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Role of glutathione peroxidase 1 in glucose and lipid metabolism-related diseases

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Abstract

Glutathione peroxidase 1 (GPX1) is a selenium-dependent enzyme that reduces intracellular hydrogen peroxide and lipid peroxides. While past research explored regulations of gene expression and biochemical function of this selenoperoxidase, GPX1 has recently been implicated in the onset and development of chronic diseases. Clinical data have shown associations of human *GPX1* gene variants with elevated risks of diabetes. Knockout and overexpression of *Gpx1* in mice may induce types 1 and 2 diabetes-like phenotypes, respectively. This review assembles the latest advances in this new field of selenium biology, and attempts to postulate signal and molecular mechanisms mediating the role of GPX1 in glucose and lipid metabolism-related diseases. Potential therapies by harnessing the beneficial effects of this ubiquitous redox-modulating enzyme are briefly discussed.

Graphical Abstract

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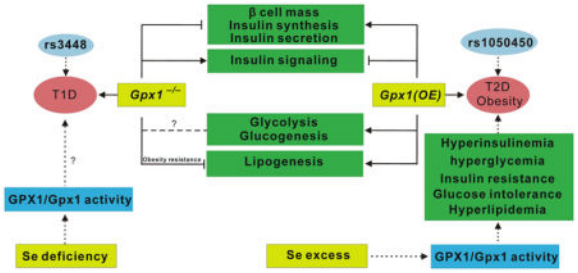

Keywords

Diabetes; Glucose; Glutathione peroxidase 1; Lipid; Selenium

Introduction

Diabetes resulted in a total of 1.6 million deaths in 2015 [1], and is projected to be the seventh leading cause of death by 2030 [2]. The prevalence of diabetes is rapidly rising not only in developed countries but also in middle- and low-income nations [3]. Overdosing or deprivation of dietary selenium (Se) is associated with increased risks of type 2 diabetes (T2D), following a U-shaped curve [4–6]. Although nutritional essentiality of Se and cellular glutathione peroxidase 1 (GPX1) were both identified in 1957 [7–9], GPX1 had not been known until 1972 as the very first selenoprotein and selenoperoxidase to help link these two important discoveries [7, 10–12]. However, a virtually exclusive focus on the redox-modulating functions of GPX1 and the “undoubted” belief in its benefit, similar to that of other antioxidants, to insulin sensitivity and function have made the novel finding of T2D-like phenotypes in the *Gpx1*-overexpressing mice initially counterintuitive [13–16]. Nevertheless, that metabolic paradox has prompted interests in potential roles of the redox enzymes such as GPX1 in glucose and lipid metabolism [10, 17–19]. Subsequently, a new research field has been created during the past decade or so [20–23] to explore the role and mechanism of GPX1 in regulating insulin synthesis, secretion, and sensitivity, glucose homeostasis, lipogenesis, and lipolysis and in the onset and progression of diabetes.

Diet-mediated *GPX1* expression on glucose and lipid metabolism

Selenium deficiency

Dietary Se deficiency decreased *GPX1* gene and protein expression in different tissues of several mammalian species [24–35]. While the deficiency did not affect body weights of mice [36], it decreased blood glucose concentration and hepatic concentrations of total cholesterol (TC), triglyceride (TG), and nonesterified free fatty acid (NEFA) in 5-month old mice [13, 15, 37], compared with the Se-adequate controls. Dietary Se deficiency decreased hepatic mRNA abundances of lipogenesis-related genes such as cytochrome P450, family 7, subfamily a, polypeptide 1 (*Cyp7a1*), sterol regulatory element binding transcription factor 1a (*Srebp1a*) and 2 (*Srebp2*), and hepatic activities of glucokinase (Gk) and phosphoenolpyruvate carboxykinase (Pepck) in the muscle of mice [14, 15, 37]. Meanwhile, dietary Se deficiency enhanced pancreatic islet mRNA abundances of catalase (*Cat*), transcription factor C-fos (*Cfos*), hepatic nuclear factor 4, alpha (*Hnf4α*), forkhead box o1

(*Foxo1*), glucokinase (*Gk1*), insulin 1 (*Ins1*), and transformation related protein 53 (*Trp53*) in the 5-month old mice. In rats, dietary Se deficiency decreased Gpx activity in erythrocytes of dams on day 19 of gestation and in the liver of dams on day 14 postpartum, but elevated mRNA abundances of insulin receptor substrate 2 (*Irs2*) in the liver of dams on day 14 postpartum. In pigs, dietary Se deficiency did not affect plasma glucose or insulin concentration, but decreased plasma concentration of TC [34, 38].

Because broiler chicks are fast growing and susceptible to dietary Se deficiency [25, 26, 39], and also contain much higher blood glucose concentrations than mammalian species, they may serve as a unique model to study roles of Se and GPX1 in glucose and insulin metabolism. Feeding chicks an Se-deficient diet for 15 weeks decreased TC and TG, but elevated insulin and glucose concentrations in their plasma [39]. While the Se deficiency enhanced mRNA abundances of forkhead box a 2 (*FOXA2*), glucagon (*GCG*), and insulin receptor substrate 1 (*IRS1*) in the liver [39], it decreased transcript numbers of 16 insulin-related genes in three tissues. These genes include *IRS2,* insulin (*INS*)*,* pancreatic and duodenal homeobox factor 1 *(PDX1),* protein tyrosine phosphatase, non-receptor type 1 (*PTPN1*), and solute carrier family 2, facilitated glucose transporter member 2 (*SLC2A2*) in the liver; AKT serine/threonine kinase 1 (*AKT1*)*,* B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)*, FOXO1, FOXA2,* insulin receptor (*INSR*)*, IRS1, IRS2, INS,* neuronal differentiation 1 (*NEUROD1*)*, PTPN1*, phosphoinositide 3-kinase (*PI3K*)*, SLC2A2,* and uncoupling protein (*UCP*) in the muscle, and *AKT1, FOXA2*, Hnf1 homeobox a (*HNF1A*), *HNF4α, INSR,* and *PDX1* in the pancreas. In summary, dietary Se deficiency dys-regulated glucose homeostasis and altered expression of many insulin- and lipogenesis-related genes in the liver, muscle, and pancreas of both mammalian and avian species.

Selenium supranutrition

Rats—Compared with those fed 0.3 mg Se/kg diet [33], dams of rats fed 3.0 mg Se/kg diet had greater Gpx activities in the erythrocytes on day 19 of gestation and in the liver on day 14 postpartum. Supranutritional Se induced hyperinsulinemia, insulin resistance, and glucose intolerance in the dams at late gestation and/or day 14 postpartum as well as in the offspring at the age of 112 days old. These impairments concurred with decreased transcript and/or protein levels of insulin signaling proteins in the liver and muscle of dams and/or pups. Compared with the 0.3 mg Se/kg diet, the 3.0 mg Se/kg diet resulted in 50% decreases in transcripts of *Akt2*, *Insr*, and *Irs1* and 36% decrease in the transcript of *Foxo1* in the liver of the offspring. The decreased hepatic transcripts of *Insr* and *Akt2* were verified by approximately 60% decreases in the respective proteins Insr and Akt. Although the transcripts of these genes in the muscle was not significantly altered by the high-Se diet, the treatment decreased the expression of *Irs2* and phosphatidylglycerol phospholipase (*Pgc1*) in the muscle of dams on day 14 postpartum. Meanwhile, *Foxo1* expression was decreased by both Se depletion and supranutrition.

Pigs—Compared with those fed 0.3 mg Se/kg diet [40], pigs fed 3.0 mg Se/kg diet had GPX activities in the liver and muscle enhanced by 21 and 57%, respectively. However, there were no significant differences in the transcript levels of *GPX1* in the two tissues between the two diets. Pigs fed 1.0 mg Se/kg had 23–28% lower plasma TG and(or) TC

concentrations than did those fed 0.3 mg Se/kg. Pigs fed 3.0 mg Se/kg diet had doubled plasma insulin concentration at week 11 than pigs fed 0.3 mg Se/kg diet. Their TC and TG concentrations in the adipose tissue were 2.4-fold and 41% greater, respectively, than those fed 0.3 mg Se/kg. Likewise, hepatic concentrations of TC, TG, and NEFA in pigs fed 3.0 mg Se/kg diet were 40%, 2.3-fold, and 63% greater, respectively, than those fed 0.3 mg Se/kg. However, no such differences in the lipid profiles of the muscle tissue were seen between these two levels of dietary Se. Compared with those fed the 0.3 mg Se/kg diet, pig fed 3.0 mg Se/kg diet showed up-regulations of *SREBP1* (59%) and fatty acid synthase (*FASN*) (doubled) in the liver and peroxisome proliferator-activated receptor gamma (*PPARG*) and *TRP53* (42–48%) in the muscle, and down-regulations of *CYP7A1* (88%) in the liver and *ACC1* (51%) and *FASN* (57%) in the muscle, respectively.

Chicks—In broiler chicks [41], a high Se (3.0 mg Se/kg) diet elevated plasma GPX activity by 37% at week 4 and muscle GPX activities by about 1.8-, 2.2- and 2.8-fold at week 2, 4, and 6, respectively, compared with the 0.3 mg Se/kg diet. Meanwhile, the high Se diet resulted in 38% higher GPX activity in the pancreas compared with that in the 0.3 mg Se/kg group at week 2 [41]. Broilers fed 3.0 mg Se/kg exhibited a lower fasting plasma glucose concentration, but higher plasma insulin concentration compared with those fed the 0.3 mg Se/kg at week 2. Plasma concentrations of TC and TG were also higher in broilers fed 3.0 mg Se/kg than those fed 0.3 mg Se/kg. The 3.0 mg Se/kg diet increased muscle transcripts of *FOXO1*, *HNF4α*, *IRS2*, and *PI3K*, hepatic transcripts of *GCG, HNF4α, and SLC2A2*, and pancreatic transcripts of *HNF4α, and IRS2* at week 6. In contrast, the 3.0 mg Se/kg diet downregulated insulin signaling-related genes of *AKT1*, *FOXA2*, *INS*, *PI3K*, and *UCP* in the pancreas and *AKT1*, *GCG*, and *INSR* in the muscle at the same time. Meanwhile, hepatic transcripts of *GCG* were elevated by the Se supranutrition and deficiency in broiler chicks. Pancreatic transcripts of *AKT1*, and *FOXA2*, muscle transcripts of *AKT1*, and *INSR* in the chicks were downregulated by the Se supranutrition and deficiency in the same direction. In contrast, muscle transcripts of *FOXO1* and *IRS2*, hepatic transcript of *SLC2A2*, and pancreatic transcript of *HNF4α* were affected by the Se supranutrition and deficiency in opposite ways. Organic sources of Se from 2-hydroxy-4-methylselenobutanoic acid and Se-enriched yeast seemed to be more effective in restoring hepatic *GPX1* transcript and GPX activity in tissues than sodium selenite in broiler chicks [42]. However, differences of these Se forms in affecting glucose and lipid metabolism remain unclear.

Humans—Blood or plasma Se, instead of GPX(1) activity, has often been measure to assess body Se status in human population studies. A recent review [43] indicated that five out of eight cross-sectional studies had shown positive associations between serum/plasma Se and T2D or fasting circulating glucose. Among the five randomized controlled trials (RCTs) with Se supplementation, three trials, including the well-known Se and Vitamin E Cancer Prevention Trial [44], showed no effect, one showed lower fasting serum insulin and homeostasis model assessment of insulin resistance, and only one, the Nutritional Prevention of Cancer study conducted in the dermatology outpatients, showed an increased incidence of T2D [45]. But, Algotar et al. [46]failed to observe the same positive effect of Se on diabetes prevention at a later time. The Selenium and Celecoxib Trial for the prevention of colorectal adenoma recurrence suggested that Se supplementation might increase the risk of T2D in

older participants following removal of adenomas [47]. A recent case control study reported that high serum Se concentrations were associated with increased risks for diabetes mellitus, independent of central obesity and insulin resistance [48].

Higher risks of dyslipidemia were associated with higher circulating Se concentrations in the observation trials from all the three times of National Health and Nutrition Examination Survey conducted between 1988–2012 in US [49–51], as well as from the populations of Lebanon [52], Taiwan [53], Britain [54], Finland [55], and Spain [56, 57]. But results from the Se supplementation trials were inconsistent, similar to those for the glucose metabolism. Supplementing Se at 100 μg/day for 6 months increased the cord blood concentrations of TG in a small group of pregnant women (n = 34 for supplementation vs 32 for placebo) [58]. While supplementing antioxidants including Se increased for > 7 years the risk of dyslipidemia in women [59]. However, supplementing Se to the Britain [60] and Chinese [61] adults improved their blood lipid profiles. In addition, the 1988–94 US survey showed that higher levels of serum Apo B and Apo A1 were associated with the highest vs. the lowest serum Se concentrations [49]. Serum lipoprotein (A) concentrations were positively correlated with Se in a 140 adult male population [62]. Notably, those who performed the Spanish trial [56] supported a hypothesis that regulations of blood Se and lipid profiles shared common pathways. Overall, results on the associations of Se with glucose and lipid metabolism from the human studies are inconsistent or even conflicting. Large randomized controlled trials are needed to confirm the pro-diabetic or pro-dyslipidemic potential of excessive Se and GPX1.

Fat, Vitamin E, and other factors

High-fat intake—Although *GPX1* mRNA, protein, and activity were highly responsive to dietary Se changes in different tissues of various species [25, 29, 30, 33–35, 42, 63], its mRNA was not changed by a high-fat diet in the heart, hypothalamus, kidney, liver, muscle, pancreas, perirenal adipose tissue (PAT), pituitary, subcutaneous adipose tissue (SAT), or thyroid [64, 65] of pigs. However, several other selenoprotein genes including *DIO2*, *SELENOI*, *SELENOS*, *SELENOV*, and *TXNRD1* in the thyroid; *SELENOF* in the liver; *SELENOO* in the kidney; *GPX4*, *GPX6*, *DIO1*, and *SELENOV* in the muscle; *GPX4* and *SELENOM* in the pituitary; and *GPX3* in the hypothalamus were up-regulated by the high fat diet in pigs. Meanwhile, *DIO1*, *SELENOH*, *SELENOI*, *SELENOK*, *SELENOM*, *SELENOW*, and *TXNRD1* in the pancreas; *SELENOH*, *SELENOI*, and *TXNRD1* in the hypothalamus; *SELENOI*, *SELENOM*, and *MSRB1* in the subcutaneous fat; *SELENOH*, *SELENOK*, *SELENOP, SELENOV,* and *SELENOW* in the perirenal fat; *GPX3, GPX6, DIO3,* and *SELENOV* in the liver; *SELENOI,* and *TXNRD1* in the pituitary; *SELENOM* in the kidney were down-regulated by the high fat diet in these pigs.

Compared with the control, pigs fed the high fat diet had greater concentrations of serum TG, TC, low density lipoprotein and NEFA [64, 65]. The high fat diet up-regulated 5 lipogenesis-related genes in 3 tissues. These genes included agouti signaling protein (*ASIP*), agouti related protein (*AGRP*), and resistin (*RETN*) in the skeletal muscle; uncoupling protein 3 (*UCP3*) in the thyroid; and uncoupling protein 2 (*UCP2*) in the pituitary. In contrast, 11 genes were downregulated in 6 tissues. These changes included *AGRP* in the

liver, kidney, and PAT; leptin receptor (*LEPR*) in the liver, kidney, and SAT; adiponectin receptor 2 (*ADIPOR2*) in the kidney, PAT, and SAT; and fatty acid binding protein 4 (*FABP4*) in the PAT, pituitary, and hypothalamus. In addition, adiponectin (*ADIPOQ*) was downregulated in the PAT and SAT. Genes that were affected in single tissues include *ASIP*, fatty acid binding protein 3 (*FABP3*), *RETN*, and *UCP2* in the liver; fatty acid binding protein 1 (*FABP1*) in the PAT; and *FASN* in the SAT. Apparently, these high fat diet–mediated changes of lipogenesis-related gene expression were not directly related to *GPX1* mRNA or activity.

Vitamin E—Vitamin E has a close relationship with Se in regulating lipid metabolism [44, 66, 67]. The observation that diabetes leads to high concentrations of organic peroxides, and cholesterol, and the fact that vitamin E protects fatty acids from oxidation or peroxidation implicate it as a possible inhibitor of diabetogenesis [68]. In fact, supplementing the diabetic group with vitamin E and Se for 5 weeks led to a significant increase in GPX activities in plasma [69] and decreases in plasma concentrations of malondialdehyde (MDA) and oxidized low-density lipoprotein (LDL) [69]. In contrast, vitamin E supplementation (all-rac-α-tocopheryl acetate at 50 mg/kg) to a vitamin E deficient diet for chicks led to ~30–50% decreases in transcripts of *GPX1, SELENOI*, *TXNRD1*, and *TXNRD2* in the liver [25], despite no effect on the liver GPX1 activity. Notably, the same treatment in another study did not affect GPX1 protein, but decreased GPX4 protein and transcripts of *SELENOF* and *SELENOW* in the muscle of Se-adequate chicks [26]. The same treatment also elevated transcript of muscle *SELENOM*, regardless of the Se status of chicks.

Feeding young adult mice high levels of dietary vitamin E (all-rac-α-tocopheryl acetate at 750 or 7,500 mg/kg) could not replace the protection by Gpx1 against the paraquat-induced lethality [70], although hepatic Gpx activities were elevated by ~40% in the $Gpx1^{-/-}$ mice and by 17~24% the wild-type mice compared with those fed 0 or 75 mg of all-rac-α-tocopheryl acetate//kg. Contrary to the chick results, hepatic Gpx4 activities in both $Gpx1^{-/-}$ and wild-type mice showed dose-dependent increases (36 and 48%, respectively) in response to the increases in dietary vitamin E supplementation. Apparently, supplemental dietary vitamin E at the nutrient requirement and higher levels could affect the transcript, protein, and activity of several selenoproteins including Gpx4. However, its impacts may be species, tissue, and selenoprotein-dependent, and the functional implication for the interaction of Se and vitamin E remains unclear. Recent studies have illustrated the involvement of Gpx4 in the ferroptotic cell death that entails cellular iron accumulation and lipid peroxidation, and $Gpx4^{-/-}$ cells could be rescued from the cell death by vitamin E [71].

Other factors—Zinc finger protein 143 (ZNF143) transcription factor mediated cell survival through upregulation of the GPX1 activity at the mitochondrial respiratory dysfunction [72]. A novel upregulation of *Gpx1* by knockout of regenerating islet-derived 3 beta (Reg3β) aggravated acetaminophen-induced hepatic protein nitration, while the knockout enhanced Gpx1 activity via selenocysteine lyase upregulation [73]. Skeletal muscle *Gpx1* expression in mice was altered by both exercise and dyslipidemia through changes in DNA methylation [74].

Genetically-altered *GPX1* expression on glucose and lipid metabolism

Gpx1 knockout

Compared with wild type mice, *Gpx1*$^{-/-}$ mice had lower pancreatic β-cell mass, hypoinsulinemia, mild hyperglycemia, and impaired ATP production and glucose-stimulated insulin secretion(GSIS) in islet [16] (Figure 1). The molecular mechanism was associated with decreased Pdx1 and elevated Ucp2 in pancreas [16]. Knockout of *Gpx1*, contrary to the overexpression of *Gpx1*, improved insulin sensitivity [16]. This was because appropriate amount of intracellular reactive oxygen species (ROS) is important to control the activity of protein phosphatases. Consistently, the improved insulin sensitivity in the *Gpx1*$^{-/-}$ mice were associated with elevated intracellular hydroperoxides and phosphorylation of p53 and p38-AMP-activated protein kinase (Mapk) in the islets and enhanced PI3K/Akt signaling and glucose uptake in the muscle. Meanwhile, *Gpx1*$^{-/-}$ mice were protected from the high-fat diet-induced insulin resistance by a mechanism related to enhanced oxidation of the PI3K antagonist phosphatase and tensin homolog (Pten) [75].

Gpx1$^{-/-}$ mice showed decreased expression of gluconeogenic genes such as glucose-6-phosphatase (*G6pc*) and phosphoenolpyruvate carboxykinase (*Pepck*), increased glucose uptake by white gastric and diaphragm skeletal muscles through membrane docking of glucose transporter 4 (Glut4) upon Akt substrate of 160 kDa (As160) phosphorylation on Thr642 [pAS160(Thr642)], and enhanced insulin-induced oxidation β fibroblast cells [75]. In line with the elevated PI3K/Akt signaling in the *Gpx1*$^{-/-}$ muscle, the phosphorylation (Thr642) of the AS160, a Rab GTPase that regulates Glut4 docking on the plasma membrane for glucose uptake, was increased, whereas glycogen synthase Ser-640/641 phosphorylation was reduced (a consequence of Akt phosphorylating and inhibiting glycogen synthase kinase 3). No significant change in insulin-induced PI3K/Akt signaling was seen in the liver or adipose tissue of the *Gpx1*$^{-/-}$ mice. In another study [76], *Gpx1*$^{-/-}$ mice fed an obesogenic high-fat diet for 12 weeks exhibited systemic oxidative stress and hyperglycemia, but had unaltered whole body insulin sensitivity, improved hepatic insulin signaling, and decreased whole body glucose production, hepatic steatosis and damage, plasma insulin, and glucose stimulated insulin secretion. The attenuated insulin secretion was associated with the decreased islet β cell Pdx1 and insulin production, elevated pancreatic Ptp (protein tyrosine phosphatase) oxidation, and accelerated Y701 phosphorylation of signal transducer and activator of transcription 1 (Stat1).

In hepatocyte-specific *Gpx1* knockout mice [77], insulin induced a combined change in the liver via the PI3K/Akt2 pathway in the postprandial state: decreased transcription of gluconeogenic genes of *Pck1* and *G6pc* and increased transcription of *Gk1* and other genes that promote glycogen storage or glycolysis. This combination coordinately repressed hepatic glucose production and prevented postprandial hyperglycaemia. In the fasting state, expression of *G6pc* and *Pck1* was also decreased in the liver of these mice, accompanied by a 7.2-fold increase in the *Gk1* transcript. Because Gk catalyzes the conversion of glucose to G6P and serves as the first step of glycolysis or glycogen synthesis, hepatic glycogen storage was elevated in these mice. In addition, the expression of pyruvate dehydrogenase kinase 4 (*Pdk4*) was decreased, whereas hepatocyte basal and insulin-induced H_2O_2

generations were exacerbated by the Gpx1 deficiency. Moreover, the insulin-induced phosphorylation of insulin receptor-Y1162/Y1163 and Akt-S473 was enhanced. These results were consistent with that the GPX1 deficiency repressed hepatic glucose production and promoted glucose storage and utilization without altering lipogenesis [18].

Gpx1 overexpression

GPX1 overproduction may be beneficial if diabetes or obese are developed. However, excessive GPX1 activity is actually deleterious to normal metabolism. Figure 1 illustrates molecular and biochemical mechanisms for the T2D-like phenotypes induced by *Gpx1* overexpression [*Gpx1*(OE)] in mice [13, 15, 37, 78]. The over-produced Gpx1 activity in the pancreatic islets enhanced β cell mass and insulin synthesis and secretion via modulations of key genes and proteins at the epigenetic, transcript, and/or protein levels. These effects led to hypersecretion of insulin and hyperinsulinemia. Meanwhile, *Gpx1* overexpression also impaired insulin responsiveness in the liver and muscle and disturbed lipogenesis, glycolysis, and gluconeogenesis in these tissues. The attenuated phosphorylations of Insr and Akt in both liver and muscle after insulin stimulation were associated with over-quenching intracellular ROS that are required for inhibiting protein phosphatases [13, 15, 78, 79]. This subsequently contributed to insulin resistance in these mice. Dietary Se deficiency actually improved the T2D-like phenotypes in the *Gpx1*(OE) mice [37]. The improvement was mediated by reversing gene expression of key factors involved in insulin synthesis and secretion (*Beta2*, *Cfos*, *Foxa2*, *Pregluc*, *Ins1*, *Trp53*, and *Sur1*) to the wild type levels. Dietary Se deficiency also downregulated hepatic gene expression of two rate-limiting enzymes for lipogenesis (*Acc1* and *Gk1*), and lowered activities of hepatic Gk and muscle Pepck in these mice.

As discussed above, elevated GPX1 activity was associated with excessive dietary Se intakes and insulin resistance in various species [33, 34, 40, 41]. Because the *Gpx1* overexpression induced insulin resistance via diminishing intracellular ROS, elevating other antioxidant enzymes or antioxidants may cause similar problems [68, 80]. Overall, the development of T2D-like phenotypes in the *Gpx1*(OE) mice offers a unique model for the study of redox control and insulin resistance [81, 82].

GPX1 on high-fat diet/diabetic-related atherosclerosis

Recent clinical studies have suggested a major protective role for GPX1 against atherosclerosis [83–85]. Lack of functional Gpx1 accelerated diabetes-associated atherosclerosis via upregulation of pro-inflammatory and pro-fibrotic pathway in ApoE-deficient mice [86]. However, a specific deficiency in Gpx1 did not cause changes in biomarkers of oxidative damage or increased atherosclerosis in a murine model with the high fat diet-induced atherogenesis [87]. Thus, effects of Gpx1 and high fat diet in the presence and absence of ApoE deficiency were different. In ApoE-deficient mice, deficiency of Gpx1 accelerated the progression of atherosclerosis [88]. Likewise, lack of Gpx1 accelerated atherosclerosis and upregulated proatherogenic pathways in diabetic ApoE/Gpx1 double-knockout mice, thereby establishing Gpx1 as an important therapeutic target [89, 90]. Ebselen reduced atherosclerotic lesions in most regions of the diabetic ApoE-deficient aorta, except for the aortic sinus, suggesting its effectiveness as a potential antiatherogenic

therapy of diabetic-macrovascular disease. Ebselen might elicit its effect via modulation of transcription factors such as NF-κB and AP-1 [89, 90].

Atherosclerotic lesions within the aortic sinus region, as well as arch, thoracic, and abdominal lesions, were significantly increased in diabetic ApoE/Gpx1 double-knockout mice aortas compared with diabetic ApoE-deficient mice aortas [86]. This was associated with increased staining for smooth muscle cells (SMCs) and macrophages, consistent with increased SMC migration and macrophage infiltration. Furthermore, a range of molecules implicated in the progression and development of atherosclerosis, including vascular cell adhesion molecule-1(VCAM1), vascular endothelial growth factor and connective tissue growth factor, cytokines, growth factors, and receptors for advanced glycation end products, were increased by the absence of Gpx1 [86]. Furthermore, plasmalogen enrichment via batyl alcohol supplementation attenuated atherosclerosis in ApoE and ApoE/Gpx1 double deficient mice, with a greater effect in the latter group [91]. Plasmalogen enrichment may represent a viable therapeutic strategy to prevent atherosclerosis and reduce cardiovascular disease risk, particularly under conditions of elevated oxidative stress and inflammation [91].

Subcellular location of GPX1 and its interaction with other GPX enzymes

Immunogold ultrastructural staining showed that GPX1 exists not only in cytosol but also in the mitochondria and nucleus [20, 92]. Cytosol GPX1 overexpression reversed the tumor cell growth inhibition caused by manganese-dependent superoxide dismutase overexpression, altered intracellular GSH, GSSG, and ROS [92], and attenuated degradation of the inhibitory subunit a of NF-κB [92]. The *GPX1* gene codes for both the cytosolic and mitochondrial forms of the enzyme [93, 94]. Liver is highly dependent on *GPX1* for its mitochondrial antioxidant defenses [95]. Knockout or overexpression of *Gpx1* did not produce significant changes in the other forms of GPX, implying an independent expression of these selenoperoxidases [96, 97]. The relationship between Gpx1 and steroidogenesis was confirmed by the immunocytochemical localization of the enzyme in the rat adrenal cortical cells [22], and both cytosol- and mitochondrial-Gpx1 were modified by lipoperoxidative damage in those cells. It seemed that the pattern of Gpx1 staining was a sensitive and specific indicator of oxidative damage in the cells [98, 99].

Expression of GPX2 is mainly in the gastrointestinal epithelium, but is also localized in the epithelium lining of the lung, bladder, and breast[100]. This enzyme has been detected only in cytosol. Knockout of *Gpx2* in mice induced an increase in *Gpx1* expression that could only compensate partially for the loss of Gpx2 in the colon [101]. The $Gpx2^{-/-}$ mice were susceptible to allergic airway inflammation [102]. A double knockout of *Gpx1* and *Gpx2* produced a worse impairment of the intestinal integrity, than the single knockout, resulting in spontaneous developments of ileocolitis [103] and colon cancer [104]. Both symptoms could be efficiently prevented by bringing back one allele of *Gpx2* but not *Gpx1* [105].

As the only extracellular isoform of the GPX family, GPX3 is detectable in the plasma and in extracellular body fluids such as chamber water of the eye, thyroid colloid lumen, and amniotic fluid [106]. Liver Se concentration and cytosolic GPX activity were not altered by

the knockout of *Gpx3* [107]. Three forms of GPX4 proteins are expressed by the *Gpx4* gene: a long form (lGPX4), a short form (sGPX4), and a nuclear form (nGPX4) [108]. The lGPX4 has a mitochondrial signal at the N terminus, and is believed to be targeted to mitochondria [109]. The sGPX4 protein is synthesized using the second translation start codon and is believed to be the non-mitochondrial GPX4 protein found in cytoplasm, nucleus, and microsome. The nGPX4 protein is encoded from an alternative first exon called exon Ib and is expressed mainly in sperm nuclei. nGPX4 proteins are dispensable for both somatic functions and fertility [110]. Likewise, there was no change in the expression of GPXs in the liver of 1 day old *Gpx4*-deficient mice [111]. Moreover, GPX6 has been found only in the olfactory epithelium [112].

Polymorphisms of human GPX1 on glucose and lipid metabolism

There are a number of recognized single nucleotide polymorphisms (SNP) of *GPX1* associated with obesity and insulin resistance in humans (Table 1). A well-known missense mutation of rs1050450 (C to T substitution) results in the substitution of leucine for proline at codon 198 (or 200) of the GPX1 protein [85, 113]. A few studies have shown the leucine allele to be associated with outcomes of oxidative stress, central obesity and insulin resistance, with some sex-related differences [114, 115]. Male T allele (leucine) carriers had a higher metabolic syndrome prevalence, with higher waist-hip ratios, serum TG and insulin, homeostasis model assessment of β cell function, and systolic and diastolic blood pressures [115, 116]. Female T allele carriers showed higher body fat mass, serum insulin, and homeostasis model assessment of insulin resistance [114]. Nutritional supplementation of Se from Brazil nuts was associated with higher DNA damage in the leucine carriers [114]. The *GPX1* Pro200Leu polymorphism (rs1050450) was associated with morbid obesity, independently of the presence of prediabetes or diabetes in women from central Mexico [117]. Carriers of the T allele also had higher levels of lipoperoxides and MDA in LDLs [118].

A combination of Pro198Leu SNP (rs1050450) with the copy number variant Ala^5/Ala^6 at codon 7–11 decreased the activity of the enzyme by 40% *in vitro* [85]. The same study demonstrated that the combination of two other SNPs (-602A/G and 2C/T) decreased the transcriptional activity of GPX1 by 25% [85]. These data suggest that the T allele was associated with lower GPX activity and a possible higher oxidative stress status, aggravating the obesity-associated phenotypes. The genotype distribution of *GPX1* Pro198Leu variant in the Chinese population (the frequency of T allele is 14%) was different from that in the Swedes (the frequency of T allele is 9.0%) [119, 120]. Pro198Leu polymorphism of *GPX1* raised the risk of T2D in Han Chinese of Shanghai. The T allele was a risk factor of T2D but not of diabetic coronary heart disease [120]. Another *GPX1* variant, T-allele of rs3448, was associated with kidney complications in T1D patients [21], which was consistent with the implication of GPX1 in the protection against renal oxidative stress in those patients [121].

Conclusion and perspective

Overall, this review highlights the dual role of GPX1 in glucose and lipid metabolism and the related human health implications. As the most abundant isoform of the GPX family,

GPX1 exerts its impacts via regulating gene expression, protein function, and enzyme activities of key factors involved in both macro- and micro-nutrient metabolism [97, 122, 123]. The combined effects of the Gpx1 overexpression [14, 15, 20, 44, 124] in the insulin-producing and insulin-responsive tissues lead to metabolic phenotypes similar to T2D [37, 78, 79]. Meanwhile, the T1D-like phenotypes in the *Gpx1*$^{-/-}$ mice [16, 75] seem to be reciprocal. These two extremes underscore the importance to maintain an appropriate expression and activity of this selenoperoxidase for controlling redox balance and glucose and lipid metabolism [13, 17, 97, 124–126]. Excessive ROS accumulation, due to *Gpx1* deficiency, inhibits gene expression or protein production of key transcriptional factors like Pdx1, leading to lowered islet β cell mass, insulin synthesis, and insulin secretion [37, 78]. However, the physiological level of ROS is essential to control protein phosphatase activity for insulin signaling. Overly diminishing intracellular ROS by *Gpx1* overexpression desensitizes insulin signaling [4, 21, 77, 123]. Along with the chronic hyperinsulinemia resultant from the dysregulated islet β cell mass, insulin synthesis, and insulin secretion, this desensitization leads to insulin resistance in the *Gpx1*(OE) mice [13, 79].

Illustrating the associations of GPX1 polymorphisms with risks of diabetes and obesity in different populations [113, 115–118] highlights GPX1 as a novel, key regulator of insulin physiology and energy metabolism. Diabetic patients with decreased GPX1 function, due to *GPX1* polymorphism, had an increased risk for cardiovascular diseases [83–85]. The deficiency of GPX1 accelerated diabetic atherosclerosis in the ApoE-knockout mice [86], and the acceleration concurred with an increased nitrotyrosine formation and transcriptional changes of inflammatory and profibrotic factors [86]. Ebselen was shown to reduce diabetes-associated atherosclerosis [89]. This well-known GPX1 mimic has also been successfully used to decrease oxidative injuries [89, 127], to prevent noise-induced hearing loss [128], and reduce neurotoxicity in a variety of animal models in which GPX1 deficiency caused opposite effects [129].

Ebselen has been shown to improve GSIS in islets of *Gpx1*$^{-/-}$ mice [127]. The rescue results from a coordinated transcriptional regulation of four key GSIS regulators via the PGC-1α-mediated signaling pathway, and supports the notion that excessive ROS inhibits GSIS [130] and ebselen removes this inhibition by acting as a GPX mimetic to scavenge the elevated intracellular H_2O_2 due to the lack of Gpx1. Likewise, the SOD mimic, copper diisopropylsalicylate, that catalyzes H_2O_2 production from superoxide, also rescued the defected GSIS in the superoxide dismutase-1 (Sod1) knockout mouse pancreatic islets. This suggested that the lack or blocking of enzymatic production of H_2O_2 from superoxide in the *Sod1*$^{-/-}$ islets impaired GSIS. Because an adequate amount of H_2O_2 is required to initiate GSIS [131], the Sod1-deficient islets might not produce sufficient H_2O_2 or have appropriate ratios of H_2O_2 to superoxide to support GSIS. Thus, the SOD mimic treatment could have rescued GSIS by restoring H_2O_2 generation. However, this H_2O_2 restoring notion could not explain the positive effect of ebselen (supposed to decrease H_2O_2) on GSIS in the Sod1-deficent islets. Meanwhile, the SOD mimic affected the gene expression of the Pgc-1α pathway in a different or just opposite way from that of ebselen in the same type of islets (double knockouts of *Gpx1* and *Sod1*) [127]. These findings not only have illustrated that GPX1 and SOD1, as two important intracellular antioxidant enzymes, function distinguishably in regulating insulin secretion, but also underscored the ROS concentration-

or redox balance-dependent effects of their mimics. This complexity highlights the necessities and opportunities of discretional applications of various antioxidant enzyme mimics in treating insulin-related disorders [15].

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Abbreviations used

ACC1	acetylcoenzyme A carboxylase 1
ASIP	agouti signaling protein
BETA2	transcription factor Beta 2
CYP7a1	cytochrome P450, family 7, subfamily a, polypeptide 1
cFOS	transcription factor C-fos
FASN	fatty acid synthase
FOXA22	forkhead box protein A2
GK1	glucokinase
INSR	insulin receptor
GPX1	glutathione peroxidase 1
GPX1(OE)	GPX1 overexpression
GSIS	glucose-stimulated insulin secretion
LDL	low-density lipoprotein
NEFA	nonesterified free fatty acid
PAT	perirenal adipose tissue
PDX1	pancreatic and duodenal homeobox 1
PEPCK	phosphoenolpyruvate carboxykinase
ROS	reactive oxygen species
SAT	subcutaneous adipose tissue
Se	selenium
SLC2A2	solute carrier family 2 member 2
SNPs	single nucleotide polymorphisms

SREBPs	sterol regulatory element-binding proteins
SUR1	sulfonylurea receptor 1
T1D	type 1 diabetes
T2D	type 2 diabetes
TC	total cholesterol, TG, triglyceride
Trp53	transformation related protein 53

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Highlights

- Supranutrition of Se is associated with hyperglycemia and hyperinsulinemia
- Knockout of Gpx1 induces metabolic changes similar to type 1 diabetes
- Overexpression of Gpx1 produces type 2 diabetes-like phenotypes
- Human *GPX1* polymorphism links to risks of diabetes and obesity

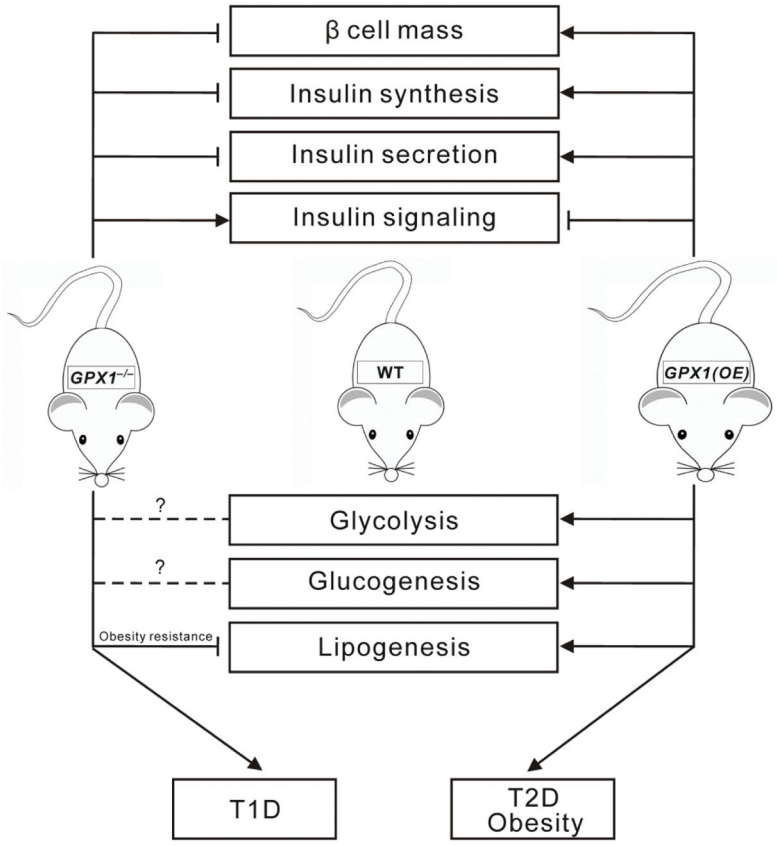

Figure 1.

Roles of glutathione peroxidase 1 (Gpx1) in insulin physiology, glucose, lipid, and protein metabolism. Overexpression of *Gpx1* [*Gpx1*(OE)] induced hypertrophy of β cells, hyperinsulinemia, hyper secretion of insulin, hyperglycemia, hyperlipidemia, insulin resistance, and obesity. In contrast, knockout of *Gpx1* ($Gpx1^{-/-}$) led to hypotrophy of β-cells, hypoinsulinemia, hyposecretion of insulin, and elevated insulin sensitivity. Lines ending with arrows, activation or increase; Lines ending with cross bars, inhibition or decrease; Dash with question mark, unknown function; T1D, type 1 diabetes; T2D, type 2 diabetes;

Table 1

Genetic variants in human *GPX1* associated with diabetes/obesity-related phenotypes

Analyzed variant(dbSNP)	Other designation	Metabolic phenotype	Reference
rs1050450	594C/T, Pro198Leu	The CT/TT genotype had higher waist-hip ratios, triacylglycerol concentrations, homeostasis model assessment for β-cell function, and systolic and diastolic blood pressures in men	[115]
		The CT/TT genotype had higher body fat mass, insulin and HOMA-IR in women	[115]
		Leu carriers had higher lipoperoxides and MDA in LDL	[118]
		Leu carriers showed higher DNA damage after Se supplementation	[114]
		Leu carriers had higher lipoperoxides and MDA in LDL, lower GPX activity	[113]
		Erythrocyte GPX activity was lowered with the T allele dose	[113]
	Pro198Leu	The variant T allele was associated with a higher risk of developing diabetic peripheral neuropathy	[116]
	Ala^5/Ala^6+ Pro198Leu	Ala^6/198Leu polymorphism had a 40% decrease in GPX1 activity	[85]
	-602A/G+2C/T	25% decrease in transcriptional activity	[85]
	Pro200Leu	linked to morbid obesity in central Mexican women	[117]
rs8179169	Arg5Pro	Had an effect on erythrocyte Se, with lower concentrations in individuals with the GC genotype	[132]
rs3448	XT/CC	The CT/TT allele was associated with higher plasma concentrations of isoprostane and advanced oxidation protein products	[21]

GPX1, glutathione peroxidase 1; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, Low-density lipoprotein; MDA, malondialdehyde; Se, selenium.