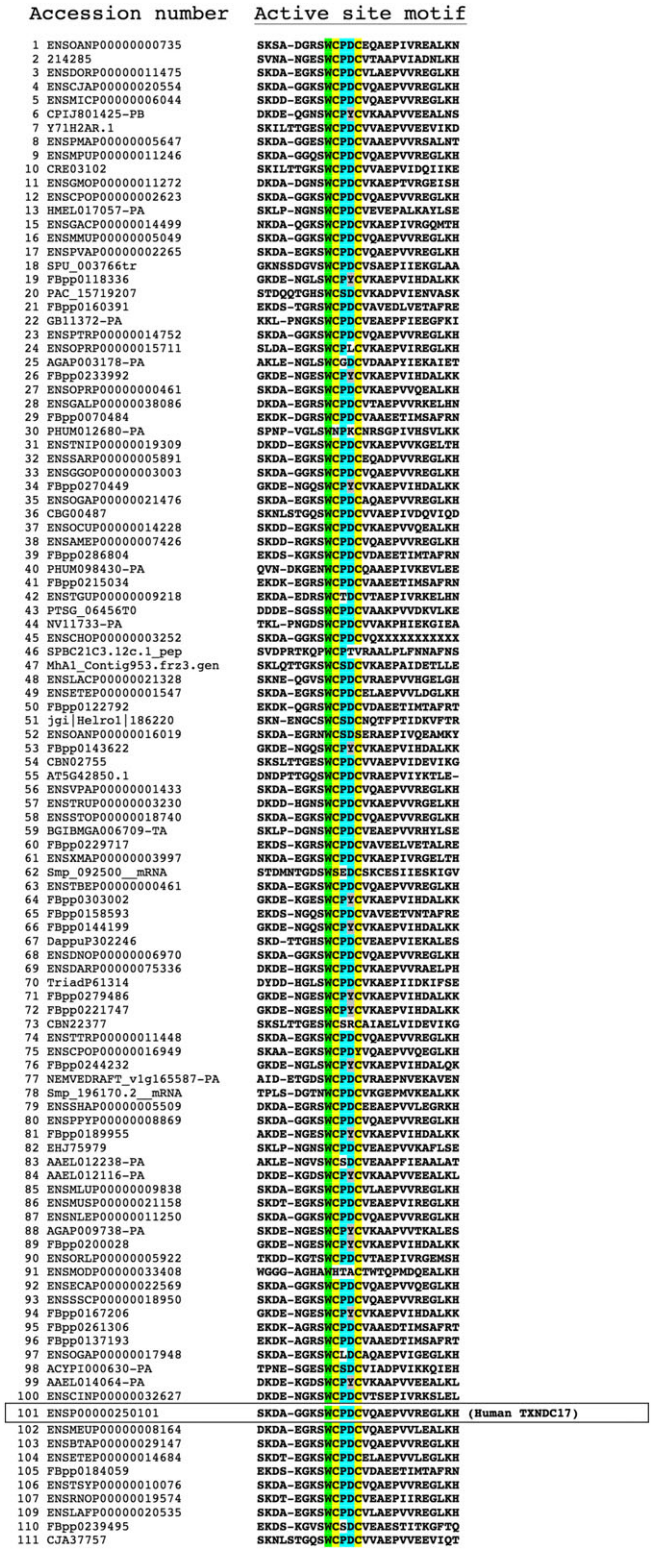
Potential roles of TRP14 (TXNDC17) in signalling

Identification and characterizations of TRP14 as a regulator of NF-κB signalling

Mammalian TRP14 has 123 amino acids and was detected in 2000 by a procedure used to search for proteins containing redox-sensitive cysteine residues with low pKa in rat brains (Kim *et al.*, 2000). Human TRP14 was subsequently discovered in 2004 by Rhee and co-workers, who characterized TRP14 as a cytosolic protein that is expressed in most cells and tissues, has a low redox potential and, interestingly, is reduced by cytosolic TrxR1 but, in contrast to Trx1, is unable to reduce ribonucleotide reductase subunit M2 (RRM2), peroxiredoxins or methionine sulfoxide reductase, thus suggesting different functions from those of Trx1 (Jeong *et al.*, 2004). The active site motif of human TRP14 is WCPDC (instead of WCGPC as found in Trx1), and in 2004, the Rhee group also solved the crystal structure of TRP14 at 1.8 Å resolution (PDB entry 1WOU), showing that although TRP14 only shares 20% sequence identity with Trx1, the topological structures of the two proteins are very similar. However, in the vicinity of the active site in TRP14, there is an extended loop, an additional α-helix, and a different distribution of charged residues compared to Trx1, which may explain the differences in substrate specificities between the two oxidoreductases (Woo *et al.*, 2004). It was also shown in 2004, again by Rhee *et al.*, that TRP14 suppresses **TNF-α**-induced activation of NF-κB, JNK and p38 MAPKs, while TRP14 in contrast to Trx1 did not regulate the activities of apoptosis signal-regulating kinase-1 (Jeong *et al.*, 2004b). The authors later showed that the TRP14-mediated suppression of NF-κB activation was uniquely related to its reduction of dynein light chain LC8 (Jung *et al.*, 2008; Jeong *et al.*, 2009).

Further evolutionary insights regarding TRP14 functions

Early on, it was noted that TRP14 orthologues are found in a large number of species, from bacteria, plants, yeast and mammals, and in an alignment of TRP14 sequences from 42 different species the unusual WCPDC active site was completely conserved (Jeong *et al.*, 2004; Jeong *et al.*, 2009). In the decade that has passed since those analyses, many more organisms have been sequenced, and the TRP14 family of sequences has thus grown considerably. When 111 sequences of TRP14 from 89 compiled animal sequences were analysed at the curated TreeFam database of EMBL-EBI (http://www.treefam.org/family/TF313854) (Li *et al.*, 2006; Ruan *et al.*, 2008), it became evident that TRP14 orthologues are widely distributed throughout the animal kingdom. However, an analysis of the active site motifs of these sequences revealed that the WCPDC active site is not completely conserved. In some of the sequences, it is instead WCPYC (Figure 1); this motif is the sequence of a typical dithiol glutaredoxin active site (Åslund *et al.*, 1997; Holmgren *et al.*, 1998; Fernandes and Holmgren, 2004; Foloppe and Nilsson, 2004; Lillig *et al.*, 2008). At present, it is not clear whether such 'WCPYC' active site proteins, otherwise being closely related to TRP14 sequences, should be considered as glutaredoxins or TRP14 variant proteins. An important definition of a glutaredoxin is that it utilizes glutathione during catalysis (Åslund *et al.*, 1997; Holmgren *et al.*, 1998; Fernandes and Holmgren, 2004; Lillig *et al.*, 2008), and those TRP14 variant proteins thereby need to be enzymatically characterized, before they can be fully classified as being either glutaredoxins or TRP14 proteins. Some additional insights into the potential functions of TRP14 can, however, be deduced from a number of biochemical characterizations of TRP14 that have thus far been made with non-mammalian TRP14 proteins.



	Accession number	Active site motif
1	ENSOANP00000000735	SKSA-DGRSWCPDCEQAEPIVREALKN
2	214285	SVNA-NGESWCPDCVTAAPVIADNLKH
3	ENSDORP00000011475	SKDA-EGKSWCPDCVLAEPVVREGLKH
4	ENSCJAP00000020554	SKDA-GGKSWCPDCVQAEPVVREGLKH
5	ENSMICP00000006044	SKDD-EGKSWCPDCVQAEPVVREGLKH
6	CPIJ801425-PB	DKDE-QGNSWCPYCVKAAPVVEEALNS
7	Y71H2AR.1	SKILTTGESWCPDCVVAEPVVEEVIKD
8	ENSPMAP00000005647	SKDA-GGESWCPDCVAAEPVVRSALNT
9	ENSMPUP00000011246	SKDA-GGQSWCPDCVQAEPVVREGLKH
10	CRE03102	SKILTTGKSWCPDCVVAEPVIDQIIKE
11	ENSGMOP00000011272	DKDA-DGNSWCPDCVKAEPTVRGEISH
12	ENSCPOP00000002623	SKDA-GGKSWCPDCVQAEPVVREGLKH
13	HMEL017057-PA	SKLP-NGNSWCPDCVEVEPALKAYLSE
15	ENSGACP00000014499	NKDA-QGKSWCPDCVKAEPIVRGQMTH
16	ENSMMUP00000005049	SKDA-GGKSWCPDCVQAEPVVREGLKH
17	ENSPVAP00000002265	SKDA-EGKSWCPDCVQAEPVVREGLKH
18	SPU_003766tr	GKNSSDGVSWCPDCVSAEPIIEKGLAA
19	FBpp0118336	GKDE-NGLSWCPYCVKAEPVIHDALKK
20	PAC_15719207	STDQQTGHSWCSDCVKADPVIENVASK
21	FBpp0160391	EKDS-TGRSWCPDCVAVEDLVETAFRE
22	GB11372-PA	KKL-PNGKSWCPDCVEAEPFIEEGFKI
23	ENSPTRP00000014752	SKDA-GGKSWCPDCVQAEPVVREGLKH
24	ENSOPRP00000015711	SLDA-EGKSWCPLCVKAEPVIREGLKH
25	AGAP003178-PA	AKLE-NGLSWCGDCVDAAPYIEKAIET
26	FBpp0233992	GKDE-NGESWCPYCVKAEPVIHDALKK
27	ENSOPRP00000000461	SKDA-EGKSWCPDCVKAEPVVQEALKH
28	ENSGALP00000038086	DKDA-EGRSWCPDCVTAEPVVRKELHN
29	FBpp0070484	EKDK-DGRSWCPDCVAAEETIMSAFRN
30	PHUM012680-PA	SPNP-VGLSWNPKCNRSGPIVHSVLKK
31	ENSTNIP00000019309	DKDD-EGKSWCPDCVKAEPVVKGELTH
32	ENSSARP00000005891	SKDA-EGKSWCPDCEQADPVVREGLKH
33	ENSGGOP00000003003	SKDA-GGKSWCPDCVQAEPVVREGLKH
34	FBpp0270449	GKDE-NGQSWCPYCVKAEPVIHDALKK
35	ENSOGAP00000021476	SKDA-EGKSWCPDCAQAEPVVREGLKH
36	CBG00487	SKNLSTGQSWCPDCVVAEPIVDQVIQD
37	ENSOCUP00000014228	SKDD-EGKSWCPDCVKAEPVVQEALKH
38	ENSAMEP00000007426	SKDD-RGKSWCPDCVQAEPVVREGLKH
39	FBpp0286804	EKDS-KGKSWCPDCVDAEETIMTAFRN
40	PHUM098430-PA	QVN-DKGENWCPDCQAAEPIVKEVLEE
41	FBpp0215034	EKDK-EGRSWCPDCVAAEETIMSAFRN
42	ENSTGUP00000009218	EKDA-EDRSWCTDCVTAEPIVRKELHN
43	PTSG_06456T0	DDDE-SGSSWCPDCVAAKPVVDKVLKE
44	NV11733-PA	TKL-PNGDSWCPDCVVAKPHIEKGIEA
45	ENSCHOP00000003252	SKDA-GGKSWCPDCVQXXXXXXXXXXX
46	SPBC21C3.12c.1_pep	SVDPRTKQPWCPTVRAALPLFNNAFNS
47	MhA1_Contig953.frz3.gen	SKLQTTGKSWCSDCVKAEPAIDETLLE
48	ENSLACP00000021328	SKNE-QGVSWCPDCVRAEPVVHGELGH
49	ENSETEP00000001547	SKDA-EGKSWCPDCELAEPVVLDGLKH
50	FBpp0122792	EKDK-QGRSWCPDCVDAEETIMTAFRT
51	jgi|Helro1|186220	SKN-ENGCSWCSDCNQTFPTIDKVFTR
52	ENSOANP00000016019	SKDA-EGRNWCSDSERAEPIVQEAMKY
53	FBpp0143622	GKDE-NGQSWCPYCVKAEPVIHDALKK
54	CBN02755	SKSLTTGESWCPDCVVAEPVIDEVIKG
55	AT5G42850.1	DNDPTTGQSWCPDCVRAEPVIKKTLE-
56	ENSVPAP00000001433	SKDA-EGKSWCPDCVQAEPVVREGLKH
57	ENSTRUP00000003230	DKDD-HGNSWCPDCVKAEPVVRGELKH
58	ENSSTOP00000018740	SKDA-EGKSWCPDCVQAEPVVREGLKH
59	BGIBMGA006709-TA	SKLP-DGNSWCPDCVEAEPVVRHYLSE
60	FBpp0229717	EKDS-KGRSWCPDCVAVEELVETALRE
61	ENSXMAP00000003997	NKDA-EGKSWCPDCVKAEPIVRGELTH
62	Smp_092500__mRNA	STDMNTGDSWSEDCSKCESIIESKIGV
63	ENSTBEP00000000461	SKDA-EGKSWCPDCVQAEPVVREGLKH
64	FBpp0303002	GKDE-KGESWCPYCVKAEPVIHDALKK
65	FBpp0158593	EKDS-NGQSWCPDCVAVEETVNTAFRE
66	FBpp0144199	GKDE-NGQSWCPYCVKAEPVIHDALKK
67	DappuP302246	SKD-TTGHSWCPDCVEAEPVIEKALES
68	ENSDNOP00000006970	SKDA-GGKSWCPDCVQAEPVVREGLKH
69	ENSDARP00000075336	DKDE-HGKSWCPDCVKAEPVVRAELPH
70	TriadP61314	DYDD-HGLSWCPDCVKAEPIIDKIFSE
71	FBpp0279486	GKDE-NGESWCPYCVKAEPVIHDALKK
72	FBpp0221747	GKDE-NGESWCPYCVKAEPVIHDALKK
73	CBN22377	SKSLTTGESWCSRCAIAELVIDEVIKG
74	ENSTTRP00000011448	SKDA-EGKSWCPDCVQAEPVVREGLKH
75	ENSCPOP00000016949	SKAA-EGKSWCPDYVQAEPVVQEGLKH
76	FBpp0244232	GKDE-NGLSWCPYCVKAEPVIHDALQK
77	NEMVEDRAFT_v1g165587-PA	AID-ETGDSWCPDCVRAEPNVEKAVEN
78	Smp_196170.2__mRNA	TPLS-DGTNWCPDCVKGEPMVKEALKK
79	ENSSHAP00000005509	DKDA-EGRSWCPDCEEAEPVVLEGRKH
80	ENSPPYP00000008869	SKDA-GGKSWCPDCVQAEPVVREGLKH
81	FBpp0189955	AKDE-NGESWCPYCVKAEPVIHDALKK
82	EHJ75979	SKLP-NGNSWCPDCVEAEPVVKAFLSE
83	AAEL012238-PA	AKLE-NGVSWCSDCVEAAPFIEAALAT
84	AAEL012116-PA	DKDE-KGDSWCPYCVKAAPVVEEALKL
85	ENSMLUP00000009838	SKDA-EGKSWCPDCVLAEPVVREGLKH
86	ENSMUSP00000021158	SKDT-EGKSWCPDCVEAEPVIREGLKH
87	ENSNLEP00000011250	SKDA-GGKSWCPDCVQAEPVVREGLKH
88	AGAP009738-PA	SKDE-NGESWCPYCVKAAPVVTKALES
89	FBpp0200028	GKDE-NGESWCPYCVKAEPVIHDALKK
90	ENSORLP00000005922	TKDD-KGTSWCPDCVTAEPIVRGEMSH
91	ENSMODP00000033408	WGGG-AGHAWHTACTWTQPMDQEALKH
92	ENSECAP00000022569	SKDA-GGKSWCPDCVQAEPVVQEGLKH
93	ENSSSCP00000018950	SKDA-EGKSWCPDCVQAEPVVREGLKH
94	FBpp0167206	GKDE-NGESWCPYCVKAEPVIHDALKK
95	FBpp0261306	EKDK-AGRSWCPDCVAAEDTIMSAFRT
96	FBpp0137193	EKDK-AGRSWCPDCVAAEDTIMSAFRT
97	ENSOGAP00000017948	SKDA-EGKSWCLDCAQAEPVIGEGLKH
98	ACYPI000630-PA	TPNE-SGESWCSDCVIADPVIKKQIEH
99	AAEL014064-PA	DKDE-KGDSWCPYCVKAAPVVEEALKL
100	ENSCINP00000032627	DKDE-NGKSWCPDCVTSEPIVRKSLEL
101	ENSP00000250101	SKDA-GGKSWCPDCVQAEPVVREGLKH (Human TXNDC17)
102	ENSMEUP00000008164	DKDA-EGRSWCPDCVQAEPVVLEALKH
103	ENSBTAP00000029147	SKDA-EGKSWCPDCVQAEPVVREGLKH
104	ENSETEP00000014684	SKDT-EGKSWCPDCELAEPVVLEGLKH
105	FBpp0184059	EKDS-KGKSWCPDCVDAEETIMTAFRN
106	ENSTSYP00000010076	SKDA-EGKSWCPDCVQAEPVVREGLKH
107	ENSRNOP00000019574	SKDT-EGKSWCPDCVEAEPIIREGLKH
109	ENSLAFP00000020535	SKDA-EGKSWCPDCVLAEPVVREGLKH
110	FBpp0239495	EKDS-KGVSWCSDCVEAESTITKGFTQ
111	CJA37757	SKNLSTGQSWCPDCVVAEPVVEEVIQT

Figure 1

Evolutionary conservation of TRP14 in animals. The accession numbers and amino acid sequences of the region around the active site WCPDC motif are shown for 111 sequences of TRP14 from 89 species, as generated through the curated TreeFam server (see references and details in the text). The human sequence is boxed for reference. Note that the tryptophan in the active site motif is fully conserved throughout these animal species (green). The two active site cysteine residues (yellow) are almost fully conserved, while a few sequences have monothiol active site motifs with only a single Cys residue. The intervening Pro-Asp amino acids are also conserved in most species (blue), although in some, Asp is substituted by Tyr (grey), thus resulting in a WCPYC active site motif as typically found in glutaredoxins. See text for further details.

In 2007, a TRP14-encoding gene named AmphiTRP14 was identified in the amphioxus *Brahciostom belcheri*, which became the first non-mammalian TRP14 to be characterized (Jiang *et al*., 2007). AmphiTRP14 shows 56% identity with human TRP14 and is, as in human TRP14, a 123 amino acid protein having a WCPDC active site motif and an estimated molecular weight of 14 kDa. The protein was found to be expressed mainly in hepatic caecum, ovary and hind-gut of the amphioxus (Jiang *et al*., 2007). Another TRP14 orthologue was characterized in the clam *Venerupis philippinarum*, where it was expressed in all tissues but at highest levels in the hepatopancreas and other organs associated with environmental exposure such as gills, hemocytes and mantles (Wang *et al*., 2011). Interestingly, the expression of that protein was up-regulated upon exposure to high levels of cadmium or copper, suggesting that it may have a role in antioxidant responses against metal stress in the clam (Wang *et al*., 2011).

TRP14 was also identified in the fish group *Epinephelus coioides*. Similar to TRP14 orthologues of other species, it has 123 amino acids with the conserved active site motif WCPDC, and is widely expressed in different organs of the fish, displaying high levels in the liver, muscle, brain, kidney, skin and gill. Interestingly, in that study, it was shown that transcripts for this TRP14 were up-regulated when the fish was challenged with the pathogenic Singapore grouper iridovirus, again possibly suggesting some protective function of TRP14 (Wei *et al*., 2013).

Based upon these analyses of TRP14 orthologues in species other than humans, it is reasoned that TRP14 has a role in protection against challenges with oxidative stress, toxic compounds or viral infections. The fact that the protein is so well preserved during evolution points towards some vital but yet unrecognized role of TRP14 in the survival of cells and organisms. The possibility that TRP14 is not a direct antioxidant, but rather an important redox signalling protein that orchestrates protective responses, should not be disregarded, especially considering its lack of direct support of the activities of antioxidant enzymes such as peroxiredoxins or methionine sulfoxide reductases (Jeong *et al*., 2004). Some recently discovered redox activities of TRP14 should be considered when assessing the possible functional roles of this protein, as shall be discussed next. Several of the activities are also schematically summarized in Figure 2.

Cystine reduction by human TRP14

An important antioxidant, protective and cell–cell communicative function of cells is system x_C^--mediated uptake of **cystine** in exchange with **glutamate**, with intracellular cystine providing an important source of cysteine for synthesis of glutathione (Conrad and Sato, 2012; Lewerenz *et al*., 2013). It is in this context that TRP14 could have a potentially important role in that it efficiently reduces the disulfide of cystine, to liberate two cysteine molecules, in a reaction propelled by TrxR1 and NADPH (Pader *et al*., 2014). Human TRP14 has been shown to be a good substrate for TrxR1, which reduces the active site disulfide of TRP14 to a dithiol using NADPH, while TRP14 is not a substrate for mitochondrial TrxR2 (Jeong *et al*., 2004; Woo *et al*., 2004). Interestingly, when coupled to cystine reduction, TRP14 becomes an even better substrate for TrxR1 than Trx1, with the catalytic efficiency (k_{cat}/K_m) for TRP14 (2217 $min^{-1}\cdot\mu M^{-1}$) being fivefold higher than that for Trx1 (418 $min^{-1}\cdot\mu M^{-1}$) (Pader *et al*., 2014). Moreover, if another substrate of Trx1 other than cystine is present that can be reduced by Trx1 but not by TRP14, then Trx1-mediated cystine reduction easily becomes blocked, while TRP14 reduction of cystine continues with high efficiency (Pader *et al*., 2014). These observations possibly suggest that one important role of TRP14, compatible with its involvement in the protection against metal stress or viral infections as implied above, may relate to its catalysis of cystine reduction. Furthermore, several other findings suggest that TRP14 is uniquely positioned to have a role in the control of redox signalling events.

Specific roles of TRP14 in redox signalling

Redox signalling implies the control of cellular functions by enzymatically regulated oxidation or reduction of redox active moieties in key signalling proteins (Winterbourn and Hampton, 2008; Brigelius-Flohe and Flohe, 2011; Groitl and Jakob, 2014; Sies, 2014; Yoshihara *et al*., 2014; Sobotta *et al*., 2015; Winterbourn and Hampton, 2015; Ye *et al*., 2015). TRP14 can control several distinct steps of redox regulatory pathways, as summarized here.

- NF-κB signalling

  NF-κB has critical functions in processes such as inflammation, immunity, cell proliferation, differentiation and survival (Hayden and Ghosh, 2004; Hayden and Ghosh, 2012). TRP14 was initially discovered in 2004 as a suppressor of NF-κB signalling, as discussed above. Trx1 has also been shown to play different roles in redox regulation of several transcriptional factors, including NF-κB (Matthews *et al*., 1992; Mitomo *et al*., 1994; Heilman and Watson, 2008). However, TRP14 seems to be a more potent regulator of NF-κB signalling than Trx1, although TRP14 is expressed at lower levels than Trx in cells (Jeong *et al*., 2004a). In order to try to identify potential cellular substrates of TRP14, a trapping method using an active site monothiol mutant was employed, as typically used for Trx substrates (Motohashi *et al*., 2001). In that analysis, three potential substrates of TRP14 were identified: LC8, cofilin and ribosomal protein L30, with the reduction of LC8 being suggested to mediate the suppression of NF-κB signalling by TRP14 (Jeong *et al*., 2004b; Jung *et al*., 2008). It was later shown that TRP14 counteracts osteoclast differentiation, which also seems to be an activity that relates to its suppression of NF-κB activation (Hong *et al*., 2014). The mode of TRP14-mediated suppression of NF-κB is believed to occur through activation of LC8 by reduction of a disulfide in the protein; the reduced LC8 then binds to IκB to prevent its phosphorylation (Jung *et al*., 2008).

- STAT3 signalling

  By examining the regulation of TRP14 through Chip analyses coupled with a luciferase assay, the transcription factor **STAT3** was found to bind the promoter region of the TRP14-encoding gene *TXNDC17* (Zhang *et al*., 2016). Furthermore, cells became resistant to **paclitaxel** (Taxol) treatment after either overexpression of TRP14 or stimulation of phosphorylation of STAT3, which in turn correlated with the induction of autophagy (Zhang *et al*., 2016). These

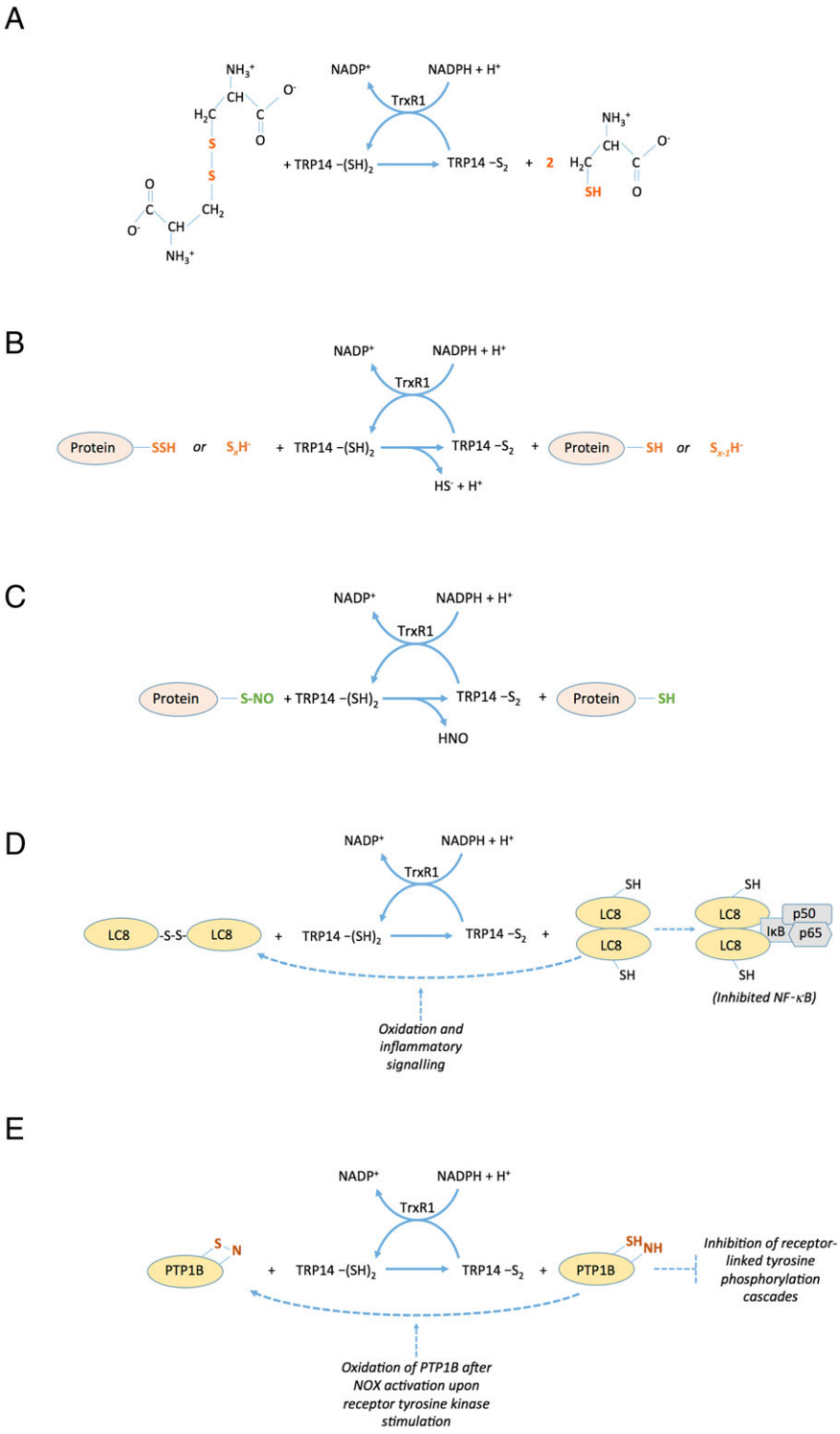


Figure 2

Schematic summary of selected enzymatic reactions catalyzed by TRP14. As is further discussed in the text, TRP14 lacks enzymatic activity with several classic Trx substrates including ribonucleotide reductase, methionine sulfoxide reductases or peroxiredoxins. However, several other enzymatic activities of TRP14, coupled to its own NADPH-dependent reduction from an active site disulfide to a dithiol by TrxR1, were described in recent years. Some of these are summarized here, with the key features in the different substrates being reduced by TRP14 indicated in colour. The activities include (A) reduction of cystine into two molecules of cysteine, (B) reduction of persulfidated proteins or inorganic polysulfides, (C) reduction of nitrosylated Cys residues (S-nitrosolyated moieties) in proteins, (D) reduction of a disulfide in LC8 that activates LC8 as an inhibitor of NF-κB through interactions of reduced LC8 with IκB and (E) reduction of a presumed sulfenylamide motif in oxidized PTP1B that promotes its phosphatase activity, which inhibits receptor-linked tyrosine phosphorylation cascades.

findings suggest that TRP14 is linked to STAT3 signalling, but the full interrelationships between TRP14 and STAT3 signalling are yet unclear. It should be noted that NF-κB and STAT3 interact and overlap in their signalling pathways (Fan *et al*., 2013), suggesting that TRP14 can also be indirectly linked to both pathways by being affected, or regulating, either one of these pathways. It is also noteworthy that STAT3 is directly regulated by peroxiredoxin 2 (Sobotta *et al*., 2015), which in turn is reduced by Trx1 but not by TRP14 (Jeong *et al*., 2004). These observations suggest that although TRP14 can modulate several pathways of redox signalling, some of these pathways (such as those involving STAT3) can be intricately modulated by many members of the thioredoxin system. The exact roles of TRP14 in this signalling need further scrutiny and may also, noteworthy, be both cell-, tissue- and organism-specific.

- Control of autophagy through beclin-1 (BECN1)

It was found that TRP14 supports the induction of autophagy, as a mechanism of resistance of cancer cells to paclitaxel (Taxol) in a manner dependent upon BECN1. Upon treatment with paclitaxel, an up-regulation in the expression of both proteins was found. However, when TRP14 expression was lowered using siRNA, the up-regulation of BECN1 in cells exposed to paclitaxel was prevented, thus suggesting a potential regulation of BECN1 expression by TRP14 (Zhang *et al*., 2015; Zhang *et al*., 2016; Zhen *et al*., 2017). The mechanisms of autophagy as well as BECN1 expression are known to be intimately linked with and affected by oxidative stress and redox signalling pathways (Navarro-Yepes *et al*., 2014), but it is yet too early to speculate on exactly how TRP14 directly regulates BECN1 and other processes linked to autophagy.

- Control of cysteine nitrosylation

One interesting mechanism of redox signalling is that linked to **NO** and nitrosylation (also called nitrosation) of target cysteine residues in key signalling proteins. Although it may be argued that *any* reactive cysteine residue can be modified by several different oxidative insults, such as glutathionylation, overoxidation and electrophilic attack, and that nitrosylation may be intrinsically unstable (Wolhuter and Eaton, 2017; Wolhuter *et al*., 2018), there are nonetheless a vast number of reports suggesting that nitrosylation of cysteine residues may be an important mechanism for control of cell function (Benhar *et al*., 2009; Wolhuter and Eaton, 2017; Wolhuter *et al*., 2018). It has long been known that Trx1 can control the nitrosylation state of cysteine residues, both by direct reduction of cysteine S-nitrosolyated (SNO) groups and by transnitrosylation mechanisms (Benhar *et al*., 2008; Hashemy and Holmgren, 2008; Benhar *et al*., 2009; Sengupta and Holmgren, 2013; Benhar, 2015; Benhar, 2016). It is thus interesting to note that TRP14 is also efficient at reducing nitrosylated cysteine residues (Pader *et al*., 2014). Whether Trx1 and TRP14 have different nitrosylated target proteins, or if one of the two proteins is more dominant than the other in regulating nitrosylation status, is not yet known.

- Hydrogen sulfide signalling as well as regulation of protein-tyrosine phosphatase 1B (PTP1B)

Hydrogen sulfide signalling is currently a rapidly expanding research field, with implications in a wide variety of redox signalling systems. There are many mechanisms by which hydrogen sulfide can alter cellular function in a regulated manner. One important mechanism is the formation of persulfidated cysteine residues, that is the addition of one or several sulfur atoms to the sulfur of cysteine through formation of disulfide bonds (Kabil *et al*., 2014; Nagy, 2015; Kasamatsu *et al*., 2016; Akaike *et al*., 2017; Alvarez *et al*., 2017). It is thus interesting, in relation to the potential functions of TRP14, that TRP14 is efficient at reducing persulfide moieties on cysteine residues in selected target proteins (Doka *et al*., 2016). Not only can TRP14 reduce persulfidated proteins, as well as inorganic polysulfide compounds in pure systems, but cells with knockdown of TRP14 were also found to display higher levels of endogenous persulfidated proteins, especially after having been challenged with polysulfide (Doka *et al*., 2016). The reduction of protein persulfides by TRP14 is also interesting in light of the fact that TRP14 can reactivate oxidized forms of protein-tyrosine phosphatase **PTP1B** (Dagnell *et al*., 2013), an important modulator of signalling pathways linked to activation of the tyrosine kinase receptor superfamily (Haj *et al*., 2003), which has been found to be regulated by persulfidation (Krishnan *et al*., 2011). It should also be considered that a stable form of PTP1B oxidation is that containing a sulfenylamide motif (Salmeen *et al*., 2003), which is the form of PTP1B that was believed to be reduced by TRP14 (Dagnell *et al*., 2013). It should, however, be noted that Trx1, TrxR1 and the glutathione system can also reduce many persulfidated proteins (Doka *et al*., 2016; Wedmann *et al*., 2016), as well as regulating PTP1B (Schwertassek *et al*., 2014; Dagnell *et al*., 2017). Hence, the importance and specific role(s) of TRP14 in this overall context, if any, remain to be determined.

Additional as yet uncharacterized functions of TRP14?

Less than 20 publications can today be found in PubMed on TRP14 (TXNRD17), and with such few studies published on this protein, it is highly likely that additional unknown functions of TRP14 will be revealed in the coming years. Recently, it was suggested that the clot gene of *Drosophila melanogaster*, essential for synthesis of the red eye pigment of the fly, encodes for a TRP14 orthologue (Kim, 2018). However, the protein has a typical glutaredoxin active site motif (WCPYC) and indeed exerts high glutaredoxin-like activities, although it has a predicted overall structure closely similar to TRP14 and also interacts with NF-κB signalling (Kim, 2018). Thus, the clot protein seems to have features of both glutaredoxins and TRP14. Perhaps it becomes a matter of semantics what protein class it should be considered to belong to.

The fact that TRP14 has such different substrate specificities than Trx1, while both proteins are efficiently supported by cytosolic TrxR1, suggests that TRP14 may have specific but yet unrecognized roles in cells. One such role may

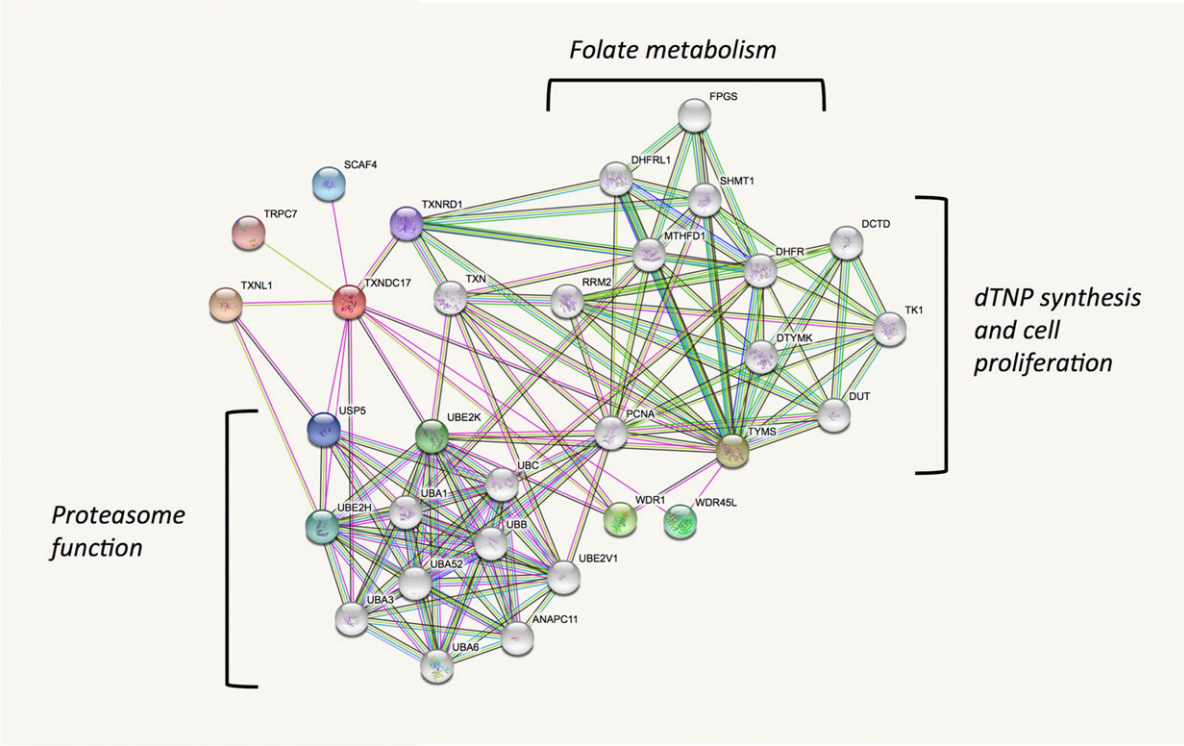


Figure 3

Predicted functional protein partners of TRP14 and its relation to Trx1 according to STRING analysis. The figure summarizes predicted functional protein partners using human TRP14 as query (TXNDC17, red), with the proteins predicted to directly interact with TRP14 shown in coloured nodes and the second shell of interactors shown in non-coloured nodes. The proposed interactions are those indicated with lines. For full description of the construction of this figure and the prediction basis, please see the text and cited references. Note that TRP14 is correctly predicted to interact with TrxR1 (TXNRD1) and indirectly, through TrxR1, with Trx1 (TXN). The functional overlap between Trx1 and TRP14 is otherwise predicted to be very low, with Trx1 interacting with a cluster of proteins involved in dTNP synthesis and proliferation or folate metabolism, while TRP14 is predicted to possibly interact with ubiquination status and proteasome function, as indicated in the figure. See text for further details.

perhaps be deduced by analyses of the protein in the STRING database, which was designed with the purpose of identifying possible functions of proteins by analysing co-expression, fusion genes or physical interactions with other proteins, as reported throughout large database sources (von Mering *et al.*, 2003; Szklarczyk *et al.*, 2017). Performing a STRING analysis for human TRP14 (TXNDC17) indeed gives an interesting result. It is clear that both TRP14 and Trx1 (TXN) are found in an analysis using TRP14 as a query, with the two proteins being linked through TrxR1 (TXNRD1) as a common denominator. More interesting, however, is that the majority of the other proteins predicted to interact with TRP14, or with Trx1, fall into distinct categories rather well separated from each other. For Trx1, the STRING analysis suggests interactions with several proteins involved in the synthesis of deoxyribonucleotides and cell proliferation, with RRM2 being a well-known and important Trx1 substrate in this context (Arner and Holmgren, 2000; Padovani *et al.*, 2001; Nordlund and Reichard, 2006). It is also interesting to note that Trx1 and TrxR1 are suggested to interact with several enzymes involved in folate metabolism, which may possibly relate to the recently discovered rather strong links between the thioredoxin system and the methionine/homocysteine cycle and thus indirectly folate metabolism (Eriksson *et al.*, 2015; Prigge *et al.*, 2017; Miller *et al.*, 2018). TRP14, however, does not evidently cluster with these systems but seems instead to be predominantly suggested to interact with a number of enzymes that support ubiquitin status and thus proteasome function (Figure 3). Perhaps TRP14 can thereby have functions explaining potential links between TrxR1 activities and proteasome function (Wang *et al.*, 2014; Nagakannan *et al.*, 2016). It should, however, be emphasized that these predictions are primarily based upon database analyses and must be validated experimentally, but could nonetheless suggest lines of forthcoming research further probing the cellular roles of TRP14 in control of redox signalling.

Conclusions

TRP14 is a ubiquitous cytosolic redox active protein, well-conserved and present from bacteria to mammals. Its conservation during evolution suggests that this protein should be important for cell or organism survival, but much is still unknown about its roles. Being effectively reduced by TrxR1 but not supporting classic substrates of Trx1 makes TRP14 a perfect candidate for regulation of redox signalling, with unique characteristics complementing those of Trx1. The

confirmed activities of TRP14 in NF-κB regulation, autophagy, persulfide reduction, PTP1B activation, SNO reduction and more implicate TRP14 to be of importance in redox signalling, but at present, little is known about its exact effects and the activities where it may have a predominant role over other redox active proteins. Further studies of TRP14 functions are thus warranted, and forthcoming results on the functions of this protein are likely to be interesting in the context of redox signalling.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b).

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Conflict of interest

The authors declare no conflicts of interest.

References

Akaike T, Ida T, Wei FY, Nishida M, Kumagai Y, Alam MM *et al.* (2017). Cysteinyl-tRNA synthetase governs cysteine polysulfidation and mitochondrial bioenergetics. Nat Commun 8: 1177.

Alexander SPH, Fabbro D, Kelly E, Marrion NV, Peters JA, Faccenda E *et al.* (2017a). The Concise Guide to PHARMACOLOGY 2017/18: Enzymes. Br J Pharmacol 174: S272–S359.

Alexander SPH, Kelly E, Marrion NV, Peters JA, Faccenda E, Harding SD *et al.* (2017b). The Concise Guide to PHARMACOLOGY 2017/18: Overview. Br J Pharmacol 174: S1–S16.

Alvarez L, Bianco CL, Toscano JP, Lin J, Akaike T, Fukuto JM (2017). Chemical biology of hydropersulfides and related species: possible roles in cellular protection and redox signaling. Antioxid Redox Signal 27: 622–633.

Arner ES, Holmgren A (2000). Physiological functions of thioredoxin and thioredoxin reductase. Eur J Biochem 267: 6102–6109.

Benhar M (2015). Nitric oxide and the thioredoxin system: a complex interplay in redox regulation. Biochim Biophys Acta 1850: 2476–2484.

Benhar M (2016). Emerging roles of protein S-nitrosylation in macrophages and cancer cells. Curr Med Chem 23: 2602–2617.

Benhar M, Forrester MT, Hess DT, Stamler JS (2008). Regulated protein denitrosylation by cytosolic and mitochondrial thioredoxins. Science 320: 1050–1054.

Benhar M, Forrester MT, Stamler JS (2009). Protein denitrosylation: enzymatic mechanisms and cellular functions. Nat Rev Mol Cell Biol 10: 721–732.

Brigelius-Flohe R, Flohe L (2011). Basic principles and emerging concepts in the redox control of transcription factors. Antioxid Redox Signal 15: 2335–2381.

Conrad M, Sato H (2012). The oxidative stress-inducible cystine/glutamate antiporter, system x (c) (−): cystine supplier and beyond. Amino Acids 42: 231–246.

Dagnell M, Frijhoff J, Pader I, Augsten M, Boivin B, Xu J *et al.* (2013). Selective activation of oxidized PTP1B by the thioredoxin system modulates PDGF-β receptor tyrosine kinase signaling. Proc Natl Acad Sci U S A 110: 13398–13403.

Dagnell M, Pace PE, Cheng Q, Frijhoff J, Ostman A, Arner ESJ *et al.* (2017). Thioredoxin reductase 1 and NADPH directly protect protein tyrosine phosphatase 1B from inactivation during H_2O_2 exposure. J Biol Chem 292: 14371–14380.

Dammeyer P, Arner ES (2011). Human protein atlas of redox systems – what can be learnt? Biochim Biophys Acta 1810: 111–138.

Deponte M (2013). Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes. Biochimica et Biophysica Acta (BBA) - General Subjects 1830: 3217–3266.

Doka E, Pader I, Biro A, Johansson K, Cheng Q, Ballago K *et al.* (2016). A novel persulfide detection method reveals protein persulfide- and polysulfide-reducing functions of thioredoxin and glutathione systems. Sci Adv 2: e1500968.

Eriksson S, Prigge JR, Talago EA, Arner ESJ, Schmidt EE (2015). Dietary methionine can sustain cytosolic redox homeostasis in the mouse liver. Nat Commun 6: 6479.

Fan Y, Mao R, Yang J (2013). NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. Protein Cell 4: 176–185.

Fernandes AP, Holmgren A (2004). Glutaredoxins: glutathione-dependent redox enzymes with functions far beyond a simple thioredoxin backup system. Antioxid Redox Signal 6: 63–74.

Foloppe N, Nilsson L (2004). The glutaredoxin -C-P-Y-C- motif: influence of peripheral residues. Structure 12: 289–300.

Funato Y, Miki H (2007). Nucleoredoxin, a novel thioredoxin family member involved in cell growth and differentiation. Antioxid Redox Signal 9: 1035–1057.

Groitl B, Jakob U (2014). Thiol-based redox switches. Biochim Biophys Acta 1844: 1335–1343.

Gromer S, Urig S, Becker K (2004). The thioredoxin system–from science to clinic. Med Res Rev 24: 40–89.

Haj FG, Markova B, Klaman LD, Bohmer FD, Neel BG (2003). Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatase-1B. J Biol Chem 278: 739–744.

Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S *et al.* (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 46: D1091–D1106.

Hashemy SI, Holmgren A (2008). Regulation of the catalytic activity and structure of human thioredoxin 1 via oxidation and S-nitrosylation of cysteine residues. J Biol Chem 283: 21890–21898.

Hayden MS, Ghosh S (2004). Signaling to NF-kappaB. Genes Dev 18: 2195–2224.

Hayden MS, Ghosh S (2012). NF-κB, the first quarter-century: remarkable progress and outstanding questions. Genes Dev 26: 203–234.

Heilman J, Watson W (2008). Thioredoxin reductase modulates NFkB signaling at the nuclear compartment. Cancer Res 68: 5268.

Holmgren A (1995). Thioredoxin structure and mechanism: conformational changes on oxidation of the active-site sulfhydryls to a disulfide. [Review]. Structure 3: 239–243.

Holmgren A, Arnér E, Åslund F, Björnstedt M, Liangwei Z, Ljung J *et al*. (1998). Redox regulation by the thioredoxin and glutaredoxin systems. In: Montagnier L, Olivier R, Pasquier C (eds). Oxidative Stress, Cancer, AIDS and Neurodegenerative Diseases. Marcel Dekker, Inc.: New York, pp. 229–246.

Holmstrom KM, Finkel T (2014). Cellular mechanisms and physiological consequences of redox-dependent signalling. Nat Rev Mol Cell Biol 15: 411–421.

Hong S, Huh JE, Lee SY, Shim JK, Rhee SG, Jeong W (2014). TRP14 inhibits osteoclast differentiation via its catalytic activity. Mol Cell Biol 34: 3515–3524.

Jeong W, Chang T-S, Boja ES, Fales HM, Rhee S (2004a). Roles of TRP14, a thioredoxin-related protein in tumor necrosis factor-α signaling pathways. J Biol Chem 279: 3151–3159.

Jeong W, Chang TS, Boja ES, Fales HM, Rhee SG (2004b). Roles of TRP14, a thioredoxin-related protein in tumor necrosis factor-alpha signaling pathways. J Biol Chem 279: 3151–3159.

Jeong W, Jung Y, Kim H, Park SJ, Rhee SG (2009). Thioredoxin-related protein 14, a new member of the thioredoxin family with disulfide reductase activity: implication in the redox regulation of TNF-alpha signaling. Free Radic Biol Med 47: 1294–1303.

Jeong W, Yoon HW, Lee SR, Rhee SG (2004). Identification and characterization of TRP14, a thioredoxin-related protein of 14 kDa. New insights into the specificity of thioredoxin function. J Biol Chem 279: 3142–3150.

Jiang S, Zhang S, Vuthiphandchai V, Nimrat S (2007). Human TRP14 gene homologue from amphioxus Branchiostoma belcheri: identification, evolution, expression and functional characterization. J Anat 210: 555–564.

Jimenez A, Pelto-Huikko M, Gustafsson JA, Miranda-Vizuete A (2006). Characterization of human thioredoxin-like-1: potential involvement in the cellular response against glucose deprivation. FEBS Lett 580: 960–967.

Jung Y, Kim H, Min SH, Rhee SG, Jeong W (2008). Dynein light chain LC8 negatively regulates NF-kappaB through the redox-dependent interaction with IkappaBalpha. J Biol Chem 283: 23863–23871.

Kabil O, Vitvitsky V, Banerjee R (2014). Sulfur as a signaling nutrient through hydrogen sulfide. Annu Rev Nutr 34: 171–205.

Kasamatsu S, Nishimura A, Morita M, Matsunaga T, Abdul Hamid H, Akaike T (2016). Redox signaling regulated by cysteine persulfide and protein polysulfidation. Molecules 21.

Kim JR, Yoon HW, Kwon KS, Lee SR, Rhee SG (2000). Identification of proteins containing cysteine residues that are sensitive to oxidation by hydrogen peroxide at neutral pH. Anal Biochem 283: 214–221.

Kim K (2018). Structure-based analysis of clot as a thioredoxin-related protein of 14 kDa in drosophila via experimental and computational approaches. Biotechnol Appl Biochem 65: 338–345.

Krishnan N, Fu C, Pappin DJ, Tonks NK (2011). H2S-induced sulfhydration of the phosphatase PTP1B and its role in the endoplasmic reticulum stress response. Sci Signal 4: ra86.

Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW *et al*. (2013). The cystine/glutamate antiporter system x(c)(−) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 18: 522–555.

Li H, Coghlan A, Ruan J, Coin LJ, Heriche JK, Osmotherly L *et al*. (2006). TreeFam: a curated database of phylogenetic trees of animal gene families. Nucleic Acids Res 34: D572–D580.

Lillig CH, Berndt C, Holmgren A (2008). Glutaredoxin systems. Biochim Biophys Acta 1780: 1304–1317.

Martin JL (1995). Thioredoxin-a fold for all reasons. Structure 3: 245–250.

Matthews JR, Wakasugi N, Virelizier JL, Yodoi J, Hay RT (1992). Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bond involving cysteine 62. Nucleic Acids Res 20: 3821–3830.

Miller CG, Holmgren A, Arner ESJ, Schmidt EE (2018). NADPH-dependent and -independent disulfide reductase systems. Free Radic Biol Med. https://doi.org/10.1016/j.freeradbiomed.2018.03.051.

Miranda-Vizuete A, Sadek CM, Jimenez A, Krause WJ, Sutovsky P, Oko R (2004). The mammalian testis-specific thioredoxin system. Antioxid Redox Signal 6: 25–40.

Mitomo K, Nakayama K, Fujimoto K, Sun X, Seki S, Yamamoto K (1994). Two different cellular redox systems regulate the DNA-binding activity of the p50 subunit of NF-κB in vitro. Gene 145: 197–203.

Motohashi K, Kondoh A, Stumpp MT, Hisabori T (2001). Comprehensive survey of proteins targeted by chloroplast thioredoxin. Proc Natl Acad Sci 98: 11224–11229.

Nagakannan P, Iqbal MA, Yeung A, Thliveris JA, Rastegar M, Ghavami S *et al*. (2016). Perturbation of redox balance after thioredoxin reductase deficiency interrupts autophagy-lysosomal degradation pathway and enhances cell death in nutritionally stressed SH-SY5Y cells. Free Radic Biol Med 101: 53–70.

Nagy P (2015). Mechanistic chemical perspective of hydrogen sulfide signaling. Methods Enzymol 554: 3–29.

Navarro-Yepes J, Burns M, Anandhan A, Khalimonchuk O, del Razo LM, Quintanilla-Vega B *et al*. (2014). Oxidative stress, redox signaling, and autophagy: cell death versus survival. Antioxid Redox Signal 21: 66–85.

Nordlund P, Reichard P (2006). Ribonucleotide reductases. Annu Rev Biochem 75: 681–706.

Pader I, Sengupta R, Cebula M, Xu J, Lundberg JO, Holmgren A *et al*. (2014). Thioredoxin-related protein of 14 kDa is an efficient L-cystine reductase and S-denitrosylase. Proc Natl Acad Sci U S A 111: 6964–6969.

Padovani D, Mulliez E, Fontecave M (2001). Activation of class III ribonucleotide reductase by thioredoxin. J Biol Chem 276: 9587–9589.

Prigge JR, Coppo L, Martin SS, Ogata F, Miller CG, Bruschwein MD *et al*. (2017). Hepatocyte hyperproliferation upon liver-specific co-disruption of thioredoxin-1, thioredoxin reductase-1, and glutathione reductase. Cell Rep 19: 2771–2781.

Ruan J, Li H, Chen Z, Coghlan A, Coin LJ, Guo Y *et al*. (2008). TreeFam: 2008 update. Nucleic Acids Res 36: D735–D740.

Salmeen A, Andersen JN, Myers MP, Meng TC, Hinks JA, Tonks NK *et al*. (2003). Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate. Nature 423: 769–773.

Schwertassek U, Haque A, Krishnan N, Greiner R, Weingarten L, Dick TP *et al*. (2014). Reactivation of oxidized PTP1B and PTEN by thioredoxin 1. FEBS J 281: 3545–3558.

Sengupta R, Holmgren A (2013). Thioredoxin and thioredoxin reductase in relation to reversible S-nitrosylation. Antioxid Redox Signal 18: 259–269.

Sies H (2014). Role of metabolic H2O2 generation: redox signaling and oxidative stress. J Biol Chem 289: 8735–8741.

Sobotta MC, Liou W, Stocker S, Talwar D, Oehler M, Ruppert T *et al*. (2015). Peroxiredoxin-2 and STAT3 form a redox relay for H2O2 signaling. Nat Chem Biol 11: 64–70.

Su D, Berndt C, Fomenko DE, Holmgren A, Gladyshev VN (2007). A conserved cis-proline precludes metal binding by the active site thiolates in members of the thioredoxin family of proteins. Biochemistry 46: 6903–6910.

Szklarczyk D, Morris JH, Cook H, Kuhn M, Wyder S, Simonovic M *et al*. (2017). The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. Nucleic Acids Res 45: D362–D368.

Toppo S, Flohe L, Ursini F, Vanin S, Maiorino M (2009). Catalytic mechanisms and specificities of glutathione peroxidases: variations of a basic scheme. Biochim Biophys Acta 1790: 1486–1500.

Trachootham D, Lu W, Ogasawara MA, Valle N, Huang P (2008). Redox regulation of cell survival. Antioxid Redox Signal 10: 1343–1374.

von Mering C, Huynen M, Jaeggi D, Schmidt S, Bork P, Snel B (2003). STRING: a database of predicted functional associations between proteins. Nucleic Acids Res 31: 258–261.

Wang Q, Ning X, Chen L, Pei D, Zhao J, Zhang L *et al*. (2011). Responses of thioredoxin 1 and thioredoxin-related protein 14 mRNAs to cadmium and copper stresses in Venerupis philippinarum. Comp Biochem Physiol C Toxicol Pharmacol 154: 154–160.

Wang X, Stafford W, Mazurkiewicz M, Fryknas M, Brjnic S, Zhang X *et al*. (2014). The 19S deubiquitinase inhibitor b-AP15 is enriched in cells and elicits rapid commitment to cell death. Mol Pharmacol 85: 932–945.

Wedmann R, Onderka C, Wei S, Szijarto IA, Miljkovic JL, Mitrovic A *et al*. (2016). Improved tag-switch method reveals that thioredoxin acts as depersulfidase and controls the intracellular levels of protein persulfidation. Chem Sci 7: 3414–3426.

Wei J, Ji H, Guo M, Yan Y, Qin Q (2013). Identification and characterization of TRP14, a thioredoxin-related protein of 14 kDa from orange-spotted grouper, Epinephelus coioides. Fish Shellfish Immunol 35: 1670–1676.

Winterbourn CC, Hampton MB (2008). Thiol chemistry and specificity in redox signaling. Free Radic Biol Med 45: 549–561.

Winterbourn CC, Hampton MB (2015). Redox biology: signaling via a peroxiredoxin sensor. Nat Chem Biol 11: 5–6.

Wolhuter K, Eaton P (2017). How widespread is stable protein S-nitrosylation as an end-effector of protein regulation? Free Radic Biol Med 109: 156–166.

Wolhuter K, Whitwell HJ, Switzer CH, Burgoyne JR, Timms JF, Eaton P (2018). Evidence against stable protein S-nitrosylation as a widespread mechanism of post-translational regulation. Mol Cell 69: 438–450 e435.

Woo JR, Kim SJ, Jeong W, Cho YH, Lee SC, Chung YJ *et al*. (2004). Structural basis of cellular redox regulation by human TRP14. J Biol Chem 279: 48120–48125.

Ye ZW, Zhang J, Townsend DM, Tew KD (2015). Oxidative stress, redox regulation and diseases of cellular differentiation. Biochim Biophys Acta 1850: 1607–1621.

Yoshihara E, Masaki S, Matsuo Y, Chen Z, Tian H, Yodoi J (2014). Thioredoxin/Txnip: redoxisome, as a redox switch for the pathogenesis of diseases. Front Immunol 4: 514.

Zhang SF, Wang XY, Fu ZQ, Peng QH, Zhang JY, Ye F *et al*. (2015). TXNDC17 promotes paclitaxel resistance via inducing autophagy in ovarian cancer. Autophagy 11: 225–238.

Zhang Z, Wang A, Li H, Zhi H, Lu F (2016). STAT3-dependent TXNDC17 expression mediates Taxol resistance through inducing autophagy in human colorectal cancer cells. Gene 584: 75–82.

Zhen Z, Yang K, Ye L, You Z, Chen R, Liu Y *et al*. (2017). Suberoylanilide hydroxamic acid sensitizes neuroblastoma to paclitaxel by inhibiting thioredoxin-related protein 14-mediated autophagy. Cancer Sci 108: 1485–1492.

Åslund F, Berndt KD, Holmgren A (1997). Redox potentials of glutaredoxins and other thiol-disulfide oxidoreductases of the thioredoxin superfamily determined by direct protein-protein redox equilibria. J Biol Chem 272: 30780–30786.