PARADOXICAL ROLES OF ANTIOXIDANT ENZYMES: BASIC MECHANISMS AND HEALTH IMPLICATIONS

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759 references, 9 tables, and 13 figures

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ABSTRACT: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated from aerobic metabolism, as a result of accidental electron leakage as well as regulated enzymatic processes. Because ROS/RNS can induce oxidative injury and act in redox signaling, enzymes metabolizing them will inherently promote either health or disease, depending upon the physiological context. It is thus misleading to consider conventionally-called antioxidant enzymes to be largely, if not exclusively, health-protective. Because such notion is nonetheless common, we herein attempt to rationalize why this simplistic view should be avoided. First we give an updated summary of physiological phenotypes triggered in mouse models of overexpression or knockout of major antioxidant enzymes. Subsequently, we focus on a series of striking cases that demonstrate "paradoxical" outcomes, i.e. increased fitness upon deletion of antioxidant enzymes or disease triggered by their overexpression. We elaborate mechanisms by which these phenotypes are mediated via chemical, biological, and metabolic interactions of the antioxidant enzymes with their substrates, downstream events and cellular context. Furthermore, we propose novel treatments of antioxidant enzymes-related human diseases by deliberate targeting dual roles of the pertaining enzymes, and outlined potential of "antioxidant" nutrients and phytochemicals, via regulating the expression or function of antioxidant enzymes, in preventing, treating, or aggravating chronic diseases. We conclude that "paradoxical" roles of antioxidant enzymes in physiology, health, and disease derive from sophisticated molecular mechanisms of redox biology and metabolic homeostasis. Simply viewing antioxidant enzymes always beneficial is not only conceptually misleading but also clinically hazardous if such notions underpin medical treatment protocols based upon modulation of redox pathways.

Key Words: Antioxidant Enzyme, Knockout, Overexpression, Oxidative Stress, Redox Signaling

I. INTRODUCTION

Antioxidant enzymes are often discussed in scientific research and daily life as key players of metabolism that promote healthy cells, tissues and organisms. The term best relates to enzymes that lower the levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), or counteract their downstream cellular effects of excessive oxidation. ROS and RNS are produced from aerobic biogenesis or by oxidative enzymes, and being chemically reactive they have the capacity to damage cellular components. Nature has evolved three layers of antioxidant defense in the body. Small molecular antioxidants, including uric acid, glutathione (GSH), and vitamins C and E, offer the first line of defense to scavenge ROS/RNS directly and thus prevent or delay the initiation of various oxidative stresses. Damage-removing or repairing enzymes function as the last defense to regenerate biomolecules damaged from oxidative injury. Between these two layers, antioxidant enzymes serve as an intermediate defense to detoxify ROS/RNS into less reactive species. Superoxide (O_2^-) and hydrogen peroxide (H_2O_2) represent arguably the best-known and most-produced ROS, with the former scavenged by superoxide dismutases (SOD)[1] and the latter by catalase (CAT), glutathione peroxidases (GPX), and peroxiredoxins (PRX). Thioredoxin reductases (TrxR) are in addition required to maintain functions of thioredoxins (Trx), PRX, methionine sulfoxide reductases (Msr) and many other redox-regulatory enzymes/proteins by regenerating protein thiols (411) in parallel with glutaredoxins (Grx)

[1]Genes and proteins are in this article typically named according to HUGO (http://www.genenames.org) and MGI (http://www.informatics.jax.org/mgihome/nomen/gene.shtml) guidelines for human and mouse, respectively, unless other names or abbreviations are by convention more prevalent in the literature. In some cases mice have been studied with overexpression from human transgenes, which may be somewhat confusing in terms of nomenclature. We believe, however, that the references given in the Tables of this review article will serve as useful reference material for any reader interested in the exact gene constructs that are being discussed.

utilizing GSH to catalyze reduction of protein disulfide substrates (180, 395), These ROS-metabolizing and reductive enzymes, which also play important roles in RNS homeostasis, are widely considered to be the major antioxidant enzymes and are the focus of this review article.

During the past two decades, developments of antioxidant enzyme gene knockout and overexpression mouse models (**Table 1**) have enabled us to not only verify "anticipated" metabolic health-promoting functions of these enzymes, but also to reveal often neglected "paradoxical" roles of antioxidant enzymes triggering metabolic disorders. It has indeed become clear that many antioxidant enzymes are more than just protective ROS/RNS scavengers. They regulate many redox signaling pathways and may also exhibit pro-oxidant functions or functions independent of their redox activities.

A number of chronic diseases are associated with genetic or metabolic alterations of antioxidant enzymes, displaying *either* lower or increased activities, depending upon the actual enzyme and disease. Meanwhile, certain "antioxidant" nutrients and phytochemicals are able to regulate antioxidant enzyme expressions or functions with health implications. Therefore it is important to have a better understanding of the "paradoxical" functions of antioxidant enzymes in physiology, which explain how their overexpression can promote disease or their deletion can be health-promoting. It is our goal that this review will help to support awareness of the involved molecular mechanisms and thus be useful in advancing a more balanced view of antioxidant enzyme and redox biology in medicine.

II. IMPACTS OF KNOCKOUT AND OVEREXPRESSION

Superoxide- and H_2O_2-metabolizing enzymes, including SOD, catalase, GPX and PRX, are generally considered to be the primary antioxidant enzyme defense system in the body. However, the only antioxidant enzymes that have thus far been found to be essential for mouse embryonic development and thus lethal when genetically deleted are GPX4 (68, 293, 725), the two genes for cytosolic and mitochondrial TrxR, *Txnrd1* (51, 305) and *Txnrd2* (123), their cognate substrate Trxs, *Txn1* (438) and *Txn2* (490), as well as an essential gene for synthesis of GSH (604). Deletion of the *Trsp1* (encoding selenocysteine tRNA ($tRNA^{[Ser]Sec}$) gene that is required for synthesis of all selenoproteins is also embryonically lethal (54). Genetic deletion of several other antioxidant enzymes trigger strong phenotypes even if not being embryonically lethal, while certain antioxidant enzymes seem to have an impact only under severe oxidative stress or in specific tissues.

While the SOD family represents the only enzymes able to scavenge O_2^-, catalyzing its disproportionation into O_2 and H_2O_2, multiple classes of enzymes detoxify H_2O_2 or organic peroxides. Catalases scavenge H_2O_2 by catalyzing its disproportionation into O_2 and H_2O. Some selenoproteins and thiol peroxidase such as GPXs, and PRXs, catalyze the 2-electron reduction of peroxides to form water using reducing equivalents from GSH or Trx, respectively. The functions of GPXs and PRXs are thus intimately coupled to those of glutathione reductase (GR) and TrxR, enzymes that catalyze the reduction of oxidized GSH (GSSG) and Trx, respectively, using reducing equivalents from NADPH (185, 411). In addition, exciting progress has been made in understanding functions of Se-dependent methionine-R-sulfoxide reductase 1 (MsrB1)

that is a Trx-dependent enzyme. Much progress has also been made in the understanding of selenoprotein P (Sepp1) and *Trsp* gene that are both crucial entities for Se homeostasis and functions of all selenoproteins. Because prior reviews have discussed many of the detailed phenotypes in mice with knockout or overexpression of different antioxidant enzymes (62, 69, 71, 80, 122, 337, 361, 377, 499), we will provide herein only an updated synopsis on the same subject, as a basis for the subsequent chapter focusing on their "paradoxical" roles.

A. Superoxide Dismutase Family

1. SOD1

Knockout of *Sod1* does not cause embryonic lethality in mice, but results in impairment of the reproduction function of both males and females. Whereas the males produce sperm with decreased motility and fertilizing ability (207, 658), the females display a marked increase in postimplantation embryonic lethality (264) associated with elevated two-cell arrest or cell death (334). The *Sod1*$^{-/-}$ mice develop anemia (299) and type 1-like diabetes (684). These mice also show a reduced lifespan, a high incidence of hepatocarcinogenesis in late life, and oxidative damage-accelerated spontaneous mutations in liver and kidney (73, 167). Although mice overexpressing SOD1 are apparently normal with a reduced mutation frequency in cerebellum (357), these animals exhibit certain abnormalities found in patients with Down's syndrome (23, 24, 524, 580).

Knockout and overexpression of *SOD1/Sod1* exert negative and positive impacts, respectively, on mouse susceptibility or resistance to neurodegenerative disorders, cerebral and myocardial injuries, diabetic syndrome, and tissue intoxications and dysfunctions (**Table 2**). However, most, if not all, of the reported "mechanisms" are associations between phenotypes and genetic manipulations, without genuine knowledge of the exact molecular mechanisms that lead to the observed phenotypes. Importantly, the association of SOD1 mutations with familial amyotrophic lateral sclerosis (ALS) does not seem to be due to effects on enzyme activity but rather an increased propensity for protein aggregation (203, 373, 474, 491). Impacts of *Sod1* knockout or *SOD1* overexpression in mice on neurodegenerative disorders may be related to effects on Aβ oligomerization (477), dopaminergic neurodegeneration (746), lipid peroxidation (536, 647), and protein nitration (294). In cell studies, altering the enzyme affects dopamine autoxidation and changes of GSH (242), and neuroinflammation driven by activation of nuclear factor-κB (NFκB), release of nitric oxide (NO), and proinflammatory cytokines (153).

Overexpression of *SOD1* protects against various brain and neurological injuries by: 1) attenuating the mitochondria-mediated apoptosis pathway (e.g., release of cytochrome c and nuclear translocation of endonuclease G) (624, 737); 2) suppressing the induced expression of matrix metalloproteinases (467); and 3) activating Akt/glycogen synthase kinase 3β (GSK-3β) survival signaling (169, 313). Meanwhile, the protection against cerebral ischemia is conferred in part by up-regulating Akt and down-regulating p38 mitogen-activated protein kinase (MAPK), and NFκB (100). In contrast, *Sod1* knockout potentiates mice to ischemic injuries by activating NFκB (100), and lung dysfunction by increasing nuclear factor of activated T-cells (NFAT) and NFATc3 activities (546). Sod1 knockout can also trigger kidney dysfunction by enhancing the

oxidative stress-induced phosphorylation and the conversion of iron responsive protein-1 (IRP1) to the iron responsive element (IRE)-binding form, which may accelerate the reabsorption of iron by renal tubular cells (734). Inhibition of matrix protein synthesis induced by high glucose (129) and the NO-O_2^- interaction (148) contributes to the protection of SOD1 overexpression against diabetic nephrophathy. Seemingly, several, if not all, of these SOD1-altered phenotypes are associated with specific redox signaling effects, rather than a direct free radical scavenging.

2. SOD2

Sod2$^{-/-}$ mice, unlike *Sod1*$^{-/-}$ mice, develop cardiomyopathy and neonatal or perinatal lethality, despite variations in postnatal survival time and neuronal injury (370, 392). Thus, the reported phenotypes of *Sod2* knockout are mostly derived from haplodeficiency or tissue-specific inactivation of the gene. While *Sod1*$^{-/-}$ female mice become infertile (264), ovaries from postnatal *Sod2*$^{-/-}$ mice undergo normal folliculogenesis and can produce viable offspring when transplanted to the bursa of wild-type hosts, suggesting the enzyme dispensable for the ovarian function (443). Interestingly, strain-dependent overexpression of SOD2 is associated with growth retardation and decreased fertility in transgenic mice (542) (**Table 3**). Although the *Sod2*$^{+/-}$ mice are viable and no more sensitive to hyperoxia (304), their mitochondria show decreased respiratory capability and elevated induction of the permeability transition (697).

Likewise, knockout and overexpression of *Sod2/SOD2* produces negative and positive impacts, respectively, on mouse susceptibility or resistance to a number of acute or chronic disorders (**Table 3**). Such opposite effects of the enzyme on neurodegenerative disorders are related to

regulating mitochondrial ROS generation and function, shifting the amyloidogenic Aβ composition (435), slowing amyloid deposition and memory deficit (164, 435), and modulating dopaminergic neurodegeneration (11, 342). Similarly, the effects on ischemic cerebral injuries are through regulations of blood-brain barrier, matrix metalloproteinases (MMPs), and inflammatory responses (425). Knockout of *Sod2* aggravates cellular senescence and aging (653, 675), though overexpression of *Sod2/SOD2* fails to extend life span despite preserving age-associated loss of mitochondrial function (308, 374). Overexpression of the enzyme protects against diabetes and complication through improved mitochondrial respiration and integrity and decreased iNOS and NO production (50, 226, 273, 351, 408, 597). Interestingly, old *Sod2*$^{+/-}$ *Gpx1*$^{-/-}$ mice have an elevated incidence of neoplasms (750), suggesting that knockout of multiple antioxidant enzymes can have synergistic effects on carcinogenesis.

3. SOD3

Knockout of *Sod3*, unlike *Sod1* or *Sod2*, does not affect mouse development and lifespan or further worsen the shortened lifespan of *Sod1*$^{-/-}$ mice, suggesting limited overlapping roles between these enzymes (81, 593). Respective protective and detrimental outcomes from overexpression and knockout of *SOD3/Sod3* are seen in brain, heart and vascular system, kidney, lung and immune system, as well as in ischemic injuries and carcinogenesis (**Table 4)**.

This extracellular SOD isoenzyme plays a pivotal role in protecting against a number of lung disorders including oxidative injury, inflammation, and fibrosis (7, 8, 81, 189, 212, 248, 318, 492, 528, 539, 625, 672). Different from those lacking Sod1, Sod2, or catalase, the *Sod3*$^{-/-}$ mice are

susceptible to hyperoxia and induced oxidative injury (81). Protective roles of the enzyme in pulmonary fibrosis have been thoroughly reviewed (205), and its unique importance in pulmonary function is attributed to its extracellular localization, the pathological importance of extracellular matrix expression, and cytokine release elicited by extracellular ROS. Involved signaling events include modulation of transforming growth factor beta (TGF-β) and early growth response protein 1 (Egr-1) expression (672), preserving angiogenesis (528), and maintaining NO bioavailability and subsequent modulating cGMP and NFκB activity (7). The unique protection by SOD3 against lung oxidative insults offers potential of administrating of the enzyme to relieve pulmonary disorders (205). Moreover, the distribution of SOD3, rather than the total SOD activity, in the extracellular space is crucial for protecting heart against the pressure overload as this insult renders the *Sod3*$^{-/-}$ mice elevated myocardial O_2^- production and nitrotyrosine formation, increases of ventricular collagen I & III, MMP-2 and -9, and decreases in ratio of GSH/GSSG (glutathione disulfide) (414). Knockout of *Sod3* renders mice susceptible to the collagen-induced arthritis (570), while overexpression of *SOD3* in mouse synovial tissue attenuates the inflammatory arthritis (736), via opposite modulations of the production of the pro-inflammatory cytokines such as IL-1β and TNFα, and MMPs. Knockout of *Sod3* also impairs renal-vascular function, in part by decreasing Akt and eNOS phosphorylation and heme oxygenase 1 activity (326).

B. Catalase

Catalase is ubiquitously expressed, and is predominantly located in peroxisomes of all types of mammalian cells with the exception of erythrocytes (669) and human vascular cells (607). A

certain activity of catalase is also detected in mitochondria of rat heart (541). In humans, acatalesemia is a comparatively common genetic disease with near-total lack of catalase, which is typically considered to be asymptomatic but may be associated with increased risk of a number of diseases (224). *Cat*$^{-/-}$ mice show normal development and fertility (268), and are not more susceptible to the hyperoxia-induced lung injury than the wild-type controls. Overexpression of catalase in mitochondria prolongs the lifespan of mice and attenuates age-associated pathological changes (137, 504, 584, 654). The overall outcomes of *Cat* knockout are rather limited, especially in comparison with those associated with *Sod*. This may in part be due to the fact that GPX and PRX (90, 184) play major roles in removing H_2O_2 at relatively low concentrations in the cells, whereas the contribution of catalase increases when intracellular H_2O_2 is high (428).

In contrast, promotion of health by *CAT/Cat* overexpression has been shown in many tissues and conditions (**Table 5**). Overexpression of *CAT* protects against cardiovascular injuries or dysfunction (424, 723, 724), which is particularly relevant due to the lack of the enzyme activity in the human vascular smooth muscle and endothelial cells (607). Aortas from apolipoprotein E knockout mice overexpressing *CAT* show smaller and relatively early stages of atherosclerotic lesions compared with the control (722). Cardiac-specific overexpression of rat *Cat* attenuates the paraquat-induced myocardial geometric and contractile alteration by alleviating JNK-mediated endoplasmic reticulum stress (208), prolongs lifespan, and suppresses aging-induced cardiomyocyte contractile dysfunction and protein damage (712). Also, this specific overexpression of rat *Cat* rescues the anthrax lethal toxin- or lipopolysaccharide-induced cardiac contractile dysfunction by alleviating oxidative stress, autophagy, and mitochondrial injury (317,

660). The elevated catalase antagonizes the alcohol dehydrogenase-associated contractile depression after acute ethanol exposure in murine myocytes, partially through improving intracellular Ca^{2+} handling and ablation of alcohol dehydrogenase-amplified JNK activation and Erk de-activation (748, 749). Comparatively, the endothelium specific overexpression of *CAT* shows a weak protection against myocardial or vascular ischemia/reperfusion injury, despite preserving the responsiveness of the heart to adrenergic stimulation (704). Knockout of *Cat* accelerates diabetic renal injury through upregulation of TGF-β and collagen secretion (289), whereas overexpression of *Cat* protects against the pathogenesis via attenuation of angiotensinogen and Bax function and normalized expression of angiotensin converting enzyme 2 (ACE-2) (58, 603).

C. Glutathione Peroxidase Family

GPX enzymes utilize reducing equivalents from GSH to reduce peroxides (60, 94, 185). Eight isoforms of GPX are known, of which five are selenoproteins (GPX1-4 and GPX6). The three selenium-independent GPX enzymes rely upon thiol rather than selenol chemistry. Among the GPX enzymes, GPX1 is the most abundant and ubiquitous isoform. GPX6 is found as a selenoprotein only in humans, while the orthologous Gpx6 has a catalytic cysteine (Cys) in mice and several other species (353). Several recent reviews have summarized physiological roles of GPX enzymes in relation to other selenoproteins (61, 360, 361, 554). Our discussion herein mainly summarizes the key findings from genetic mouse models.

1. GPX1

Gpx1 is not essential for survival or reproduction, despite its protection against cataract and slight growth retardation (110, 141, 172, 265). Knockout of *Gpx1* sensitizes mice to pro-oxidant-induced oxidative injuries, whereas overexpression of the enzyme confers extra protection against such injuries in various tissues (**Table 6**). The elevated susceptibility of the *Gpx1*$^{-/-}$ mice to various acute oxidative injuries, including increased lethality induced by high doses of paraquat and diquat, relates to accelerated oxidation of NAD(P)H, proteins, and lipids (108, 111, 141, 195, 196). The importance and mechanism for Gpx1 protection depends upon the intensity of stress as well as antioxidant status of the challenged animals (108, 111, 141, 195, 196, 376) but high levels of dietary vitamin E do not replace protection of Gpx1 (113). It should also be noted that Gpx1 is one of the most Se-responsive selenoproteins, whereby low dietary Se intake rapidly lowers its expression in most tissues (631), suggesting that the Se status of the control mice will affect the comparative outcome of Gpx1 removal.

Protections against disease conditions by GPX1 are illustrated by increased susceptibility of *Gpx1*$^{-/-}$ mice and resistance of *Gpx1* overexpressing mice to various oxidative insults, including ischemia/reperfusion and hypoxic ischemic injury in the brain, heart, and liver (128, 195, 341, 397, 564, 595, 691, 732). Furthermore, Gpx1 protects against cardiomyopathy induced by coxsackievirus B_3 through suppression of viral genome mutation (37), atherosclerosis in a pro-diabetic *ApoE*$^{-/-}$ mouse model (115, 384, 652), doxorubicin-induced and angiotensin II-mediated functional declines and cardiac hypertrophy (15, 206, 714, 733), defective blood flow and epithelial progenitor circulation in a model of ischemia-induced angiogenesis (202), diabetic

nephropathy in association with fibrosis and inflammation (115, 640, 641), and detrimental effects of cigarette smoking or influenza A infection in the lung (165, 726).

Although the exact molecular mechanisms for involvement of Gpx1 in the above-described pathogeneses are largely unknown, the existing evidences point out ROS scavenging and redox signaling as the main modes of action. The *Gpx1*$^{-/-}$ mouse brain shows elevated oxidative stress, caspase-3 cleavage, and 3-nitrotyrosine formation (128, 341). The decreased migration of endothelial progenitor cells in the *Gpx1*$^{-/-}$ mice toward vascular endothelial growth factor (VEGF) and capability of these cells in promoting the formation of vascular network are indeed related to the elevated intracellular ROS levels (202). The protection of Gpx1 against diabetic nephropathy is associated with decreases of hydroperoxides, 8-isoprostane, nitrotyrosine, 4-hydroxynonenal, and proteins implicated in fibrosis and inflammation (115, 640, 641).

2. GPX2

GPX2 was first found in the gastrointestinal tissues (117). There are no *Gpx2* transgenic mouse lines reported (**Table 1**). Like the *Gpx1*$^{-/-}$ mice, *Gpx2*$^{-/-}$ mice appear normal unless they are stressed by oxidative challenges (678). The Gpx1 expression is up-regulated in the colon and ileum of *Gpx2*$^{-/-}$ mice (186), which may explain why they do not develop cancer spontaneously but develop squamous cell tumor when additional stress such as UV exposure is employed (678). Likewise, spontaneous polyps are developed in *Gpx1*$^{-/-}$*Gpx2*$^{-/-}$ mice, probably due to elevated intestinal lipid peroxidation with onset of inflammatory bowel disease (118, 174) (**Table 7)**. Notably, nuclear factor (erythroid-derived 2) (NF-E2)-related factor (NRF2), a redox-sensing

transcription factor, may counteract oxidative injuries partially through up-regulation of Gpx2, at least in lung (613). Given its high expression in the gastrointestinal tract, GPX2 likely exerts antioxidant or anti-tumorigenic functions there, in association with GPX1 and NRF2. However, a basic question still remains as whether knockout of *Gpx2* itself elevates intracellular H_2O_2 levels or affects NRF2 (352).

3. GPX3

GPX3 is mainly synthesized in proximal convoluted tubule cells of kidney (22). While the majority of renal GPX3 is secreted into plasma, some retains at the basement membranes to account for 20% of total selenium in kidneys (429, 505). Independent of its peroxidase activity, this enzyme transfers Se from the dams to the fetus (72), while Sepp1 instead of Gpx3 provides Se to neonates via the milk (257). Knockout of *Gpx3* and overexpression of *GPX3* in mice produce essentially opposite impacts on ROS-related events (**Table 7**). The *Gpx3*$^{-/-}$ mice display cerebral infarctions, along with elevated oxidative stress, blood clot, the induction of P-selectin, and lowered plasma cGMP level (311) and colitis-associated carcinoma with increased inflammation in the colon (32). Overexpression of *GPX3* renders mice resistant to acetaminophen (APAP) overdose (458) but leads to hyperthermia (457). Thus, some physiological effects of *Gpx3/GPX3* modulation can be viewed as unexpected if the enzyme would solely have a role in extracellular H_2O_2 scavenging. It is thereby possible that it has yet unrecognized physiological functions that are not directly related to the extracellular enzymatic activity.

4. GPX4

GPX4 has three isoforms in cytosol, mitochondria, and sperm nucleus, and enzymatically exhibits substrate preference toward phospholipid hydroperoxide (667). Interacting with guanine-rich sequencing-binding factor 1, GPX4 suppresses lipid peroxidation and apoptosis during embryogenesis (664). Because the global knockout of *Gpx4* renders embryonic lethality, tissue-specific and Gpx4 isoform-specific conditional knockout mice have been generated (**Table 7**). Collectively, increased levels of lipid peroxides by localized Gpx4 deficiency lead to: 1) endothelial cell death and thrombus formation in a vitamin E-dependent manner (707); 2) 12/15-lipoxygenase dependent apoptosis-inducing factor (AIF) translocation and neuronal apoptosis (590); 3) mitochondrial potential decline and infertility of spermatozoa (292); and 4) defective photoreceptor maturation (663). Recently it was shown that cell death by ferroptosis is triggered upon genetic removal of *Gpx4* in either kidney (194) or T cells (441). Clearly, Gpx4 is important for protections against the detrimental effects of lipid peroxidation, but the enzyme also has an intriguing peroxidase-independent structural role in sperm maturation (667).

Results from isoform-specific knockout of *Gpx4* indicate that: 1) mitochondrial Gpx4 protects against apoptosis during hindbrain development (52); 2) mitochondrial Gpx4 suppresses protein thiol content, and is essential for male fertility (581); and 3) nuclear Gpx4 is essential for atrium formation (52), but indispensable for sperm maturation (581). Because the mitochondrial or nuclear *Gpx4*$^{-/-}$ mice are viable, the cytosolic Gpx4 confers the embryonic lethality phenotype of the global *Gpx4* knockout. Reciprocally, overexpression of *GPX4/Gpx4* in the global *Gpx4*$^{-/-}$ mice, detected only in liver and heart, can rescue their embryonic lethality and attenuate the

induced mitochondrial potential declines (393, 548) (**Table 7**). Similarly, the mitochondrion-specific *Gpx4* overexpression maintains mitochondrial membrane potentials and protects against ischemia/reperfusion in the heart (136).

D. Thioredoxin Reductase (TrxR) Family

TrxRs are a family of NADPH-dependent selenoproteins, which play important roles as key propagators of the Trx system and thus several Trx-dependent enzymes, including PRX, Msr, ribonucleotide reductase (RNR), sulfiredoxin, and more (17, 122, 412, 423, 571). Three mammalian genes encode different TrxR isoforms, in mice being *Txnrd1* encoding cytosolic TrxR1 (215, 325, 507), *Txnrd2* encoding mitochondrial TrxR2 (also called TR3) (325, 454, 565, 628) and *Txnrd3* encoding thioredoxin glutathione reductase that is mainly expressed in spermatids of the testis and seems to be important for spermatogenesis (211, 623, 626, 627, 659).

All *Txnrd* genes are transcribed in a complex manner, resulting in divergent forms of each isoenzyme that differ from each other mainly in their N-terminal domains (88, 95, 139, 211, 442, 455, 507, 572, 573, 622, 629), potentially reflecting many levels of regulation. The phenotypes of mouse knockout models targeting the *Txnrd1* and *Txnrd2* genes are summarized in **Table 8.** No knockout models targeting *Txnrd3* have yet been reported and overexpression of TrxR isoenzymes is difficult to obtain, due to their intricate expression patterns.

1. TrxR1

The full *Txnrd1*$^{-/-}$ knockout mice display early embryonic lethality, with one study reporting lethality between embryonic days 8.5 and 10.5 mainly due to decreased cellular proliferation (305), and the other study embryonic death before day 8.5 with a lack of formation of mesoderm (51). Differences in genetic targeting between these studies, one removing the last exon of the gene (305) and the other removing the first exon (51), may possibly help to explain the different phenotypes. Notably, the knockout in mice of the *Trx1* gene encoding Trx1 (see below) that is the presumed main substrate of TrxR1, gives even earlier embryonic death than upon TrxR1 removal (438). This suggests that functions of TrxR1 and Trx1 are not always directly linked in a physiological setting, which may be due to the fact that the GSH system can also keep Trx1 reduced through Grx activities (162). It is, however, clear that TrxR1 is an essential enzyme for embryonic development in mice.

Heart-specific *Txnrd1*$^{-/-}$ mice are normal (305), as are mice with neuron-specific deletion of the enzyme (617). Interestingly, however, expression of the enzyme in glial cells is essential for normal development of the central nervous system (617). When deleted in either hepatocytes, mouse embryonic fibroblasts or B-cell lymphoma cells, the Nrf2-driven and mainly GSH-dependent enzyme systems are typically strongly upregulated (302, 430, 520, 535, 634). In fact, it was found that the Nrf2 induction can be so strong upon TrxR1 deletion or inhibition that cells become even more resistant to certain events of oxidative challenge, than those having normal expression of TrxR1 (63, 405, 634) . These apparently paradoxical impacts on mouse susceptibility to stress upon TrxR1 removal will be further elaborated in the following chapters.

2. TrxR2

Similarly to TrxR1, the mainly mitochondrial isoenzyme TrxR2 is essential for embryonic development. Interestingly, however, *Txnrd2* knockout yields early embryonic death in a more tissue specific manner, presenting liver apoptosis, impaired hematopoiesis and insufficient heart development (123). Knockout of mitochondrial Trx2 that is presumed to be the main substrate of TrxR2, however, displays a more severe phenotype with massive widespread apoptosis and open anterior neural tube (490). This illustrates that the functions of TrxR2 are not always directly linked to those of Trx2, which is similar to the situation with Trx1 and TrxR1 (see above).

There was a lack of overt phenotype when TrxR2 was conditionally knocked out in the nervous system (617) or in B- and T-cells (209), while its conditional knockout in heart produced obvious detrimental effects (123, 280). Recently, it was also shown that TrxR2 knockout in tumor cells prevented tumor growth because of a lack of hypoxia-inducing factor (HIF) function and JNK activation (254). These observations suggest that although most cells and tissues are dependent upon mitochondrial function, the physiological effects of genetic deletion of the mitochondrial TrxR2 enzyme are more specific than what would be explained by a generally impaired mitochondrial function in the whole organism.

E. Additional Mouse Models for Knockouts of Selenoproteins

Most, if not all, of the 24-25 selenoproteins in the mammalian proteomes (353) presumably have redox activity. Readers are referred to other recent reviews for a full survey of these proteins (84, 124, 250, 322, 360). However, in the context of this article it is worth considering MsrB1, a

Trx1-dependent selenoenzyme, and Sepp1, as their physiological antioxidant roles have been studied using several genetic mouse models. Knockout of *MsrB1* renders mice prone to lipid peroxidation and protein oxidation in tissues as well as defective actin polymerization in macrophages upon lipopolysaccharide challenge (190, 371) (**Table 9**). Neuronal protection by Sepp1, a predominant extracellular selenoprotein that delivers selenium from liver to other tissues and has peroxidase activity (576, 639), may be attributed to its selenium transport function, because deletion of its C-terminal region being rich in selenocysteine residues (amino acids 240-361) was sufficient to produce severe neurodegeneration in mice (258, 533, 583). Liver-specific expression of *SEPP1* in *Sepp1*$^{-/-}$ mice enhances their brain selenium content and rescues the neurological defects (559), further supporting the important role of this selenoprotein in the selenium transport.

The redox activity of all selenoenzymes depends on the function of selenocysteine (Sec), which is cotranslationally incorporated at re-defined specific UGA codons in a process that requires $tRNA^{[Ser]Sec}$, the transcriptional product of the *Trsp* gene. Because *Trsp*$^{-/-}$ mice are embryonically lethal (54), various conditional knockouts and variants of *Trsp* have been made to study roles and regulations of selenoproteins in specific tissues, resulting in several interesting phenotypes (**Table 9**). Intriguingly, knockout of *Trsp* in endothelial cells causes embryonic lethality and in muscle and liver induces postnatal death (76, 609). Global or conditional *Trsp*$^{-/-}$ mice expressing wild-type or mutant *Trsp* transgene have also been generated (78, 591). These *Trsp*-altered mouse models help understand tissue-specific functions of selenium, and allow for recapitulation of mechanisms behind the classical selenium-deficiency syndrome, Kashin-Beck disease (161). A recent review (361) offers detailed discussion on the pleiotropic effects of *Trsp* targeting that

460 are likely to be derived from the combined effects of modulation of multiple selenoproteins at
461 once.
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463 **F. Thioredoxin Family**
464
465 Trxs are small thiol-disulfide oxidoreductases with a Cys-Gly-Pro-Cys active site and are present
466 in all living cells. The reduced forms with a dithiol motif in the active site catalyze disulfide
467 reduction reactions, generating oxidized forms of Trx with a disulfide in the active site, which is
468 again reduced by NADPH via TrxRs (276, 396). The isoforms of Trx have a broad range of
469 functions in mammalian cells (18), including to serve as electron donors for Prxs that are
470 controllers of the intracellular redox state together with GSH (274), and being major protein S-
471 denitrosylases (91). The structure of Trxs comprises a central core of β-strands surrounded by α-
472 helices that defines the Trx-fold, now known to be present in a large number of proteins denoted
473 the Trx superfamily of proteins. This includes Grx (395), glutathione S-transferases, GPXs,
474 PRXs and proteins of the protein disulfide isomerases (PDI) family, which are all built from Trx
475 domains (21). In the context of this review the main results of genetic mouse experiments for
476 analyses of Trx1, Trx2, Grx1 and Grx2 are discussed as follows.
477
478 **1. Trx1**
479
480 Trx1 (encoded by *Txn* in mice) is ubiquitously expressed in the cytosol/nucleus, and has a large
481 number of functions in cellular redox control and antioxidant defense (18). One of those
482 functions is to provide reducing power to RNR that is essential for DNA synthesis. Because the

global knockout of *Txn* in mice induces early embryonic lethality (437), shortly after implantation with differentiation and morphogenesis defects, studies in adult mice were instead enabled using a dominant-negative mutant line in which the active site Cys-32 and Cys-35 residues were altered to Ser (dnTrx-Tg) (140). These functionally Trx1-deficient mice display decreased Trx activity in the lung and are sensitive to ambient air at room temperature. These mice experience genotoxic stress, as evidenced by decreased activities of aconitase and NADH dehydrogenase, lower mitochondrial energy production, but increased levels of p53 and Gadd45α expression. These dnTrx-Tg mice are also manifested with increased levels of pro-inflammatory cytokines (140), which are aggravated by exposure to hyperoxia. In contrast, overexpression of enzymatically active Trx1 in the lung (140) helps maintain redox balance and mitochondrial function with decreased inflammation. Mice overexpressing *TXN* have increased resistance to a range of oxidative stress insults (643). In addition, Trx1 has been shown to protect against joint destruction in a murine model of arthritis (657). Overexpression of the protein furthermore seems to promote fetal growth by reducing oxidative stress in the placenta (665), prevent diabetic embryopathy (314), and extend mainly the earlier part of the life span in mice with a prolonged youth phenotype (527).

Trx1 is secreted from cells under inflammation and oxidative stress and is detectable in plasma (482). Of particular interest is that the extracellular Trx1 is taken up by cells and has been proposed as an effective antioxidant therapy (439, 483, 688). Its presumed antioxidant and anti-apoptotic properties are tightly coupled with the reduced form of Trx1 binding to thioredoxin interacting protein 1(TXNIP) (475, 735) or apoptosis signaling kinase (ASK1) (290, 310). Extracellular Trx1 is however also found in plasma as a truncated form called Trx80, resulting

from α-secretase cleavage (213) and known to act as an inflammatory mediator (Th1) via effects on the immune system and monocytes (522). Both Trx1 and Trx80 seem to have a positive effects protecting from Alzheimer´s disease in the brain (213). Because Trx80 lacks redox activity together with TrxR1 (523) and since extracellular forms of these proteins are likely to remain oxidized, it is possible and even likely that some of their physiological roles are unrelated to redox activities.

2. Trx2

Trx2, with a mitochondrial leader sequence, is targeted to the mitochondria, where it plays a crucial role in controlling of ROS by acting as a reductant of Prx3 in concert with the GSH system and Grx2 (240, 744). Knockout of the *Trx2* gene (490) induces embryonic lethality with massively increased apoptosis and exencephaly with open anterior neural tube. Cardiac specific deletion of Trx2 (283) produces spontaneous dilated cardiomyopathy at one month of age, with increased heart size, reduced ventricular wall thickness, and progressive decline in left ventricular contractile function result in mortality due to heart failure at young age. In cardiomyocyte-specific $Trx2^{-/-}$ mice, mitochondrial function and ATP production are declined and ASK1-dependent apoptosis accelerated. Interestingly, humans with dilated cardiomyopathy have lowered Trx2 protein levels in heart tissue, suggesting that these mice could be a good model of the human disease (283).

3. Grx1

Grx1 catalyzes GSH-disulfide oxidoreduction reactions (275), deglutathionylation of S-gluthionylated proteins (277) and reduction of Trx1 by GSH when TrxR is inactivated (162). Surprisingly, knockout of *Grx1* (267) results in only a mild phenotype without major effects on ischemia reperfusion injuries. However, knockout of the gene offers protection against inflammation or defective revascularization in diabetes (4, 270), which will be further elaborated in the following chapter.

4. Grx2

Grx2 is encoded by a gene resulting in splice variants including Grx2a located in mitochondria and Grx2c in the cytosol/nucleus. Knockout of *Grx2* (710) induces early onset of age-dependent cataract in mice. Grx2 is also required to control mitochondrial function since knockout affects cardiac muscle (426, 427), giving rise to larger hearts and high blood pressure.

G. Peroxiredoxin Family

The PRX enzymes are a family of abundantly present 20-30 kDa peroxidases (185, 562, 706). These homodimeric proteins fall into three varieties distinguished by their reaction mechanisms and the number of cysteine residues required for catalysis: typical 2-Cys (in mammals PRX1-4), atypical 2-Cys (mammalian PRX5), and 1-Cys (mammalian PRX6) (561, 594, 706). Both types of 2-Cys PRX utilize the reducing power of NADPH via the Trx/TrxR system to reduce their active site disulfides, formed upon catalysis with peroxide reduction, back to active dithiols. On the other hand, 1-Cys PRX, mainly utilize GSH as the reducing agent (706). Furthermore, the various PRX isoforms exhibit different subcellular localizations (271, 706). As the PRX enzymes

551 are highly abundant, accounting for as much as 1% of soluble cellular protein (673, 706) and are
552 excessively reactive with H_2O_2, they are likely to be critical for both oxidative stress protection
553 as well as redox signaling (562, 616, 698, 699).
554
555 **1. Effects of Prx knockout**
556
557 Mice lacking Prx1–4 and 6 are viable, but exhibit increased ROS levels and sensitivity to
558 oxidative insults (300, 375, 389, 461, 484, 683). In general, both *Prx1*$^{-/-}$ and *Prx2*$^{-/-}$ mice appear
559 healthy and are fertile, but have hemolytic anemia and increased atherosclerotic plaques (339,
560 518), suggesting that Prx1 and Prx2 protect red blood cells from oxidative stress (375, 484).
561 Indeed, they exhibit splenomegaly, Heinz bodies in their blood, and morphologically abnormal
562 red blood cells, which are high in ROS (375, 484). *Prx3*$^{-/-}$ mice are healthy in appearance and
563 could grow to maturity, but exhibit elevated intracellular ROS, including in lung tissue (389).
564 Intratracheal inoculation of lipopolysaccharide to the *Prx3*$^{-/-}$ mice results in pronounced lung
565 inflammation (389). Likewise, *Prx6*$^{-/-}$ mice also appear normal, but are very sensitive to
566 oxidative insults (461, 683).
567
568 **2. Effects of Prx overexpression**
569
570 Overexpression of the PRX enzyme genes generally confers protection against different forms of
571 oxidative stress. For instance, overexpression of *Prx3* in heart mitochondria of mice suppressed
572 cardiac failure after myocardial infarction (440). In addition, the *Prx3* overexpressing mice have
573 lower mitochondrial H_2O_2 concentrations and are protected against hyperglycemia and glucose

intolerance (102). Overexpression of *Prx2* inhibits the ischemic damage of neurons (56). Overexpression of *PRX4* in the pancreas of mice suppresses the TRAIL-mediated apoptosis, protects pancreatic islet β-cells against injury caused by single high-dose streptozotocin (STZ)-induced insulitis, and attenuates inflammation (155). When *Prx6* is overexpressed, development of cataract in mouse and rat lenses are significantly delayed (355). These transgenic mice exhibit extra resistance to the lung injury induced by hyperoxia (687). However, global *Prx6* overexpression does not protect against diet-induced atherosclerosis despite lowering levels of H_2O_2 (531).

III. PARADOXICAL OUTCOMES

Although knockout of several antioxidant enzymes is detrimental and their overproduction beneficial to health, the opposite impacts have also been increasingly observed. This chapter describes a series of such apparently "paradoxical" cases that reveal metabolic benefits of deleting major antioxidant enzymes, or harmful effects of overexpressing them.

A. SOD Family

1. Elevated resistance to APAP toxicity by knockout of *Sod1*

APAP, also known as acetaminophen or paracetamol, is the active component of Tylenol and many other over-the-counter analgesics. A life-threatening hepatotoxicity of APAP overdose depends upon the liver enzyme CYP2E1 (cytochrome P450 2E1) that catalyzes biotransformation of APAP to a highly reactive intermediate, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which in turn can cause depletion of hepatic GSH and excessive liver necrosis (306). Interestingly, genetic deletion of several antioxidant enzymes yields increased APAP resistance in mice, which has been reported for Gstp1 (255), TrxR1 (see below) and Sod1.

While an intraperitoneal injection of 600 mg APAP/kg results in 75% mortality in wild-type mice within 20 h, all such treated *Sod1*$^{-/-}$ mice survive for the entire 70 h duration of study (379). Moreover, the *Sod1*$^{-/-}$ mice survived nearly three times as long as, and showed much less hepatic injuries, than wild-type mice following both higher (1,200 mg/kg) and lower (300 mg/kg) doses of APAP injection, respectively. As shown in **FIGURE 1**, this astonishing resistance to APAP

intoxication is associated with at least four separate mechanisms. Firstly, these mice have a 50% reduction in activity of the NAPQI-producing enzyme CYP2E1 (cytochrome P450 2E1) in liver. The down-regulated CYP2E1 activity thus helps attenuate NAPQI formation and the resultant GSH depletion and protein adduct formation. Indeed, hepatocytes isolated from *Sod1*$^{-/-}$*Gpx1*$^{-/-}$ mice display a lower susceptibility to APAP-induced cell death, but higher susceptibility to NAPQI toxicity as compared with cells from wild-type mice (754). Secondly, hepatic protein nitration plays a crucial role in mediating APAP-induced hepatotoxicity (343). Knockout of *Sod1* nearly completely blocks APAP-induced hepatic protein nitration (379). This is intriguing as the enzyme knockout or depletion presumably elicits elevated O_2^- production and thus subsequent peroxynitrite formation for protein nitration, provided that NO is available. Strikingly, SOD1 was previously shown to catalyze peroxynitrite-mediated nitrotyrosine formation in vitro (298). Later, the enzyme was demonstrated to be required for the protein nitration mediated by APAP or LPS in murine liver (758). Thirdly, compensatory inductions of other protective antioxidant enzymes (379, 756) and, fourthly a blunted cell death signaling (757) also attribute to the APAP resistance of the *Sod1*$^{-/-}$ mice. Seemingly, the above-described Sod1 deficiency-derived protection against the APAP overdose is cytosolic-specific. The mitochondrial *Sod2*$^{+/-}$ mice are actually more prone to the APAP-induced liver toxicity than their wild-type controls, potentially through prolonged JNK activation, exaggerated mitochondrial dysfunction with nuclear DNA fragmentation and necrosis (200, 545). It remains unclear whether *Sod2*$^{+/-}$ mice are altered with expression of CYP2E1 and metabolism of APAP. However, SOD2 may serve a more important role than SOD1 as mitochondrion is a main target of the APAP toxicity. As the protein level of hepatic CYP2E1 in the *Sod1*$^{-/-}$ is not altered (379), the activity loss probably results from an oxidative modifcation. However, another group failed to detect similar decreases in the baseline

activity of CYP2E1 in *Sod1*$^{-/-}$ mice, despite conflicting effects of ethanol on the enzyme activity between their own studies (133, 329).

2. Protection against irradiation-induced neuronal damages by knockout of *Sod*

Knockout of *Sod1* or *Sod2* decreases a baseline of neurogenesis, but ameliorates radiation-induced decline of neurogenesis (183, 286) (**FIGURE 2**). Following irradiation, *Sod2*$^{+/-}$ mice preserve normal hippocampal-dependent cognitive functions and normal differentiation pattern for newborn neurons and astroglia, which otherwise are damaged in irradiated wild-type mice. However, irradiation leads to a disproportional reduction in newborn neurons of the *Sod2*$^{+/-}$ mice following behavioral training, suggesting that *Sod2* haploinsufficiency renders newborn neurons susceptible to metabolic stress (126). In contrast, irradiation of *Sod3*$^{-/-}$ mice enhances hippocampus-dependent cognition and decreases hippocampal nitrotyrosine formation (540). These results suggest that chronically-elevated O_2^- anion levels and/or the lower production of H_2O_2 resulting from *Sod3* knockout, may be protective against irradiation-induced damages in neurogenesis and cognition. In line with this result, overexpression of SOD3 impairs long-term learning and potentiation in hippocampal area CA1, further suggesting that O_2^-, rather than being considered exclusively neurotoxic, may also be a signaling molecule necessary for normal neuronal function (644).The underlying molecular mechanisms and signaling pathways for these phenotypes await further investigation. Likewise, knockout of *Sod1* enhances recovery after closed head injury-induced brain trauma in mice, which is associated with attenuated activation of NFκB and subsequent decreased death-promoting signals due to down-regulated H_2O_2 production (41).

3. Neurological disorders associated with overexpression of *SOD1/Sod1*

SOD1 expression is associated with two types of neurological diseases: Down's syndrome (with elevated SOD activity) and ALS (associated with *SOD1* mutations) (569, 612). Indeed, *SOD1*-overexpressing mice manifest certain abnormalities that resemble physiological effects seen in Down's syndrome, including withdrawal and destruction of some terminal axons and development of multiple small terminals (23, 24), a defect in platelet's dense granule responsible for the uptake and storage of blood serotonin (580), thymus and bone marrow abnormalities (524), and an impairment of hippocampal long-term potentiation (201). Meanwhile, *SOD1* overexpression causes mitochondrial vacuolization, axonal degeneration, and premature motor neuron death, and accelerates motor neuron degeneration in mice expressing an ALS-inducing *SOD1* mutant (303). The *SOD1* overexpression also impairs muscle function and leads to typical signs of muscular dystrophy in mice (525, 550). In fact, transgenic mice overexpressing *SOD1* display aberrant protein expression profiles in neurons and mitochondria of hippocampus (605, 606), indicating that elevated SOD1 activity in Down's Syndrome is not just a side-effect or a compensation in response to the increased oxidative stress, but may be part of the cause for the pathophysiology.

Overexpression of *SOD1* impairs peripheral nerve regeneration and increases development of neuropathic pain after sciatic nerve injury with a disturbed inflammatory reaction at the injury site (350), exacerbates abnormalities in hematopoiesis and radiosensitivity in a mouse model of ataxia-telangiectasia (529), and promotes aging as indexed by mitochondrial DNA deletion in the acoustic nerve of transgenic mice (120). Neurons from the *SOD1* overexpressing mice exhibit

676 higher susceptibility to kainic acid-mediated excitotoxicity, associated with a chronic pro-
677 oxidant state as manifested by decreased cellular GSH and altered Ca homeostasis (30). All these
678 negative impacts, along with known biochemical and neurological mechanisms, of SOD1
679 overexpression on various neurological disorders are summarized in **FIGURE 3**.
680
681 In contrast, other studies have shown either negligible effects of *Sod1* overexpression on
682 toxicities induced by neurotoxins including kainite, glutamate and N-methyl-D-aspartate
683 (NMDA) (347, 729) or even protections against similar insults in vivo (260, 586) and in vitro (53,
684 92). These seemingly contradictory findings may be confounded in part with differences in
685 extents of Sod1 overexpression, acute vs. chronic experimental settings, the timing of
686 observation, and the cellular capacity of H_2O_2 catabolism at the testing condition. For example,
687 when treated with a O_2^- donor, overexpression of *SOD1* increases neuronal vulnerability due to
688 increased H_2O_2 accumulation, while overexpression of the gene in astrocytes that exhibit a
689 greater H_2O_2 catabolism capacity than do neurons actually leads to an increased resistance to O_2^-
690 toxicity (104). Therefore, the "paradoxical" function of SOD1/*Sod1* overexpression in the central
691 nervous system may largely rely on: 1) whether the generated extra H_2O_2 results in a burden
692 beyond affordable cellular clearing capacity; 2) whether the induced burst of O_2^- is more
693 detrimental to cell survival than the converted extra amount of H_2O_2; and 3) whether effects of
694 the enzyme expression are unrelated to its enzymatic activity.
695
696 **4. Impaired immune functions and detrimental effects by overexpression of *SOD1/Sod1***
697

Overexpression of *SOD1* in intraperitoneal macrophages decreases their microbicidal and fungicidal activity, along with increased intracellular production and release of H_2O_2, decreased extracellular release of O_2^-, and inhibited NO production following endotoxin stimulation (456). It was intriguing why enzymatically derived NO production became decreased when O_2^- anion levels were diminished. The authors noted that nitrocompound metabolism in macrophages was affected by the overproduction of SOD1, but did not give mechanistic explanations. Possibly the reduced activities of NFκB and Erk1/2 in the *SOD1* overexpressing macrophages, which are upstream regulators of iNOS, lead to downregulation of iNOS expression and thus lower NO production. However, this hypothesis remains to be experimentally confirmed. Transgenic mice overexpressing *SOD1* show no increased resistance to TNFα-induced endotoxic shock (144), but a higher sensitivity to malaria infection as reflected by an earlier onset and increased rate of mortality (220), and activation-induced DNA fragmentation in their splenic T cells (513).

Doubling the expression of *SOD1* does not extend, but instead causes a slight reduction of lifespan in mice (284). Likely due to elevated chronic oxidative stress, *Sod1* overexpression leads to an increased heart rate variability (646) and accelerates the loss of cone function (668). Contrary to its protection against most of ischemic injuries, overexpression of *SOD1* in the in-utero ischemia/reperfusion in pregnancy led to brain damages in both adult and fetal mice (383). *Sod1*$^{-/-}$ mice exposed to chronic ethanol consumption exhibit decreased alcohol dehydrogenase activity and little induced CYP2E1 activity, which suppresses ethanol metabolism and precludes the resultant steatosis (133), while these mice are more susceptible to the acute ethanol-induced liver injury (329). This apparently contrasting impact of Sod1 knockout on injuries associated

with either acute or chronic ethanol intake underscore the stress-type and/or temporal-dependence of the function and (patho)physiological relevance of this enzyme.

5. Diverse effects of *SOD2*/*Sod2* overexpression on alcohol intoxication and cancer cell survival

While overexpression of *Sod2* protects against liver mitochondrial DNA depletion and respiratory complex dysfunction after alcohol binge exposure via inhibition of the formation of peroxynitrite (433), the overexpression aggravates prolonged (7 weeks) alcohol intake-induced hepatic toxicity (368, 433) (**FIGURE 4**). The prolonged ethanol intake selectively triggered hepatic iron elevation, lipid peroxidation, respiratory complex I protein carbonyls and dysfunction, mitochondrial DNA lesion and depletion in Sod2 overexpressing mice. Because administration of an iron chelator (deferoxamine) prevents all these adverse effects, hepatic iron accumulation is likely the crucial factor for the metabolic disorder (368). It has been suggested that alcohol administration decreases the expression of hepcidin, leading to abnormally active duodenal ferroportin and increased intestinal absorption of iron, which gradually increases hepatic iron accumulation (246). Although it remains unclear why in the referenced study (368) the iron overload was only found in Sod2 overexpressing mice, elevated Sod2 activity was linked to hepatic iron accumulation through modulation of iron homeostasis proteins in alcoholic patients (481, 633).

A proposed mechanism for aggravated hepatotoxicity by Sod2 overexpression may be as follows: the hepatic iron overload could lead to a decreased mitochondrial manganese uptake and

743 increased mis-incorporation of iron in the active site, forming Fe-substituted Sod2. The Fe-Sod2
744 is stable and lacks superoxide dismutase activity, but gains hydroxyl radical generating activity
745 in the presence of hydroxyl radicals derived from H_2O_2, which in turn is generated by the
746 manganese-Sod. Consequently, increased production of hydroxyl radicals could lead to the
747 above-mentioned lipid peroxidation and other oxidative injuries (368). Apparently, increased
748 hepatic iron and H_2O_2 might also generate hydroxyl radicals through Fenton reactions. The
749 anticipated diminished O_2^- anion levels due to Sod2 overexpression might furthermore remove
750 its beneficial roles in limiting propagation of lipid peroxidation and blunt alcohol-induced
751 increases of iNOS and subsequent up-regulation of peroxisome proliferator activated receptor
752 gamma coactivator 1 (PGC-1), which otherwise promotes mitochondrial DNA replication (368).
753 Another contributing factor could be the decrease in the mitochondrial transcription factor A
754 (Tfam) in *Sod2* overexpressing mice following alcohol administration. However, further studies
755 are required to clarify the different cause-effect relationships with regards to the observed
756 phenotypes. It should be noted that in rats, overexpression of *Sod2* in liver prevents steatosis,
757 inflammation, necrosis, and apoptosis following prolonged alcohol (4 weeks) administration
758 (694). Thus, there may also be different impact between species of *Sod2* overexpression on
759 ethanol metabolism and intoxication.
760
761 Recently, differential roles SOD2 have been proposed between early and late stages of
762 carcinogenesis. At the early stage, a lower SOD2 level may facilitate transformed phenotypes by
763 potentiating mitochondrial defects, whereas at the later stage a higher SOD2 level protects cell
764 from mitochondrial injury and contributes to tumor growth and metastasis (149). The roles of
765 SOD2 become further complicated when cancer cells are challenged with increased oxidative

stress. Overexpression of *SOD2* in HeLa cervical cancer cells promotes their growth when growth factors are withdrawal, suggesting that SOD2 may promote tumor-cell survival in vivo at conditions unfavorable to cell growth by counteracting the intracellular oxidative processes that can additively impair cell growth and viability (514). Moreover, overexpression of *SOD2* promotes survival of cancer cells treated with radiation, cytokines or drugs (263, 387, 432, 469, 632), likely through activation of NFκB and AP-1 signaling by the SOD2-mediated conversion of H_2O_2. Therefore, overexpression of *SOD2* may promote cancer due to increased cancer cell resistance to the cytotoxicity of therapeutic treatments.

B. Catalase

1. Diabetic developments induced by catalase overexpression

The β cell-specific overexpression of rat *Cat* in non-diabetic background mice shows no detrimental effects on islet function (717) and protects against the diabetogenic effect of STZ (99, 717). However, this type of overexpression provides no protection against cytokine-mediated toxicity in isolated islets, despite a suppression of ROS formation (99, 717). Interestingly, overexpression of *CAT* in mitochondria, compared with that in cytoplasm, confers stronger protections against the cytokine-induced cytotoxicity in insulin-producing cells (230, 407), indicating an important role of mitochondrial ROS in the cytokine toxicity of autoimmune diabetes.

Strikingly, β cell-specific overexpression of *Cat* in nonobese diabetic mice accelerates spontaneous diabetes onset in males and cyclophosphamide-induced diabetes in both males and females, and sensitizes isolated islets to cytokine injuries. **FIGURE 5** depicts several described divergent effects of catalase overexpression on susceptibilities to diabetes, but none of these effects are fully understood mechanistically. There was a down-regulation of Akt/Foxo1/Pdx1 survival pathway in islets associated with the cyclophosphamide-induced autoimmune type 1 diabetes (390). It was suggested that insulin/IGF-1 mediated phosphorylation of Akt might be down-regulated by PTP-1B (a tyrosine phosphatase) that is inhibited by ROS (H_2O_2) and catalase overexpression prevented the ROS inhibition of PTP-1B (390, 574). Although there are no direct experimental data to support these notions, maintaining adequate intracellular H_2O_2 may be needed for activating protective responses of β cells in autoimmune type 1 diabetes.

In contrast, *Cat* overexpression consistently protects against diabetic nephropathy (58, 603) or insulin resistance-induced cardiac contractile dysfunctions (160). Overexpression of *Cat* also attenuates high glucose-induced reduction of endothelial cell tight-junction proteins and the subsequent brain blood barrier (BBB) dysfunction in diabetes (402). These data suggest differential roles of catalase in pancreas and other organs in diabetic vs. physiological conditions.

2. Cell type-dependent inhibition of proliferation by catalase overexpression

Elevating catalase activity, similar to that of Sod, may alter the sensitivity of cancer cells to chemotherapy (216, 416). Overexpressing *CAT* in the cytosolic and especially in the mitochondrial compartments of HepG2 cells potentiates TNF-α-induced apoptosis by promoting

activation of caspases-3 and -8 (26). In contrast, overexpression of *Cat* in a murine lymphoid cell line enhances resistance to dexamethasone-induced apoptosis and exhibits increased net tumor growth in nude mice, which is associated with a delay of mitochondrial cytochrome c release and altered glucose and energy metabolism (648, 649). Overexpression of *CAT* inhibits proliferation of endothelial cells (740) and vascular smooth muscle cells (66, 602) by suppressing Erk1/2 and p38 MAPK signaling (602) and promoting a Cox2-dependent apoptosis (66). This highlights the need for a physiological level of endogenous H_2O_2 for survival and proliferation of vascular cells. Interestingly, the proliferation rate is elevated in vascular smooth muscle cells of *Sod1*$^{+/-}$ and *Sod2*$^{+/-}$ mice, along with higher activity of divergent mitogenic signaling pathways. The heterozygosity of *Sod1* leads to preferential activation of Erk1/2 and p38 MAPK, while that of *Sod2* causes activation of JAK/STAT pathway in smooth muscle cells (422). This opposite outcome is intriguing, because overexpression of *Cat* presumably diminishes intracellular H_2O_2 whose formation would be supposed to be lower due to the *Sod* haplodeficiency. Nevertheless, these diverse effects underscore the physiological importance to tightly regulate intracellular H_2O_2 levels for control of vascular cell proliferation. Furthermore, specific overexpression of *CAT* in myeloid lineage cells impairs perfusion recovery associated with fewer neovascularization and blunted inflammatory response following a femoral artery ligation, suggesting that H_2O_2 derived from myeloid cells such as macrophages plays a key role in promoting neovascularization in response to ischemia and in the development of ischemia-induced inflammation (269). Notably, decreases of H_2O_2 levels upon overexpression of catalase were verified by direct assays in vascular smooth muscle cells and myeloid cells in the above-mentioned studies, but only by indirect methods in endothelial cells and lymphoid cells.

C. GPX Family

1. Improved insulin sensitivity and decreased insulin synthesis upon knockouts of *Gpx1* and *Sod1*

While knockouts of *Gpx1* and *Sod1* impair islet function, pancreas integrity, and body glucose homeostasis, these mice present improved insulin sensitivity in liver and muscle (680, 684). This improvement is mainly associated with an increased phosphorylation of muscle Akt at Thr^{308} and Ser^{473} after injection of insulin (684) (**FIGURE 6**). Presumably, this "unanticipated" benefit is attributed to elevated intracellular ROS that inhibit protein phosphatase activities and thereby attenuate dephosphorylation of Akt (33, 680). Moreover, an increased IRβ protein in the liver of the *Sod1*$^{-/-}$, but not in the *Gpx1*$^{-/-}$, mice may also contribute to the improvement (684). Meanwhile, *Gpx1*$^{-/-}$ mice are resistant to the high fat diet-induced insulin resistance and show favorable responses including decreased-expression of gluconeogenic genes (*G6pc, Pck1* and *Fp1),* increased glucose uptake by white gastric and diaphragm skeletal muscles through membrane docking of glucose transporter 4 upon AS160 phosphorylation on Thr^{642}, and enhanced insulin-induced oxidation of phosphatase and tensin homolog (Pten) and PI3K/Akt signaling (406) in their embryonic fibroblast cells.

Comparatively, the *Sod1* knockout exerts stronger impacts on insulin synthesis and secretion, glucose and lipid metabolism, and islet integrity than that of *Gpx1* (684). Simultaneous ablation of both enzymes does not result in additive or severer metabolic outcomes. The *Sod1*$^{-/-}$ mice show more apparent pancreatitis than the *Gpx1*$^{-/-}$ mice that are more susceptible to the cerulein-

induced amylase increase. Although hypoinsulinemia and decreased pancreatic β cell mass are caused by knockouts of both of *Gpx1* and *Sod1* via down-regulation of the key transcription factor Pdx1 in pancreatic islets, the former seems to decrease only Pdx1 protein whereas the latter exerts suppressions at three levels of the Pdx1 regulation: epigenetic, mRNA, and protein (684) (**FIGURE 7**). Likewise, knockout of *Sod1*, but not *Gpx1*, up-regulates protein phosphatase 2b/sterol responsive element binding protein (SREBP)-mediated lipogenesis and down-regulates the AMPK-mediated gluconeogenesis (680). Apparently, there are several overlapping as well as distinctive mechanisms for Sod1 and Gpx1 in regulation of glucose homeostasis and lipid metabolism (378). It should also be noted that reductive stress may be as destructive as oxidative stress in the etiology of diabetes and obesity (753).

2. **Potentiation of the peroxynitrite-induced toxicity by GPX1/Gpx1**

Peroxynitrite represents a major RNS formed from reaction of O_2^- with NO, which occurs at a diffusion-limited rate (39). Although peroxynitrite induces nitration in a variety of biomolecules, a major activity indicator is the nitrosylation of protein tyrosine residues (39). Peroxynitrite-mediated protein nitration is indeed involved in the pathogenesis of many human diseases (297, 530). Impacts and mechanisms of the influence of GPX1 activity on peroxynitrite-induced oxidative damage have been studied in different systems (198, 610). **FIGURE 8** summarizes "paradoxical" roles and mechanisms of bovine GPX1, *Gpx1* knockout, and *GPX1* overexpression in coping with the PN-mediated protein nitration and toxicity in these systems.

Using a cell-free system, Sies et al found that GPX1 can serve as a peroxynitrite reductase (610). However, that function of GPX1 could not be verified by Fu et al. (198) using primary

881 hepatocytes isolated from *Gpx1*$^{-/-}$ mice. In stark contrast, *Gpx1*$^{-/-}$ hepatocytes are instead
882 extremely resistant to peroxynitrite-induced DNA fragmentation, cytochrome c release and
883 caspase-3 activation, GSH depletion, protein nitration, and cell death (198). Interestingly,
884 treating hepatocytes with *S*-nitroso-*N*-acetyl-penicillamine (SNAP; a NO donor) in addition to
885 diquat (O_2^-/H_2O_2 donor) produces synergistic cytotoxicity, and protein nitration induced by these
886 two pro-oxidants together is attenuated in *Gpx1*$^{-/-}$ cells (197). While knockout of *Gpx1* in mice
887 exerts partial protection on the APAP- or LPS-induced hepatic toxicity and protein nitration (343,
888 755, 756), overexpressing *GPX1* sensitizes mice to the APAP-induced hepatotoxicity and
889 lethality (458). The metabolism of APAP in *GPX1* overexpressing mice leads to a substantial
890 decrease in the replenishment of GSH in liver and blood compared with the controls. In contrast,
891 overexpressing *GPX3* and *Sod1* in the same study renders mice resistant to the APAP toxicity.
892 These observations again underscore the complexity or unpredictability of seemingly similar
893 antioxidant enzymes in coping with a given oxidative insult.
894
895 3. **Protection against kainic acid-induced lethality and seizure by *Gpx1* knockout**
896
897 Kainic acid is an analog of glutamate that is widely used to induce limbic seizures and model the
898 disease of epilepsy in rodents (40, 217). Administration of the compound activates NMDA
899 receptors in hippocampus and other vulnerable brain regions (31, 43). As an event following
900 NMDA activation (364, 365), there is increased oxidative stress including formations of O_2^-, NO,
901 and peroxynitrite in the central nervous system after the kainic acid injection (217, 452, 568).
902 Thus, antioxidants such as ascorbate, GSH and EUK-134 (a synthetic SOD and catalase mimic)
903 can decrease the neurotoxic effects of kainic acid and its seizure-associated neuropathology (421,
904 575). Strikingly, *Gpx1*$^{-/-}$ mice are much more resistant to kainic acid-induced seizure (frequency

and interval), neuronal injury, and lethality compared with wild-type controls (309). This increased resistance involves inactivation of the NMDA receptor via thiol oxidation of its NMDA receptor-1 subunit, possibly due to elevated H_2O_2 levels in the brain of *Gpx1*$^{-/-}$ mice, and subsequent attenuation or block of the kainic acid-induced oxidative injuries (309) (**FIGURE 9)**. As described above, neurons from *SOD1* overexpressing mice exhibit elevated susceptibility to the kainic acid-mediated excitotoxicity (30). Therefore, certain levels of ROS or chronic oxidation in the brain are needed for a functional NMDA receptor, with long-term use of antioxidants possibly thereby leading to detrimental rather than protective effects.

4. Type 2 diabetes-like phenotypes induced by *Gpx1* overexpression

Global overexpression of *Gpx1* in non-obese or non-diabetic mice results in hyperinsulinemia, hyperglycemia, hyperlipidemia, insulin resistance, β cell hypertrophy, and obesity at 6 months of age (445). Diet restriction can prevent all these phenotypes except for hyperinsulinemia and hyper-secretion of insulin after glucose-stimulation (686). Thus, these two phenotypes represent primary effects of Gpx1 over-production and seem to be mediated by up-regulation of a key transcription factor (Pdx1) for β cell differentiation and insulin synthesis and secretion, as well as down-regulation of the insulin secretion inhibitor mitochondrial uncoupling protein 2 (Ucp2). The insulin resistance in these *Gpx1* overexpressing mice may be attributed to less oxidative inhibition of protein tyrosine phosphatases due to diminished intracellular ROS (H_2O_2) levels upon higher Gpx1 activity, leading to accelerated dephosphorylation of IRβ and Akt after insulin stimulation (445, 686). Meanwhile, *Gpx1* overexpression also affects transcripts, proteins, and functions of other pro-insulin genes, lipogenesis rate-limiting enzyme genes, and key glycolysis (GK) and gluconeogenesis (PEPCK) enzymes in islets, liver, and muscle (526, 721). **FIGURE**

10 highlights the major pathways and modes of action in relation to insulin production and insulin responses, illustrating how Gpx1 overexpression can induce type 2 diabetes-like phenotypes. Dietary Se deficiency precludes Gpx1 overproduction in these mice and partially rescues their metabolic syndromes by modulating or reversing these molecular and biochemical changes (721). Similarly, dietary Se levels have indeed been shown to affect glucose metabolism and insulin sensitivity (362). However, β cell-specific overexpression of *GPX1* in *db/db* mice with mutated leptin receptor rescues β-cell dysfunction with reversed signs of diabetes at 20 weeks of age (229, 244). It should be noted that islets have relatively low baseline Gpx1 activity but display one of the highest overproductions of Gpx1 activity among all tissues in the global *Gpx1* overexpressing mice. Collectively, it seems clear that GPX1/Gpx1 overproduction is beneficial at diabetic or obese pathophysiological conditions, but becomes deleterious if triggered in healthy mice with normal metabolic status.

5. Intriguing roles of GPX enzymes in carcinogenesis

A number of studies have revealed cancer type-, stage-, and tissue-dependent impacts of GPX enzymes on carcinogenesis (**FIGURE 11**). Global *GPX1* overexpression sensitizes mice to skin tumor formation induced by 7,12-dimethylbenz(a)anthracene/12-O-tetradecanoylphorbol-13-acetate (DMBA/TPA) (413), whereas adenoviral delivery of *GPX1* to pancreatic tumor xenografts actually suppresses the tumor growth in nude mice (403). While mechanisms for differential roles of GPX1 between skin and pancreatic tumors remains elusive, a deficiency of Gpx1 in cancer-free naked mole rats (323) suggests the enzyme to be dispensable for cancer prevention at least in this particular species. As discussed in Chapter II, chronic colitis (174) and inflammation-driven intestinal cancer (118) are observed in *Gpx1*$^{-/-}$*Gpx2*$^{-/-}$ mice (118, 174), but

not in *Gpx2*$^{-/-}$ mice unless additional stress is employed (678). This implies dose-dependent or overlapping roles of the two Gpx enzymes in this regard.

Roles of GPX2 in carcinogenesis vary with cellular metabolic contexts (61, 473). In healthy (normal or precancerous) cells, the enzyme helps maintain self-renewing of the gastrointestinal epithelium, suppress inflammatory processes, and thereby inhibit carcinogenesis (61). Loss of *Gpx2* induces apoptosis, mitosis, and elevated *Gpx1* expression in the intestine of mice (62, 186). In cancerous cells, however, the anti-apoptosis function of the enzyme may promote their growth and migration. After being treated with intestinal carcinogens azoxymethane/dextran sulfate, *Gpx2*$^{-/-}$ mice fed a selenium-inadequate diet (0.08 mg Se/kg) showed increased tumor numbers but decreased sizes, compared with the wild-type controls (352). The elevated tumor numbers may reflect Gpx2-derived protection against carcinogenesis at the early stage of tumor formation, whereas the declined tumor sizes imply promotion of Gpx2 on tumor growth during the lates stages of tumorigenesis. In addition, up-regulation of GPX2 in colorectal cancer (59, 187) and activation by cancer-associated NRF2 and Wnt pathways (28, 336) further suggest that the enzyme may indeed be involved in the pathophysiolical processes.

Several studies have collectively demonstrated both positive and negative impact of GPX3 on carcinogenesis (62). While knockout of *Gpx3* sensitizes mice to chemical-induced, colitis-associated carcinoma (32), knockdown of the gene by shRNA in leukemia stem cells decreased their competitiveness and self-renewal capability (256). Apparently, most of the findings on the roles of GPX enzymes in carcinogenesis await full elucidation of the molecular and cell biological mechanisms.

D. Paradoxical effects of TrxR1 targeting by genetic modulation or drug treatment

Although TrxR1 is an essential enzyme for mouse embryogenesis, the enzyme can be conditionally deleted in a wide range of differentiated tissues without apparent phenotype (**Table 8**, see above) and fully inhibited for at least a week in mice by gold compound treatment without overt toxicity (615). Strikingly, genetic deletion or full inhibition of TrxR1 can instead protect cells and tissues from oxidative challenges. As in the case of global knockout of *Sod1*, liver-specific *Txnrd1*$^{-/-}$ mice become highly resistant to APAP-induced hepatotoxicity (302, 520). It was also found that the TrxR1 enzyme, together with GSH, is a prime target for inhibition by NAPQI, which should help explain why APAP-derived NADPQI becomes more toxic than what is seen upon mere GSH depletion using inhibition of GSH synthesis (302, 520). The protective effects of TrxR1 deletion against APAP challenge are likely to be explained by compensatory up-regulation of many Nrf2 targets in mice with hepatocytes lacking *Txnrd1* with more robust GSH biosynthesis, glutathionylation, and glucuronidation systems following APAP overdose (302, 520). Indeed, "priming" of tissues for oxidative injuries by prior inhibition of TrxR1 has also been shown in lung tissue, where inhibition of the enzyme leads to better resistance to hyperoxia (63, 405), in most or all of these cases presumed to involve activation of the cell protective Nrf2 pathway (89).

Similar paradoxical roles of TrxR1 exist in carcinogenesis. Although liver-specific *Txnrd1*$^{-/-}$ mice were reported to display a much greater tumor incidence (90 vs 16%) compared with wild-type mice after diethylnitrosamine induction (79), the Trx/TrxR1 system has also been found to

promote tumor growth (19, 251). Tumors arising in mice after injection of *Txnrd1*-knockdown Lewis lung carcinoma (LLC1) cells are of much smaller in size than those from mice injected with the control, malignant cells; and most importantly, these knockdown LLC1 cells lose their targeting construct or show attenuated metastasis (251, 730). The mechanisms by which the enzyme can either be cancer preventive or promoting cancer progression are not fully understood, but are likely to relate to different stages of carcinogenesis and perhaps also differ between cancer types. It is known that over-expression of TrxR1 in cancer cells correlates with tumorigenic properties and down-regulation of the enzyme inhibits growth of human hepatocarcinoma cells (204). As mentioned above, knockdown of TrxR1 in lung carcinoma cells reverses their tumorigenicity and invasive potential in a xenograft model (730). Therefore, TrxR1 enzymes have been suggested as potential targets for development of anticancer drugs (410, 485, 666). As loss of *Txnrd1* renders tumors highly susceptible to pharmacologic GSH deprivation, a concomitant inhibition of both GSH and TxrR systems was recently proposed to be a strategy to kill tumor cells (245, 430). In this context it should be noted that drug-targeted inhibition may not only inhibit TrxR1, but can also convert the enzyme to a pro-oxidant NADPH oxidase upon selective modification of its Sec residue (13).

We conclude that TrxR1 can exert "paradoxical" effects in three separate forms of the enzyme, i.e. no matter whether it is overexpressed, knocked down or targeted by low molecular weight inhibiting compounds, either beneficial or detrimental physiological effects can be triggered depending upon cellular context. This is summarized in **FIGURE 12** and its diverse effects should be considered in studies aimed at understanding the physiological roles of this enzyme.

2. E. Hazard of Trx overexpression and benefit of Grx knockout

Increased Trx1 potentiates cadmium toxicity (218), whereas ablation of *Grx1* renders mice resistant to the LPS- induced inflammation and macrophage activation associated with enhanced S-glutathionylation (4). The latter also enhances resolution of airway hyper-responsiveness and mucus metaplasia in allergic mice (270). Because the gene knockout also attenuates inflammation and expression of proinflammatory mediators in the lung, S-gluathionylation of specific target proteins may be beneficial to attenuate airway hyperrepsonsiveness like in asthma. Thus, inhibitors of Grx1 may be of interest clinically. Plasma Grx1 concentration is increased in patients with diabetes (163). This may be linked to defective revascularization in diabetes, since Grx1 overexpressing mice have elevated soluble vascular endothelial growth factor receptor 1 and attenuated post-ischemia limb revascularization (478).

IV. MECHANISMS AND METABOLIC RELEVANCE

The apparently paradoxical outcomes in several cases of antioxidant enzyme overexpression or genetic deletion studies clearly challenge the "prevailing" view that these enzymes are only beneficial, or that ROS/RNS are solely toxic byproducts of aerobic metabolism. It is clear that controlled production of ROS/RNS is important in signaling and that under certain conditions, antioxidant enzymes exhibit pro-oxidant activities. In all aspects of redox biology, spatial-, tissue- and temporal-specific dependences are crucial, which will also have an impact upon the physiological functions of antioxidant enzymes (307, 465, 656).

The exact mechanisms for "paradoxical" outcomes of antioxidant enzyme knockout or overexpression should undoubtedly derive from the interplay of three factors: 1) the properties and roles of their ROS/RNS substrates and products; 2) the activities and functions of the antioxidant enzymes and 3) the metabolic contexts in which these entities interact. Accordingly, we will here discuss a series of chemical, molecular, biochemical, and physiological mechanisms that need to be considered and that may help to explain the observed paradoxical roles of antioxidant enzymes. Contributions of reductant substrates such as GSH to the paradox are discussed in the context of antioxidant enzyme catalysis.

A. Multi-faced Chemical Reactivity and Metabolic Roles of ROS/RNS

1. Dose-dependent impacts of ROS/RNS

Whereas excessive levels of ROS and RNS trigger oxidative stress, appropriate levels of ROS/RNS are required for redox signaling. Apparently, antioxidant enzymes are needed to suppress excessive production of ROS and RNS. Under certain conditions, however, insufficient ROS/RNS or elevated cellular reductants can be detrimental, or, conversely, elevated ROS/RNS may be beneficial. This explains in part dose-dependent effects of ROS/RNS or roles of their metabolizing enzymes. Transgenic mice with 2- to 3-fold increased Sod2 activity in major organs are phenotypically normal and fertile (542), while a higher overexpression of the enzyme to 2.5- to 8.7-fold activity above normal decreases body size and female fertility, and causes male infertility. Transgenic lines overexpressing 60- or 100-fold catalase activity are more resistant to doxorubicin-induced cardiac injury, but further overexpression to 200-fold or higher fails to provide protection (319). While the precise molecular explanations to these observations are unknown, they likely involve effects of site-specific localization, reactivity, steady-state levels of H_2O_2, as well as differential induction of compensatory pathways, as discussed below.

2. Detrimental effects of insufficient peroxides on redox signaling

Of the primary ROS, H_2O_2 is perhaps the most important for signaling (560), with both O_2^- and hydroxyl radicals having limited half-life and reactivity profiles unsuitable for diffusible signals (135, 192, 193). H_2O_2 is an ideal signaling agent because of its relatively long lifetime and selectivity for targeting of particular protein microenvironments (135, 181, 192, 193, 700). It can oxidize thiol groups of specific Cys residues to disulfides (S-S), sulfenic (S-OH), sulfinic (SO_2H), and sulfonic (SO_3H) acids (404). Over-oxidation to sulfonic acid is not implicated in redox signaling, but contributes to oxidative stress due to its irreversibility. Peroxide sensing proteins

that utilize uniquely reactive Cys residues may include transcriptional factors (20, 487), kinases (651), phosphatases (451), ion channels (521), ubiquitin and small ubiquitin-related modifier (SUMO)-conjugating enzymes, ligases and adapter proteins (55, 157, 450, 743), as well as various metabolic enzymes (466). Most likely of all proteins to react with H_2O_2 are however peroxidases, such as GPXs or PRXs, which in turn may propagate the oxidative signal to specific downstream targets in cells (698, 699).

Many signal transduction pathways are hard-wired to redox signaling networks, due to the large number of kinases and phosphatases having reactive Cys residues that affect their activities (70, 192, 193, 673). Deliberately-produced peroxides can oxidize catalytic Cys residues in various protein tyrosine phosphatases (PTPs), thereby inactivating them (34, 146, 577, 650, 670). This in turn serves to enhance activation of related signaling pathways by preventing the PTPs-catalyzed de-phosphorylation of specific phosphorylated tyrosine residues. Apparently, this type of inhibition can be removed by a hyperactivity of peroxide-scavenging enzymes. As in the case of *Gpx1*-overexpressing mice that develop type 2 diabetes-like phenotypes (445, 686), the over-produced Gpx1 diminishes intracellular ROS production, reverts the inhibition of PTPs, accelerates dephosphorylation of IR and Akt after insulin stimulation, and thereby leads to insulin resistance. In contrast, knockout of *Gpx1* causes accumulation of intracellular peroxide, which, via the same pathways, improves insulin sensitivity and renders the mice more resistant to high-diet induced insulin resistance (406, 684). However, the specific dose, temporal dynamics, and targeting protein phosphatases for the action of H_2O_2 in redox signaling remain largely unclear.

3. Mixed effects of peroxynitrite in cell signaling

Peroxynitrite-mediated signaling pathways are not as firmly established as those involving H_2O_2. Traditional "antioxidant" ROS-scavenging enzymes like SOD1 and GPXs have been implicated in peroxynitrite metabolism and are supposed to affect the related signaling pathways. Peroxynitrite can upregulate Src tyrosine kinases, the Akt pathway, and various mitogen-activated kinases (512). Because many mitogen-activated kinases like p38 and c-Jun are implicated in pro-apoptotic pathways, peroxynitrite is considered to be a pro-death signaling molecule. In addition, peroxynitrite has also been implicated in hypoxic signaling. Under hypoxia, cytochrome c oxidase exhibits nitrite reductase activity, reducing nitrite to nitric oxide instead of oxygen to water (85, 86). This nitric oxide then reacts with O_2^- to form peroxynitrite, which can oxidize yet to be determined protein targets that signal adaptation to hypoxia (158, 534). As discussed in greater detail below, SOD1 can either increase or decrease peroxynitrite via its ability to control O_2^- fluxes. Thus, paradoxical outcomes of *Sod1* knockout or *SOD1* overexpression may be in part derived from the unpredictable consequences of peroxynitrite modulation (298, 512, 758). The same may also be true for the case of GPX1 (197-199) but the precise roles and mechanisms of SOD1 and GPX1 in regulating peroxynitrite-mediated signaling are unclear.

B. Paradox-related Properties of Antioxidant Enzymes

1. Pro-oxidant catalysis

Despite their well-known ROS/RNS scavenging capacity, some antioxidant enzymes may also promote oxidative/nitrosative stress. One example is the conversion of TrxR1 to a prooxidant enzyme upon targeting of its Sec residue by inhibitors, as discussed above. Another illustrative example relates to the peroxidase activity exhibited by SOD1 (398, 399, 551, 745). The peroxidase cycle of SOD1 involves peroxide reducing the Cu(II) center to form O_2^- radical and Cu(I), followed by another molecule of peroxide re-oxidizing Cu(I) to form Cu(II) and hydroxyl radical. These reactions can occur under severe peroxide stress, with the resulting hydroxyl radicals subsequently being able to irreversibly oxidize metal coordinating His residues and thereby inactivate SOD1 (728). In the presence of carbonate, hydroxyl radicals can also oxidize carbonate to form carbonate radicals, which can in turn oxidize a variety of other substrates, including azide, urate, and nitrite (448, 745). However, it remains unclear to which extent this chemistry happens *in vivo*, but how much this contributes to the SOD1 toxicity.

In some circumstances, SOD1 can also promote aberrant protein nitration, either by enhancing peroxynitrite production or by directly activating it for tyrosine nitration. Beckman and colleagues demonstrated that human SOD1 mutants that are zinc deficient, either due to mutations associated with ALS or by other interventions that limit zinc to the protein, are better at catalyzing the reduction of dioxygen to O_2^-, thus providing a pool of O_2^- that can react with nitric oxide to form peroxynitrite (173, 655). This peroxynitrite can then go on to nitrosylate and irreversibly damage various biomolecules, serving as another mechanistic basis for a toxic gain of function associated with various ALS-associated the mutants of SOD1.

Beckman and Koppenol have also proposed that intact human SOD1 can activate peroxynitrite to nitrosylate protein tyrosine residues (38, 39). The mechanism would involve Cu(II)-catalyzed heterolytic cleavage of peroxynitrite into the nitronium cation and CuO, with the former being a potent nitrosylating agent. Indeed, Lei and co-workers demonstrated that there is a diminished or blocked protein nitration in *Sod1*$^{-/-}$ mice treated with APAP (379). They proposed that the block of hepatic protein nitration in those mice might partially explain their resistance to the APAP overdose. Adding functional holo-SOD1, but not apo-SOD1, to liver homogenates of the *Sod1*$^{-/-}$ mice mixed with a bolus of peroxynitrite indeed resulted in increased protein nitration (758).

Likewise, GPX1 bears pro-oxidant potential. Several groups have demonstrated that this enzyme can aggravate nitrosative stress in mouse models (199, 343, 376, 377, 379, 458). This effect opposes the role of GPX1 in preventing nitrosative stress by catalyzing reduction of peroxynitrite into nitrite using reducing equivalents from GSH (610). Although the precise mechanisms remain poorly understood (191, 197), attenuated protein nitration should help explain the increased resistance of *Gpx1*$^{-/-}$ hepatocytes to peroxynitrate toxicity and lack of potentiation or even protection conferred by *Gpx1* knockout against APAP hepatotoxicity (199, 343, 376, 377, 379, 458).

2. "Unwanted" modulation of reducing equivalents

Excessive enzymatic removal of ROS/RNS may lead to other detrimental downstream effects. For example, consumption of GSH as a reductant substrate deplete cells of GSH and thus outweigh the benefits of GSH-dependent ROS scavenging enzymes (199, 379, 458). Although

un-catalyzed reduction of peroxide by GSH is slow (700), GPX1 is very efficient at catalyzing this reaction (235). However, GSH can directly scavenge other more reactive species, like hydroxyl radicals, HOCl, peroxynitrite, and carbonate radicals (235). It can also regenerate antioxidants vitamins C and E. This may partially explains why overproduction of GPX1/Gpx1 can result in greater sensitivity to the destructive reactivity of APAP metabolites (199, 379, 458).

Meanwhile, elevating GSH may also be detrimental via mechanisms that involve S-glutathionylation and inactivation of various key proteins. For instance, GAPDH (462), eNOS (96, 431), certain tyrosine phosphatases (1), MAPK phosphatase 1 (331), mitochondrial thymidine kinase 2 (630), and protein disulfide isomerase (715) have all been reported to be inactivated by glutathionylation. This may either protect such enzymes from further damage, but can inhibits their function. While the precise pathways and mechanisms are yet unclear, NRF2 is emerging as a major regulator of oxidative and reductive extreme conditions in metabolism (57, 321). Upon a rise of ROS levels above normal, NRF2 helps to up-regulate GSH synthase and GSSG reductase, G6PD of the pentose phosphate pathway, as well as antioxidant enzymes like TrxR1, SOD and catalases. While initially activated to protect against oxidative stress, hyperactivity of NRF2 can however result in a shift towards reductive stress, due to over-abundance of anti-oxidant factors and GSH that can lead to cardiomyopathy and hypertrophy (543). It is possible that the detrimental effects of reductive stress can be associated with elevated S-glutathionylation (227) and/or inappropriate suppression of critical ROS-dependent signaling pathways. The effects of antioxidant enzyme overexpression in this context remain to be better characterized.

3. Stress source and intensity-dependent roles

As ROS scavengers, both Gpx1 and Sod1 protect mice against the lethality and toxicity caused by ROS-generating diquat and paraquat (111, 113, 168, 199). However, the opposite is true when mice are treated with the RNS-generating APAP and kainic acids (309, 379). Indeed, the ultimate metabolic outcome from overexpression or knockout of a particular antioxidant enzyme should be decided by how the enzyme will alter the relative production and fate of ROS and RNS in a given context. Good examples are the impacts of SOD overproduction on cardiovascular diseases or myocardial ischemic injuries. First, elevated SOD may help to preserve NO bioavailability, by preventing its reaction with O_2^- to form peroxynitrite, and thus allow NO to serve as a vessel relaxation factor to protect the cardiac function and survival (83, 493). On the other hand, the hyperactivity of SOD may promote formation of H_2O_2 which then triggers downstream signaling responses that may inhibit vascular pathogenesis (747). However, the role of vascular H_2O_2 can also depend upon the location, as exemplified with H_2O_2 derived from overproduced SOD3 anchored to endothelial cells, which promotes VEGFR2 signaling and then potentially aggravates angiogenesis-dependent vascular diseases (508).

Knockouts of *Txnrd1*, *Gpx1* and *Sod1* produce different phenotypes of glucose and lipid metabolism in mice (302, 680, 684). While the knockout of *Sod1* elevates endogenously-derived intracellular O_2^-, the mice display similar impairments in islet physiology, but distinct signaling mechanism compared with the *Gpx1*$^{-/-}$ mice with elevated intracellular peroxides. As shown in **FIGURE 7,** *Sod1* knockout down-regulates Pdx1 at three levels: epigenetic, gene, and protein, whereas the *Gpx1* knockout affects only the Pdx1 protein. Interestingly, both knockouts suppress

GSIS by elevating Ucp2 expression with decreased ATP production and affecting the mitochondrial potential in islets (684). Interestingly, only the GPX mimic ebselen, but not the SOD mimic copper diisopropylsalicylate (CuDIPs), rescues impaired GSIS in islets of all test genotypes including *Gpx1*$^{-/-}$ and *Sod1*$^{-/-}$ (684). The effects of ebselen seemed to be mediated via peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) while, in contrast, CuDIPs improves insulin secretion only in *Sod1*$^{-/-}$ islets with suppressed gene expression of the PGC-1α pathway (685). These results demonstrate that Gpx1 and Sod1, via their respective ability to modulate different species of ROS, can differentially affect redox-sensitive pathways in regulating GSIS. However, the "sensor" in the target signal molecules or regulators that distinguish and react with the local changes of O_2^- and peroxide needs unveiling.

Even for the same oxidative insult, the necessity and mechanism of a given antioxidant enzyme will vary with stress intensity and antioxidant status. When mice are injected with a high dose of paraquat (50 mg/kg body weight) or diquat (24 mg/kg), Gpx1 becomes absolutely essential to promote mouse survival by protecting against the depletion of NADPH and redox collapse (113, 195). In contrast, *Gpx1*$^{-/-}$ mice tolerate low doses of paraquat (12.5 mg/kg) and diquat (6 mg/kg) well if they are fed adequate selenium to saturate the expression of other selenoproteins (111, 196). Still, minute amounts of Gpx1 activity, raised by injection of selenium in selenium-deficient mice, becomes protective against a moderate dose of paraquat-induced hepatic necrosis and apoptosis (112). Comparatively, knockout of *Sod1* in the mice enhances sensitivity to oxidative injury induced by a similar dose of paraquat (10 mg/kg) (264), implicating that generation of O_2^- contributes more to the paraquat-induced oxidative toxicity.

4. Compensatory inductions

"Hidden helpers" or compensatory responses induced by altering the expression of antioxidant enzymes may also help to explain the mechanisms of the observed phenotypes. The protection conferred by the *Sod1* knockout against the APAP toxicity is associated with a 50% activity reduction in a key APAP-biotransforming enzyme, CYP2E1 (379), which catalyzes the formation of toxic metabolites of APAP. The *Sod1* knockout also results in a 40% reduction of GPX1 activity (684), which may also add to the resistance of the *Sod1*$^{-/-}$ mice to the drug overdose (756).

As elaborated above, NRF2 is a redox-sensitive transcription factor that controls protective responses to oxidative stress (419, 463). The protein is normally sequestered in the cytosol by Keap1 and marked for proteasomal degradation. Under oxidative stress, Keap1 becomes oxidized and NRF2 can then translocate to the nucleus where it initiates transcription of selected antioxidant enzyme genes (419, 496). In the *Sod1*$^{-/-}$ mice, a greater fraction of Nrf2 is localized in the nucleus and up-regulates gene expression of many antioxidant proteins including glutathione S-transferases, sulfiredoxins, TrxR1, GSH synthases and other reductases (239). The up-regulation of these enzymes provides an increased antioxidant capacity in *Sod1*$^{-/-}$ mice against the APAP-derived oxidative stress. Likewise, the liver specific knockout of *Txnrd1* enhances mouse resistance to the APAP toxicity by up-regulation of the Nrf2-target genes and proteins, with more robust GSH biosynthesis, glutathionylation, and glucuronidation systems (302, 520). The increased resistance to acute lung injury induced by endotoxin in acatalasemic mice (759) results from the H_2O_2-mediated down-regulation of cytokine expression in macrophages via

inhibition of NFκB activation. With these compensatory mechanisms revealing intricate pathways of physiological coordination to cope with redox imbalances, caution should be given to evaluate functions of antioxidant enzymes as absolute or isolated entities, as they will always be context-dependent.

5. Overlapping and coordinated functions

Catalase and GPX1 are two major antioxidant enzymes that are both responsible for removal of H_2O_2 although via distinct mechanisms (94, 184). Double-knockout mice deficient in both of these enzymes were generated to reveal insights into the overlap between these potentially redundant H_2O_2-detoxification systems (333). Interestingly, hepatic lipid peroxidation is not elevated in mice deficient in Gpx1 alone compared with that of wild-type mice (113), yet it is increased in mice lacking both Gpx1 and catalase (333).

In other cases, intrinsic expression of multiple isoforms of the same antioxidant enzymes in cells makes interpretations of oxidant-mediated diseases difficult. GPX1 is ubiquitous in all types of cells and GPX2 is in epithelium of the gastrointestinal tract (60, 117, 177). *Gpx1*$^{-/-}$ and *Gpx2*$^{-/-}$ mice are grossly normal. However, *Gpx1*$^{-/-}$*Gpx2*$^{-/-}$ mice develop spontaneous ileocolitis and intestinal cancer (118, 174, 175). This occurrence of cancer is also associated with an increased rate of mutation in the intestine (372). Collectively, these results suggest that the two enzymes cooperatively attenuate intestinal flora-induced inflammation by removing H_2O_2 and alkyl hydroperoxides, thereby suppressing the vicious cycles of the inflammatory response and oxidant-mediated mutations and cancer.

Over-production of either SOD2 or Cat , each having its distinct target of ROS, in pancreatic β cells of mice significantly delays but does not prevent the onset of diabetes induced by STZ compared with wild-type mice (99). However, the STZ-triggered increase in blood glucose is more effectively attenuated by overexpression of both enzymes in mice, suggesting that both O_2^- and H_2O_2 contribute to the dysfunction and death of pancreatic β cells caused by STZ. In contrast, double knockouts of *Sod1* and *Gpx1* did not produce more aggravated effects than the single knockout of *Sod1* on mouse susceptibility to pro-oxidant toxicity, loss of islet beta cell mass and insulin synthesis, and dysregulation of glucose metabolism (376, 684, 758). Thus, overlapping or coordination between antioxidant enzymes is not a universal feature.

Double knockouts of antioxidant enzymes can also yield unexpected novel insights into mammalian redox control. This was recently exemplified when *Txnrd1* was conditionally deleted from hepatocytes in mice lacking a functional *Gsr* gene, thus leading to livers lacking both of the two major cytosolic NADPH dependent oxidoreductases TrxR1 and GR, presumed to be required for essentially all NADPH dependent reductive activities in the cytosol. These mice were, surprisingly, found to be both viable and fertile. The reductive power was instead supplied solely by dietary methionine that became converted to GSH, which was likely used in single-turnover reactions and thus these livers avoid the reliance on NADPH (171).

6. **Non-redox functions**

SOD1 has been shown to play roles in copper and zinc metabolism (132, 690, 709). In Baker's yeast, overexpression or deletion of SOD1 affects the cell resistance or sensitivity to copper and zinc toxicity or deprivation, respectively (132, 709). More recent work suggests that SOD1 is also important for communicating the cellular stress response to low zinc (278, 709). Most interestingly, a group have demonstrated (656) a role for SOD1 in cell signaling independent of its role in O_2^- disproportionation. They found that under oxidative stress, SOD1 translocated to the nucleus where it acted as a transcriptional activator of genes involved in oxidative resistance and repairing. Indeed, yeast cells expressing an allele of SOD1 that cannot get into the nucleus are more sensitive to oxidative stress. SOD1 represents ~1% of total cellular protein (~10-50 μM), and less than 1% of total SOD1 enzyme may be needed to protect against various oxidative insults (127, 557). Thus, the recently-discovered novel functions of SOD1, besides O_2^- scavenging, help explain its high cellular abundance and perhaps its paradoxical roles.

Another antioxidant enzyme that exhibits non-redox functions is PRX1 (307). The enzyme forms oligomeric species that exhibit chaperonin activity upon oxidation of certain Cys to sulfinic acid. Such a mechanism enables the PRX family enzymes, which are better at scavenging low concentrations of peroxide, to be converted to chaperones to ensure proper protein folding under severe oxidative stress and high peroxide fluxes (409, 560, 705). Undoubtedly, the discovery of SOD1 as a novel transcriptional factor and PRX1 as a chaperone offers a new direction to elucidate the underlying mechanism for paradoxical roles of antioxidant enzymes. Additional non-redox functions of antioxidant enzymes include the role of Gpx4 as a structural protein in sperm mentioned above, or the cytokine-like properties of extracellular Trx1 or Trx80. It is possible, perhaps even likely, that additional non-redox related functions of classically

considered antioxidant enzymes will be discovered, which should help in interpreting the phenotypes seen upon their genetic deletion or overexpression.

C. Metabolic Context and Reaction Environment Affecting Roles of Antioxidant Enzymes

1. Physiological vs. pathophysiological conditions

Antioxidant enzymes may exert different impact in physiological compared to pathological processes. While overexpressing *Gpx1* induces type 2 diabetes-like phenotypes in mice without diabetic or obese-prone genetic background (445), the β cell-specific overexpression of *GPX1* in *ob/ob* mice actually, in stark contrast, reverses hyperglycemia and improves β-cell volume and granulation (244). Similarly, knockout of *Gpx1* impairs insulin synthesis and secretion in mice fed the normal diet (684), but enhances mouse resistance to a high-fat diet-induced insulin resistance (406). Therefore, roles of antioxidant enzymes under "normal" and "diseased" conditions should not be extrapolated or inferred from each other.

2. Temporal dependence of physiological effects

Short-term benefits of antioxidant enzyme alterations may lead to long-term harms, and *vice versa*. Indeed, overexpression of *Gpx1* alone or in combination with *SOD1* and *SOD3* protects mouse islets from oxidative injury and improves islet graft function (480). However, the long-term over-production of Gpx1 results in hyperinsulinemia, insulin resistance, and obesity (684). In contrast, knockout of *Sod1* offers extra resistance to APAP overdose and insulin sensitivity in

the young adult mice (379, 684), but leads to hepatocarcinogenesis in later life (167). When the hippocampal long-term potentiation (LTP), one of the major cellular mechanisms for learning and memory ability, is impaired in young (2-months old) *SOD1* overexpressing mice (201), the aged (2-years old) transgenic mice actually exhibit an enlarged LTP (316) and consequently a better performance in spatial memory (315) compared with the wild-type mice. These differences implied a strong age-dependence for the effects of the Sod1 deficiency and/or Sod1-derived peroxide based on the brain function.

3. Subcellular location-dependence effects

Sub-cellular localizations of particular antioxidant enzymes have profound effects on their roles, which need to be considered in interpretations of the mechanistic results. Overexpressing extracellular *GPX3* protects mice from the APAP toxicity, while the overexpression of intracellular *GPX1* sensitizes mice to the toxicity (458). Likewise, the β-cell specific overexpression of cytoplasmic *Cat* and the metallothionein gene, but not the mitochondrial *Sod2*, accelerates the cyclophosphamide-induced and spontaneously-developed diabetes in the non-obese diabetic male mice (390). Overexpression of *CAT* in mitochondria, but not in the peroxisomes or nuclei, extends the median and maximal lifespan of the mice by 20% (584). This indicates that the interactions between ROS/RNS and their metabolizing enzymes should not be extrapolated from different subcellular compartments.

Likewise, peroxide-derived from the yeast SOD1 protein that is proximal to a membrane bound casein kinase is required to regulate energy metabolism in response to oxygen and glucose

availability (557). The yeast SOD1 protein that is not targeted to the cytosol, or other SOD isoforms that are targeted to the cytosol like mitochondrial SOD2 or Candida Albicans SOD3 are unable to regulate casein kinase signaling. Similarly, a small fraction of cytosolic PRX1 and PRX2 is associated with lipid rafts proximal to NADPH oxidase enzymes. Only the lipid raft associated PRX1, but not cytosolic PRX1, is found to be phosphorylated at Tyr194 by a protein tyrosine kinase (PTK) of the Src family when cells are stimulated by growth factors (705). Phosphorylation of PRX1 near membranes has the effect of inactivating the enzyme, which promotes peroxide-mediated signals to propagate.

4. Cell-compartmentalization and tissue heterogeneity of transgenes

Different types of cell may not respond the same toward similar changes of antioxidant enzymes. While the cardiac-specific overexpression of *CAT*/*Cat* generates many benefits for prolonging lifespan and protecting against cardiac injuries (208, 317, 660, 712, 748, 749), the same specific overexpression in the endothelium shows little protection against myocardial or vascular ischemia/reperfusion injury (704). In either tissue-specific overexpression of a given antioxidant enzyme, such as catalase in cardiomyocytes and pancreatic β cells (319, 717), or ubiquitous overexpression of an antioxidant enzyme in mice, the intended overexpression may be very heterogeneous in different types of cells within an organ. Likewise, extents of a global overexpression of a transgene in mouse tissues may be restricted to certain organs, but not as widely spread as the corresponding endogenous mouse genes or the genes whose promoters are used in the transgene constructs (such as the human β-actin promoter) (266, 494, 509, 716, 727).

The heterogeneity of transgene expression cannot be appropriately assessed when homogenate of the entire organ is used for expression study. To circumvent this problem, large genomic fragments containing the genes of interest have been used to overexpress *SOD1* and *CAT* (103). However, whether the specificity of transgene expression can also be applied to each individual type of cells within each organ is still an open question.

Heterogeneity of transgene expression is also shown even in mice carrying an identical transgene. For example, the same 14.5-kb genomic fragment containing the entire human *SOD1* gene has been used independently by several laboratories to generate transgenic mice (87, 170, 231, 681). Although the *SOD1* overexpression protects heart against an *in vitro* model of ischemia/reperfusion in two independent lines of transgenic mice, the cell specificity of overexpression in these mice is quite different. The gene is overexpressed in both endothelial cells and cardiomyocytes in one line of transgenic mice (681), but exclusively in coronary vascular cells including endothelial cells and smooth muscle cells but not cardiomyocytes in another line (106). Therefore, immune-histochemical studies are needed to identify the types of cells expressing the transgene in the target organs, and more than one line of transgenic mice carrying the same transgene should be employed in physiological studies to ensure reproducibility of the experiments. The latter approach is even more critical when homozygous transgenic mice are used in the experiments, because the transgene occasionally disrupts the expression of a normal mouse gene at the site of integration by the mechanism referred to as "insertional mutagenesis," leading to a phenotype that is unrelated to the expression of the transgene (708). As a given antioxidant enzyme may not be sufficiently overexpressed in

targeted cells within an organ that are vulnerable to a particular oxidant-mediated injury, a negative result does not rule out the enzyme function in defense against the injury in those cells.

Furthermore, the tissue heterogeneity of the transgene expression may also affect human implications of findings from a particular animal model. Noteworthy, SOD3 in human aorta accounts for approximately 50% of the total SOD activity, whereas the enzyme in rat aorta represents only 5% of the total SOD activity due to a key amino acid difference that affects tissue binding in vessels (178, 619). As a result, the rat essentially lacks vascular SOD3 and, consequently, the observed protection of SOD3 against vascular diseases in rat models may be easily over-interpreted.

5. Genetic background of mouse models

Most transgenic and knockout mice are initially generated in a mixed genetic background (272, 515) and it will take 10 to 12 generations of backcrossing to become congenic. Because this crossing may take several years, most of the phenotypic studies, at least initially, are performed on mice in a mixed genetic background. Such studies should be interpreted with caution, since the genetic background of the mice may contribute to the observed phenotypes. For example, strain C57BL/6J (B6) mice are more susceptible to hyperoxia-induced lung injury than C3H/HeJ (C3) mice (287). Further studies using linkage analysis have shown that the B6 mice carry a nucleotide substitution in the promoter region of the *Nrf2* gene (116). This *Nrf2* polymorphism co-segregates with the susceptible phenotype of B6 mice to hyperoxia. Therefore, when *SOD2* transgenic mice in a B6 X C3 mixed genetic background are used for study of hyperoxia-induced

lung injury, tolerance to exposure is determined by both the origin of the *Nrf2* allele and expression of the *SOD2* transgene (266). Therefore, control experiments should be conducted for functional studies in mice with the identical genetic background, preferably littermates of the experimental mice.

6. Heterozygous mouse models and human relevance

To date, most of the phenotypic studies have been performed using homozygous knockout mice (if viable) in comparison with wild-type mice. However, studies using heterozygous mice with a partial deficiency may be more relevant to human diseases, since humans being fully devoid of a protein or enzyme are very rare. Although relatively limited studies have documented the phenotypes of such mice that express approximately a half of the normal amount of enzyme, some results are very intriguing. For example, under normal physiological conditions, the time to development of malignant tumors in *Prx1*$^{+/-}$ mice is between those of *Prx1*$^{-/-}$ and wild-type mice. In addition, hemolytic anemia was first observed in the *Prx1*$^{+/-}$ mice at 12 months of age compared with 9 months of the null mice, whereas wild-type mice are free of this disease (484). Therefore, a partial deficiency in Prx1 results in phenotypes being intermediate between complete deficiency and normal in mice. On the contrary, while *Sod1*$^{-/-}$ females show a declined fertility (489), the fertility of the *Sod1*$^{+/-}$ females are normal (264, 443). In response to trauma-induced dysfunction of mitochondrial respiration in brain, *Cat*$^{+/-}$ mice are as vulnerable as *Cat*$^{-/-}$ mice (268). In contrast, the phenotype of *Sod1*$^{+/-}$ mice resembles that of wild-type mice in response to acute paraquat toxicity (10 mg/kg body weight) (264). Therefore, the effect of a partial deficiency in antioxidant enzyme on untreated mice and oxidant-mediated disease models

varies from gene to gene. While future research on the physiological role of antioxidant enzymes should consider more partial knockdown or knockout models, current findings from the homozygous knockout mouse models need to be verified in human studies.

In summary, we have postulated a series of mechanisms in this chapter that should underpin the "paradoxical" outcomes of antioxidant enzyme deletion or overexpression. **FIGURE 13** highlights the central concept that effects of antioxidant enzyme modulation arise from a complex interplay between the activities of the antioxidant enzymes with their ROS/RNS substrates (and reductants such as GSH), as well as the importance of the environmental context in which they operate. It is our hope that this figure, along with our deliberations, prompt readers to recognize that the mechanisms by which nature masterfully orchestrates these seemingly paradoxical events are evolved to maintain redox homeostasis, and are critical towards understanding both health and disease.

V. HEALTH AND NUTRITION IMPLICATIONS

A. Antioxidant Enzymes in relation to Human Diseases

Catalase-deficient patients, classified as acatalasemic or hypocatalasemic, are found in many countries (495). These patients can have different alterations of the catalase gene including substitution (692, 693), deletion (262), and insertion (222, 225). Being apparently healthy, patients with acatalasemia may display increased risks of a progressive oral gangrene (166, 637, 638) and type 2 diabetes mellitus, especially in females (223). Still, the rather common occurrence of this autosomal recessive disease and its mild symptomatology suggests that catalase has mainly redundant activities with regards to human H_2O_2 removal pathways.

Two well-known neurodegenerative diseases: familial ALS and Down's syndrome, exemplify the significant health implications of antioxidant enzymes in a "paradoxical" manner. While dominantly-inherited mutations of *SOD1* gene account for 20% of the familial ALS cases (569), the pathophysiology seems to be due to a gain of mutant protein toxicity independent of the normal enzymatic activity of SOD1. Several lines of transgenic mice expressing *Sod1* mutants have indeed displayed pathological characteristics reminiscent of those seen in ALS (67). The Down's syndrome patients usually display a 50% increase in SOD activity (14, 131, 612). Although transgenic mouse models have been developed for this disease (23, 24, 524, 580), the underlying mechanisms of SOD1 toxicity in Down's syndrome are not understood (143, 366). In addition, mutations of *SOD2* in humans are associated with idiopathic cardiomyopathy, sporadic motor neuron defect and cancer (261). However, *Sod2*$^{-/-}$ mice generated by targeted disruption

1504 only partially recapitulate these human symptoms; rather, these mice display metabolic
1505 phenotypes including fatty liver and cardiomyopathy (388). Indeed, polymorphisms of SOD
1506 enzymes, catalase and GPX1 have been implicated in association with a number of human
1507 metabolic disorders such as diabetes and cardiovascular diseases, as well as cancers [reviewed in
1508 (130, 253)]
1509
1510 Altered nutritional selenium intake has long been implied in several diseases that are believed to
1511 be explained mainly by aberrant selenoprotein functions (554). The first examples of genetically
1512 and molecularly defined diseases of insufficient selenoprotein synthesis were found to relate to
1513 mutations in the selenium-binding protein-2 involved in translational insertion of Sec into
1514 selenoprotein and leading to complex diseases with hypothyroidism as a main symptom (25, 150,
1515 582). These patients are however only partially deficient in selenoproteins and considering that
1516 deletion of *Trsp* and some of the selenoproteins in mice is embryonically lethal (see above) it is
1517 unlikely that patients would survive with a total lack of selenoprotein synthesis, but additional
1518 polymorphisms and other aberrations in specific selenoproteins are likely to be discovered in
1519 relation to disease.
1520
1521 Among the genetic variants of GPX enzymes, *GPX1*Pro198Leu polymorphism is the most
1522 studied case. In a small randomized trial with 37 morbidly obese women (BMI > 45), this variant
1523 precluded the protection against DNA breaks by daily supplementation of one Brazil nut daily
1524 (290 µg Se/day) for 8 weeks (121). Furthermore, the same variation is associated with decreased
1525 selenium status in Alzheimer's patients (75), lowered GPX activity and increased breast cancer
1526 risk in Danish women (553), predisposition to colorectal adenomas or carcinomas based on the

Norwegian cohort NORCCAP (241), and increased prevalence of cardiovascular disease on the cohort of 184 Japanese with type-2 diabetes (238). These associations appear to be specific, as no such relationship was found between the same variant and the risk of basal cell carcinoma in the cohort of 317 Danish (677). Another *GPX1* variant (C198T) lowering the enzyme activity was identified in the South Indian population, which resulted in increased incidences of type 2 diabetes (C/T, 1.4-fold and T/T, 1.8-fold) (547).

Several single nucleotide polymorphisms on *GPX2* are found to affect Barrett's esophagus and esophageal adenocarcinoma (479). Polymorphisms of *GPX3* are known to suppress the expression of this gene and serve as a risk factor for thrombosis in cerebral veins (676). In the 3'-untranslated region of *GPX4*, the T/C variation at position 718 is linked to cancer susceptibility, with the T variant being associated with a lower risk for developing colorectal cancer (44). Likewise, polymorphisms in transcription factor binding sites of the *PRX6* promoter are associated with less favorable overall survival in breast cancer patients (589).

B. Novel Treatments of Antioxidant Enzyme-related Diseases

The impact of antioxidant enzymes in disease may possibly offer novel treatment options for redox-related diseases, provided that the molecular mechanisms are known and can be specifically targeted. RNA interference (RNAi) technologies may thus possibly be developed for treatment of ALS originated from single nucleotide polymorphisms in *SOD1* (472, 569). Mice expressing the missense mutant *SOD1*G93A-targeting shRNA were created to prove the principle of therapeutic potential (154, 544, 552, 566, 713).

Commonly used drugs for treating cardiovascular diseases, such as β-adrenocepter blocker carvedilo, ACEs, and statins (2, 738), bear SOD-like activities that suppress O_2^-. A GPX mimic may be used to improve GSIS impaired by the GPX1 deficiency (685). Overexpressing one or several antioxidant enzyme genes proves effective to prolong the survival of islet graft against the anticipated host oxidative attack (480). When large doses of chemotherapeutic agents or radiation induce severe oxidative stress, treating the patients with antioxidant enzyme mimics may help restore their redox homeostasis (359).

Meanwhile, there have been many studies aiming for virally mediated approaches to increase expression of antioxidant enzymes for protective effects in models of hypertension, restenosis, myocardial infarction, stroke, and other diseases [see (711) for a review]. For example, a gene delivery of antioxidant enzymes such as GPX1 and SOD1 was shown to attenuate oxidative stress in the brain of rodent models of HIV-associated neurocognitive disorders, Parkinson's disease, and diabetic complications (5, 6, 453, 564). Similarly, gene delivery for expression of SOD3 protects against the monocrotaline-induced hypertension in the lung of rats (312). However, the safety and efficacy of gene therapy are still a concern, and therapeutic potentials of viral delivery of antioxidant enzyme genes to specific tissues remains an open question.

In contrast, inhibiting a given antioxidant enzyme or specifically silencing its gene expression may help treat disorders related to a gain of enzymatic function. As stated above, there is a great potential of using RNAi to specifically suppress the toxic mutant of *Sod1* gene associated with ALS (154, 544, 552, 566, 713). In addition, microRNA (miRNA), regulators of mRNA stability

and translation, has been recently proposed as biomarkers for a variety of diseases (449). Although numerous miRNAs targeting antioxidant enzymes have been identified in cultured cells (243, 682), little is known about the reciprocal interactions between antioxidant enzymes and miRNA expression during pathogenesis.

Many types of drug-resistant cancer cells express high levels of antioxidant enzymes such as SOD, GPX, and PRX (64, 517). Pre-treating these cells with specific antioxidant enzyme antagonists or genetically silencing the target gene shall improve the anti-cancer drug efficacy (741). Similarly, pre-conditioning the antioxidant enzyme status may help minimize toxicities of commonly used drugs. Theoretically, hepatotoxicity of APAP may be attenuated if the patients are treated with TrxR1, SOD1 or GPX1 inhibitors, perhaps along with some GPX3 mimic, before administration. This notion is based on the fact that knockout of *Txnrd1*, *Sod1* or *Gpx1* renders mice resistant to the drug-induced protein nitration and toxicity (see above), but overexpression of *GPX3* protects against APAP hepatotoxicity (458).

Targeting of antioxidant enzymes may possibly also be applied to treat chronic diseases such as type 2 diabetes. Insulin resistance is the hallmark of the disease, and is inversely related to the oxidative inhibition of protein phosphatases in GSIS. When *Gpx1* overexpression diminishes of intracellular H_2O_2 and lifts the oxidative inhibition of protein phosphatases, causing insulin resistance (445), knockout of *Gpx1* and *Sod1* alone or together improved insulin sensitivity via the opposite mechanism (684). Therefore, the injected insulin could be more effective in lowering blood glucose, if GPX1 and SOD1 are temporarily down-regulated prior to insulin

administration. Clearly, such clinical protocols based upon findings from mouse experiments need to be studied and duly verified in human studies.

C. Antioxidant Nutrients

1. Perception and mixed outcomes of intervention trials

Antioxidant nutrients in foods often refer to vitamins C and E, carotenoids (particularly β-carotene), and certain trace elements such as selenium and zinc. Antioxidants are widely used to preserve food and beverages and to promote value-added product sales because of their perceived health benefits (182, 233). Indeed, many people believe that "antioxidant is good, more antioxidant is better" (234). However, more than 100 nutritional intervention trials conducted during the past 20 years (45-47) have shown disappointing outcomes of administering high or pharmacological doses of dietary antioxidant nutrients (46, 221, 233, 235, 537). In contrast, supra-nutrition of selenium and elevated serum selenium concentrations are associated with increased risk of type 2 diabetes (9, 119, 134, 363, 620). Although a re-analysis of the data from the large Se and Vitamin E Cancer Prevention (SELECT) trial (400) found the risk for increased prevalence of diabetes to be attributed to vitamin E supplementation (340), this controversial finding underscores the potential risk of over-dosing antioxidant nutrients. It also points out the need for a thorough understanding of selenium biology before large nutritional selenium trials are initiated or when their results are to be interpreted (249, 555).

2. Mode of actions by antioxidant nutrients

Antioxidant nutrients may contribute to overall antioxidant defence and interact with antioxidant enzymes in several ways. First, some of these nutrients like vitamins C and E directly scavenge ROS and RNS. Secondly, some of them serve as co-factors of antioxidant enzymes. Examples include selenium in the form of Sec in GPX, copper, zinc, and manganese in SOD, and iron in catalase. Dietary selenium deficiency is related to several diseases as is selenium toxicity (554). While iron and zinc deficiencies are quite common, deficiencies of manganese and copper are rare in humans. However, supplementing these nutrients to adequate subjects does not likely elevate their pertaining antioxidant enzyme activities because the activities are supposed to be saturated by those nutrients at the requirement levels. That fact may partially explain the lack of positive effects of long-term supplementation of antioxidant nutrients in adequate subjects. Thirdly, antioxidant nutrients regulate antioxidant enzyme gene expression and protein production. For example, dietary vitamin E seems to down-regulate certain selenoprotein gene expressions (282) and up-regulate SOD activity (506). However, optimal intakes of antioxidant nutrients for the balance between body antioxidant enzymes and ROS/RNS still remain elusive.

3. Effects of phytochemicals on antioxidant enzymes

Plant foods contain a diverse range of secondary metabolites of bioactive molecules (phytochemicals) (380). Although these low molecular weight compounds do not seem to decrease systemic oxidative damage, polyphenols, carotenoids and tocopherols may reach high concentrations in the gastrointestinal tract and exert effects there (236, 237). Moreover, some of these phytochemicals (e.g., polyphenols) can exert pro-oxidant effects.

As discussed above, NRF2 plays a key role in maintenance of cellular redox homeostasis under oxidative stress (49, 328, 464). Phytochemicals such as EGCG, curcumin and isothiocyanates may induce oxidative or covalent modification of thiols in cysteine residues of NRF2, resulting in dissociation of NRF2 from Keap1 and its translocation to the nucleus where NRF2 can regulate gene expression of more than 200 antioxidant and phase II detoxifying enzymes (74, 252, 645). Thus, using naturally-occurring phytochemicals to up-regulate NRF2 may be a strategy for preventing or treating chronic diseases due to insufficient NRF2 activities (49, 156, 214). However, many of these compounds also inhibit TrxR1 (89) and the resulting long-term impact on disease must be better understood before guidelines on prevention through supplementation with phytochemicals should be given.

NRF2 can exert different roles in effects of various phytochemicals on cancer prevention and development (29, 35, 145, 420, 460, 464, 488, 596). Many phytochemicals characterized as NRF2 inducers (751) can be either chemopreventive or oncogenic (618). This has promoted scientists to search for NRF2 inhibitors. For example, brusatol isolated from the seeds of *Brucea sumatrana*, may inhibit NRF2 and enhance the efficacy of chemotherapeutic drugs in a mouse xennograft model (558). A coffee alkaloid trigonelline inhibits NRF2 and renders pancreatic cancer cells susceptible to anti-cancer drug-induced apoptosis (16). Meanwhile, NRF2 can act as a protooncogene (596), suggested that protective effects of its activities might exist only in normal non-cancerous cells and tissues. Overexpression of *Nrf2* indeed causes chemoresistance (742), whereas NRF2 inhibitors can overcome it (488). The complex nature between interactions

of phytochemicals with NRF2 will require a genuinely-personalized use of such compounds for cancer prevention or treatment (49, 210).

VII. CLOSING REMARKS

Strict control of ROS and RNS at physiological levels is essential to avoid disease, neither too much nor too little being good. Recently, James Watson hypothesized that several chronic diseases such as diabetes, dementias, cardiovascular disease and certain types of cancers may all be linked to a failure to generate sufficient ROS (689). Another, complementary, theory is the Triage theory proposed by Bruce Ames underscoring that distortions in trace element usage by age underpins several diseases, which thereby also includes effects on several antioxidant enzymes (10, 444).

In this review, we have attempted to provide comprehensive analyses of the paradoxical functions of SOD, catalase, GPX, TrxR, Trx, Grx, and PRX enzymes, along with other selenoproteins and selenoprotein synthesis-related *Trsp*, in metabolism, health, and disease. While paradoxes associated with these enzymes signify an alternative requirement for the body to maintain metabolic balance, harmony, and homeostasis, our understanding of the underlying mechanisms is far from clear. We do not know how antioxidant enzymes respond to demands for a tight control of their substrates or products in specific tissues or whole body. We know very little of novel functions of antioxidant enzymes independent of redox modulation. Their pro-oxidant catalytic potential and mechanism are not fully recognized or understood. Likewise, little is revealed regarding feedback mechanism of individual antioxidant enzymes and global coordination of different enzyme families in coping with various ROS/RNS-initiated events.

Because most of our discussions are based on animal experiments, many of the findings need to be verified in humans. It is clear that a number of human diseases are associated with genetic defects or polymorphism in specific antioxidant enzymes. However, specific, sensitive, and reliable indicators of *in vivo* redox status are yet explored to identify the optimal range of the antioxidant enzyme activities and ROS/RNS tone required by individuals according to personal genetic makeup, life style, and living environment. While mechanisms outlined in this review for the paradoxical roles of antioxidant enzymes may lead to alternative therapy strategies, the challenge will be to identify surfeits and deficits among the complex array of given diseases to design the most effective treatment. Antioxidant nutrients and phytochemicals can affect production of ROS/RNS, functions of antioxidant enzymes, and the balance between the two. It remains to be found out when and how these supplements are beneficial, wasteful, or even detrimental. In conclusion, antioxidant enzymes and their ROS/RNS substrates represent a pair of natural complements. Basic mechanisms and clinical implications for their interdependence and counterbalance in physiology and health warrant intensive research.

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DISCLOSURES

None of the authors has any disclosure related to this review.

FIGURE LEGENDS

FIGURE 1. Protective mechanisms conferred by the *Sod1* knockout against APAP toxicity**.** The associated mechanisms include: 1) inhibition of protein nitration; 2) up-regulation of GR and TrxR activities; 3) down-regulation of microsomal P450 enzyme CYP2E1 activity, decreasing NAPQI production and the subsequent GSH depletion; and 4) inhibition of cell death signaling. Collectively, the *Sod1*$^{-/-}$ mice, as shown in the bottom graph, display a 100% survival rate over 70 h, while 75% of the wild-type mice die within 20 h after an intraperitoneal injection of 600 mg APAP/kg of body weight (from reference 379). APAP, acetaminophen; Bcl-X_L, B-cell lymphoma-extra large; CYP2E1, cytochrome P450 2E1; GR, glutathione reductase; GSH, glutathione; IκBε, inhibitor of NFκB, epsilon; JNK, c-jun N-terminal kinase; NAPQI, *N*-acetyl-*p*-benzoquinoneimine; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; p21, cyclin-dependent kinase interacting protein 1; PARP, poly(ADP-ribose) polymerase; and TrxR, thioredoxin reductase.

FIGURE 2. Protections conferred by knockouts and haploid insufficiencies of *Sod1*, *Sod2,* and *Sod3* against neural and cognitive damages induced by irradiation and brain trauma. Whereas mechanisms for the protections against the irradiation-induced damages await further investigation, the enhanced recovery from the brain trauma in the *Sod1*$^{-/-}$ mice is associated with attenuated H_2O_2 production and the subsequent NFκB activation. NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells.

FIGURE 3. Induction or potentiation of various neurological disorders by SOD1 overexpression. While mice overexpressing SOD1 develop signs of Down's syndrome and muscular dystrophy, the overexpression promotes or exacerbates pathogeneses of other listed disorders including amyotrophic lateral sclerosis that is induced by the overexpression of mutant SOD1. Respective biochemical and neurological mechanisms for the impacts of SOD1 overexpression, along with their change directions (up and down arrows), are schematically shown for each of the disorders. GSH, glutathione.

FIGURE 4. Aggravation of prolonged alcohol intake-induced hepatic toxicity by Sod2 overexpression. The main proposed mechanism is that Sod2 overexpression leads to accumulation of hepatic iron that partially replaces manganese in the active site of Sod2 to form Fe-Sod2. Consequently, Fe-Sod2 catalyzes production of hydroxyl radicals from H_2O_2 that cause lipid peroxidation and mitochondrial damage. Likely, the increased hepatic iron and H_2O_2 may also enhance production of hydroxyl radicals through Fenton reactions. In fact, the exacerbated effect of Sod2 overexpression can be prevented by iron chelators. Meanwhile, the anticipated diminished levels of superoxide anion may remove its beneficial role in limiting the propagation of lipid peroxidation and blunt the ethanol induction of iNOS and subsequent up-regulation of PGC-1, leading to mtDNA depletion. Fe-Sod2, iron-substituted superoxide dismutase 2; iNOS, inducible nitric oxide synthase; mtDNA, mitochondrial DNA; NO, nitric oxide; and PGC-1, peroxisome proliferator activated receptor gamma coactivator 1.

FIGURE 5. Divergent effects of catalase overexpression on susceptibility to diabetes. The β-cell specific overexpression of catalase in non-obese diabetic mice leads to early onset of

spontaneous diabetes in male mice, with accelerated occurrence of diabetes by inhibition of the Akt-Foxo1-Pdx1 survival pathway in islets following cyclophosphamide administration. In contrast, such overexpression prevents diabetogenic effects of streptozotocin in non-diabetic mice. In insulin-producing cells, finally, overexpression of catalase in mitochondria renders strong resistances to cytokine-induced cytotoxicity, whereas its overexpression in cytoplasm leads to weak protection. Akt, protein kinase B; Foxo1, forkhead box O1; and Pdx1, pancreatic and duodenal homeobox 1.

FIGURE 6. Comparative mechanisms for improved insulin sensitivity in *Sod1*$^{-/-}$ and *Gpx1*$^{-/-}$ mice. Knockout of *Sod1* elevates hepatic IRβ protein and muscle Akt phosphorylation after insulin stimulation, whereas knockout of *Gpx1* induces only the latter. Meanwhile, embryonic fibroblast cells from *Gpx1*$^{-/-}$ mice are manifested with enhanced Pten oxidation and PI3K/Akt activation after insulin addition. These changes are presumably (dashed arrows) upstream of Akt phosphorylation and result in improved insulin sensitivity. However, such impact of *Sod1* deletion has not been tested yet (question mark). In addition, *Gpx1*$^{-/-}$ mice fed a high fat diet display, following insulin challenge, enhanced glucose update through membrane docking of glucose transporter 4 upon AS160 phosphorylation on Thr^{642}. Akt, protein kinase B; AS160, the 160 kDa substrate of Akt; IRβ, β subunit of insulin receptor; PI3K, phosphatidylinositol-3-kinase; and Pten, phosphatase and tensin homolog.

FIGURE 7. Distinctive mechanisms between knockouts of *Sod1* and *Gpx1* in lowering pancreatic islet β cell mass and plasma insulin concentration via down-regulation of the key transcription factor Pdx1. While knockout of *Gpx1* decreases only the Pdx1 protein in islets,

knockout of *Sod1* exerts suppression at three levels of Pdx1 regulation: epigenetic, mRNA, and protein. The down regulation of Pdx1 mRNA and protein upon *Sod1* knockout coincides with decreased mRNA and protein levels of Foxa2, a transactivator of Pdx1, as well as attenuated binding of Foxa2, H_3 acetylation, and H_3K_4, trimethylation in the proximal region of the *Pdx1* promoter. Foxa2, forkhead box A2; H_3, histone-3; K_4, lysine-4; ORF, open reading frame; and Pdx1, pancreatic and duodenal homeobox 1.

FIGURE 8. Paradoxical roles of bovine GPX1, *Gpx1* knockout, and *GPX1* overexpression in coping with PN-mediated protein nitration and toxicity in cell-free system, primary hepatocytes, and mice. Different insult-mediated responses with net impacts of enzyme expression, and reported or proposed mechanisms are summarized in this figure. APAP, acetaminophen; DQ, diquat; GSH, glutathione; GST, glutathione S-transferase; PN, peroxynitrite; and SNAP, *S*-nitroso-*N*-acetyl-penicillamine.

FIGURE 9. Mechanisms of protection conferred by *Gpx1* knockout against kainic acid-induced neurotoxicity. Gpx1 deficiency may elevate H_2O_2 production that can oxidize thiols in the NMDA receptor-1 subunit, which deactivates the NMDA receptor and subsequently attenuates or blocks kainic acid-induced oxidative stress and injuries. This oxidative stress can also be protected by antioxidants. EUK-134, a synthetic SOD and catalase mimic; GSH, glutathione; and NMDA, *N*-methyl-*D*-aspartate.

FIGURE 10. Molecular and biochemical mechanisms for the type 2 diabetes-like phenotypes induced by Gpx1 overexpression in mice**.** The diminished H_2O_2 accumulation in pancreatic islets may enhance β cell mass and insulin synthesis and secretion via modulation of key signaling

genes and proteins at epigenetic, mRNA, and(or) protein levels. These effects lead to hyperinsulinemia and hyper-secretion of insulin. Meanwhile, Gpx1 overexpression also impairs insulin responsiveness in liver and muscle and disturbs lipogenesis, glycolysis, and gluconeogenesis in those tissues. The reported modes of action for those impacts include modulation of key gene expression, protein function, and enzyme activities. The outcomes from these effects in insulin-responsive tissues are reflected by insulin resistance, hyperglycemia, hyperlipidemia, and obesity. The overall phenotypes from GPx1 overexpression in either insulin producing or insulin responsive tissues, resemble type 2 diabetes. Representative key factors for each of the main pathways or phenotypes are listed in brackets. *Acc1*, acetyl-coenzyme A carboxylase 1; *Beta2*, neurogenic differentiation 1; *Cat*, catalase; *Cfos,* fbj murine osteosarcoma viral oncogene homolog; *Fasn*, fatty acid synthase; *Foxa2*, forkhead box a2; *Ins1*, Insulin 1; IRβ, the β-subunit of insulin receptor; *Kir6.2*, the KCNJ11 subunit of ATP-sensitive K^+ channel; *p53,* transformation related protein 53; *Pdx1*, pancreatic and duodenal homeobox 1; *Pparγ*, peroxisome proliferator-activated receptor γ; *Pregluc,* Preproglucagon; *Sur1*, sulfonylurea receptor; *Ucp2*, uncoupling protein 2; Akt, protein kinase B; GK, glucokinase; PEPCK, phosphoenolpyruvate carboxykinase; and $\Delta\psi$, mitochondrial membrane potential.

FIGURE 11. Intriguing roles of GPX isoenzymes in carcinogenesis. Overexpression of GPX1 in mice promotes DMBA/TPA-induced skin cancer, whereas adenoviral delivery of GPX1 to pancreatic tumor xenografts slows tumor growth in nude mice. This contrast illustrates tissue- or stage-specific roles of GPX1 in carcinogenesis. As depicted in the middle yellow box, Nrf2 and β-catenin that are associated with cancer, were shown to up-regulate GPX2 expression in cultured human cells. Knockout of *Gpx2* either stimulates or inhibits AOM-DSS-induced intestinal tumorigenesis at early or late stages, respectively. The relative stage-specific effects

1831 are indicated on the pink-colored triangle box, exemplifying the temporal dependence of the
1832 GPX enzyme in carcinogenesis. In addition, knockout of *Gpx3* in mice promotes AOM/DSS-
1833 induced colitis-associated carcinoma, but knockdown of the enzyme by shRNA inhibits leukemia
1834 stem cell renewal. This comparison illustrates the cancer type- and(or) model-specific role of the
1835 GPX enzyme in carcinogenesis. AOM/DSS, azoxymethane/dextran sodium sulfate; DMBA/TPA,
1836 7,12-dimethylbenz[a]anthracene/12-*O*-tetradecanoylphorbol-13-acetate; Nrf2, NF-E2-related
1837 factor 2; and shRNA, small hairpin RNA.
1838
1839 **FIGURE 12.** Paradoxical effects of TrxR1 overexpression, genetic loss or drug inhibition. Three
1840 separate states of TrxR1 can have either beneficial (top) or detrimental (bottom) effects in
1841 mammals, as summarized in this figure. Native TrxR1 promotes cell viability through diverse
1842 functions of the Trx system, including support of Prxs, Msrs, and RNR as well as modulation of
1843 redox signaling pathways. However, cancer cells may also rely on TrxR1 activity to proliferate
1844 and the enzyme can thus promote cancer progress as well as metastases. Genetic targeting of
1845 TrxR1 is embryonically lethal, while conditional knockout in differentiated tissues such as
1846 hepatocytes result in Nrf2 activation and an increased resistance to oxidative challenges. When
1847 targeted by inhibitors, the TrxR1 enzyme can also gain an NADPH oxidase activity in addition to
1848 loss of its native Trx1 reducing capacity, which further activates Nrf2 but can also trigger cancer
1849 cell death, toxic side effects in normal tissues and increased dependence upon GSH for survival.
1850 APAP, acetaminophen; Msrs, methionine sulfoxide reductases; NAPQI, *N*-acetyl-*p*-
1851 benzoquinoneimine; Nrf2, NF-E2-related factor 2; Prxs, peroxiredoxins; RNR, ribonucleotide
1852 reductase; Trx, thioredoxin; and TrxR1, thioredoxin reductase-1.
1853

FIGURE 13. Scheme of mechanisms of paradoxical outcomes upon modulation of antioxidant enzyme status. In general, either detrimental or beneficial impacts of antioxidant enzyme overexpression or knockout arise from complex interplays among redox active enzymes, their substrates, and the enzymatic reaction environment. Different ROS/RNS species and antioxidant enzymes discussed in this review are illustrated, along with their representative features (in black text) of chemistry, free radical biology, and metabolism that may all trigger paradoxical outcomes. Specifically, the dose, reactivity, and localization of ROS/RNS substrates can lead to differential impacts on oxidative stress and redox signaling pathways. Impacts and mechanisms of reductant substrates (e.g., GSH) in the "paradox" are shown in the context of antioxidant enzyme catalysis. The antioxidant enzymes can themselves contribute to the paradoxical outcomes by acting as pro-oxidants, either by catalyzing production of certain ROS/RNS or over-consuming reducing equivalents, depleting ROS/RNS required for signaling, acting on non-canonical substrates, exhibiting non-redox functions, inducing compensatory responses, or having overlapping functions with other enzymes. The environmental context, i.e. physiological (non-stress) or pathophysiological (metabolic stress, oxidative injury, nutrient deficiency, or drug toxicity) state, the experimental model, as well as spatial or time constraints, will determine the final phenotype. Thus, apparent paradoxes in antioxidant enzyme overexpression and knockout studies should be viewed in a well-defined physiological context as a combined interactions of all of these factors. Cat, catalase, Gpx, glutathione peroxidase; Grx, glutaredoxin; MsR, methionine sulfoxide reductase; Prx, peroxiredoxin; ROS, reactive oxygen species; RNS, reactive nitrogen species; Sepp1, selenoprotein P; Trsp, selenocysteine tRNA gene; Sod, superoxide dismutase; Trx, thioredoxin; and TrxR, thioredoxin reductase.

Table 1 Commonly-used mouse models for antioxidant enzyme overexpressing and knockout

Enzyme/ Protein	Overexpression			Knockout		
	Nature of the transgene	Altered site	Reference	Disrupted gene	Altered site	Reference
Cu,Zn-superoxide dismutase (SOD1)	The entire human *SOD1* gene contained in a 14.5-kb genomic fragment	Brain, liver, heart, and lung	(87, 170, 681)	*Sod1*	Global	(264, 285, 443, 556)
	The entire human *SOD1* gene contained in a 64-kb genomic fragment	Brain, heart, kidney, liver, lung, skeletal muscle, and spleen	(103)			
Mn-superoxide dismutase (SOD2)	A human SOD2 expression construct driven by 3.7 kb of the promoter and 5' flanking sequences of the human surfactant protein C gene	Lung	(703)	*Sod2*	Global and tissue-specific	(291, 370, 392, 563, 621)
	A human SOD2 expression construct controlled by 3 kb of 5' flanking sequence plus 5' untranslated region and intron 1 of the human β-actin gene.	Brain, eye, heart, lung, skeletal muscle, spleen, and tongue	(266, 494, 727)			
	The entire mouse *Sod2* gene contained in a 14-kb genomic fragment	Brain, heart, kidney, liver, and lung	(542)			
	A human SOD2 expression construct driven by 570 bp of 5' flanking sequence and promoter of the rat insulin I gene	Pancreatic β-cells	(99)			
	A human SOD2 expression vector controlled by a 2-kb promoter and 10-kb enhancer of the mouse Tie2 (a vascular endothelial-specific receptor tyrosine kinase) gene	Endothelial cells	(226)			
	A human SOD2 expression construct controlled by a 5.5-kb mouse genomic fragment containing the last intron of the β-myosin heavy chain (MHC) gene to exon 3 of the α-MHC gene	Heart	(597)			
Extracellular superoxide dismutase (SOD3)	A human SOD3 expression construct controlled by 3 kb of 5' flanking sequence plus 5' untranslated region and intron 1 of the human β-actin gene.	Brain, heart, and skeletal muscle	(509)	*Sod3*	Global	(81)
	A human SOD3 expression construct driven by 3.7 kb of the promoter and 5' flanking sequences of the human surfactant protein C gene	Lung	(189)			
Catalase	A rat CAT expression construct	Heart	(319)	*Cat*	Global	(268)

(CAT)	downstream of a 5.5-kb mouse genomic fragment containing the last intron of the β-myosin heavy chain (MHC) gene to exon 3 of the α-MHC gene					
	A human CAT expression construct controlled by a 2.8-kb mouse α-fetoprotein enhancer element I fused to 1.8 kb of the human β-globin promoter	Liver and gut	(486)			
	A rat CAT expression construct driven by 570 bp of 5' flanking sequence and promoter of the rat insulin I gene	Pancreatic β-cells	(717)			
	Three human CAT expression constructs (peroxisome-, nucleus-, and mitochondria-targeted) driven by the cytomegalovirus enhancer element and a chicken β-actin promoter	Brain, heart, kidney, skeletal muscle, and spleen	(584, 585)			
	The entire human *CAT* gene contained in a 80-kb genomic fragment	Brain, heart, kidney, liver, lung, skeletal muscle, and spleen	(103)			
Glutathione peroxidase 1 (GPX1)	A human GPX1 expression construct controlled by the promoter, exon 1, and intron 1 of the mouse hydroxymethylglutaryl-coenzyme A reductase gene	Brain, heart, kidney, and liver	(457)	*Gpx1*	Global	(141, 172, 265)
	A human GPX1 expression construct controlled by rat insulin II promoter	Pancreas	(244)			
	The entire mouse *Gpx1* gene contained in a 5.3-kb genomic fragment	Brain, eye, heart, lung, skeletal muscle, spleen, pancreas, and tongue	(109, 716, 733)			
Gastrointestinal glutathione peroxidase (GPX2)				*Gpx2*	Global	(176, 186)
Glutathione peroxidase 3 (GPX3)	A human GPX3 expression construct controlled by the promoter, exon 1, and intron 1 of the mouse hydroxymethylglutaryl-coenzyme A reductase gene	Kidney, brain, and lung	(457)	*Gpx3*	Global	(311)
Phospholipid hydroperoxide glutathione	A rat mitochondria-targeted Gpx4 expression driven by the human cytomegalovirus	Mitochondria of the heart	(136)	*Gpx4*	Global, neurons, spermatoc	(52, 292, 293, 581,

peroxidase (GPX4)	immediate early enhancer and chicken β-actin promoter				ytes, cytosol, mitochon dria, nucleus	590, 725)
	A 50-kb genomic clone containing the entire human *GPX4* gene	Cerebral cortex, heart, skeletal muscle, kidney, liver and testes	(548)			
Peroxiredoxin I (PRX1)				*Prx1*	Global	(338, 484)
Peroxiredoxin II (PRX2)				*Prx2*	Global	(375)
Peroxiredoxin III (PRX3)	A rat Prx3 expression construct driven by the cytomegalovirus promoter	Mitochondria of the heart	(440)	*Prx3*	Global	(389)
Peroxiredoxin IV (PRX4)	A human PRX4 expression construct driven by the enhancer and promoter of the human cytomegalovirus immediate early gene	Brain, heart, kidney, pancreas, and testis	(155)	*Prx4*	Global	(300)
Peroxiredoxin VI (PRX6)	A 16.8-kb genomic fragment containing the entire mouse *Prx6* gene isolated from 129SvJ mice	Intestine, kidney, liver, lung, and epithelial cells of all tissues	(531)	*Prx6*	Global	(461, 683)
Thioredoxin 1 (TXN1 or TRX1)	A human TXN1 expression construct controlled by the human insulin promoter and exons and introns of the rabbit β globin gene	Pancreas	(281)	*Txn1/Trx1*	Global	(438)
	A human TXN1 expression construct driven by 3 kb of 5' flanking sequence plus 5' untranslated region and intron 1 of the human β-actin gene.	Brain, heart, kidney, liver, lung, , skeletal muscle, spleen, and tongue	(3, 661)			
	The structure of the human TXN1 transgene is not described.	Brain, heart, kidney, liver, lung, and skin	(636)			
Thioredoxin 2 (TXN2 or TRX2)	The structure of the human TXN2 transgene is not described	Heart	(696)	*Txn2/Trx2*	Global	(490)
Thioredoxin reductase 1 (TrxR1)				*Txnrd1*	Global, neurons, liver, heart	(79, 305)
Thioredoxin reductase 2 (TrxR2)				*Txnrd2*	Global, neurons, heart	(123, 330)
Selenoprotein P (SEPP1)				*Sepp1*	Global	(259, 583)
Glutaredoxin 1 (Grx1or Glrx1			(478)	*Glrx1*	global	(4, 267, 270)
Glutaredoxin 2 (Grx2 or Glrx2)				*Grx2*	global	(426, 427, 710)

Selenocysteine tRNA (Trsp)	A 1.93-kb genomic DNA containing the entire mouse *Trsp* gene with mutations of T→C at position 9 and A→G at position 37	Brain, kidney, liver, and testes	(471)	*Trsp*	Global and 12 tissue-specific knockout	(54, 356)
Methionine sulfoxide reductase A (MSRA)	Three mouse MsrA expression constructs (wild-type, mitochondria-targeted, and cytosolic) controlled by the cytomegalovirus enhancer and chicken β-actin promoter.	Liver, skin fibroblasts	(752)	*MsrA*	Global	(468)
Methionine sulfoxide reductase B (MSRB)				*MsrB1*	Global	(190)

Table 2. Physiological impacts or pathological responses of superoxide dismutase-1 overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Overexpression	Brain and neurological system	Ameliorate brain injuries induced by cold or subarachnoid hemorrhage (in rats) via suppressing MMP-2 and MMP-9 or activation of Akt/GSK-3β.	(93, 169, 313, 467)
		Protect vulnerable motor neurons after spinal cord injury via attenuating the mitochondrial apoptosis pathway (in rats)	(624, 737)
		Attenuate kainic acid-induced neurotoxicity in hippocampus and striatum	(260, 586)
		Alleviate phenotypes of Parkinson's disease by elevating dopamine and suppressing lipid peroxidation, protein nitration	(294, 536, 647)
	Vascular system	Protect against post-angioplasty response and neointimal formation (adenovirus-mediated gene overexpression in rabbit tissue)	(358)
	Lung	Alleviate pulmonary oxygen toxicity and prolong survival	(695)
		Resistant to allergen-induced changes in airway control	(369)
	Ischemic injury	Protect against cerebral ischemic injury (in mice/rats)	(100, 345, 476)
		Render the heart resistant to myocardial ischemia/reperfusion injuries and protect against ischemia-reperfusion injury, inflammatory responses and apoptosis in cardiac graft	(106, 642, 681)
	Diabetes	Protect against diabetogenesis and diabetic nephropathy by suppressing glomerular nitrotyrosine formation and matrix protein synthesis	(129, 148, 354)
		Abolish maternal diabetes-induced embryopathy, block maternal hyperglycemia-induced activation of PKCα/βII and PKCδ and lipid peroxidation	(232, 391, 679)
	Cancer	Reduce mutation frequency in cerebellum	(357)
Knockout	Brain and neurological system	Undergo marked hypertrophy and altered responses to acetylcholine in cerebral arterioles	(36, 152)
		Vulnerable to axonal injury such as axotomy and ischemic insults, and altered calcium homeostasis in spinal motor neurons	(556, 611)
		Increase susceptibility to MPTP-induced phenotypes of Parkinson's disease	(746)
		Drive phenotypes of Alzheimer's disease such as Aβ oligomerization and memory loss	(477)
		Display a modified distribution of fiber types and fiber loss, muscle atrophy and weakness	(348, 349, 367)
	Vascular system	Lead to dysfunctions in endothelial-dependent vasodilation and myogenic tone, and accelerated vascular aging in endothelial progenitor cells	(125, 151, 152, 228, 674)
	Lung	Increase NFAT activity and NFATc3 nuclear localization resulted from elevated superoxide/H_2O_2 ratio, induce spontaneous pulmonary hypertension in pulmonary arteries	(546)
	Liver	Alter hepatic gluconeogenesis, glycolysis, and lipogenesis, and induce lipid accumulation by impaired lipoprotein secretion	(662, 680)
		Enhance sensitivity to acute paraquat and alcohol-induced liver toxicity	(264, 329)
	Ischemic injury	Impair neovascularization induced by hindlimb ischemia	(228)
		Aggravate ischemia/reperfusion-induced myocardial, hippocampal and renal injuries (in mice/rats)	(100, 719, 731)
	Diabetes	Accelerate diabetic renal injury	(147)
		Impair islet function, pancreas integrity, and body glucose homeostasis by elevating islet superoxide, upregulating p53 phosphorylation and downregulating Foxa2/Pdx1 pathway	(684)
		Increase susceptibility to ocular disorders such as cataract and progressive retinal cell loss	(247, 295, 500-503)
	Immune response	Increase susceptibility to the experimental autoimmune encephalomyelitis	(436)
		cause anemia and autoantibody production by elevating oxidative stress in erythrocytes	(299)

	Kidney	Exhibit an increase in phosphorylation of iron regulatory protein 1(IRP1) in kidney, leading to increased binding to iron-responsive elements (IREs)	(734)
		Susceptible to hydronephrosis- and salt-induced hypertension and histopathological changes	(82)
	Cancer	Show reduced lifespan and increased carcinogenesis in late life with oxidative damage-accelerated spontaneous mutations in liver and kidney	(73, 167)
	Others	Lead to embryonic two-cell arrest or cell death, and impaired sperm motility and fertilizing ability	(207, 334, 658)
		Induce age-related dysfunction of the lacrimal gland, potentiate hearing loss, cochlear pathology, bone stiffness/strength, skin morphology and wound healing	(301, 346, 446, 614)

Table 3. Physiological impacts and pathological responses of superoxide dismutase-2 overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Overexpression	Brain and neurological system	Attenuate MPTP-induced phenotypes of Parkinson's disease	(342)
		Attenuate phenotypes of Alzheimer's disease by reducing hippocampal oxidative stress, modulating Aβ deposition and composition, and slowing memory deficit	(164, 435)
	Lung	Prevent hypoxia-mediated decrease in Na,K-ATPase and alveolar fluid reabsorption (adenovirus-mediated gene overexpression in rats)	(401)
	Liver	Protect against liver mitochondrial DNA depletion and respiratory complex dysfunction after an alcohol binge	(433)
	Diabetes	Ameliorate high-fat diet-induced insulin resistance in rat skeletal muscle (electroporation delivery of expression vector to rat muscle)	(50)
		Prevent retinal VEGF expression and retinopathy in diabetic mice	(226, 351)
		Normalize contractility in diabetic cardiomyocytes with improved mitochondrial respiration	(597)
	Ischemic injury	Reduce ischemia/reperfusion-induced vascular endothelial cell death and protects against blood-brain barrier damage	(425)
		Reduces neuronal vulnerability to forebrain ischemia (injection of astrocyte-specific expression vector to rat brain)	(718)
		Protect against myocardial ischemia/reperfusion-induced injury	(107)
	Aging	Preserve age-associated loss of mitochondrial DNA mass and function of ATP generation	(308, 374)
Knockout	Brain and neurological system	Show selective cerebral vascular dysfunction and accelerated disorganization of distal nerve axons following nerve injury	(179, 459)
		Exacerbate phenotypes of Alzheimer disease, Parkinson's disease and ALS	(11, 12, 385)
		Exhibit neurodegenerative phenotypes including frequent, spontaneous motor seizures	(188, 394)
	Liver	Exaggerate APAP-induced liver toxicity, mitochondrial dysfunction and DNA fragmentation	(200, 545)
	Diabetes	Result in severe central nervous system degeneration and subsequent gait deformities, seizures, and perinatal lethality in type 2 diabetes	(497)
	Heart	Induce cardiac mitochondrial dysfunction, severe lipid peroxidation and spontaneous apoptosis in myocardium, and maladaptive cardiac hypertrophy	(563, 621, 671)
	Vascular system	Lead to increased vascular oxidative stress with aging and endothelial dysfunction in large and mesenteric arteries	(65, 138, 498, 720)
		Up-regulate transferrin receptor and down-regulate mitochondrial biogenesis and metabolism in erythroid cells	(434)
	Kidney	Develop hypertension, mild renal damage and interstitial inflammation in aged mice	(516, 567)
	Cancer	Elevate incidence of neoplasms in aging *Sod2*$^{+/-}$*Gpx1*$^{-/-}$ mice	(750)
	Ischemic injury	Increased susceptibility to cerebral ischemia/reperfusion with activation of MMPs, inflammation, blood-brain barrier breakdown and high brain hemorrhage rates	(425)
	Aging	Lead to reduced lifespan and premature onset of aging-related phenotypes	(653, 675)
	Others	Reduce contractile muscle function and aerobic exercise capacity during aging	(335, 417, 418)
		Ocular pathology including progressive retinal thinning	(578)
		A significant decrease in the respiratory capability and an increased rate of induction of the permeability transition in mitochondria	(697)

Table 4. Physiological impacts and pathological responses of superoxide dismutase-3 overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Overexpression	Brain and neurological system	Protect against brain injury induced by subarachnoid hemorrhage, hyperoxia or cold	(447, 510, 739)
		Improve behavioral outcome from closed head injury	(532)
		Protect against aging-induced memory and cognitive impairments	(381, 382)
	Vascular system	Reduce cuff-induced arterial neointimal formation (adenovirus-mediated gene expression in rat tissue)	(511)
	Lung	Attenuate pulmonary oxygen toxicity by increasing cGMP activity and reducing of NFκB activation (aerosolized delivery of expression plasmid to neonatal rabbits) or by attenuating neutrophil inflammatory responses	(7, 189)
		Preserve pulmonary angiogenesis by retaining VEGF, VEGFR1, VEGFR2 and PECAM-1	(528)
		Inhibit the development of hypoxia- or fibrosis-induced pulmonary hypertension and vascular remodeling, and ameliorate established pulmonary hypertension	(8, 492, 672)
		Attenuate radiation-, endotoxin (adenovirus-mediated expression)-, influenza- or air pollutant-induced lung injury	(212, 248, 318, 539, 625)
	Immune response	Attenuate inflammatory arthritis by suppressing the production of proinflammatory cytokines and MMPs	(736)
	Ischemic injury	Increased resistance to heart or cerebral ischemia/reperfusion injuries	(97, 98, 493, 598, 600)
		Improve recovery from surgical hind-limb ischemia (adenovirus-mediated gene expression)	(579)
	Cancer	Inhibit chemical-induced skin carcinogenesis	(332)
Knockout	Heart	Exacerbate pressure overload-induced left ventricular hypertrophy and dysfunction	(414)
	Lung	Increased susceptibility to hyperoxia	(81)
	Kidney	Exhibit renal histopathological abnormalities, hypertension, endothelial dysfunction, and reduced eNOS and Akt activity	(326)
	Immune response	Increased susceptibility to the collagen-induced arthritis	(570)
	Ischemic injury	Worsen the outcome from cerebral or skeletal muscle ischemia/reperfusion	(519, 599)

Table 5. Physiological impacts and pathological responses of catalase overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Overexpression	Heart	Preserve the responsiveness of the heart to adrenergic stimulation	(704)
		Attenuate cardiac contractile dysfunction induced by paraquat, anthrax, LPS, acute ethanol, or hypoxia-reoxygenation, through alleviating events such as JNK-mediated ER stress	(105, 208, 317, 660, 748, 749)
		Prevent progressive myocardial remodeling, including myocyte hypertrophy, apoptosis, and interstitial fibrosis due to overexpression of Gαq	(538)
		Protect against acute and chronic doxorubicin-induced cardiotoxicity	(319, 320)
	Vascular system	Prevent pathological mechanical changes underlying abdominal aortic aneurysm formation	(424)
		Reduce pressure response to norepinephrine or angiotensin II by eliminating H_2O_2 in arterial wall	(723)
		Inhibit toxin-accelerated atherosclerosis in the hypercholesterolemic *ApoE*$^{-/-}$ mice	(722, 724)
	Kidney	Inhibit the development of hypertension and renal injury in the angiotensinogen transgenic mice	(219)
	Ischemic injury	Render the heart resistant to myocardial ischemia/reperfusion injury	(386)
	Diabetes	Increase resistance to STZ-induced β-cell injury and diabetic effect including an attenuation of renal angiotensinogen and proapoptotic gene expression	(58, 99, 717)
		Cardiac overexpression rescues insulin resistance-induced cardiac contractile dysfunction	(160)
		Prevent hypertension and progression of nephropathy by attenuating renal oxidative stress and normalizing ACE-2 expression in type 1 diabetes	(603)
	Aging	Mitochondrial overexpression prolongs lifespan with delayed age-associated pathologies including cardiac aging and cataract, decreases malignant nonhematopoietic tumor burden in old mice and enhances hippocampus-dependent memory with a reduction of anxiety	(137, 504, 584, 654)
		Cardiac overexpression prolongs lifespan and attenuates aging-induced cardiomyocyte contractile dysfunction and protein carbonyl formation	(712)
Knockout	Brain	Show a decreased efficiency in brain mitochondrial respiration following cortical oxidative injury	(268)
	Kidney	Render remnant kidneys increased susceptibility to oxidant tissue injury and progressive renal fibrosis after nephrectomy	(344)
	Diabetes	Accelerate STZ-induced diabetic renal injury with increased expression of glomerular TGF-β and collagen α1	(289)

Table 6. Physiological impacts and pathological responses of glutathione peroxidase-1 overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Overexpression	Brain and neurological system	Protect against 6-OHDA-induced neurotoxicity, trauma-induced mitochondrial dysfunction, cerebral/ischemia reperfusion and hypoxic ischemic injury	(42, 564, 595, 691, 716)
	Heart	Resistant to ischemia/reperfusion injury and doxorubicin-induced cardiomyopathy and mitochondrial dysfunction	(714, 733)
	Liver	Protect against paraquat-induced hepatotoxicity	(111)
		Enhanced susceptibility to acetaminophen toxicity	(458)
	Diabetes and metabolic disorders	Contribute to hyperinsulinemia in association with the transcription factor PDX1 and mitochondrial uncoupling protein 2	(686)
		β-cell-specific overexpression of human GPX1 rescues β-cell dysfunction and reverses diabetes in 20-week-old *db/db* obesity mice	(229, 244)
		Gpx1 overexpression mice are obese	(445)
Knockout	Brain and neurological system	Exacerbate neuronal toxicity induced by Aβ, malonate, 3-nitropropionic acid, and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine	(128, 341)
		Resistant to kainic acid-induced seizure and neurodegeneration	(309)
	Heart	Susceptible to ischemia/reperfusion injury in male mice	(397, 732)
		Mutate the benign coxsackievirus B3 and induce myocarditis	(37)
		Susceptible to doxorubicin- and angiotensin II-induced aortic and cardiac dysfunction and oxidative stress	(15, 206)
		Accelerated progression of atherosclerosis under a diabetic $ApoE^{-/-}$ background on a high fat diet (21% fat, 0.15% cholesterol)	(384, 652)
	Liver and kidney	Enhanced susceptibility to diquat- and paraquat-induced oxidative stress	(110, 112, 114, 199)
		Resistance to peroxynitrite-mediated hepatic toxicity	(199)
		Accelerated diabetic nephropathy in the $ApoE^{-/-}$ model of diabetes	(115, 640, 641)
	Lung	Enhanced oxidation and lung inflammation after cigarette smoking or influenza A infection	(165, 726)
	Aging	No apparent phenotype except for cataract	(142, 265)
	Carcinogenesis	$Gpx1^{-/-}Gpx2^{-/-}$ mice have spontaneous polyps formation and inflammation-induced tumor formation in the gastrointestinal tract	(174)

Table 7. Physiological impacts and pathological responses of glutathione peroxidases 2-4 overexpression and knockout in mice

	Organ/ Condition	Phenotype	Reference
Over expressi	Heart	Mitochondrial Gpx4 (rat) attenuates ischemia/reperfusion cardiac injury	(136)
	Liver	Human GPX4 protects against diquat-induced apoptosis and oxidative stress	(393, 548)
		Increased expression of human GPX3 in the plasma by 50% renders the mice resistant to APAP-induced hepatotoxicity and a thermosensitive phenotype	(457, 458)
Knockout	Brain and neurological system	*Gpx3*$^{-/-}$: display cerebral infarctions	(311)
		Gpx4$^{+/-}$: accumulate oxidized lipids and senile plagues	(101)
		Mitochondrial *Gpx4*$^{-/-}$: apoptosis-induced cerebral degeneration in the hindbrain	(52)
		Gpx4$^{-/-}$ (neuron-specific): neurodegeneration, corrected by α-tocopherol	(590)
		Gpx4$^{-/-}$ (endothelium-specific): vitamin E-dependent suppression of angiogenesis in aortic explants	(707)
		Nuclear *Gpx4*$^{-/-}$: retardation in atrium formation	(52)
	Carcinogenesis	*Gpx2*$^{-/-}$: severe inflammation and colon carcinoma induced by AOM/DSS; prone to UV-induced squamous cell tumor	(352, 678)
		Gpx3$^{-/-}$: prone to colitis-associated carcinoma and increased inflammation in the colon	(32)
	Aging	*Gpx4*$^{+/-}$: a slight lifespan extension (1029 vs 963 days)	(549)
	Others	*Gpx4*$^{-/-}$ (photoreceptor-specific): degeneration and apoptotic death of photoreceptor cells	(663)
		Gpx4$^{-/-}$ (spermatocytes-specific): infertility; reduced forward mobility and mitochondrial membrane potential in the spermatozoa	(292)
		Mitochondrial Gpx4$^{-/-}$: infertility; impaired sperm quality and severe structural abnormalities in the midpiece of spermatozoa	(581)

Table 8. Physiological impacts and pathological responses of thioredoxin reductases knockout in mice

***Gene*/Isoenzyme/ Deletion**	**Organ (Genetic model)**	**Phenotype**	**Reference**
***Txnrd1* (TrxR1, TR1)**			
Knockout	Ubiquitous deletion	Early embryonic lethality	(51, 305)
	Heart (*MLC2a*-driven knockout)	No apparent phenotype and no effect on infarct size after cardiac ischemic/reperfusion injury	(280, 305)
	Nervous system (*Nestin*-driven knockout)	Smaller mice with ataxia and tremor, cerebellar hypoplasia, ectopically located and abnormal Purkinje cells, disorganized Bergmann glial network.	(617)
	Neurons (*Tα1*-driven knockout)	No apparent phenotype	(617)
	Liver (*Alb*-driven knockout)	Strong upregulation of *Nrf2*-targeted genes, no apparent growth defect in non-treated liver but metabolic switch with accumulation of glycogen or lipids and significantly increased resistance to acetaminophen challenge	(302, 520, 535, 634)
	B-cell lymphoma (*mb-1*-driven knockout in *λ-myc* lymphoma model)	No effect on tumor growth except induction of an absolute requirement of the tumors on GSH upon *Txnrd1* knockout	(430)
	Hepatocellular carcinoma (induced by diethylnitrosamine in *Alb*-driven knockout)	Strongly increased propensity for hepatocarcinogenesis	(79)
***Txnrd2* (TrxR2, TR2)**			
Knockout	Ubiquitous	Early embryonic lethality with impaired heart development, anemia, lack of hematopoiesis and liver apoptosis	(123)
	Nervous system (*Nestin*-driven knockout)	No apparent phenotype	(617)
	Heart (*MLC2a*-driven knockout)	Congestive heart failure with signs of dilated cardiomyopathy, death within hours after birth	(123)
	Heart (tamoxifen-induced *α-myosin* heavy chain-driven knockout)	Impaired cardiac function at rest and more severe injuries after cardiac ischemia/reperfusion, with NAC treatment normalizing the observed phenotypes	(280)
	B- and T-cells (CD4- and CD19-driven knockouts)	No apparent phenotype	(209)

Table 9. Physiological impacts and pathological responses of overexpression, knockout, and transgene of other selenium-dependent proteins and *Trsp* in mice

	Models	Phenotypes	Reference
***Trsp* transgene**	Lacking the STAF-binding site	Tissue-specific decrease in selenoprotein expression (brain, muscle > lung, spleen > liver, kidney; no change in heart and testes)	(77)
	Mutation at position 37 (A →G)	Tissue- and selenoprotein-specific changes in selenoprotein expression (↓GPX1, ↑TrxR1, liver > testes); pyogranulomatous inflammation in various tissues	(470, 471)
		mTOR-dependent increase of muscle growth after exercise	(279)
		Severe neurological defects and mortality in these mice on a Se-deficient or high Se (2.25 ppm) diet	(324)
		Increased susceptibility to azoxymethane-, diethylnitrosamine-, and *C3(1)*-induced carcinogenesis in intestines, liver, and prostate, respectively; no changes on *TGFα*-induced hepatocarcinogenesis	(159, 296, 324, 470)
		Increased X-ray-induced micronuclei formation in the erythrocytes	(27)
		Defective immune responses after the lungs were targeted with viral infection of influenza	(601)
***Trsp* conditional knockout**	Hematopoietic cells (*Mx1*-driven)	Prone to hemolytic anemia and defective oxidative homeostasis	(327)
	Macrophage (*LysM*-driven)	Increased oxidative stress, induction of Nrf2 expression, defective immune response and expression of fibrosis-associated genes	(635)
	T cells (*Lck*-driven)	Defective T cell maturation and antibody responses upon T cell receptor stimulation	(608)
	Neuron (*Tα1*-driven)	Defects in interneuron development and cerebellar hypoplasia, increased striatal neuronal loss with movement disorder, and seizure due to spontaneous epileptiform activity	(588, 701, 702)
	Endothelial cells (*TieTeK2*-driven)	Embryonic lethal. 14.5 days embryos are smaller with underdeveloped vascular system, limbs, tail and head	(609)
	Osteo-chondroprogenitor (*Col2a1*-driven)	Growth retardation and delayed skeletal ossification reminiscent of Kashin-Beck disease	(161)
	Skin (*K14*-driven)	Small body size, alopecia, flaky and fragile skin, and early regression of hair follicles	(592)
	Heart and skeletal muscle (*MCK*-driven)	Die 12 days after birth with acute myocardial failure	(609)
	Mammary gland (*MMTV*- or *Wap*-driven)	Increased mammary carcinogenesis	(288)
	Liver (*Alb*-driven)	Premature death at 1-3 months of age, no changes in brain Se levels, and increased apolipoprotein E and cholesterol levels in plasma	(76, 587, 591)
	Kidney (*NPHS2*-driven)	No effect on streptozotocin-induced diabetes	(48)
	Prostate epithelium (*ARR2PB*-driven)	Early onset of intraepithelial neoplasia	(415)
***Trsp* knockout**	Mutant G37 transgene under global $Trsp^{-/-}$	Reduced fertility in males and litter size in females	(78)
	A34 or G37 transgene in liver-specific $Trsp^{-/-}$	Reversal of the elevated levels of apolipoprotein E and cholesterol in the plasma	(591)
	$Sepp1^{-/-}$	Neuronal degeneration, loss of 55% Se in the brain, degenerated and dystrophic axons in the cervical spinal cords and the brainstem	(259, 533, 583)
	$Sepp1^{\Delta 240\text{-}361}$	Decreased Se levels in the brain	(258)
	$MsrB1^{-/-}$	Oxidation of protein, lipid, and GSH in liver and kidney; actin fragmentation	(190, 371)

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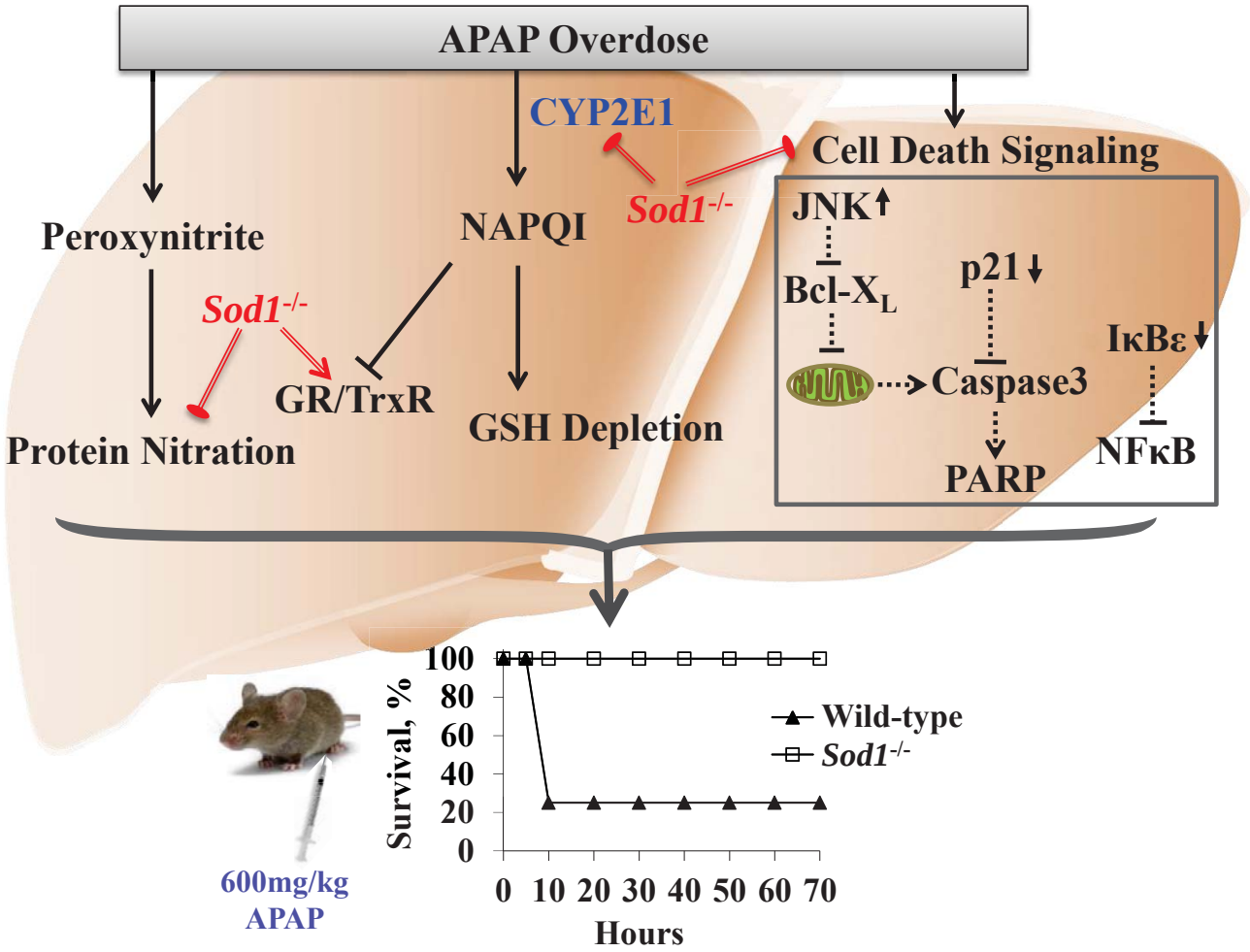
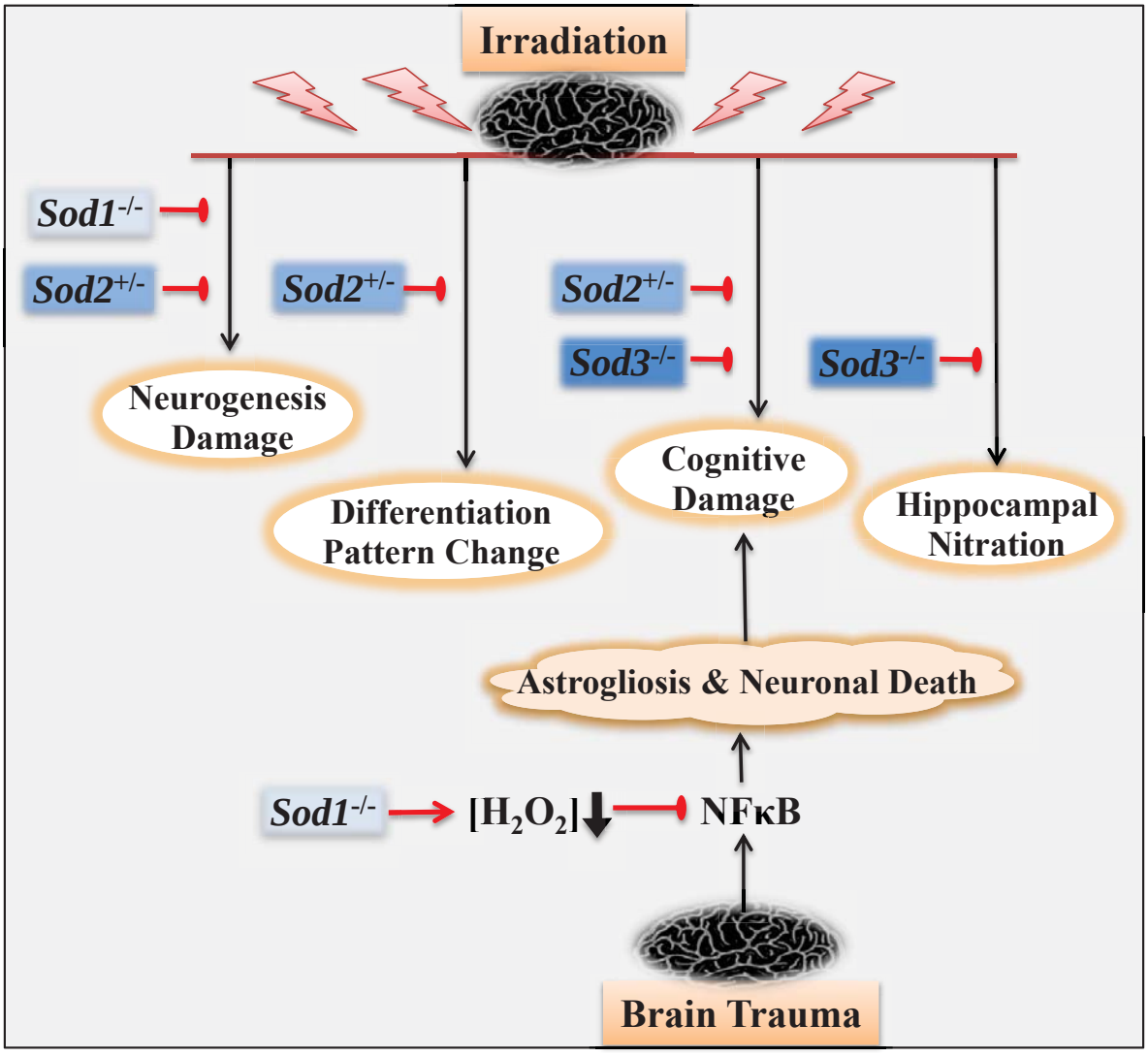
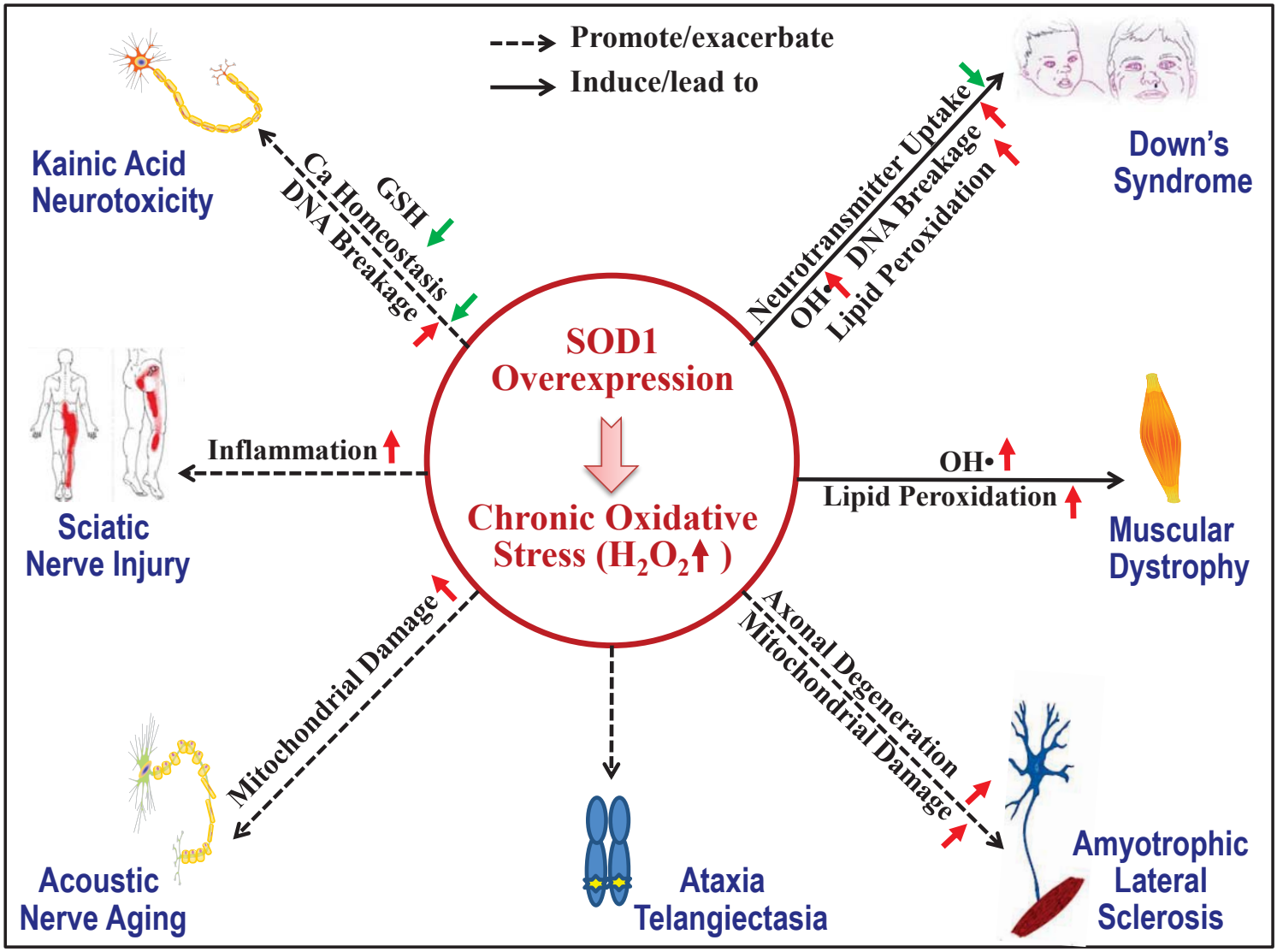

APAP Overdose
CYP2E1
Cell Death Signaling
Peroxynitrite
NAPQI
Sod1-/-
JNK
Bcl-XL
p21
IκBε
Sod1-/-
GR/TrxR
Caspase3
Protein Nitration
GSH Depletion
PARP
NFκB
600mg/kg
APAP
Survival, %
100
80
60
40
20
0
0 10 20 30 40 50 60 70
Hours
Wild-type
Sod1-/-

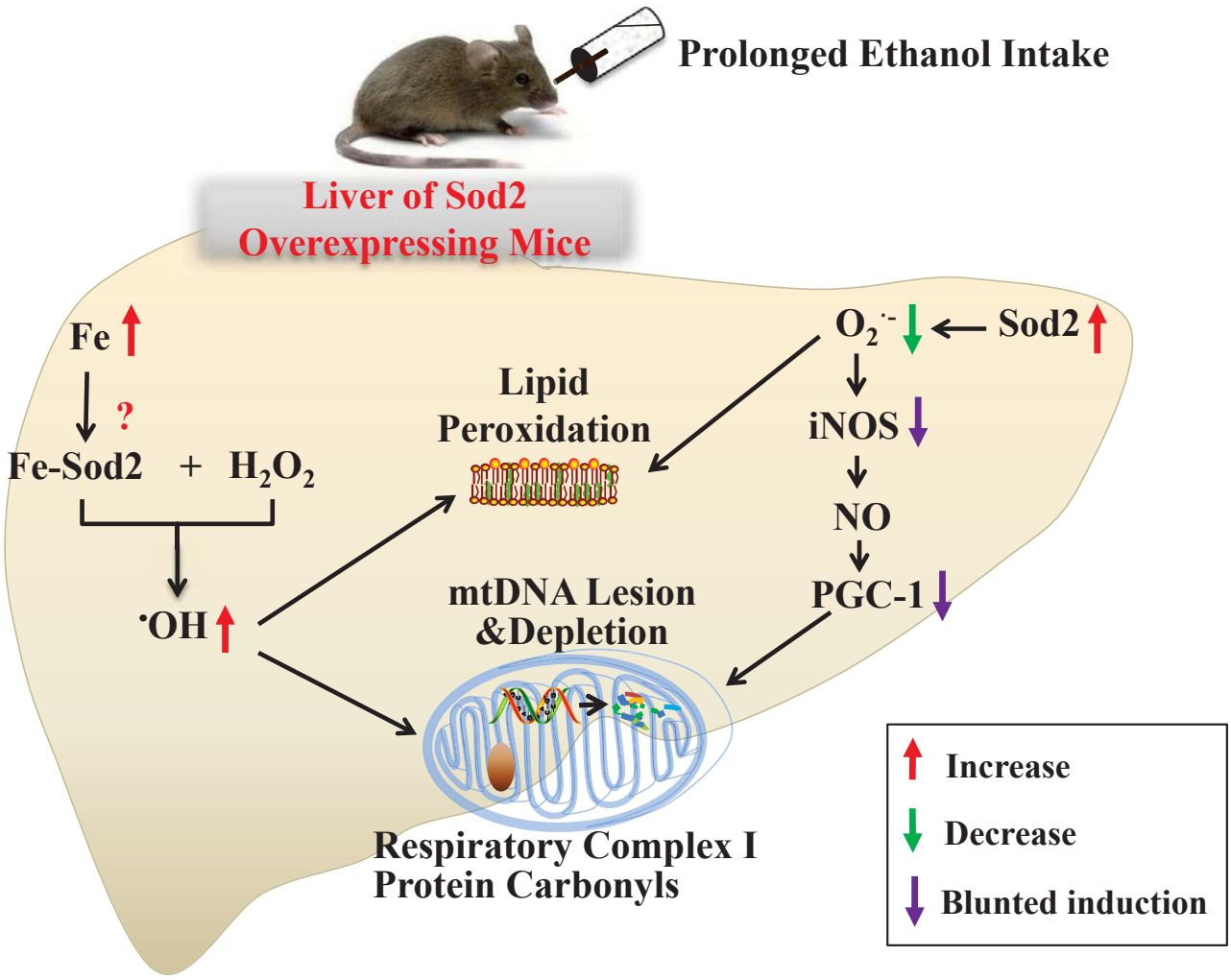
F1


Irradiation
Sod1-/-
Sod2+/-
Sod2+/-
Sod2+/-
Sod3-/-
Sod3-/-
Neurogenesis Damage
Differentiation Pattern Change
Cognitive Damage
Hippocampal Nitration
Astrogliosis & Neuronal Death
Sod1-/-
[H2O2]
NFκB
Brain Trauma

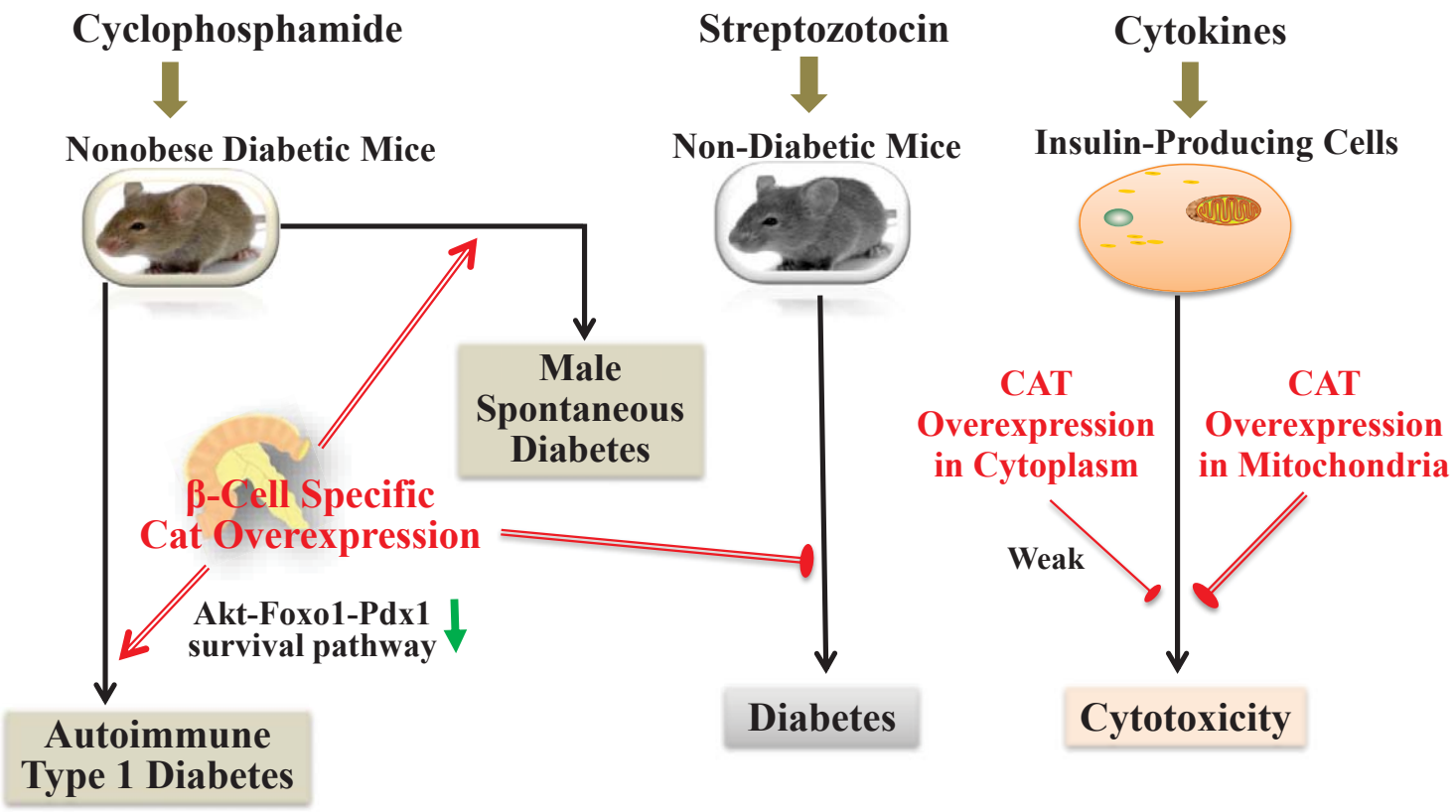
F2


Promote/exacerbate
Induce/lead to
Kainic Acid Neurotoxicity
Ca Homeostasis
DNA Breakage
GSH
Down's Syndrome
Neurotransmitter Uptake
OH•
DNA Breakage
Lipid Peroxidation
SOD1 Overexpression
Chronic Oxidative Stress (H_2O_2)
Inflammation
Sciatic Nerve Injury
OH•
Lipid Peroxidation
Muscular Dystrophy
Mitochondrial Damage
Acoustic Nerve Aging
Ataxia Telangiectasia
Axonal Degeneration
Mitochondrial Damage
Amyotrophic Lateral Sclerosis

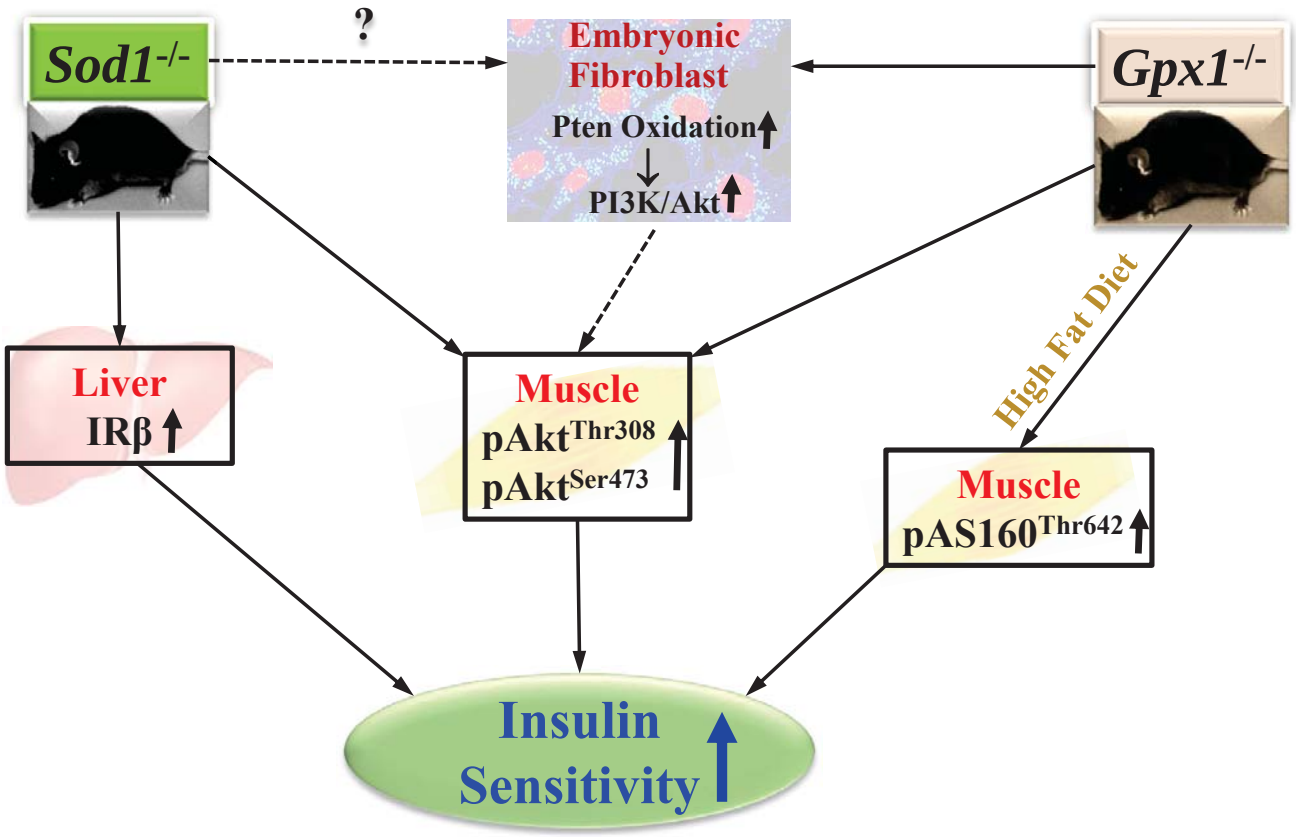
F3


Prolonged Ethanol Intake
Liver of Sod2 Overexpressing Mice
Fe
?
Fe-Sod2 + H_2O_2
·OH
Lipid Peroxidation
$O_2^{\cdot-}$
Sod2
iNOS
NO
PGC-1
mtDNA Lesion &Depletion
Respiratory Complex I Protein Carbonyls
Increase
Decrease
Blunted induction

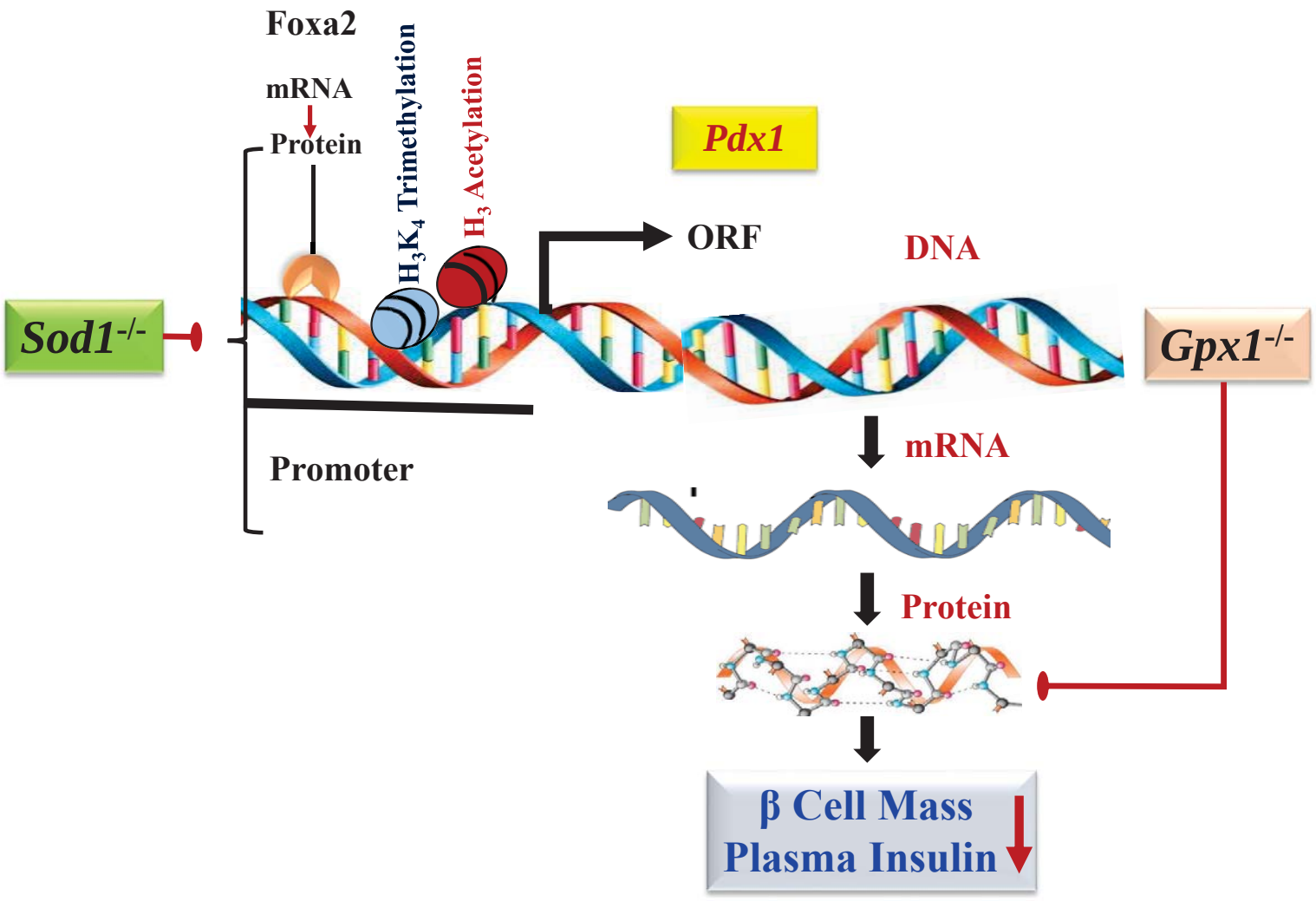
F4


Cyclophosphamide
Nonobese Diabetic Mice
Streptozotocin
Non-Diabetic Mice
Cytokines
Insulin-Producing Cells
Male Spontaneous Diabetes
β-Cell Specific Cat Overexpression
Akt-Foxo1-Pdx1 survival pathway
CAT Overexpression in Cytoplasm
CAT Overexpression in Mitochondria
Weak
Autoimmune Type 1 Diabetes
Diabetes
Cytotoxicity

F5


Sod1-/-
?
Embryonic Fibroblast
Pten Oxidation
PI3K/Akt
Gpx1-/-
Liver
IRβ
Muscle
pAktThr308
pAktSer473
High Fat Diet
Muscle
pAS160Thr642
Insulin Sensitivity

F6

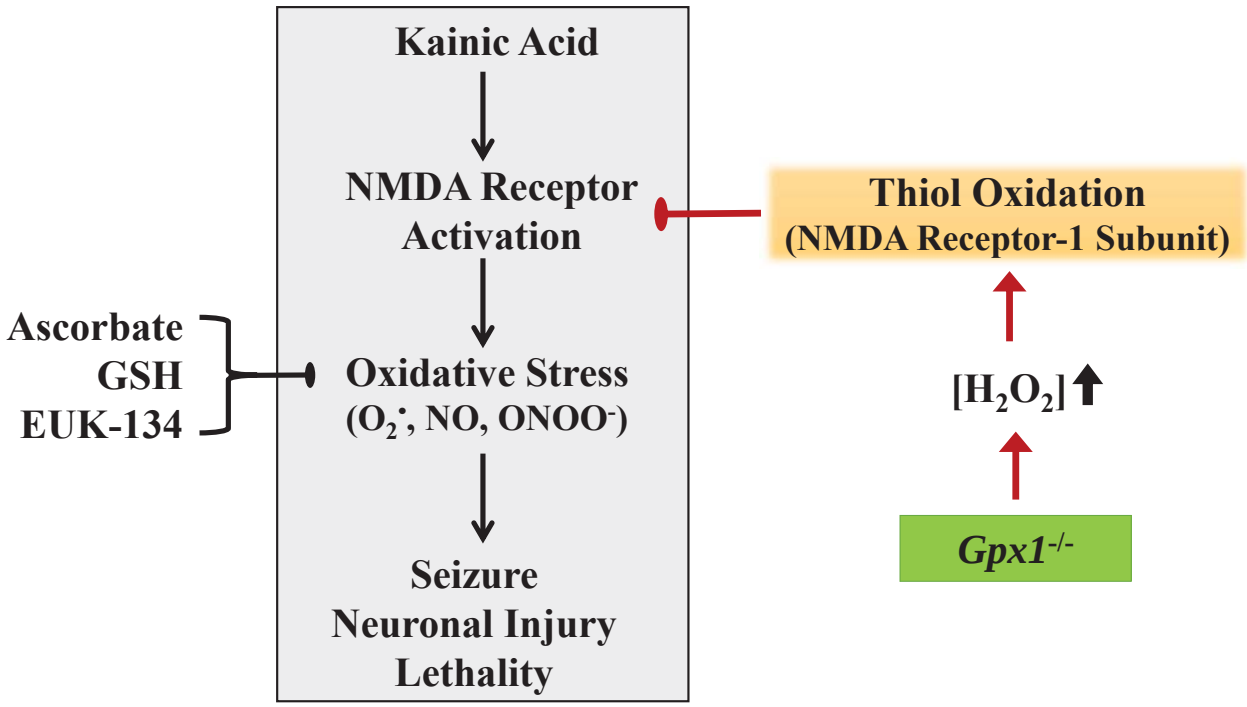

Foxa2
mRNA
Protein
H_3K_4 Trimethylation
H_3 Acetylation
Pdx1
ORF
DNA
Sod1-/-
Gpx1-/-
Promoter
mRNA
Protein
β Cell Mass
Plasma Insulin

F7

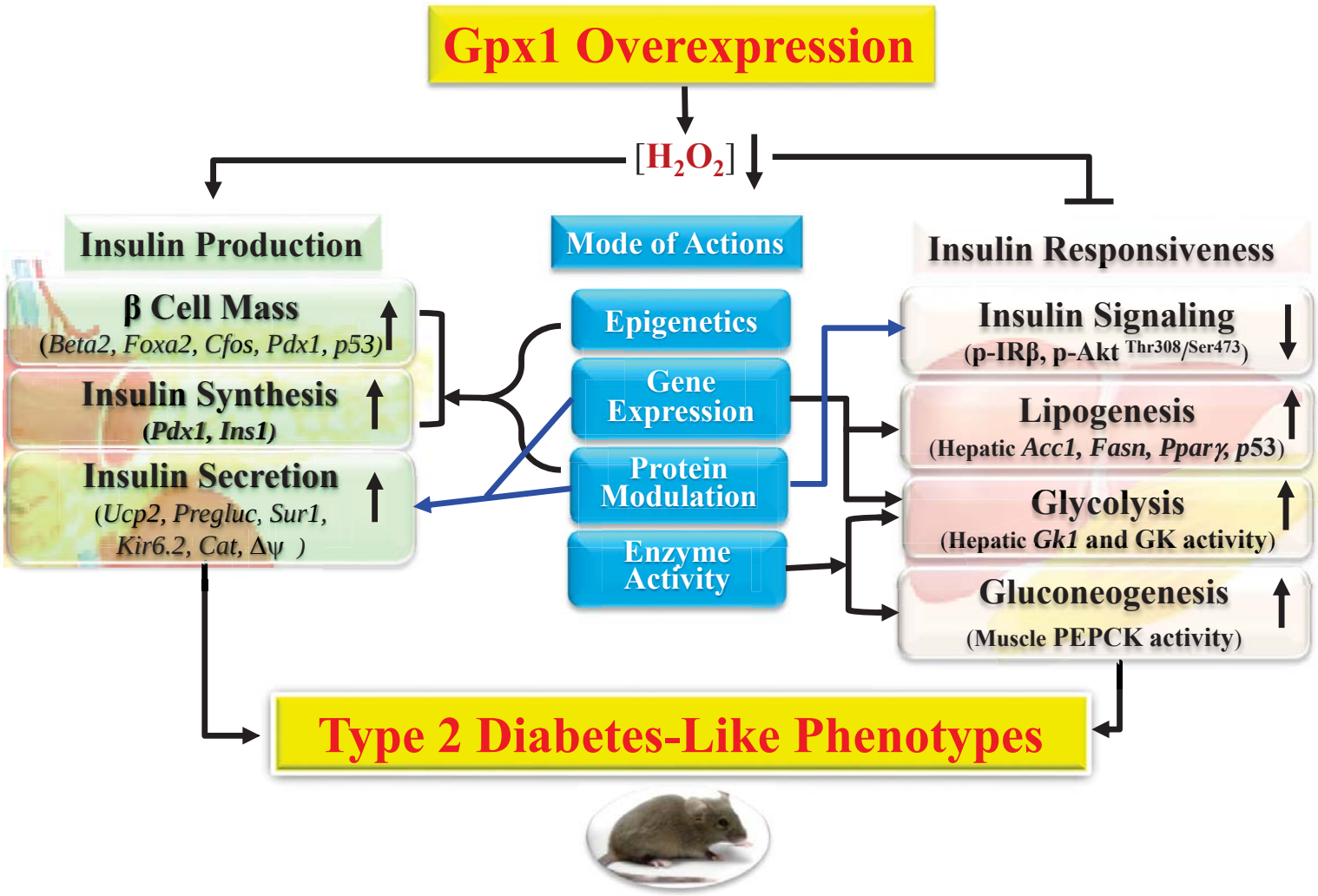
Condition	Insult	Impact	Mechanism
Cell-Free System	Bovine GPX1 ⊣ PN → Protein Nitration	Protection	As PN Reductase
Primary Hepatocytes	PN → DNA Fragmentation, Caspase-3 Activation, Protein Nitration, Cell Death; *Gpx1*$^{-/-}$ ⊣ SNAP +DQ → Protein Nitration	Protection Protection	GSH Sparing Sod2 Induction?
Mice	*Gpx1*$^{-/-}$ ⊣ APAP → Death, Protein Nitration, Liver Injury, Cell Death Signaling; GPX1 Overexpression ⊣ APAP → Death, Hepatotoxicity	Partial Protection Potentiation	GST Elevation? GSH Depletion

⊣ Inhibition → Promotion

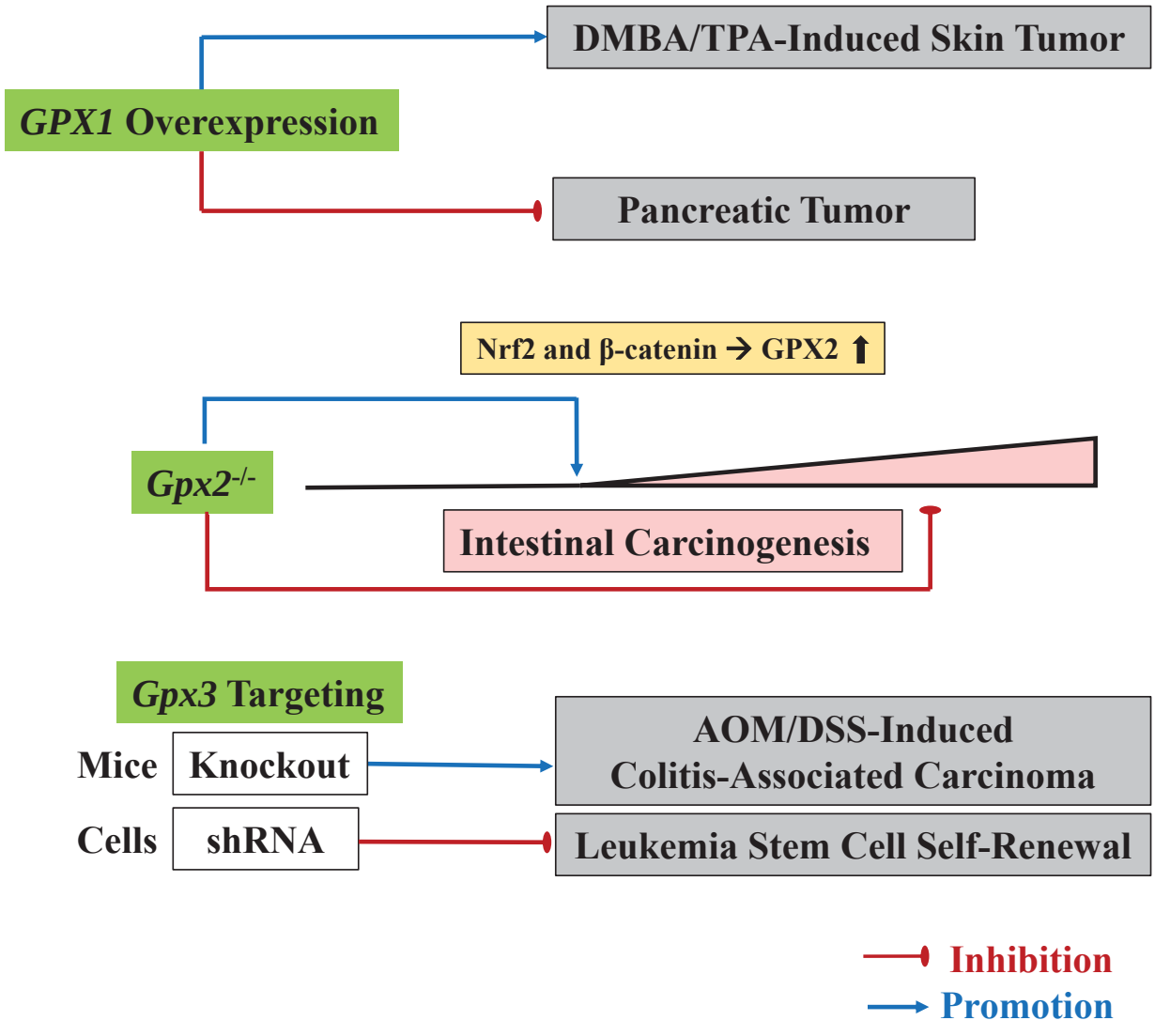
F8


Kainic Acid
NMDA Receptor Activation
Oxidative Stress ($O_2^{\bullet}$, NO, $ONOO^-$)
Seizure
Neuronal Injury
Lethality
Ascorbate
GSH
EUK-134
Thiol Oxidation
(NMDA Receptor-1 Subunit)
$[H_2O_2]$
Gpx1$^{-/-}$

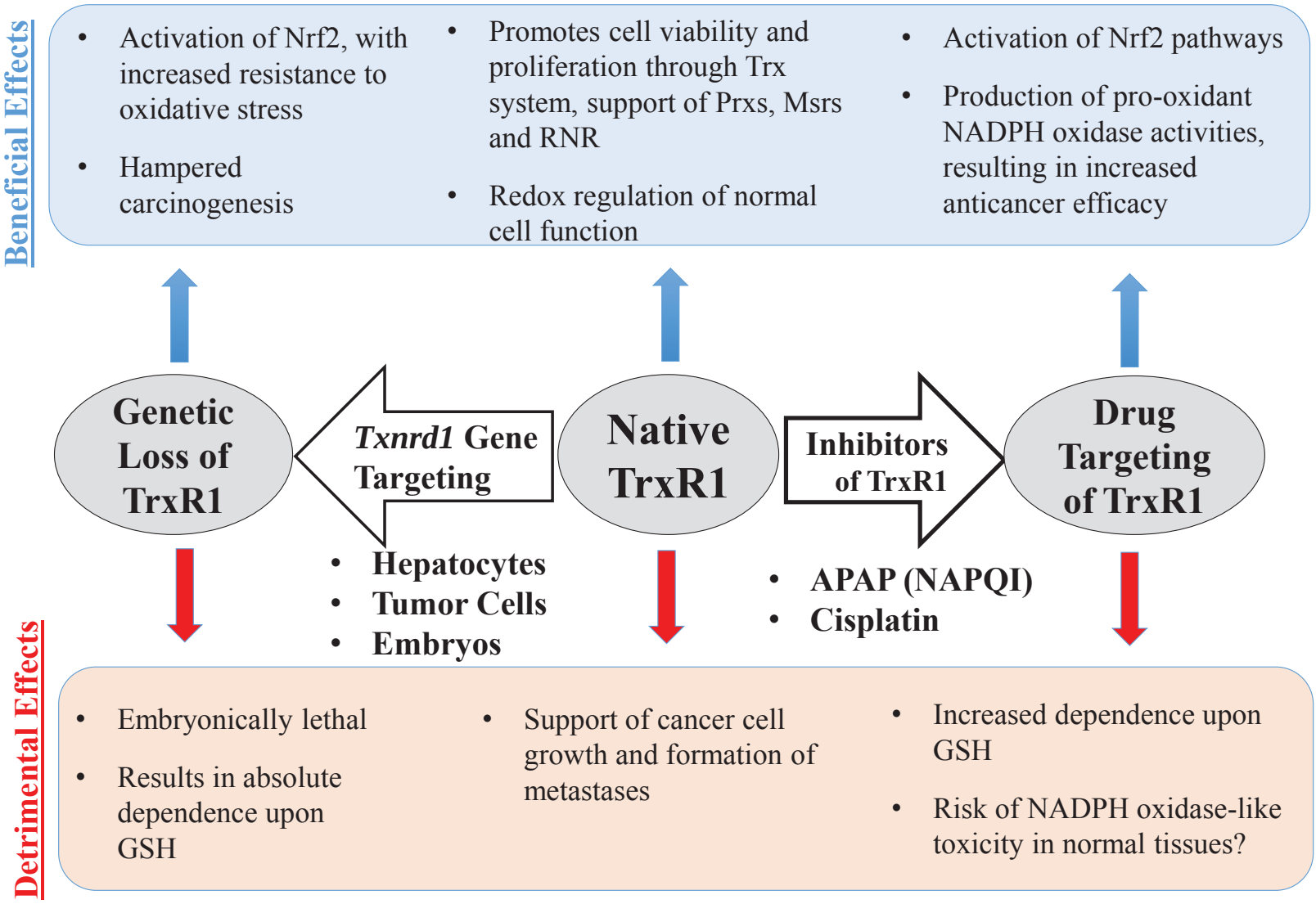
F9

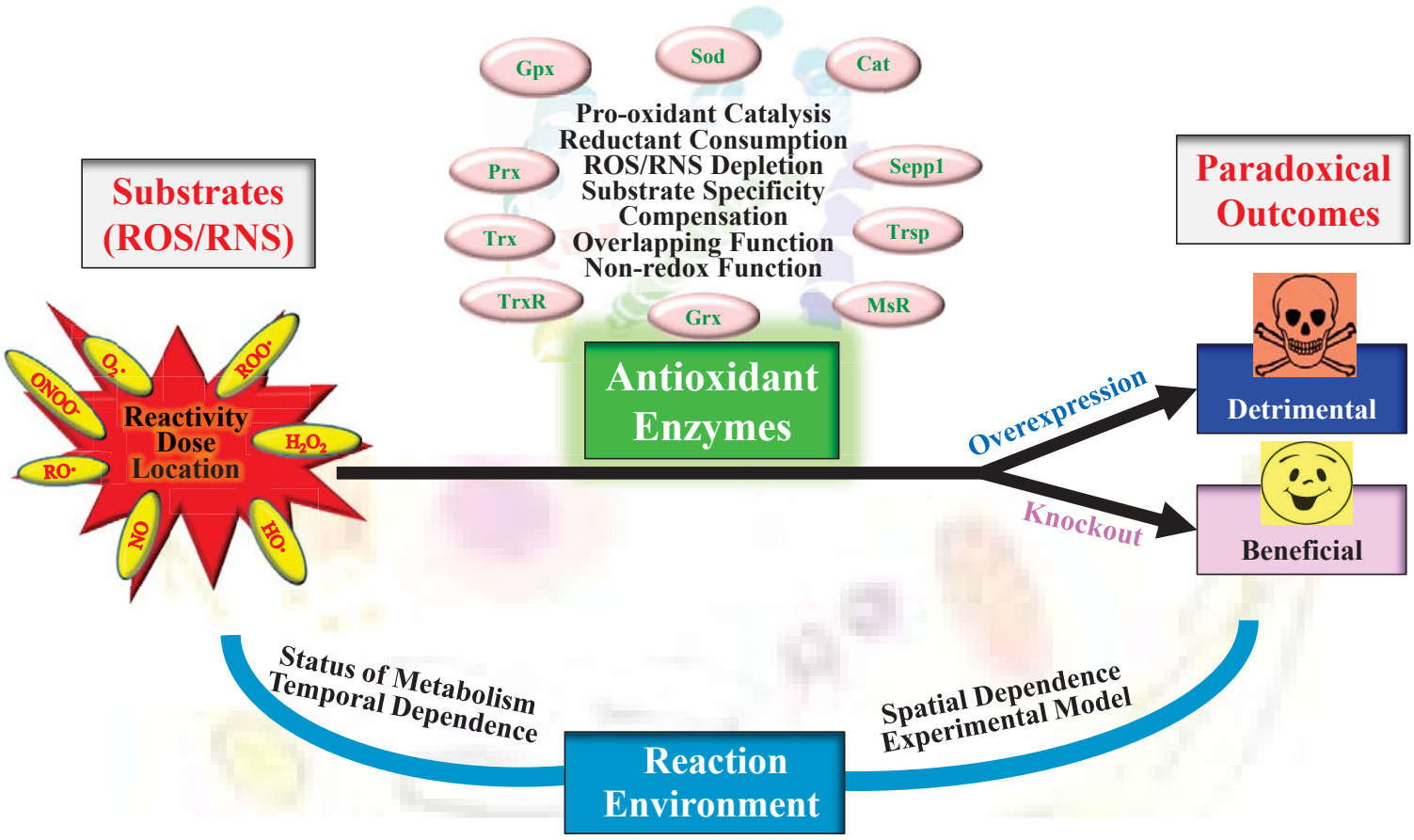

Gpx1 Overexpression
[H2O2]
Insulin Production
β Cell Mass
(Beta2, Foxa2, Cfos, Pdx1, p53)
Insulin Synthesis
(Pdx1, Ins1)
Insulin Secretion
(Ucp2, Pregluc, Sur1, Kir6.2, Cat, Δψ)
Mode of Actions
Epigenetics
Gene Expression
Protein Modulation
Enzyme Activity
Insulin Responsiveness
Insulin Signaling
(p-IRβ, p-Akt Thr308/Ser473)
Lipogenesis
(Hepatic Acc1, Fasn, Pparγ, p53)
Glycolysis
(Hepatic Gk1 and GK activity)
Gluconeogenesis
(Muscle PEPCK activity)
Type 2 Diabetes-Like Phenotypes

F10


DMBA/TPA-Induced Skin Tumor
GPX1 Overexpression
Pancreatic Tumor
Nrf2 and β-catenin → GPX2 ⬆
Gpx2-/-
Intestinal Carcinogenesis
Gpx3 Targeting
Mice
Knockout
Cells
shRNA
AOM/DSS-Induced Colitis-Associated Carcinoma
Leukemia Stem Cell Self-Renewal
Inhibition
Promotion

F11


Beneficial Effects
Activation of Nrf2, with increased resistance to oxidative stress
Hampered carcinogenesis
Promotes cell viability and proliferation through Trx system, support of Prxs, Msrs and RNR
Redox regulation of normal cell function
Activation of Nrf2 pathways
Production of pro-oxidant NADPH oxidase activities, resulting in increased anticancer efficacy
Genetic Loss of TrxR1
Txnrd1 Gene Targeting
Native TrxR1
Inhibitors of TrxR1
Drug Targeting of TrxR1
Hepatocytes
Tumor Cells
Embryos
APAP (NAPQI)
Cisplatin
Detrimental Effects
Embryonically lethal
Results in absolute dependence upon GSH
Support of cancer cell growth and formation of metastases
Increased dependence upon GSH
Risk of NADPH oxidase-like toxicity in normal tissues?


Substrates (ROS/RNS)
Reactivity
Dose
Location
$O_2^{\cdot}$
ROO·
H_2O_2
HO·
NO
RO·
ONOO⁻
Gpx
Sod
Cat
Prx
Sepp1
Trx
Trsp
TrxR
Grx
MsR
Pro-oxidant Catalysis
Reductant Consumption
ROS/RNS Depletion
Substrate Specificity
Compensation
Overlapping Function
Non-redox Function
Antioxidant Enzymes
Overexpression
Knockout
Paradoxical Outcomes
Detrimental
Beneficial
Status of Metabolism
Temporal Dependence
Spatial Dependence
Experimental Model
Reaction Environment

F13