Cellular and Molecular Life Sciences (2018) 75:1567–1586
https://doi.org/10.1007/s00018-018-2745-8

REVIEW

The role of the thioredoxin/thioredoxin reductase system in the metabolic syndrome: towards a possible prognostic marker?

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Received: 18 October 2017 / Revised: 13 December 2017 / Accepted: 3 January 2018 / Published online: 11 January 2018

Abstract

Mammalian thioredoxin reductase (TrxR) is a selenoprotein with three existing isoenzymes (TrxR1, TrxR2, and TrxR3), which is found primarily intracellularly but also in extracellular fluids. The main substrate thioredoxin (Trx) is similarly found (as Trx1 and Trx2) in various intracellular compartments, in blood plasma, and is the cell's major disulfide reductase. Thioredoxin reductase is necessary as a NADPH-dependent reducing agent in biochemical reactions involving Trx. Genetic and environmental factors like selenium status influence the activity of TrxR. Research shows that the Trx/TrxR system plays a significant role in the physiology of the adipose tissue, in carbohydrate metabolism, insulin production and sensitivity, blood pressure regulation, inflammation, chemotactic activity of macrophages, and atherogenesis. Based on recent research, it has been reported that the modulation of the Trx/TrxR system may be considered as a new target in the management of the metabolic syndrome, insulin resistance, and type 2 diabetes, as well as in the treatment of hypertension and atherosclerosis. In this review evidence about a possible role of this system as a marker of the metabolic syndrome is reported.

Keywords Selenium · Thioredoxin reductase · Diabetes · Obesity · Thioredoxin interacting protein

Abbreviations

HIV	Human immunodeficiency virus
NADPH	Nicotinamide adenine dinucleotide phosphate
PPAR-γ	Peroxisome-proliferator-activated receptor-gamma
Se	Selenium
Trx	Thioredoxin
TrxR	Thioredoxin reductase
TXNRD	Thioredoxin reductase

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Introduction

Thioredoxin reductase (TrxR, EC 1.8.1.9) is a selenoprotein of increasing interest in the recent years because of its role in the selenium (Se) homeostasis and its involvement in metabolic and cardiovascular diseases [1–12]. TrxR as a flavoprotein [13] is presumably vulnerable to riboflavin deficiency like glutathione reductase (GR) [14, 15]. Recent data on poultry animals revealed a role of thioredoxin (Trx) in the regulation of selenoproteins, particularly because gene expression of selenoproteins is regulated by Trx [16]. Selenium availability is another regulator of some selenoproteins, such as glutathione peroxidase 1 [17]. Furthermore, the function of Trx depends on the activity of the thioredoxin reductase [18]. This implies that the system

selenium–Trx–TrxR participates altogether in the modulation of the expression of selenoproteins [19, 20].

Early studies described a differential pattern of function in the Trx activity in different species [21].

The different species showed similar three-dimensional structures of the enzyme, but with important differences in the amino acid composition, although residues in the active site of the different thioredoxins were highly conserved, and included Gly-33, Pro-34, Cys-35, Asp-61, Asp-26, Ala-29, Trp-31, Cys-32, Pro-76, and Gly-92 [21]. The biochemical structure of the enzymatic complex TrxR and Trx has been approached several years ago [22] and reviewed recently [10, 23]. Fundamentally, Trx as a ubiquitous protein has been described through a catalytic model that should involve a protein disulfide reduction, via the interaction of a binding protein and the nucleophilic attack by cysteine residue 32 (Cys32) in the active site to form a "mixed" disulfide transition state (Fig. 1).

Thioredoxin (Trx) was originally discovered as a hydrogen donor for ribonucleotide reductase in *Escherichia coli* and, therefore, connected to the formation of DNA building blocks and DNA synthesis [24, 25]. Trx is found in all living cells, and determination of its structure from *E. coli* defined a domain called the thioredoxin fold, which is widespread in nature [26]. Thioredoxin is the founder of the thioredoxin family of proteins and contains a redox-active disulfide/dithiol, within the conserved active site CXXC [27, 28]. The most general function of Trx is to catalyze the reduction of disulfide bonds in target proteins, including ribonucleotide reductase and the oxidized form of Trx with a disulfide is reversibly reduced by the action of TrxR [29]. Collectively, NADPH, Trx, and TrxR are called the thioredoxin system. Oxygen metabolism in aerobic organisms causes reactive oxygen species requiring balancing antioxidant systems for defending the organism against irreversible damage by ROS. As such the Trx system is important because it provides reduction of the disulfide in peroxiredoxins after reduction of hydrogen peroxide and peroxides [30]. The mechanism of Trx has been identified many years ago and involves the nucleophilic attack of the N-terminal Cys residue of the active site in Trx1 (–CGPC–) and formation of a mixed disulfide intermediate (Fig. 1) followed by an attack of the cysteine-35 to resolve the mixed disulfide [31]. By using Trx1 mutated to C35S (a trapping mutant) many targets of Trx have been identified as substrates [4]. Trx can be found both in the cytosol/nucleus (Trx1) or mitochondria (Trx2) as well as Trx1 extracellularly where it acts as a co-cytokine [32]. Secretion of Trx also generates Trx80 [30] which is a truncated form of Trx1 which has immune functions by acting as a growth factor for monocytes [33] leading to a Th1 response and driving inflammation [34].

In the intracellular context, TrxR and Trx, via the assistance of NADPH (the Trx system), exerts a fundamental role in supporting the redox milieu [35]. The substrate Trx is similarly found (as Trx1 and Trx2) not only in various intracellular compartments but also in blood plasma and other extracellular fluids. Trx1 has a fundamental role in the regulation of the homeostasis of protein thiol and ROS signaling, both in the intra- and extracellular milieu. Its impairment has been recently associated with a panoply of pathologies, e.g., tumors, infection from HIV, neurodegenerative and cardiovascular diseases [36, 37]. Enhanced levels of extracellular Trx have been reported in plasma samples from individuals with various diseases, including sepsis and HIV infection [38, 39]. The pharmacological attempts to administrate Trx appears a possible success in pre-clinical trials, but a more keen reappraisal of these studies revealed that effect remains quite elusive [40, 41].

TrxR and Trx are also targeted for the prevention and treatment of cancer, autoimmune and chronic inflammatory diseases. The activity of TrxR is influenced both by genetic and environmental factors. In numerous tumors, such as acute lymphocytic leukemia, lung carcinoma, breast cancer, colorectal cancer, hepatocellular and gastric cancer, non-Hodgkin lymphoma, pancreas cancer, myeloma, an increased level of Trx or TrxR have been reported, usually in association with aggressive tumor behavior [42–45].

At least three isoenzymes are recognizable in mammals, namely the cytosolic form TrxR1 (or TXRND1), the mitochondrial TrxR2 (or TXNRD2) and the thioredoxin glutathione reductase TrxR3 (or TGR) [10]. Mitochondrial TrxRs are present in several different cell types and organs,

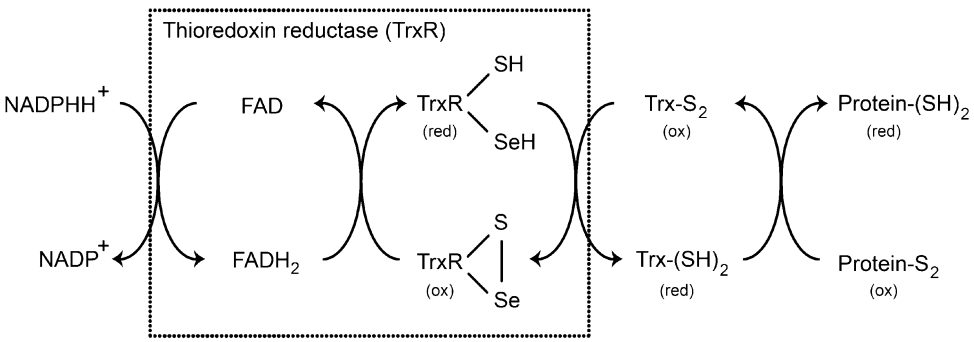

Fig. 1 Reaction sequence of TrxR-mediated reduction of protein disulfides

including skeletal muscle cells [46–48], cardiomyocytes [49–55], and endothelial cells [56, 57], where these enzymes are presumably crucial for the scavenging of the intra-mitochondrial H_2O_2 and peroxynitrite (ONOO–). Mitochondria are primary regulators of the redox homeostasis [58]. In this context, the role of Trx may be strategic [59].

The crystal structure of the Trx/TrxR complex in humans confirmed that TrxRs in mammals contains selenocysteine, in a peculiar configuration [35, 60]. The simplest description would depict a complex where one part of the molecule is a flavoprotein, while the other one is a flexible arm, which close to its end contains a cysteinyl group and a selenocysteinyl group in vicinal positions [13–62]. This configuration makes it possible for the enzyme to form chelate complexes with heavy metals, where the metal atoms are simultaneously coordinated to the Se atom of the selenol group and the sulfur (S) atom of the thiol group [35]. Thus, the adequate functioning of the enzyme is presumed to be vulnerable not only to Se and riboflavin deficiencies, but also to toxic metal exposure, e.g., arsenic (As) [63], cadmium (Cd) [64, 65], mercury (Hg) [3, 66–70], and tributyltin [64].

Thioredoxin reductase is necessary as a reducing substrate in all biochemical reactions involving Trx [71]. It plays a critical role in the mitochondrial ability to regulate redox signaling and H_2O_2 [10]. Further, it has been shown that the enzymatic complex of TrxR has a function during the progression of metabolic syndromes and cardiovascular disorders [72–75]. Recent reports suggest that the thioredoxin/thioredoxin binding reductase (Trx/TrxBP) system plays a significant role in the protection of the human cardiovascular system [76]. Also, it has been shown that in pregnant women affected by gestational diabetes, this same enzyme system (Trx/TrxBP) mediates a possible compensatory mechanism against glucotoxicity [77, 78]. Moreover, Trx2 plays a protective role during ischemic damage, as observed in an oxygen-glucose deprivation and reperfusion model in H9c2 cells [79]. Here, it is of interest that the TrxRs appear to require somewhat higher serum Se levels than other human selenoenzymes to be optimized [80]. In this context, the present article provides a review of the role of the Trx/TrxR system in metabolic diseases.

Thioredoxin, thioredoxin reductase, and metabolic syndrome: what is new?

Metabolic syndrome is usually characterized by impaired glucose tolerance, elevated blood pressure, and elevated triglyceride–HDL ratio, in addition to central obesity [81, 82], and often accompanied by nonalcoholic steatohepatitis [83]. The existing studies indicate profound changes in the Trx/TrxR system in metabolic syndrome [76, 84]. Thus, examination of metabolic syndrome patients revealed a significant postprandial increase in adipose tissue Trx mRNA levels after consumption of a diet rich in high-saturated fatty acids (HSFA) in comparison to low-fat diets. This was paralleled by a significant postprandial decrease of adipose tissue TrxR1 mRNA, presumably reflecting increased oxidative stress in response to saturated fat consumption [85]. Furthermore, circulating Trx levels were found to be significantly higher in metabolic syndrome patients compared to healthy controls, but did not vary with respect to lectin-like oxidized low-density lipoprotein receptor-1 polymorphism [86]. However, data on the role of TrxR and Trx in metabolic syndrome and its components appear contradictory. In the following sections, the interaction and the possible mechanisms of the interplay between the Trx/TrxR system and the metabolic syndrome components, including obesity, nonalcoholic steatohepatitis (NASH), insulin resistance and diabetes, hypertension, and atherosclerosis will be discussed.

Thioredoxin, thioredoxin reductase, and adipose tissue pathophysiology

Recent studies have demonstrated a significant role of the Trx system in adipocyte dysfunction and obesity [87]. It has been revealed that obese people with metabolic disturbances are characterized by significantly elevated TrxR activity and Trx content in subcutaneous tissue in comparison to metabolically healthy obese and control subjects [88]. Actually, Trx has a major role in insulin sensitivity [89–91]. Thioredoxin reductase-1 transcript levels in subcutaneous adipocytes in women are inversely associated with insulin sensitivity [92]. Moreover, it was found that adipocytes from subjects with low fat-oxidizing capacity were characterized by 1.7-fold higher expression of TrxR compared to the same values in high-fat oxidizing subjects [93]. Examination twin pairs revealed a significant (+ 30%) up-regulation of TrxR1 in subcutaneous adipose tissue of obese twins in comparison to the lean ones [94]. Adipose tissue TrxR1 expression in obese nondiabetic subjects significantly correlated with percent fat mass.

Comparative analysis of protein expression demonstrated that Trx is differentially expressed in the white adipose tissue of type 2 diabetic patients as compared to healthy controls [95]. Trx levels were also shown to be reduced in the serum of obese children in comparison to the age- and sex-matched lean subjects. Recent studies also indicate that thioredoxin-mimetic peptides (TMPs) can inhibit the inflammation associated with high-glucose levels and oxidative stress [96]. Moreover, a significant inverse correlation between serum Trx levels and systemic inflammation as assessed by complement fragment C4 has been observed, supporting the hypothesis of Trx as an anti-inflammatory factor [97].

The expression of the thioredoxin-interacting protein (TXNIP) in subcutaneous abdominal adipose tissue tended to decrease in obese adolescents in parallel with increasing rate of glucose intolerance, although this trend did not achieve statistical significance [98]. A detailed examination using whole blood from 1647 Mexican mestizo people revealed that TXNIP gene rs7211 polymorphism in this population was associated with obesity [99].

It is noteworthy here that caloric restriction resulted in a significant decrease in the expression of Trx-dependent peroxide reductase (peroxiredoxin-3) in adipose tissue of overweight and obese subjects [100]. Peroxiredoxin-3 is a key molecule regulating adipocyte oxidative stress and adipokine expression [101]. A detailed analysis of rat adipose tissues demonstrated that Trx and TrxR are produced in visceral, subcutaneous, as well as gonadal fat pads [102]. Analysis of human mesenchymal stem cell secretome at the early steps of adipocyte differentiation also revealed TrxR1 production [103]. The analysis of 3T3-L1 adipocytes proteome demonstrated a secretion of Trx, supporting the hypothesis of a significant role of the Trx system in adipocyte biology [104]. Experimental studies have shown an association between obesity and TrxR activity. In particular, ob/ob mice were characterized by increased TrxR mRNA expression in visceral adipose tissue [105]. Genetic obesity (ob/ob) in mice was characterized by significantly increased TrxR1 mRNA expression in liver and white adipose tissue [106]. The role of the Trx/TrxR system in adipocytes might serve as a master tuner of the redox detoxification and maintenance of cell survival, particularly when stressors overwhelm alternative scavenging systems to counteract a stress-derived damage.

It is in accordance with this hypothesis that overexpression of Trx1 and Trx2 prevents adiponectin-induced apoptosis mediated by reactive oxygen species (ROS) in hepatocellular carcinoma cells [107]. Adiponectin apparently acts as an inhibitor of Trx1 synthesis. In particular, adipose-KO mice with low adiponectin levels were characterized by a significant increase in serum Trx1 protein levels and activity [108]. Another ROS scavenger is catalase, and high-fat feeding accompanied by a significant upregulation of catalase expression did not significantly affect the expression of Trx and TrxR in the mouse heart [109]. A similar mechanism might explain that high-fructose feeding did not result in significant alteration of TrxR activity in testes and kidneys in rats [110]. Oppositely, Fisher-Wellman et al. [111] found that a high-fat high-sucrose diet was associated with increased body weight, body fat, and adiposity index in rats, and was also accompanied by TrxR2 up-regulation in the heart. Most probably, upregulation of TrxR2 occurs when metabolic oxidative stress is high. It is also notable that exercise by running in sedentary animals positively up-regulated TrxR2 in both heart and skeletal muscle. The authors have proposed a critical role of TrxR2 in the control of mitochondrial H_2O_2 flux during fatty acid oxidation [111]. Interestingly, high-fat (50%) feeding for 13 weeks in male C57BL/6J mice that were complicated by hepatic and systemic insulin resistance, was accompanied by a significant decrease in liver TrxR and Trx activity, and such high-fat diet was also associated with decreased liver peroxisome proliferator-activated receptor y (PPARγ) expression, hyperleptinemia, and increased expression of hepatic leptin receptor and protein-tyrosine phosphatase 1B (PTP1B).

Finally, it has been demonstrated that 4-hydroxynonenal overproduction at least partially contributes to the high-fat diet induced depression of the Trx/TrxR system [112]. Interesting data were obtained using laboratory mice overexpressing Trx1 (Tg(*TRX1*)$^{+/0}$). In particular, high-fat feeding in these Trx1 overexpressing mice resulted in a significant increase in adipose tissue mass, but these animals retained an intact glucose tolerance in contrast to the control wild-type mice [113].

In vitro studies demonstrated that TrxR1-deficient murine fibroblasts were characterized by increased glycogen storage, lipogenesis, and adipogenesis, being associated with PPARy up-regulation and increased Akt activation. Moreover, TrxR1 knockdown in human pre-adipocytes resulted in increased adipocyte differentiation [92]. It has also been demonstrated that TXNIP, an endogenous inhibitor of Trx that interacts with a cysteine motifs [104], also acts as an inhibitor of adipogenesis [105]. Correspondingly, preadipocytes and murine embryonic fibroblasts deficient in TXNIP were characterized by increased adipogenesis, whereas TXNIP overexpression resulted in an impaired adipocyte differentiation [106]. Suppression of TXNIP in adipocytes prevented the glucose-induced production of IL-1, being indicative of a role of TXNIP in diabetes-associated inflammatory response [107]. It has been reported that mRNA levels of TXNIP are increased in adipose tissue of animals with genetic ob/ob and db/db obesity [108]. A huge deal of studies reports the major role of the Se-Trx system in metabolic syndrome and adipogenesis [109–118]. A detailed study by Rajalin et al. [119] demonstrated a role of the Trx-dependent redox system in adipogenesis. The authors found that adipocyte differentiation is associated with an increase in both TrxR1 and TrxR2 activity. At the same time, it has been reported that inhibitors of adipogenesis decrease TrxR activity in differentiating, but not in mature cells [119].

What can these results inform us?

These findings are in agreement with the earlier data by Song et al. [120] who showed that Trx1 and Trx2 regulate human adipose tissue-derived mesenchymal stem cells proliferation and survival through activation of ERK1/2. It is also notable that intraperitoneal injection of aurothioglucose, that is used in animal modeling of obesity [121],

resulted in a significant decrease in TrxR activity in heart, liver, and pancreas, whereas tissue GPx1 activity was unaltered [121]. Figure 2 summarizes this overview.

Dysfunctions in brain centers of satiety and hunger have been considered fundamental in the development of obesity. In this respect, it is of particular interest that Zhao et al. [122] demonstrated that the TrxR1-related mRNA levels in hypothalamus and pituitary in obese pigs were significantly decreased, whereas thyroid TrxR1 mRNA concentrations in the animals were elevated. At the same time, overexpression of TXNIP in murine agouti-related peptide (AgRP) neurons resulted in increased susceptibility to diet-induced adiposity and obesity through decreased energy expenditure. TXNIP deficiency was associated with reduced the rate of obesity and improved blood glucose levels and leptin sensitivity [123]. Recently it has also been reported that deletion of the TrxR-resembling selenoprotein M by experimental genetic knockdown leads to leptin resistance and metabolic syndrome with obesity [124].

Experimental studies using non-rodent models also demonstrated the influence of Se status on TrxR activity in adipose tissue. In this case, it has also been shown that prolonged Se deficiency in chicken was associated with a decrease in TrxR1, TrxR2, and TrxR3 mRNA expression in subcutaneous, articular, and visceral adipose tissue [125]. Apparently, the TrxR enzymes are critically dependent on adequate Se intakes [80]. However, supra-nutritional Se intakes in pigs did not significantly alter TrxR1 expression in liver, skeletal muscle and visceral adipose tissue [126].

In sum, the reviewed observations show that the Trx/TrxR system plays a significant role in the adipose tissue physiology. A modified adipose tissue accumulation in obesity appears actually to be achieved by modulation of the Trx system (see also Fig. 1). It has been shown that Trx is essential for normal differentiation and maturation

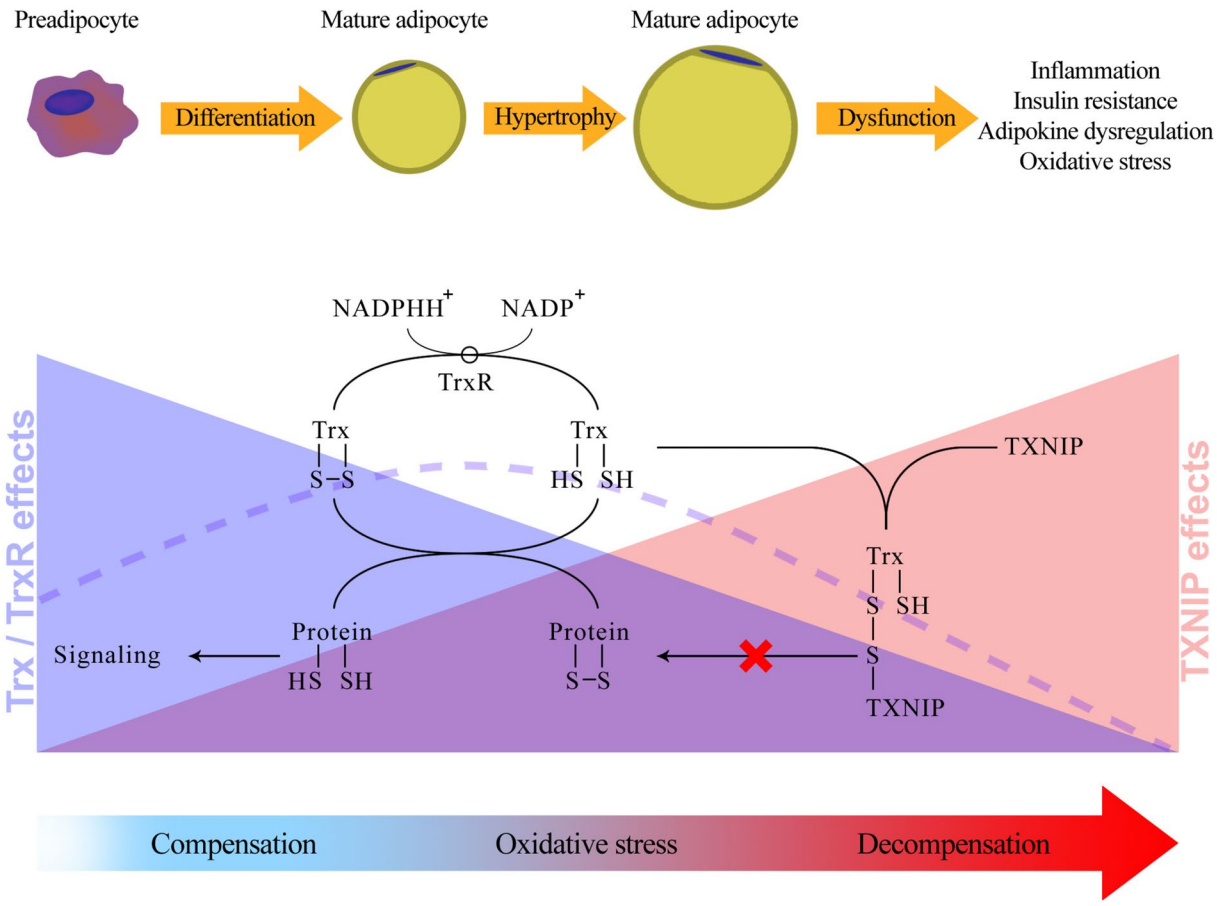

Fig. 2 The mechanistic scheme of the effect of interaction between Trx and TXNIP signaling on adipose tissue development and functioning. Normal Trx redox cycling is required for adipogenesis, whereas increased TXNIP levels appear to inhibit differentiation and maturation of adipocytes. At the same time, TXNIP signaling is associated with adipose tissue dysfunction, leading to obesity and metabolic syndrome. The dotted line is indicative of the level of Trx that seem to be increased in the early stages of adipocyte hypertrophy as a compensatory response to oxidative stress. At further stages, increased TXNIP levels, as well as increased oxidative stress and Trx requirements, result in a decrease in Trx levels

of adipocytes through the influence of various regulators, including PPARγ. Also, aberrant TXNIP signaling is associated with increased inflammatory reaction and insulin resistance in adipose tissue. Therefore, the role of the Trx system in metabolism is fundamental.

Certain contradictions in human studies regarding the levels of Trx in obese patients may be related to the stage of the disease. It is tempting to hypothesize from the available observations that adipocyte hypertrophy is associated with oxidative stress and that increased Trx production acts as a compensatory response to an altered redox environment. However, when adipose tissue escalates into an "unhealthy" state ("morbid obesity") and oxidative stress is aggravated, Trx levels significantly decrease. It is proposed that modulation of TrxR activity may at least partially mediate changes in Trx levels, and thus they represent one of the targets in treatment strategies. Finally, we wonder if this system might play a role as a possible prognostic marker of the metabolic syndrome. The role of this complex system in the development of obesity, metabolic syndrome, and atherosclerosis needs to be further explored. The observed interactions between Trx/TrxR and other metabolic pathways in adipose tissue demonstrate that it could be at least partially involved in the development of obesity-associated metabolic disturbances.

Thioredoxin reductase and non-alcoholic steatohepatitis (NASH)

Multiple studies have reported changes in the Trx/TrxR system upon the development of NASH [127, 128]. Examination of patients with simple fatty liver and NASH revealed significantly elevated levels of serum Trx in the latter. Moreover, elevated Trx and ferritin levels appeared to be potent biomarkers for distinguishing NASH from early stages of fatty liver [129]. Furthermore, the severity of NASH was reflected by raised Trx levels paralleled by increased iron accumulation in the liver [130]. Reduction of hepatic iron stores by phlebotomy significantly decreased serum Trx levels [131]. A similar relationship was reported in recent years. Another study reported a significant correlation between serum Trx levels and the severity of hepatic steatosis [132]. Correspondingly, 12-month treatment of NASH patients with highly purified eicosapentaenoic acid resulted in significantly lower values of alpha-lipoic acid (ALA), free fatty acids, soluble tumor necrosis factor (TNF) receptor 1 and 2, ferritin, and Trx levels, all being associated with improved liver histology [133]. It has also been demonstrated that patients with nonalcoholic fatty liver disease (NAFLD) were characterized by significantly elevated levels of hepatic Trx-interacting protein (TXNIP) [36].

Non-alcoholic steatohepatitis induced by methionine- and choline-deficient diet in C57BL/6 mice was associated with a significant overexpression of TXNIP gene and reduced expression of TrxR1 and TrxR2, but not TrxR3 in the liver, in comparison to the control animals [134]. In a choline-deficient model of liver steatosis, the activities of both Trx1 and TrxR in the liver was significantly increased as measured at the 14th day of choline-deficient diet consumption. Subsequently, the activity of both proteins significantly decreased to the 30th day in comparison to both initial and day 14 values [135]. A high-fat diet (HFD) also resulted in a significant increase in body and adipose tissue weight, insulin resistance, and liver steatosis due to activation of lipogenic genes, all being accompanied by increased hepatic TXNIP levels. In turn, curcumin treatment significantly improved metabolic parameters of animals and reduced hepatic TXNIP at both protein and mRNA levels [136]. Correspondingly, TXNIP deficiency in HFD-fed mice ($Txnip^{-/-}$) prevented diet-induced hepatic steatosis, lipogenesis, and inflammation [36]. In this context, it has also been demonstrated that protective effect of honey against high-fat-diet-induced non-alcoholic steatohepatitis is associated with the inhibition of TXNIP overexpression [137]. At the same time, the results of the earliest studies demonstrated that $Txnip^{-/-}$ mice were characterized by hyperlipidemia [increased triglycerides (TG), non-esterified fatty acids (NEFA), β-hydroxybutyrate] and increased liver TG, cholesterol, and cholesteryl ester (CE) due to increased lipogenic activity [138].

These reports strongly indicate a role of the Trx/TrxR complex in the reactive oxygen species involvement in the onset of metabolic syndrome characterized by NASH development. It is notable that glutathione (GSH)-deficient mice, resistant to diet-induced steatohepatitis, are characterized by a significant up-regulation of TrxR1 gene in liver [139]. Similarly, high-fat feeding of $PTEN^{flox/flox}$ [hepatocyte-specific phosphatase and tensin homolog (PTEN)-KO mice] resulted in liver steatosis, being accompanied by a significant elevation of TrxR activity [140]. Furthermore, it has been demonstrated that HFD-feeding in Wistar rats resulted in the presence of fatty liver at week nine. Simultaneously, hepatic Trx expression was significantly decreased in comparison to the control group values. The authors reported further progression of liver disorder into steatohepatitis after 13–18 weeks, accompanied by a gradual increase in Trx mRNA expression, although these values were lower than that in the control group [141]. High-fat feeding in Nrf2-deficient mice ($Nrf^{-/-}$) was associated with NASH development and even cirrhosis in contrast to wild-type controls, the latter group being protected by increased lipogenesis and better insulin sensitivity. Despite a diet-induced increase in liver TrxR expression in $Nrf2^{-/-}$ mice, the values were still significantly lower than the respective values in HFD-fed wild-type controls [142]. The effect of Nrf2 deficiency on

TrxR was also demonstrated in a model of toxin-induced steatohepatitis. In particular, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin treatment in mice resulted in a significant elevation of hepatic TrxR1 expression. The exposed $Nrf2^{-/-}$ mice were characterized by higher intensity of hepatocyte degeneration, lipid accumulation, and fibrosis in comparison to wild-type controls, accompanied by a significant decrease in TrxR1 expression [143]. It has been suggested that TrxR exerts an important protective role in the mitochondrial ROS scavenging, thereby influencing mechanisms such as apoptosis and autophagy.

Thioredoxin, thioredoxin reductase, and diabetes: an indirect correlation?

The association between the Trx/TrxR system activity and diabetes has been shown both in clinical and experimental studies. In particular, an examination of 174 diabetic patients revealed a significant increase in serum Trx levels in comparison to normoglycemic controls. However, serum Trx values did not correlate with fasting blood glucose and glycated hemoglobin (HbA_{1c}) levels [144]. A later study involving 178 adults demonstrated a significant increase in plasma Trx levels in patients with impaired glucose tolerance and diabetes mellitus. In the latter study, plasma Trx levels significantly correlated with HbA_{1c} levels, whereas glucose intolerance was found to be independently associated with high Trx levels [145]. It is also notable that Trx gene polymorphism is significantly associated with susceptibility to type 1 diabetes mellitus in the Japanese population [145, 146]. Thioredoxin reductase-1 activity was significantly increased in lymphocytes of diabetic nephropathic patients in parallel with elevated oxidative stress biomarkers. This finding allowed the authors to propose that the observed increase in TrxR activity is a cellular response to oxidative stress in diabetes [147]. A later study of the same authors demonstrated increased biomarkers of oxidative stress paralleled by an increase in Trx and TrxR1 levels in lymphocytes in diabetic nephropathic patients [148]. Reduced levels of GSH in red blood cells from of poorly controlled type 2 diabetic patients were also ascribed to a significant oxidative stress in this group of patients [149].

An upregulation of the Trx/TrxR system is presumed to act protectively against further complications of diabetes. Thus, Trx overexpression in streptozotocin-diabetic animals did not improve glycemic control or modulate phosphorus-calcium homeostasis, whereas it caused a significant decrease in bone tissue oxidative stress and partially prevented diabetes-associated reduction of bone mineral density [150].

Previous studies have revealed the potential protective effect of the Trx/TrxR system against progressive pancreatic β-cell damage. In particular, overexpression of Trx in β-cells prevented both autoimmune and streptozotocin-induced diabetes [151]. Also, Trx overexpression in db/db mice prevented weight loss and hyperinsulinism and protected β-cells from dysfunction and destruction [152]. Similarly, intravenous administration of recombinant human Trx1 in nonobese diabetic (NOD) mice reduced signs of insulitis and prevented β-cell damage [153].

However, the involvement of TXNIP may result in inhibition of the Trx system in diabetes [154]. In particular, it has been reported that very high glucose levels significantly reduced Trx activity through upregulation of TXNIP expression via the p38 mitogen-activated protein kinase (MAPK) signaling pathway [155]. Exercise resulted in increased Trx1 protein and activity in normoglycemic rats without any significant effect on TXNIP; whereas diabetes with hyperglycemia altered training-induced increase in Trx1 levels and upregulated TXNIP in rat brain [156]. An investigation by Shaked et al. [157] demonstrated that increased glucose levels in *Psammomys obesus* and isolated INS-1E β-cells resulted in a significant increase in TXNIP production, whereas the level of Trx remained unaltered. At the same time, insulin negatively regulated TXNIP production and this effect were enhanced by NO·. A recent study also demonstrated a significant insulin-induced degradation of TXNIP in adipocytes, preadipocytes, and L6 myotubes, but not in HepG2, HEK 293, or pancreatic β-cells [158].

It has been proposed that TXNIP is involved in regulation of carbohydrate metabolism [154]. In particular, TXNIP expression was negatively correlated with insulin-stimulated glucose uptake in both humans and 3T3-L1 adipocytes [159]. A later study by Chen et al. [160] demonstrated a significant protection of pancreatic islets against glucose-induced apoptosis in TXNIP-deficient HcB-19 mice. Moreover, the authors revealed a substantial increase in TXNIP expression in response to high-glucose incubation (25 mM) in INS-1 β-cells. Correspondingly, β-cell specific TXNIP deficiency resulted in increased cell mass and a significant reduction in streptozotocin-induced apoptosis through induction of Akt/Bcl-xL signaling [160]. A later study by Masson et al. [161] also demonstrated a significant increase in β-cell mass in TXNIP deficient mice. However, the relative streptozotocin-induced decrease in cell mass was greater than in the control animals. TXNIP deficient INS-1 β-cells were also characterized by increased sensitivity to streptozotocin toxicity and proinflammatory cytokines, as well as reduced glucose-induced insulin secretion [162]. The results of these studies indicate that TXNIP is involved in the control of insulin production [163].

Non-obese patients with type 2 diabetes mellitus were also characterized by significantly increased expression of TXNIP in peripheral mononuclear cells as compared to the control subjects and obese diabetics. Moreover, in the group

of people with diabetes with normal weight expression of TXNIP directly correlated with fasting blood glucose, and advanced glycation end products (AGE) and was inversely associated with HOMA-β values [163].

Experimental studies have also highlighted a role of TXNIP in the development of diabetes complications. In particular, it has been demonstrated that high glucose induces TXNIP expression and epithelial to mesenchymal transition in tubular epithelial HK-2 cells, whereas TXNIP knockdown, as well as *N*-acetylcysteine treatment, prevented glucose-induced cellular transition, ROS generation, decreased Trx activity, phosphorylation of p38 MAPK, and expression of transforming growth factor beta 1 (TGF-β1) [164]. ROS and RNS are produced in vivo and usually affect a broad spectrum of physiological and pathological processes. They both affect cellular function through redox-mediated modification of proteins.

The net effects on cells exerted by ROS and RNS are modulated by NADPH oxidases and NO synthases. In this regard, the antioxidant protein Trx and the tripeptide GSH, together with their system components, should represent the primary defenses against the reactive species [165–167]. Accumulating evidence indicates that Trx and GSH play a homeostatic role in fundamental cellular processes including DNA synthesis, protein maturation, and cellular signaling [165, 166, 168].

Taken together, the reviewed data demonstrate that TXNIP plays a significant role in the development of diabetes complications and β-cell dysfunction and death [169]. Therefore, both the Trx/TrxR-system and its antagonistic principle TXNIP have been proposed as potential targets for antidiabetic and cardiovascular therapy [37].

The protective effects of various substances in diabetes might be mediated through regulation of the Trx/TrxR system. In particular, wolfberry feeding prevented retinal damage in diabetic (db/db) mice through upregulation of retinal Trx via activation of AMP-activated protein kinase (AMPK) [170]. However, the earlier study demonstrated that 3–5 days treatment with high glucose did not result in a significant alteration in Trx/TrxR activity in retinal Muller cells, whereas glutaredoxin was up-regulated [171]. Cardioprotective effect of antidiabetic agent metformin has been ascribed to an upregulation of Trx expression, i.e., in human aortic endothelial cells via activation of the AMPK–FOXO3 pathway [172]. Similarly, probucol treatment induced increased Trx and insulin expression, as well as depressed TXNIP expression in diabetic rats [173]. Resveratrol treatment in diabetic (streptozotocin) rats significantly reduced blood glucose levels, prevented ventricular dysfunction, decreased infarction size and cardiomyocyte apoptosis, all being accompanied by induction of phosphorylated Akt and endothelial nitrous oxide (eNOS), vascular endothelial growth factor (VEGF), and Trx1, as well as activation of manganese superoxide dismutase (MnSOD) [174]. It has also been proposed that antidiabetic action of dihydrolipoic acid may be related to its interaction with TrxR [175].

Modulation of Se status has been shown to affect the relationship between Trx/TrxR in diabetes significantly. In particular, treatment of diabetic Se-deficient db/db mice with selenite was associated with reduced insulin resistance and increased liver TrxR activity [176]. Sodium selenite treatment in streptozotocin-diabetic rats prevented a diabetes-associated decrease in skeletal muscle Trx levels [177]. The diabetogenic effect of As exposure [178] may be related to the As–Se antagonism [179, 180]. Modulation of the Trx/TrxR system may also provide an additional link between diabetes and cardiovascular complications of hyperglycemia. In particular, methylglyoxal, a reactive glucose metabolite, exposure (5 mM) resulted in a significant decrease in Trx levels and TrxR inactivation in bovine aortic endothelial cells. It is also notable that the TrxR enzymes were more susceptible to inhibition by methylglyoxal than GPx [181]. Cultivation of murine cardiomyocytes in high-glucose conditions was accompanied by increased O_2- and ONOO-production, Trx1 nitration and a subsequent reduction of Trx1 activity. Simulated ischemia/reperfusion in high-glucose medium aggravated the observed effects, whereas supplementation with human Trx1 or antioxidants prevented ROS overproduction, Trx1 inhibition and cellular injury [182] Similarly, diabetic animals were characterized by increased vascular TXNIP expression and decreased Trx activity, all being prevented by insulin treatment [183]. Myocardial TrxR activity was also significantly decreased in diabetic (streptozotocin-induced) rats but not in Rac1 KO animals, being indicative of the role Rac1/NADPH oxidase signaling in the regulation of TrxR activity [184]. Finally, Trx1 gene therapy resulted in a significant increase in myocardial Trx1 expression as well as reduced fibrosis in myocardial infarction in rats with streptozotocin-induced diabetes [185].

Modulation of the Trx/TrxR system in diabetes mellitus is considered as a compensatory response to diabetes-related oxidative stress, aiming at prevention of further metabolic complications. Also, the Trx system appears to have a direct regulatory effect on carbohydrate metabolism, including insulin production, sensitivity, and β-cell death.

Thioredoxin, thioredoxin reductase, and hypertension

The existing data demonstrate that the Trx system is involved in the modulation of oxidative stress, being one of the mechanisms in the development of high blood pressure [186]. In turn, alteration of the Trx/TrxR system is expected to occur in hypertensive patients [74, 187]. A significant role of TrxR modulation in cardiovascular

diseases is supported by the finding that TrxR is the main antioxidant selenoprotein protecting human umbilical-vein endothelial cells from oxidative damage [188]. Additionally, the Trx system was proposed to be the primary redox signaling system in rat aorta even in comparison to the GSH system [189]. Later studies have confirmed a critical role of mitochondrial TrxR2 activity in endothelial cells [4].

Both clinical and experimental studies have demonstrated the association between the Trx/TrxR system and hypertension. In particular, Mansego et al. [190] have revealed significantly elevated mRNA levels of Trx1, Trx2, as well as TrxR1, TrxR2, and TrxR3 in mononuclear cells from patients with untreated hypertension. Three months of antihypertensive treatment resulted in a significant decrease of the Trx system enzymes' expression. It is also notable that the expression of proteins of the GSH system was decreased in the hypertensive patients as compared to normotensive controls [190]. Later studies of the authors have demonstrated that polymorphism c.-793T>C of the Trx gene was also associated with lower blood pressure in an adult population of central Spain [191].

The study involving 576 adults from the urban population of Vitoria, Brazil, demonstrated that polymorphisms of Trx interacting protein (TXNIP), an endogenous Trx inhibitor, associated with a higher TXNIP expression is characterized by increased blood pressure [192]. These findings confirmed the results of the previous study demonstrating a 5.5-mmHg higher diastolic blood pressure in the TXNIP T-allele carriers as compared to the homozygous carriers [193].

Experimental data are indicative of impaired induction of Trx expression in genetically hypertensive rats [194]. Studies using transgenic mice overexpressing human Trx2 (Tg^{hTrx2} mice) have demonstrated that Trx overexpression prevented angiotensin II-induced hypertension, alteration of endothelium-dependent vasorelaxation. The observed effects were associated with Trx-mediated prevention of increased O_2^{-} and H_2O_2 production, activation NADPH oxidase expression [195]. These data are in agreement with the previous indication of increased serum NO· levels, reduced vasoconstriction, and increased vasodilatation in aortas of Trx2 transgenic mice [196]. Based on these observations it was proposed that Trx2 might decrease blood pressure through reduction of mitochondrial H_2O_2 production ultimately leading to attenuation of angiotensin II-induced hypertension [197].

At the same time, infusion of angiotensin II was associated with a threefold increase in Trx expression and TrxR activity in male C57Bl/6 mice but not in female ones, is indicative of a significant influence of estrogens [198]. This finding allows proposing that modulation of the Trx system may serve as a cardiovascular protective mechanism for estrogens [75].

Treatment of aortic rings from C57BL/6 mice with TrxR inhibitor (1-chloro-2,4-dinitrobenzene; DNCB) reduced acetylcholine- and sodium nitroprusside-induced vascular relaxation via soluble guanylyl cyclase *S*-nitrosylation [199]. A later study of the authors demonstrated a significant decrease in TRxR activity and increased *S*-nitrosylation in aortic rings of angiotensin II-induced hypertensive C57BL/6 mice [200].

In vitro studies also support the role of altered the TRx/TRxR system in hypertension. In particular, in a coculture of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) reduced ROS production was abolished by TRxR inhibitor treatment, whereas NOS, cyclooxygenase-2 (COX-2), and 20-hydroxyeicosatetraenoic acid (20-HETE) inhibitors were not effective [201]. It is also notable that TrxR is capable of activating HO-1 activity in aortic endothelial cells, providing an additional link between altered TrxR activity and oxidative stress in endothelial cells in cardiovascular diseases [202]. Correspondingly, Trx gene therapy as well as the associated increase in Trx1, HO-1, and Bcl-2 expression was associated with reduced alteration of cardiomyocytes in spontaneously hypertensive rats with myocardial infarction [203].

The interplay between Trx/TrxR and nitric oxide (NO) may provide an additional mechanism for the role of the Trx system in hypertension. In particular, peroxynitrite (ONOO–), a NO· metabolite, was shown to decrease TrxR activity being associated with the upregulation of TrxR gene in endothelial cells [204]. Moreover, NO· exposure significantly decreased expression of TXNIP, an endogenous Trx inhibitor, and increased TrxR expression, all being associated with elevated Trx activity in rat pulmonary artery smooth muscle cells [205]. Another study demonstrated that exposure of pulmonary artery endothelial cells to NO· (8.5 ppm for 24 h) resulted in a significant decrease in Trx and TrxR at both mRNA and protein levels. At the same time, increased Trx expression in endothelial cells prevented NO·-induced eNOS inactivation [206]. Moreover, both Trx and TrxR were shown to prevent NO·-induced inhibition of protein kinase C in pulmonary artery endothelial cells [207].

Finally, Se supplementation was proposed to be effective against hypertension through modulation of TrxR activity [208].

Thioredoxin, thioredoxin reductase, and atherosclerosis

In parallel with hypertension progression, the Trx system appears to play a significant role in the progression of atherosclerosis in patients with metabolic syndrome [209]. It has been reported that increased TrxR activity characterizes patients with the uncomplicated coronary artery disease, although Trx activity does not differ significantly from the

controls. The selenoenzyme TrxR may exert a protective action against atherosclerosis. Thus, in a recent study, supplementation with Se in an elderly healthy Swedish population reduced cardiovascular mortality, improved cardiac function [210], as well as decreased oxidative stress [211] and inflammation [212]. An inverse association between Trx activity and Hcy levels in the high-Hcy group has been observed [213]. Serum Trx levels were shown to be higher in patients in an active stage of spastic coronary angina in comparison to inactive stage values. Moreover, treatment with calcium channel blockers resulted in decreased Trx levels in some patients [214]. Examination of asymptomatic subjects with plaques and patients with carotid atherosclerosis revealed elevated plasma Trx and peroxiredoxin-1 levels, and these levels were directly associated with intima-media thickness. Further immunohistochemical analysis showed a colocalization between p22phox NADPH oxidase subunit and Trx/paired related homeobox 1 (Prrx1) in macrophages, indicative of an association between Trx/Prrx1 and NADPH oxidase activity as a coordinated antioxidant response in a pro-oxidant environment in atherogenesis [215]. In a study of coronary heart disease patients, serum Trx levels were found to be negatively related to the Hcy levels [216].

Familial combined hyperlipidemia was associated with increased plasma Trx levels in comparison to the control values. Similarly, Trx levels were significantly higher in patients with hypercholesterolemia [217]. Further examination of hypercholesterolemic patients demonstrated that TrxR1 activity tended to increase in persons with high LDL levels, although the tendency was not significant. At the same time, the authors have shown a significant elevation of SOD/TrxR1 ratio in the high-LDL group. And the SOD/TrxR1 ratio was correlated to the oxidized LDL (oxLDL-Ab) levels, whereas TrxR1 activity was not [218]. Patients with familial hypercholesterolemia were also characterized by a significantly higher Trx expression in mononuclear cells in comparison to the control values in a fasted state. At the same time, no significant group difference was detected in TrxR1, TrxR2, and TrxR3 activity. Similarly, the expression of the proteins did not change significantly in response to oral fat load test due to a high variability of data [219].

Analysis of non-atherosclerotic human coronary arteries demonstrated that Trx is expressed in medial smooth muscle cells, whereas in atherosclerotic arteries Trx was expressed throughout the wall and especially in macrophages [220]. Correspondingly, a later study demonstrated increased Trx protein and mRNA levels both in endothelial cells and macrophages in the atherosclerotic plaques [221]. Moreover, Trx immunoreactivity was increased in macrophages of the coronary plaque from patients with an unstable plaque as compared to the stable one [222]. Further studies of the authors demonstrated that Trx immunopositive areas in atherectomy specimens were associated with Fe^{2+}/Fe^{3+} deposition and thrombosis [223]. It has also been noted that Trx levels are related to recurrent angina attacks [224]. Increased plasma Trx levels were also related to high disease activity and the frequency of angina attacks. Moreover, elevated Trx levels and smoking were considered as independent factors influencing coronary spasm [225]. Plasma Trx levels also positively correlated with small platelet aggregates in patients with acute myocardial infarction, stable exertional angina, and chest pain syndrome [226].

It has also been demonstrated that both Trx and TXNIP were overexpressed in the regions of human stable carotid plaques with CD68+ macrophage infiltration [227]. Higher plasma TXNIP levels in impaired glucose tolerance were associated with significantly increased carotid artery intima-media thickness, being indicative of the potential of the use of TXNIP as a tool for prediction of atherosclerosis in diabetic patients [122].

Experimental studies have also indicated a tight interplay between the Trx/TrxR system and atherogenesis. Notably, spontaneously hypertensive rats fed a high-cholesterol diet were characterized by increased Trx expression in comparison to the control group [228]. Increased nuclear Trx1 in mice (NLS-Trx1 Tg) was associated with carotid wall thickening increased due to disturbed flow but did not result in increased body weight or altered lipid spectrum. It has been found that Trx1 elevation was associated with increased nuclear factor kappa B (NF-κB) activation and vascular cell adhesion protein 1 (VCAM1) expression as well as with intercellular adhesion molecule 1 (ICAM1) and IL-6 expression in carotid arteries [229]. Interesting data were obtained by Dai et al. [230] who described two types of waveform stimulation, atheroprone or atheroprotective, on human umbilical vein endothelial cells. The atheroprotective flow was accompanied by elevated TrxR1 expression and certain other cytoprotective genes due to Nrf2 activation through PI3K/Akt pathway [230]. In a hypoxic pulmonary hypertension model, resveratrol showed an encouraging effect on the cardiovascular function, via the upregulation of Trx1 and the nuclear factor erythroid-2 related factor 2 (Nrf-2) [231, 232]. Hypoxic conditions reduce both the expression of Trx1 and Nrf-2 and resveratrol can revert this reduction. The stilbene can also reduce ROS production (probably because of Nrf-2 upregulation) on cultured PASMCs cells [233]. Correspondingly, it has been reported that TXNIP mediates disturbed flow-induced increase in ICAM-1 and VCAM-1 mRNA levels in endothelial cells [234]. It is noteworthy that *Txnip* ablation in mice resulted in a significant decrease in inflammatory response and adhesion molecules both in vascular smooth muscle cells and in macrophages [235].

The use of various treatment strategies to counteract atherogenesis in animal models also demonstrated that modulation of the Trx/TrxR system might at least partially mediate the therapeutic effect. A study involving high-fat fed

apolipoprotein E (ApoE)-deficient mice demonstrated that treatment with olmesartan, which is a novel AT1 receptor antagonist, reduced the development of fatty streak plaque. In turn, in vitro study showed that olmesartan treatment significantly reduced Trx concentration in cultured cells [236]. Moreover, it has been demonstrated that statins may at least partially mediate their pharmacological effect through modulation of the Trx system. In particular, atorvastatin treatment of endothelial cells resulted in a significant increase in Trx *S*-nitrosylation being accompanied by an increase in Trx activity and a significant reduction in ROS levels. At the same time, the activity of non-nitrosylated Trx (TRX(C69S)) was not modified by atorvastatin treatment [237]. Feeding rabbits with hypercholesterolemic diet resulted in hyperlipidemia, altered lipid spectrum, increased LDL oxidation, and increased serum SOD and TrxR activity, whereas treatment with carotenoid astaxanthin prevented alteration of lipid spectrum and increased in TrxR activity. At the same time, in an in vitro study astaxanthin significantly increased TrxR activity of rabbit serum [218]. Later studies demonstrated a similar effect for another carotenoid, bixin [238]. Similarly, blueberry consumption significantly decreased atherosclerotic lesion area in ApoE$^{-/-}$ mice and increased gene expression of antioxidant enzymes including TrxR in the aorta [216]. Modulation of the thioredoxin receptor system by flavonoids appears particularly intriguing, in this sense.

Modulation of the Trx system in macrophages, playing a significant role at both initial stages of atherogenesis and its progression [239], is associated with the functional changes in the cells and atherosclerosis progression. A detailed study by El Hadri et al. [240] demonstrated that Trx1 treatment significantly induced polarization of anti-inflammatory M2 macrophages and decreased LPS-induced differentiation of proinflammatory M1 macrophages. Similar results were observed in an in vivo study. In particular, administration of Trx1 to LPS-exposed hyperlipoproteinemic ApoE2.Ki mice significantly reduced atherosclerotic lesions and shifted the macrophage phenotype to M2 over M1 [240]. At the same time, inhibition of TrxR with auranofin resulted in suppression of NLRP3/IL-1β proinflammatory pathway in macrophages [241]. These data are in agreement with the previous study indicating that extracellular Trx1 significantly decreases IL-1β expression in human monocyte-derived macrophages through reduction of NF-κB activation, acting in contrast to the endogenous Trx1 that activates NF-κB signaling [242].

Modified, inactivated or truncated Trx was considered as a potent stimulator of proinflammatory activity of macrophages. In particular, truncated thioredoxin (Trx80) was shown to decrease polarization of M2 macrophages induced by IL-4 and IL4/IL-13 in vitro but significantly increased differentiation into proinflammatory M1 phenotype in response to lipopolysaccharides (LPS). A similar effect was observed after administration of truncated thioredoxin Trx80 to hyperlipoproteinemic ApoE2.Ki mice. Also, Trx80 potentiated LPS-induced atherogenesis and atherosclerotic lesion area in ApoE2.Ki mice, being accompanied by the predominance of M1 over M2 macrophages [73]. At the same time, reactive aldehyde [acrolein or 4-hydroxynonenal (HNE)] modification of Trx1 was shown to decrease enzyme activity. Also, injection of the aldehyde-modified Trx1 into the culture of endothelial cells resulted in enhanced macrophage adhesion to bovine aortic endothelial cells, being maximal in the case of HNE-modified Trx1 exposure [243].

It is also interesting that exposure of monocytes to atherosclerotic plaque lipid extract resulted in a significant increase in ROS production and a significant decrease in antioxidant enzymes activity including TrxR [244]. Of note, Hcy, similar to H_2O_2, was shown to up-regulate Trx expression in primary human monocytes via increasing NADPH oxidase activity, whereas hyperhomocysteinemia in ApoE$^{-/-}$ mice significantly reduce Trx expression, is associated with atherosclerosis. It was also demonstrated that increased Trx activity in Se-pretreated animals significantly decreased Hcy-induced monocyte chemoattractant protein-1 (MCP-1) expression. These findings allowed proposing a particular role of Trx in early stages of atherosclerosis through modulation of MCP-1 production [230]. Surprisingly, in a study using activated human endothelial-like EAhy926 cells increased TrxR1 expression induced MCP-1 production through NF-kB up-regulation, being indicative of its possible effect on macrophage migration and atherogenesis promotion [245].

Exposure of human macrophages to oxidized LDL was associated with a significant stimulation of Trx and TrxR1 expression, whereas minimally modified LDL caused non-significant changes. It is also notable that minimally modified LDL exposure was associated with increased macrophage TrxR1 and Trx expression from both healthy and atherosclerotic donors [246]. A later study demonstrated that treatment of murine macrophages with oxidized phospholipids resulted in their transformation into Mox phenotype that is characterized by Nrf2-dependent induction of TrxR1 expression. In comparison to M1 and M2 phenotypes, Mox macrophages have lower chemotactic and phagocytic activity, although presenting up to 30% of all macrophages in atherosclerotic lesions of LDLR$^{-/-}$ mice, being indicative of their important role in atherogenesis [247].

Both clinical and experimental studies demonstrate the involvement of the Trx/TrxR system in different stages of atherogenesis. Being a redox control system, the Trx/TrxR system is also capable of regulation of the inflammatory and chemotactic activity of macrophages through modulation of their phenotypes at different stages of atherosclerotic plaque formation.

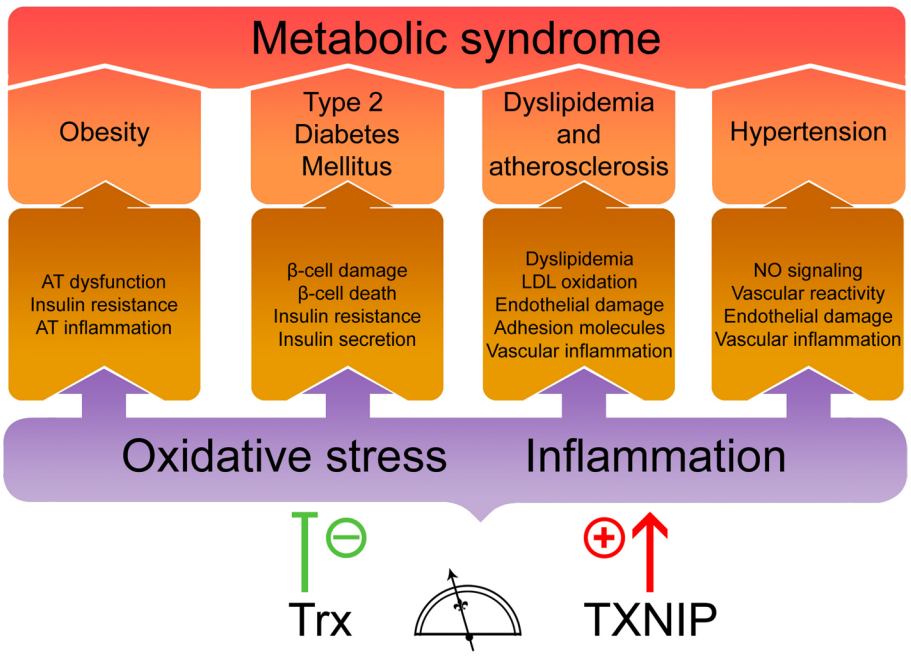

Fig. 3 The proposed effect of the balance between Trx and TXNIP effects on metabolic syndrome and its components through modulation of oxidative stress, inflammatory response (as general mechanisms of pathogenesis), and specific mechanisms of tissue dysfunction

Conclusion

The present review shows that the Trx/TrxR system plays a significant role in the cellular defense against oxidative stress, both with regard to the cytoplasmic antioxidant enzyme endowment and the mitochondrial scavenging activity and these protectors could be suggested as reporting markers of the development of the metabolic syndrome. The patterns of Trx levels change in metabolic syndrome, and these changes are presumed to be related to the role of oxidative stress in the pathogenetic cascade of this syndrome. During disease progression, oxidative stress induces a compensative increase in Trx to reduce oxidative modification of proteins. However, in the case of severe oxidative stress and metabolic disturbances, Trx levels seem to decrease, being indicative of a decompensation. Therefore, it is hypothesized that using increased Trx levels as a marker of oxidative stress is possible only in the case of adaptive responses to altered redox environment. However, in severe metabolic derangements, reduced Trx levels appear to act simply as a marker of progressive oxidative stress.

The existing data demonstrate a protective role of Trx/TrxR system in metabolic syndrome. The normal or increased activity of TrxR maintains Trx redox cycling that is required for counteraction of oxidative stress. In turn, increased TXNIP signaling is associated with activation of the inflammatory response and oxidative stress through Trx binding, contributing to the metabolic syndrome pathogenesis. Moreover, the imbalance between Trx and TXNIP signaling is also associated with specific mechanisms of metabolic syndrome pathogenesis (Fig. 3).

Although such a mechanistic approach provides explanations for the majority of associations observed, certain contradictions still exist. Therefore, further investigation of the role of Trx system in metabolic syndrome is strongly required. It is of particular interest to verify if Se supplementation may have a significant effect on the Trx–TXNIP balance, thus offering a new approach for metabolic syndrome treatment, e.g., in cases precipitated or influenced by toxic metal exposure to As, Cd, Hg, or tin compounds.

Acknowledgements This paper was financially supported by the Ministry of Education and Science of the Russian Federation on the program to improve the competitiveness of Peoples' Friendship University of Russia (RUDN University) among the world's leading research and education centers in 2016–2020.

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