Supplement A Table 1. Summary of murine Trx1 system knockout models

Gene	Organ/ cell type	Author	Knockout approach	Mean lifespan	Cell death			DNA damage	Cell proliferation and differentiation	Hypertrophy
					Apoptosis	*Autophagy and mitochondria metabolism*	*Necrosis*			
Trx-1	Embryo	Matsui et al. [1]	Constitutive gene knockout	3.5 embryonic days	Not reported	Not reported	Not reported	Not reported	Significant loss of proliferative capacity, severe growth retardation, failure to develop trophoblast and hatch from zona pellucida	Not reported
	Heart	Yamamoto et al. [70]	Suppression of endogenous Trx-1 activity by overexpression of redox inactive hTrx-1 in cardiomyocytes(-myosin heavy chain-Cre)	Not reported	Not reported	Not reported	Not reported	Yes (observed by 8-OHdG staining)	No significant changed	Concentric cardiac hypertrophy mediated via ERK pathway with preservedLV ejection fraction

		Oka et al. [43]	Cre-LoxR recombination :Trx-1$^{fl/fl}$ bred with Myh6-Creanimal	25.5 days	Yes Two-fold increase in apoptotic cells (TUNEL assay) and clCasp3 level	Enhanced mTOR oxidation with no alterations in p62 and LC3 I/II levels; Deficits in mitochondrial activity	No	Not reported	Not reported	Dilatation hypertrophy with reducedLV ejection fraction
	Liver	Prigge et al. [62]	Cre-LoxR recombination :Trx$^{fl/fl}$ with Alb-Cre mice	Similar to control	No	No	No	No	No	Enlarged nucleus
	Lung	Das [68]	constitutive sitedirected mutagenesis (Cys32 and Cys35 in the active site of Trx-1 molecule were mutated to Ser)	In basal condition – not reported;72h after hypertoxic challenge	No	No	Yes (after hyperoxic challenge)	Not reported	No	No
	Spleen	Jabbar et al. [67]	Cre-LoxP recombination :Tamoxifen-inducible general Trx-1 knockout	15 days post knockout induction	Increase in number of apoptic cells inspleen; activation of p53 pathway	Increase in expression of PINK1, PARK2, and LC3 II; Decrease in mitochondrial/nuclea rDNA ratio.	No	Not reported	Reduced cell proliferation (BrdU incorporation), Reduced colony forming units.	No

TrxR1	Brain	Ohmori etal. [100, 101]	General ENU-mutation outside of active center CRISPR-Cas9 general mutation outside of active center	Similar to control; spontaneous reversal of observed pathology at 8-9 weeks	Reversible vacuolar degeneration in midbrain, decrease in neuronal and oligodendrocyt ecount Reversible vacuolar degeneration inmidbrain,	Downregulation of mitochondrial metabolism Not reported	No Not reported	Yes (observed by 8-OHdG staining) Not reporte d	Not reported	No
	Embryo	Jakupoglu et al. [66]	Cre-LoxP recombination (excised exon 15 in TrxR1 gene)	9.5-10.5 embryoni cdays	Yes, except heart	Not reported	No	Not reported	Severe growth retardation, defective organogenesis except heart, failure of neural tube closure	No
		Bondareva et al. [2]	excising exons1 and 2 of TrxR1 gene; mutant proteinlacked both N-terminal active site cysteines (Cys^{59} and Cys^{64})	8.5 embryonic days	Not reported	Not reported	No	Not reported	Severe growth retardation, failure to gastrulate due to impaired differentiation with relatively intact proliferation capacity	No

	Liver	Suvorova et al. [74]	Cre-LoxP recombination: TrxR1$^{fl/fl}$ with Alb-Cre mouse	Similar to control	No	No	No	No	No	No
		Rollins et al. [75]			No	No	No	No	No	No
		Iverson et al. [76]			No	Repression of lipogenesis, accumulation of glycogen	No	No	No	No
		Prigge et al. [62]			No	No	No signs of necrosis after acute cholestatic injury, decreased inflammation compared to control	No	No	No
	Thymus (CD4 and CD8 thymocytes)	Muri et al. [93]	Cre-LoxP recombination :TrxR1$^{fl/fl}$ with CD4-Cre	Not reported	No	Accumulation of metabolites requiredfor nucleotide biosynthesis	No	Not reported	Reduced proliferation (according to BrdU assay), overexpression of cell cycle arrest markers	No

	Pancreas	Stancill et al. [89]	Cre-LoxP recombination :TrxR1$^{fl/fl}$ with Ins-Cre mouse	Not reported	No	Reduced glucose- and membrane depolarization-stimulated insulin secretion	No	Not reported	Lack of -cell maturation (evidenced by decreased expression of genes-indicators responsible for glucose sensing)	No
	Brain: a)neural progenitors	Soerensen et al. [105]	Cre-LoxP recombination: TrxR1^{tm1Marc} bred to Nest-Cre animal	No	No	No	No	Not reported	Cerebellar hypoplasia, decreased neuronal count, reduced arborization of Purkinje cells, disoriented glia, improper corticallayering	No
	b) neurons		TrxR1^{tm1Marc} bred to T 1-Cre animal	No	No	No	No	Not reported	No	No