Table S2. *Sod* gene knockout mouse models and their phenotypes.

Gene	Type of mutation	Genotype	Phenotype	Oxidative stress	References
Sod1	Germline mutation	*Sod1*$^{-/-}$	Grossly normal, increased incidence of hepatocarcinogenesis, distal motor axonopathy, locomotor defects, reduction in hind limb skeletal muscle mass and strength, acceleration of age-dependent skeletal muscle atrophy, hearing loss, delayed wound healing, accelerated age-related macular degeneration, a decrease in motivational behavior, impaired olfactory sexual signaling, lower fertility, increase in cellular senescence, higher levels of circulating cytokines, and a ~30% decrease in lifespan	Extensive oxidative damage in the cytoplasm	(Elchuri et al., 2005; Fischer et al., 2012; Flood et al., 1999; Garratt et al., 2014; Imamura et al., 2006; Iuchi et al., 2010; Matzuk et al., 1998; Muller et al., 2006; Reaume et al., 1996; Shi et al., 2014; Yoshihara et al., 2016; Zhang et al., 2017)
		Sod1$^{+/-}$	Viable, fertile and grossly normal, increased vulnerability to facial nerve axotomy	Oxidative stress in the liver and prostate	(Bhusari et al., 2010; Reaume et al., 1996)
Sod2	Germline mutation	*Sod2*$^{-/-}$	Die within 21 d after birth with cardiomyopathy, fatty liver, neurodegeneration, metabolic acidosis, anemia, increased susceptibility to oxygen toxicity, mitochondrial dysfunction, inhibition of ETC and TCA enzymes	Accumulation of oxidative DNA damage	(Asikainen et al., 2002; Huang et al., 2001; Lebovitz et al., 1996; Li et al., 1995; Melov et al., 1999)
		Sod2$^{+/-}$	Phenotypically normal, normal lifespan, increased cancer incidence over lifespan, decreased respiratory function	Accelerated accumulation of oxidative damage	(Lebovitz et al., 1996; Li et al., 1995; Van Remmen et al., 2001; Van Remmen et al., 2003)
	Conditional knockout	Heart and skeletal muscle (MCK-Cre;*Sod2*$^{fl/fl}$)	Growth retardation, cardiac myopathy, reduced lifespan with a median life span of 15.4 ± 4.0 wk, abnormal mitochondrial structure, loss of respiratory enzyme activities, reduced ATP production	Elevated mitochondrial ROS and oxidative damage in muscle tissues	(Nojiri et al., 2006)
		Skeletal muscle (HSA–Cre;*Sod2*$^{fl/fl}$)	Normal spontaneous motor activity and muscle strength, but reduced exercise activity, loss of enzymatic activity for mitochondrial respiratory chain complexes (especially complex II), reduced ATP production	Elevated mitochondrial ROS and an increase in oxidative DNA damage in the skeletal muscle	(Kuwahara et al., 2010)
		Type IIB skeletal muscle fibers (*TnIFastCre;Sod2*$^{fl/fl}$)	Decreased mitochondrial function, reduced complex II activity, reduced ATP production, decreased aconitase activity, impaired exercise capacity	Elevated mitochondrial oxidative stress and oxidative damage in the skeletal muscle	(Lustgarten et al., 2009; Lustgarten et al., 2011)
		Liver (Alb-Cre; *Sod2*$^{fl/fl}$)	No detected phenotype	No elevation of lipid peroxidation in the liver	(Ikegami et al., 2002)
		Liver (α-fetoprotein-Cre, *Sod2*$^{fl/fl}$)	Phenotypically normal, decreased liver to body weight ratio, sign of hepatocyte injury, increased likelihood of tumor formation in a chemically induced liver carcinogenesis model	Elevated oxidative damage in the liver	(Konzack et al., 2015; Lenart et al., 2007)

		Kidney (Ksp1.3/Cre; *Sod2*$^{fl/fl}$)	Phenotypically normal, mild renal damage and normal lifespan	Increased oxidative stress (tyrosine nitration)	(Parajuli et al., 2011)
		Cells of the neurogenic lineage mostly in the brain (nestin-Cre*;Sod2*$^{fl/fl}$)	Die by 25 d of age, growth retardation, spongiform neurodegeneration, loss of mitochondrial complex II activity	Higher intracellular superoxide levels and oxidative damage in the brain	(Izuo et al., 2015; Sasaki et al., 2011)
		Hematopoietic stem cells (vav-iCre*;Sod2*$^{fl/fl}$)	Impaired red blood cell development, systematic redistribution of iron, heme synthetic defect	An increase in superoxide in hematopoietic organs	(Case et al., 2013)
		Postnatal motor neuron (VAChT-Cre*;Sod2*$^{fl/fl}$)	No altered function in motor neurons, but accelerated disorganization of distal nerve axons following injury	No signs of oxidative damage in animals up to 1 yr after birth	(Misawa et al., 2006)
		Connective tissue (Col1α2-Cre; *Sod2*$^{fl/fl}$)	Weight loss, skin atrophy, kyphosis, muscle degeneration, and a reduced life span	Unknown	(Treiber et al., 2011)
		Mammary gland (MMTV-cre*;Sod2*$^{fl/fl}$)	Postnatal knockout: no gross abnormalities	Unknown	(Case and Domann, 2012)
		T cells (Lck-Cre*;Sod2*$^{fl/fl}$)	Increased apoptosis and aberrant T cell development and function	Elevated superoxide in the T cell population	(Case et al., 2011)
		Gastric parietal cells (Atp4b-Cre*;Sod2*$^{fl/fl}$)	Mitochondrial dysfunction and increased apoptosis in the gastric mucosa of the parietal cell	Increased gastric mucosal oxidative stress	(Jones et al., 2011)
Sod3	Germline mutation	*Sod3*$^{-/-}$	Phenotypically normal under normal conditions, reduced survival time under high oxygen tension, exaggerated response to induced hypertension	Higher level of vascular superoxide	(Carlsson et al., 1995; Jung et al., 2003)
	Inducible conditional KO	Global (*Tg*$^{cre/esr}$*;Sod3*$^{fl/fl}$)	Lung damage, die shortly after induction of *Sod3* KO	Increase of superoxide in the lung	(Gongora et al., 2008)
		Vascular smooth muscle cells (Tg$^{cre/SMMHC}$; *Sod3*$^{fl/fl}$)	Normal blood pressure, no augmented response to angiotensin II-induced hypertension	Increased vascular superoxide and reduced vascular NO levels	(Lob et al., 2011)

	Circumventricular organs (*Sod3*$^{fl/fl}$ + intracerebroventricular injection of Cre adenovirus)	An elevation of blood pressure, hypertensive response to angiotensin II	Increased vascular superoxide production, T-cell activation	(Lob et al., 2010)

References

Asikainen, T.M., T.T. Huang, E. Taskinen, A.L. Levonen, E. Carlson, R. Lapatto, C.J. Epstein, and K.O. Raivio. 2002. Increased sensitivity of homozygous Sod2 mutant mice to oxygen toxicity. Free Radic. Biol. Med. 32:175–186. PubMed https://doi.org/10.1016/S0891-5849(01)00776-6

Bhusari, S.S., J.R. Dobosy, V. Fu, N. Almassi, T. Oberley, and D.F. Jarrard. 2010. Superoxide dismutase 1 knockdown induces oxidative stress and DNA methylation loss in the prostate. Epigenetics. 5:402–409. PubMed https://doi.org/10.4161/epi.5.5.11853

Carlsson, L.M., J. Jonsson, T. Edlund, and S.L. Marklund. 1995. Mice lacking extracellular superoxide dismutase are more sensitive to hyperoxia. Proc. Natl. Acad. Sci. USA. 92:6264–6268. PubMed https://doi.org/10.1073/pnas.92.14.6264

Case, A.J., and F.E. Domann. 2012. Manganese superoxide dismutase is dispensable for post-natal development and lactation in the murine mammary gland. Free Radic. Res. 46:1361–1368. PubMed https://doi.org/10.3109/10715762.2012.715370

Case, A.J., J.L. McGill, L.T. Tygrett, T. Shirasawa, D.R. Spitz, T.J. Waldschmidt, K.L. Legge, and F.E. Domann. 2011. Elevated mitochondrial superoxide disrupts normal T cell development, impairing adaptive immune responses to an influenza challenge. Free Radic. Biol. Med. 50:448–458. PubMed https://doi.org/10.1016/j.freeradbiomed.2010.11.025

Case, A.J., J.M. Madsen, D.G. Motto, D.K. Meyerholz, and F.E. Domann. 2013. Manganese superoxide dismutase depletion in murine hematopoietic stem cells perturbs iron homeostasis, globin switching, and epigenetic control in erythrocyte precursor cells. Free Radic. Biol. Med. 56:17–27. PubMed https://doi.org/10.1016/j.freeradbiomed.2012.11.018

Elchuri, S., T.D. Oberley, W. Qi, R.S. Eisenstein, L. Jackson Roberts, H. Van Remmen, C.J. Epstein, and T.T. Huang. 2005. CuZnSOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life. Oncogene. 24:367–380. PubMed https://doi.org/10.1038/sj.onc.1208207

Fischer, L.R., Y. Li, S.A. Asress, D.P. Jones, and J.D. Glass. 2012. Absence of SOD1 leads to oxidative stress in peripheral nerve and causes a progressive distal motor axonopathy. Exp. Neurol. 233:163–171. PubMed https://doi.org/10.1016/j.expneurol.2011.09.020

Flood, D.G., A.G. Reaume, J.A. Gruner, E.K. Hoffman, J.D. Hirsch, Y.G. Lin, K.S. Dorfman, and R.W. Scott. 1999. Hindlimb motor neurons require Cu/Zn superoxide dismutase for maintenance of neuromuscular junctions. Am. J. Pathol. 155:663–672. PubMed https://doi.org/10.1016/S0002-9440(10)65162-0

Garratt, M., N. Pichaud, E.N. Glaros, A.J. Kee, and R.C. Brooks. 2014. Superoxide dismutase deficiency impairs olfactory sexual signaling and alters bioenergetic function in mice. Proc. Natl. Acad. Sci. USA. 111:8119–8124. PubMed https://doi.org/10.1073/pnas.1322282111

Gongora, M.C., H.E. Lob, U. Landmesser, T.J. Guzik, W.D. Martin, K. Ozumi, S.M. Wall, D.S. Wilson, N. Murthy, M. Gravanis, et al. 2008. Loss of extracellular superoxide dismutase leads to acute lung damage in the presence of ambient air: a potential mechanism underlying adult respiratory distress syndrome. Am. J. Pathol. 173:915–926. PubMed https://doi.org/10.2353/ajpath.2008.080119

Huang, T.T., E.J. Carlson, H.M. Kozy, S. Mantha, S.I. Goodman, P.C. Ursell, and C.J. Epstein. 2001. Genetic modification of prenatal lethality and dilated cardiomyopathy in Mn superoxide dismutase mutant mice. Free Radic. Biol. Med. 31:1101–1110. PubMed https://doi.org/10.1016/S0891-5849(01)00694-3

Ikegami, T., Y. Suzuki, T. Shimizu, K. Isono, H. Koseki, and T. Shirasawa. 2002. Model mice for tissue-specific deletion of the manganese superoxide dismutase (MnSOD) gene. Biochem. Biophys. Res. Commun. 296:729–736. PubMed https://doi.org/10.1016/S0006-291X(02)00933-6

Imamura, Y., S. Noda, K. Hashizume, K. Shinoda, M. Yamaguchi, S. Uchiyama, T. Shimizu, Y. Mizushima, T. Shirasawa, and K. Tsubota. 2006. Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proc. Natl. Acad. Sci. USA. 103:11282–11287. PubMed https://doi.org/10.1073/pnas.0602131103

Iuchi, Y., D. Roy, F. Okada, N. Kibe, S. Tsunoda, S. Suzuki, M. Takahashi, H. Yokoyama, J. Yoshitake, S. Kondo, and J. Fujii. 2010. Spontaneous skin damage and delayed wound healing in SOD1-deficient mice. Mol. Cell. Biochem. 341:181–194. PubMed https://doi.org/10.1007/s11010-010-0449-y

Izuo, N., H. Nojiri, S. Uchiyama, Y. Noda, S. Kawakami, S. Kojima, T. Sasaki, T. Shirasawa, and T. Shimizu. 2015. Brain-Specific Superoxide Dismutase 2 Deficiency Causes Perinatal Death with Spongiform Encephalopathy in Mice. Oxid. Med. Cell. Longev. 2015:238914. PubMed https://doi.org/10.1155/2015/238914

Jones, M.K., E. Zhu, E.V. Sarino, O.R. Padilla, T. Takahashi, T. Shimizu, and T. Shirasawa. 2011. Loss of parietal cell superoxide dismutase leads to gastric oxidative stress and increased injury susceptibility in mice. Am. J. Physiol. Gastrointest. Liver Physiol. 301:G537–G546. PubMed https://doi.org/10.1152/ajpgi.00177.2011

Jung, O., S.L. Marklund, H. Geiger, T. Pedrazzini, R. Busse, and R.P. Brandes. 2003. Extracellular superoxide dismutase is a major determinant of nitric oxide bioavailability: in vivo and ex vivo evidence from ecSOD-deficient mice. Circ. Res. 93:622–629. PubMed https://doi.org/10.1161/01.RES.0000092140.81594.A8

Konzack, A., M. Jakupovic, K. Kubaichuk, A. Görlach, F. Dombrowski, I. Miinalainen, R. Sormunen, and T. Kietzmann. 2015. Mitochondrial Dysfunction Due to Lack of Manganese Superoxide Dismutase Promotes Hepatocarcinogenesis. Antioxid. Redox Signal. 23:1059–1075. PubMed https://doi.org/10.1089/ars.2015.6318

Kuwahara, H., T. Horie, S. Ishikawa, C. Tsuda, S. Kawakami, Y. Noda, T. Kaneko, S. Tahara, T. Tachibana, M. Okabe, et al. 2010. Oxidative stress in skeletal muscle causes severe disturbance of exercise activity without muscle atrophy. Free Radic. Biol. Med. 48:1252–1262. PubMed https://doi.org/10.1016/j.freeradbiomed.2010.02.011

Lebovitz, R.M., H. Zhang, H. Vogel, J. Cartwright Jr., L. Dionne, N. Lu, S. Huang, and M.M. Matzuk. 1996. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proc. Natl. Acad. Sci. USA. 93:9782–9787. PubMed https://doi.org/10.1073/pnas.93.18.9782

Lenart, J., F. Dombrowski, A. Görlach, and T. Kietzmann. 2007. Deficiency of manganese superoxide dismutase in hepatocytes disrupts zonated gene expression in mouse liver. Arch. Biochem. Biophys. 462:238–244. PubMed https://doi.org/10.1016/j.abb.2007.02.007

Li, Y., T.T. Huang, E.J. Carlson, S. Melov, P.C. Ursell, J.L. Olson, L.J. Noble, M.P. Yoshimura, C. Berger, P.H. Chan, et al. 1995. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nat. Genet. 11:376–381. PubMed https://doi.org/10.1038/ng1295-376

Lob, H.E., P.J. Marvar, T.J. Guzik, S. Sharma, L.A. McCann, C. Weyand, F.J. Gordon, and D.G. Harrison. 2010. Induction of hypertension and peripheral inflammation by reduction of extracellular superoxide dismutase in the central nervous system. Hypertension. 55:277-283.

Lob, H.E., A. Vinh, L. Li, Y. Blinder, S. Offermanns, and D.G. Harrison. 2011. Role of vascular extracellular superoxide dismutase in hypertension. Hypertension. 58:232–239. PubMed https://doi.org/10.1161/HYPERTENSIONAHA.111.172718

Lustgarten, M.S., Y.C. Jang, Y. Liu, F.L. Muller, W. Qi, M. Steinhelper, S.V. Brooks, L. Larkin, T. Shimizu, T. Shirasawa, et al. 2009. Conditional knockout of Mn-SOD targeted to type IIB skeletal muscle fibers increases oxidative stress and is sufficient to alter aerobic exercise capacity. Am. J. Physiol. Cell Physiol. 297:C1520–C1532. PubMed https://doi.org/10.1152/ajpcell.00372.2009

Lustgarten, M.S., Y.C. Jang, Y. Liu, W. Qi, Y. Qin, P.L. Dahia, Y. Shi, A. Bhattacharya, F.L. Muller, T. Shimizu, et al. 2011. MnSOD deficiency results in elevated oxidative stress and decreased mitochondrial function but does not lead to muscle atrophy during aging. Aging Cell. 10:493–505. PubMed https://doi.org/10.1111/j.1474-9726.2011.00695.x

Matzuk, M.M., L. Dionne, Q. Guo, T.R. Kumar, and R.M. Lebovitz. 1998. Ovarian function in superoxide dismutase 1 and 2 knockout mice. Endocrinology. 139:4008–4011. PubMed https://doi.org/10.1210/endo.139.9.6289

Melov, S., P. Coskun, M. Patel, R. Tuinstra, B. Cottrell, A.S. Jun, T.H. Zastawny, M. Dizdaroglu, S.I. Goodman, T.T. Huang, et al. 1999. Mitochondrial disease in superoxide dismutase 2 mutant mice. Proc. Natl. Acad. Sci. USA. 96:846–851. PubMed https://doi.org/10.1073/pnas.96.3.846

Misawa, H., K. Nakata, J. Matsuura, Y. Moriwaki, K. Kawashima, T. Shimizu, T. Shirasawa, and R. Takahashi. 2006. Conditional knockout of Mn superoxide dismutase in postnatal motor neurons reveals resistance to mitochondrial generated superoxide radicals. Neurobiol. Dis. 23:169–177. PubMed https://doi.org/10.1016/j.nbd.2006.02.014

Muller, F.L., W. Song, Y. Liu, A. Chaudhuri, S. Pieke-Dahl, R. Strong, T.T. Huang, C.J. Epstein, L.J. Roberts II, M. Csete, et al. 2006. Absence of CuZn superoxide dismutase leads to elevated oxidative stress and acceleration of age-dependent skeletal muscle atrophy. Free Radic. Biol. Med. 40:1993–2004. PubMed https://doi.org/10.1016/j.freeradbiomed.2006.01.036

Nojiri, H., T. Shimizu, M. Funakoshi, O. Yamaguchi, H. Zhou, S. Kawakami, Y. Ohta, M. Sami, T. Tachibana, H. Ishikawa, et al. 2006. Oxidative stress causes heart failure with impaired mitochondrial respiration. J. Biol. Chem. 281:33789–33801. PubMed https://doi.org/10.1074/jbc.M602118200

Parajuli, N., A. Marine, S. Simmons, H. Saba, T. Mitchell, T. Shimizu, T. Shirasawa, and L.A. Macmillan-Crow. 2011. Generation and characterization of a novel kidney-specific manganese superoxide dismutase knockout mouse. Free Radic. Biol. Med. 51:406–416. PubMed https://doi.org/10.1016/j.freeradbiomed.2011.04.024

Reaume, A.G., J.L. Elliott, E.K. Hoffman, N.W. Kowall, R.J. Ferrante, D.F. Siwek, H.M. Wilcox, D.G. Flood, M.F. Beal, R.H. Brown Jr., et al. 1996. Motor neurons in Cu/Zn superoxide dismutase-deficient mice develop normally but exhibit enhanced cell death after axonal injury. Nat. Genet. 13:43–47. PubMed https://doi.org/10.1038/ng0596-43

Sasaki, T., T. Shimizu, T. Koyama, M. Sakai, S. Uchiyama, S. Kawakami, Y. Noda, T. Shirasawa, and S. Kojima. 2011. Superoxide dismutase deficiency enhances superoxide levels in brain tissues during oxygenation and hypoxia-reoxygenation. J. Neurosci. Res. 89:601–610. PubMed https://doi.org/10.1002/jnr.22581

Shi, Y., M.V. Ivannikov, M.E. Walsh, Y. Liu, Y. Zhang, C.A. Jaramillo, G.T. Macleod, and H. Van Remmen. 2014. The lack of CuZnSOD leads to impaired neurotransmitter release, neuromuscular junction destabilization and reduced muscle strength in mice. PLoS One. 9:e100834. PubMed https://doi.org/10.1371/journal.pone.0100834

Treiber, N., P. Maity, K. Singh, M. Kohn, A.F. Keist, F. Ferchiu, L. Sante, S. Frese, W. Bloch, F. Kreppel, et al. 2011. Accelerated aging phenotype in mice with conditional deficiency for mitochondrial superoxide dismutase in the connective tissue. Aging Cell. 10:239–254. PubMed https://doi.org/10.1111/j.1474-9726.2010.00658.x

Van Remmen, H., M.D. Williams, Z. Guo, L. Estlack, H. Yang, E.J. Carlson, C.J. Epstein, T.T. Huang, and A. Richardson. 2001. Knockout mice heterozygous for Sod2 show alterations in cardiac mitochondrial function and apoptosis. Am. J. Physiol. Heart Circ. Physiol. 281:H1422–H1432. PubMed https://doi.org/10.1152/ajpheart.2001.281.3.H1422

Van Remmen, H., Y. Ikeno, M. Hamilton, M. Pahlavani, N. Wolf, S.R. Thorpe, N.L. Alderson, J.W. Baynes, C.J. Epstein, T.T. Huang, et al. 2003. Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging. Physiol. Genomics. 16:29–37. PubMed https://doi.org/10.1152/physiolgenomics.00122.2003

Yoshihara, D., N. Fujiwara, N. Kitanaka, J. Kitanaka, H. Sakiyama, H. Eguchi, M. Takemura, and K. Suzuki. 2016. The absence of the SOD1 gene causes abnormal monoaminergic neurotransmission and motivational impairment-like behavior in mice. Free Radic. Res. 50:1245–1256. PubMed https://doi.org/10.1080/10715762.2016.1234048

Zhang, Y., A. Unnikrishnan, S.S. Deepa, Y. Liu, Y. Li, Y. Ikeno, D. Sosnowska, H. Van Remmen, and A. Richardson. 2017. A new role for oxidative stress in aging: The accelerated aging phenotype in Sod1-/- mice is correlated to increased cellular senescence. Redox Biol. 11:30–37. PubMed https://doi.org/10.1016/j.redox.2016.10.014