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REVIEW

Progress in the emerging role of selenoproteins in cardiovascular disease: focus on endoplasmic reticulum-resident selenoproteins

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Abstract

Cardiovascular diseases represent one of the most important health problems of developed countries. One of the main actors involved in the onset and development of cardiovascular diseases is the increased production of reactive oxygen species that, through lipid peroxidation, protein oxidation and DNA damage, induce oxidative stress and cell death. Basic and clinical research are ongoing to better understand the endogenous antioxidant mechanisms that counteract oxidative stress, which may allow to identify a possible therapeutic targeting/application in the field of stress-dependent cardiovascular pathologies. In this context, increasing attention is paid to the glutathione/glutathione-peroxidase and to the thioredoxin/thioredoxin-reductase systems, among the most potent endogenous antioxidative systems. These key enzymes, belonging to the selenoprotein family, have a well-established function in the regulation of the oxidative cell balance. The aim of the present review was to highlight the role of selenoproteins in cardiovascular diseases, introducing the emerging cardioprotective role of endoplasmic reticulum-resident members and in particular one of them, namely selenoprotein T or SELENOT. Accumulating evidence indicates that the dysfunction of different selenoproteins is involved in the susceptibility to oxidative stress and its associated cardiovascular alterations, such as congestive heart failure, coronary diseases, impaired cardiac structure and function. Some of them are under investigation as useful pathological biomarkers. In addition, SELENOT exhibited intriguing cardioprotective effects by reducing the cardiac ischemic damage, in terms of infarct size and performance. In conclusion, selenoproteins could represent valuable targets to treat and diagnose cardiovascular diseases secondary to oxidative stress, opening a new avenue in the field of related therapeutic strategies.

Keywords Selenoproteins · Cardiovascular diseases · Endoplasmic reticulum · Biomarkers · Selenoprotein T

Abbreviations

CVDs	Cardiovascular diseases
Cys	Cysteine
DIO	Iodothyronine deiodinases
ER	Endoplasmic reticulum
ERAD	ER-associated protein degradation
FGD	Familial glucocorticoid deficiency
GPX	Glutathione peroxidase
H_2O_2	Hydrogen peroxide
HbA1c	Glycated hemoglobin
HF	Heart failure
HNO	Azanone
I/R	Ischemia/reperfusion
IL-1β	Interleukin-1β
IL-6	Interleukin-6
Met	Methionine
MI	Myocardial infarction
MSRB1	Methionine sulfoxide reductase B1
NO	Nitric oxide

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$O_2^{\cdot}$	Superoxide radical
$OH^{\cdot}$	Hydroxyl radical
ONOO-	Peroxynitrite
PACAP	Pituitary adenylate cyclase-activating peptide
PCH2D	Ponto-cerebellar hypoplasia type 2D
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RSNO	*S*-Nitrosothiols
S	Sulfur
Se	Selenium
Sec	Selenocysteine
SECISBP2	SECIS binding protein 2
SELENOH	Selenoprotein H
SELENOI	Selenoprotein I
SELENOK	Selenoprotein K
SELENOM	Selenoprotein M
SELENON	Selenoprotein N
SELENOO	Selenoprotein O
SELENOP	Selenoprotein P
SELENOS	Selenoprotein S
SELENOT	Selenoprotein T
SELENOV	Selenoprotein V
SELENOW	Selenoprotein W
SELENOF	Selenoprotein F
SEPHS2	Selenophosphate synthetase 2
SEPSECS	Sep (*O*-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase
SNPs	Single nucleotide polymorphisms
STEMI	ST-segment elevation MI
TNF-α	Tumor necrosis factor-α
TRU-TCA1-1	Transfer RNA-Sec [TCA] 1-1
Trx	Thioredoxin
TXNRD	Thioredoxin reductase
UPR	Unfolded protein response

Introduction

Cardiovascular diseases (CVD) and their consequences remain the most common worldwide cause of death, accounting for more than 4 million deceases each year across Europe, and representing the most important health problem of the Western world [1, 2]. The major cardiac syndromes, myocardial infarction (MI) and heart failure (HF), are responsible for a large portion of CVD-dependent deaths; in these common diseases, cell death, occurring primarily by apoptosis or necrosis, is an important component of their pathogenesis [3]. Along with other factors, reactive oxygen species (ROS) are considered the initiators of the harm in CVD, being responsible for lipid peroxidation, protein oxidation and DNA damage. An excess of ROS results in oxidative stress and may cause cell death [4]. Accordingly, oxidative stress has been associated with diverse pathophysiological events, including CVD [5, 6].

MI is a leading cause of death in its acute phase, but the long-term morbidity and mortality are also alarmingly high [7]. Early and successful restoration of myocardial reperfusion after an ischemic event represents the most effective strategy to reduce infarct size, preserving the left ventricular systolic function and improving the clinical outcome. Paradoxically, the reperfusion strategy itself may induce further myocardial damage in a phenomenon named "lethal reperfusion-induced injury" [8, 9]. The subsequent condition results in inflammation and oxidative damage through the induction of oxidative stress rather than immediate restoration of normal function [7–9]. In addition, even if performing a successful reperfusion, mortality and morbidity are significant after an acute ST-segment elevation MI (STEMI) by electrocardiography analysis in a 1-year follow-up [10]. For these reasons, additional mechanical and pharmacological cardioprotective strategies, able to limit the reperfusion injury and further enhance the benefit of reperfusion, are urgently needed.

To preserve their integrity against oxidative stress-dependent damages and to repair deleterious structural oxidative modifications, cells employ potent endogenous antioxidative systems for ROS detoxification [11]. In mammalian cells, glutathione/glutathione peroxidase and thioredoxin/thioredoxin reductase systems constitute the principal endogenous antioxidant defense line involved in multiple redox-regulated signaling pathways [12–15]. The crucial enzymes belong to the selenoprotein family and display several fundamental functions mostly related to the oxidative cell balance control [12–15].

Several selenoproteins catalyse redox reactions by involving the oxidation of sulfhydryl groups and/or reduction of disulfides [16, 17]. As ROS-detoxifying enzymes, selenoproteins represent an array of antioxidants with different specific subcellular localization and chemical reactivities [18]. In particular, different experimental evidences show that selective selenoproteins contribute to redox regulation in CVD, displaying cardioprotection and representing promising therapeutic tools in the treatment of these pathological disorders [19, 20].

This review aims to focus on the specific function played by selenoproteins in CVD and to introduce the emerging role of one of them, namely Selenoprotein T (SELENOT), in cardioprotection, as the first results indicate that this member is crucial for the cardiovascular function.

The selenoprotein family

Distinctive structural and functional features of selenocysteine (Sec)

Selenium (Se) is an essential trace element co-translationally incorporated into the polypeptide chain as component of the

amino acid selenocysteine (Sec), the 21st amino acid in the genetic code, which is encoded by TGA [21, 22]. It has been observed that selenoproteins are found in all kingdoms of life including certain types of fungi and viruses [16, 23, 24]. Proteins including Sec in their polypeptide chain are defined as selenoproteins [14].

Sulfur (S) and Se are members of the chalcogen group of elements having very similar chemical and physical properties, that can be involved in similar chemical reactions, such as thiol/disulfide and thiol-disulfide-like (that is selenol/disulfide or thiol/selenosulfide when Se replaces S) exchange reactions [25]. Among the trace elements used as cofactors by enzymes, Se has unique properties; in fact, unlike other metal cofactors such as zinc and copper, Se is not only a part of the polypeptide chain in the form of an amino acid, but Sec can be also localized in the enzymatic catalytic site [16]. In selenoproteins, Sec function is partially preserved only when cysteine (Cys) replaces Sec; however, in most cases, the substitution of Sec with Cys leads to a detrimental reduction in the catalytic efficiency [17], as demonstrated by Zhong et al. [26] in a study by mutagenesis carried out on the rat thioredoxin reductase (TXNRD). The higher importance of Sec compared to Cys in protein function, is a debated issue, but a common view suggests the ability of Se to provide some superior chemical or physical properties able to improve the functions of the macromolecules [17]. Accordingly, unlike other amino acids, Sec is normally used only when required for protein function, supporting the idea that this amino acid is a key functional (catalytic) group in proteins. [16, 27, 28].

Additionally, Sec could have a protective effect in proteins. In fact, the one-electron oxidized product of Sec (selanyl radical), is less oxidizing compared to the cysteine-thiyl radical [29]. Consequently, the selanyl radical is not sufficient to alter proteins, while cysteine-thiyl radical can do this with a higher efficiency [29]. Accordingly, Bianco et al. [30] reported that, similarly to thiols, selenols are also target for nitroxyl (azanone, HNO); however, while HNO-induced modifications of thiols can be either reversible and irreversible, HNO-induced modifications of selenols appear to be only irreversible [30]. Other studies provided evidences about the biochemical significance of Sec-containing enzymes under oxidative conditions. For example, Snider et al. [31] compared the effect induced by several oxidant species [ROS, reactive nitrogen species (RNS) and reactive halogen oxidants] exposition on the Sec-containing TXNRD with respect to the Cys-ortholog TXNRD. These authors clearly demonstrated that the Sec-containing TXNRD results in a significantly higher capacity to resist to inactivation by oxidation, while the Cys-containing TXNRD was inactivated under the same conditions of oxidative stress.

Very recently, Ingold et al. [32] further contributed to the knowledge of the function exerted by Sec, providing additional evidence for the advantage to use Se in the form of Sec in proteins. To show this, they compared the selenolate- versus thiolate-based catalysis in mice with a targeted mutation of the catalytically active Sec to Cys in glutathione peroxidase 4 (GPX4), demonstrating that Sec-containing GPX4 prevents ferroptosis due to its resistance to irreversible inactivation mediated by overoxidation.

These findings indicate that, unlike thiol containing proteins, selenoproteins are resistant to irreversible oxidative modification, reflecting the advantage of selenolate- versus thiolate-based catalysis.

The higher reactivity of Sec compared to Cys is also indicated by the higher catalytic activity exerted by the Sec-containing enzymes, which are typically 100- to 1000-fold more active than their Cys mutants [33]. This could account for the presence of Sec in biological systems and might be the rationale of Sec selection over Cys in specific enzymes [17].

Biologically, the unique property of Sec is that, unlike the other amino acids, its biosynthesis always occurs on its own selenocysteine-specific tRNA, designated $tRNA^{[Ser]Sec}$, that controls the expression of all the Selenoprotein family, a process that is not reported for any other tRNA species [16, 27]. The gene for $tRNA^{[Ser]Sec}$ is designated as *Trsp* [34, 35] and Sec incorporation during protein synthesis is dependent on both a UGA codon in the open reading frame and a selenocysteine insertion sequence (SECIS) in the 3′-untranslated region [34]. Since two different homozygous mutations found in the human Sep (*O*-phosphoserine) tRNA:Sec tRNA synthase (SEPSECS) gene, encoding for an enzyme crucially involved in the selenocysteyl-$tRNA^{[Ser]Sec}$ synthesis [36], are associated with progressive cerebello-cerebral atrophy, an essential functional role of Sec biosynthesis can be postulated. Other mutations in SEPSECS gene have been identified in several ethnicities in the world [37, 38]. These mutations are able to generate a phenotype which is clinically similar among all patients and is now classified as ponto-cerebellar hypoplasia type 2D (PCH2D), leading to decreased selenoprotein levels and to an augmented brain susceptibility to oxidative stress [36, 39, 40].

Mutations of two other genes involved in the Sec insertion pathway are responsible for pathological conditions. In particular, mutations in SECISBP2 (SECIS binding protein 2) gene and TRU-TCA1-1 (transfer RNA-Sec [TCA] 1-1) gene, encoding $tRNA^{[Ser]Sec}$, cause a multisystem disorder with myopathic features, induced by the loss of selenoprotein N (SELENON), increased oxidative stress due to the alteration of crucial antioxidant selenoproteins (i.e. GPXs and TXNRDs) and thyroid dysfunction induced by iodothyronine deiodinases (DIOs) deficiency [39–44]. Additionally, *Trsp* gene *knockout* in mice results in embryonic lethality, indicating that selenoprotein synthesis is strictly required for mammalian life [45].

Selenoproteins and the selenoproteome

The first identified selenoprotein was the mammalian glutathione peroxidase 1 (GPX1) [46]. Subsequently, thanks to a combination of bioinformatic and experimental approaches, a large number of selenoproteins were identified in all the life kingdoms, and the full human selenoproteome, encoded by 25 selenoprotein genes was characterized [27]. Among these genes are included the glutathione peroxidases (GPXs), the thioredoxin reductases (TXNRDs) and the iodothyronine deiodinases (DIOs) [16].

GPXs are major components of the antioxidant defense and redox homeostasis, strongly involved in a wide range of physiological functions [14]. They use glutathione as a cofactor to catalyze the reduction of hydrogen peroxide (H_2O_2) and/or phospholipid hydroperoxide [14, 47]. In humans, there are eight genes encoding GPX enzymes and five of these are selenoproteins (GPX1–4, GPX6) containing Sec in the active site [27, 47].

TXNRDs, three of which have been identified in mammals (TXNRD 1–3) are members of the pyridine nucleotide-disulfide oxidoreductases that, together with thioredoxin (Trx) and NADPH, represent the major disulphide reduction system of the cell [15, 16]. The two most important features of TXNRDs are the N-terminal redox-active dithiol/disulfide in one subunit [48] and a 16-residue C-terminal elongation with the conserved selenothiol active-site in the adjacent subunit (sequence: -Gly-Cys-Sec-Gly-OH) [49]. This structure forms the redox-active center of the enzyme [48]. Several other proteins having these characteristic structural features are considered members of the Trx family.

The three mammalian DIOs (DIO1-3) are vitally involved in the regulation (activation/deactivation) of thyroid hormone activity by reductive deiodination [16]. DIO1 or DIO2 catalyze the activation of thyroid hormone by converting the prohormone thyroxine (3,5,3′,5′ tetraiodothyronine, T4) to the biologically active form, 3,5,3′-triiodothyronine (T3), while DIO3 catalyzes the irreversible inactivation of T3 and T4 to yield the inactive hormones 3,5-diiodo-L-thyronine (T2) and reverse T3 (rT3), respectively [50].

Overall, TXNRDs, GPXs and DIOs are the three-best characterized selenoprotein subfamilies. They have different enzymatic activities, but all require reductants to provide the electrons for their catalytic redox cycle [14].

The human selenoproteome also includes the methionine sulfoxide reductase B1 (MSRB1) that, together with TXNRD and GPX isoforms, synergically act to provide antioxidant defense [16]. While two other selenoproteins are crucially involved in selenoprotein synthesis (selenophosphate synthetase 2, SEPHS2) and transport (selenoprotein P, SELENOP) [16, 28], the role of many selenoproteins and their mechanisms of action (referring to selenoprotein W, SELENOW, selenoprotein T, SELENOT, selenoprotein H, SELENOH, selenoprotein V, SELENOV, selenoprotein I, SELENOI, selenoprotein F, SELENOF, selenoprotein M, SELENOM, selenoprotein K, SELENOK, selenoprotein S, SELENOS, selenoprotein O, SELENOO, and selenoprotein N, SELENON [16, 27], are still elusive.

However, the role of specific selenoproteins is emerging. After the complete identification of the selenoprotein family members in 2003 [27], which occurred after the Human Genome Project, their nomenclature was revised in 2016 [51]. Selenoproteins with characterized functions are designated according to their functions (GPXs, TXNRDs, DIOs, MSRB1 and SEPHS2). Selenoproteins without a clearly demonstrated enzymatic function, structure, tissue and cellular localization, are indicated by the common symbol SELENO followed by a specific letter [51]. Some of them, containing structures encompassing Trx folds (where Cys residues, normally present in the active site, are replaced by Sec residues), namely Trx-like proteins, include SELENOF, SELENOH, SELENOM, SELENOO, SELENOP, SELENOT, SELENOV, and SELENOW, and act in a Trx similar manner also contributing to the Trx system activity [47]. Considering the presence of the Trx fold, a thiol-based oxidoreductase activity has been postulated for these SELENO members [52]. Among them, SELENOP possesses unique features, i.e. it is the only selenoprotein with multiple Sec residues that facilitates Se transport between organs [53]. In addition, since SELENOP is transported across the blood–brain barrier [47, 54] it is the most commonly used selenoprotein as a marker of Se status [55, 56].

However, an impressive emerging interest has been given to the group of the endoplasmic reticulum (ER)-resident selenoproteins (SELENOF, SELENOK, SELENOM, SELENON, SELENOS, SELENOT). These selenoproteins predominantly contribute to the calcium ion (Ca^{2+}) signaling, the protein folding and ER-associated degradation [57–61]. In particular, Hamieh et al. demonstrated that SELENOT *knockdown* is dramatically associated with the unfolded protein response (UPR) and ER stress and lowers ER-associated protein degradation (ERAD) and hormone production [62].

Cardiovascular role of selenoproteins

Selective selenoproteins are essential for life

It is well known that, under aerobic condition, cells continuously react with ROS, such as superoxide radical ($O2^{-}$), hydrogen peroxide (H_2O_2), lipid and hydroxyl radical ($OH^{\cdot}$), which derive from several metabolic reactions, and counteract their effects through a wide range of endogenous antioxidant enzymes [63]. High and persistent ROS levels lead to a dramatic imbalance between ROS and the antioxidant defence system [64]. Under these

conditions, ROS can damage macromolecules due to their ability to react with specific amino acid residues present in the protein structure, thus inactivating their function, and with DNA and chromatin causing mutations or double-stranded breaks in a phenomena overall known as "oxidative damage" [65]. The current concept of "oxidative damage or oxidative stress" includes pathways also related to the "nitrosative stress" and, considering their implication in cellular and extracellular metabolic processes, to the "metabolic stress" [66]. So far, the definition of oxidative stress, firstly confined only to ROS, has been extended to RNS, such as nitric oxide (NO), peroxynitrite ($ONOO^-$) and S-nitrosothiols (RSNO) [66]. Today, it is widely accepted that metabolic stress has been associated with diverse patho-physiological events, including CVD [6].

In this context, while the role of many selenoproteins remains to be better established and their study is under continuous investigation and development, the fundamental role exerted by selenoproteins for life is widely accepted [45, 67]. These enzymes rapidly consume and neutralize H_2O_2, with a consequent significant decrease of H_2O_2 levels and a limitation of its transmission signal space by diffusion in the cell [68].

An important contribution regarding the mechanism by which selenoproteins are involved in antioxidant defense following oxidative stress was given by Touat-Hamici et al. [69]. These authors studied, in different cell models, the regulation of the expression of several selenoproteins secondary to H_2O_2-induced oxidative stress, in the presence of high and low selenium concentration. Interestingly, the results demonstrated that antioxidant selenoproteins, including GPX1, GPX4, TXNRD1, SELENOS, SELENOK, SEPHS2, are up-regulated by H_2O_2 when selenium is limiting. Conversely, in the presence of high selenium concentration, selenoprotein expression was not sensitive or was down-regulated in response to oxidative stress [28, 70]. These observations indicate that selenium status selectively influences the response of selenoprotein expression to oxidative stress, which induces the upregulation of UGA selenocysteine recoding efficiency and relocalization of SBP2, EFsec and L30 recoding factors from cytoplasm to nucleus [69].

In vivo studies using knockout/transgenic animal models demonstrated that selenoproteins are crucially involved in protecting the cells against oxidative stress and in maintaining the redox homeostasis [71, 72].

For instance, it has been shown that, in mice, the genetic disruption of GPX4, TXNRD1, and TXNRD2 is responsible for an embryonic lethal phenotype [73–76]. In addition, depletion of the liver SELENOP gene alters the delivery of Se to peripheral target tissues, leading to growth retardation and impaired motor coordination in mice [77, 78]. Interestingly, the more recently discovered SELENOT is the only ER-resident selenoprotein so far whose genetic ablation causes embryonic lethality in mice [79, 80].

On the other hand, genetic invalidation of other selenoproteins (for example GPX1 and MSRB1 [81, 82]) revealed that they play a key role under stressful conditions.

Noteworthy, it has been observed that a reduced selenoprotein activity is counterbalanced by a cytoprotective response mediated by the transcription factor NF-E2 related factor 2 (Nrf2), which may represent an essential compensatory response for maintaining cellular redox homeostasis and viability [67, 83]. In the same study, the importance of Trsp/Nrf2 axis was further highlighted by demonstrating the key role of selenoprotein activity and of Nrf2 gene in the oxidative homeostasis of erythrocytes and in the prevention of hemolytic anemia [84].

Selective selenoproteins are required for heart development and function

As could be expected, mutations in selenoproteins and selenoenzymes have been associated with several disorders, including CVD [85]. Considering that the mouse $tRNA^{Sec}$ *knockout* mutant exhibits an embryonic lethal phenotype [45], it is not surprising that mutations of factors taking-part in the synthesis and co-translational incorporation of Sec, such as SEPSECS can affect the selenoprotein synthesis machinery itself [36].

Accordingly, the cell-specific alteration of selenoprotein expression, using the *Cre-LoxP* technology to remove the *Trsp* gene, revealed the essential role of selenoproteins in endothelial cell development and in proper cardiac muscle function, suggesting a direct connection between the loss of selenoprotein expression in this cell type and CVD [86]. In particular, and as reviewed by Conrad et al. [73], genetic disruption in mice of the cytosolic thioredoxin reductase (TXNRD1), the mitochondrial thioredoxin reductase (TXNRD2) and glutathione peroxidase 4 (GPX4), provokes embryonic lethality, thus revealing that selonoproteins are required not only for murine embryogenesis, but also for the regulation of cellular redox metabolism [73]. These findings are extremely relevant from a cardiovascular point of view. In fact, the *knockout* of TXNRD2, which exerts an essential role in hematopoiesis, heart development, and heart function, provokes congestive HF symptoms and postnatal death in a heart-specific TXNRD2-*knockout* mouse model [75]. It is of particular interest that these mice also showed phenotypic similarities with the histopathologic phenotype of Friedreich's cardiomyopathy, that itself reflects the dilated congestive cardiomyopathy typical of severely Se-deficient patients [87]. Accordingly, the same authors described mutations in the TXNRD2 gene in a fraction of patients affected by dilated cardiomyopathy, thus revealing a novel mechanism for HF development linked to a crucial

antioxidant enzyme involved in the regulation of cellular redox state [88]. On the other hand, Prasad et al. [89] identified homozygosity for a nonsense mutation in the TXNRD2 gene associated with familial glucocorticoid deficiency (FGD), a rare autosomal recessive disorder characterized by isolated glucocorticoid deficiency without mineralocorticoid deficiency [90]. The study was carried out in an extended consanguineous Kashmiri kindred and the results attest for the fundamental role of this selenoprotein in maintaining the adrenocortical redox state [89]. In the family involved in this study, heterozygotes individuals were clinically unaffected and, unexpectedly, neither the heterozygote nor homozygote subjects, with the absence of TXNRD2, had any evidence of cardiomyopathy, except two homozygous patients who presented cardiac anomalies, probably due to other genetic or environmental factors [38, 89].

Other studies identified a critical role for TXNRD2 in preserving the morphological and functional integrity of mitochondria in aging cardiomyocytes, pointing to a critical role of this selenoprotein in the prevention of age-related functional cardiac decline [91].

Embryonic depletion of GPX isoforms is also associated with cardiac dysfunction. Indeed, mice with homozygous null mutation for the cytosolic GPX1, the most abundant GPX, show susceptibility to oxidative stress and viral myocarditis and acceleration of cardiac hypertrophy and dysfunction [92]. Wentzel et al. [93] observed that maternal diabetes causes congenital malformations and a general altered antioxidant embryonic profile in rats, and that the decreased cardiac GPX1 levels significantly contribute to an increased risk of developing congenital cardiac malformation [93]. Forgione et al. [94] demonstrated that heterozygous deficiency of GPX1 leads to endothelial dysfunction, which in turn triggers significant structural abnormalities in vascular and cardiac tissues [94]. Furthermore, mice with GPX1 deficiency exhibit a decrease in bioavailable NO [94].

As demonstrated, the gene of human GPX1 is located on chromosome 3p21.3 and contains two exons [95, 96]. An increasing body of clinical studies showed the occurrence of different polymorphisms in GPX1 associated with negative effects on the cardiovascular system, confirming the detrimental consequences linked to GPX1 alteration in the heart. In this regard, Winter et al. [97] observed that individuals with one or two ALA6 alleles of GPX1 have a modest increased risk of coronary artery disease. Functional variants in the GPX1 gene were associated with increased intima-media thickness of carotid arteries and risk of cardiovascular and peripheral vascular diseases in type 2 diabetic patients [98]. Among other single nucleotide polymorphisms (SNPs) that have been documented for this gene, the polymorphisms of the cytosine-to-thymine (C>T) substitution (rs1050450) at codon 198 and 197 generate the Pro198Leu and Pro197Leu variations [99]. Several observations suggest a possible correlation between these polymorphisms and CVD. Accordingly, a Pro197Leu substitution of the GPX1 gene correlates with a significant genetic susceptibility to coronary-arteriosclerosis in type 2 diabetes patients [100]. In line with results obtained by Hamanishi et al. [98], Oguri et al. [101] showed that the Pro198Leu polymorphism of GPX1 significantly associated with in-stent restenosis in a Japanese population. A meta-analysis study conducted by Zhang et al. [102] revealed a significant relationship of these GPX1 variants and CVD risk in East Asian populations. and a hospital-based case–control study, in a Chinese population, indicates that the GPX1 variant 198Leu allele is significantly associated with an increased risk of CAD [103]. Although other studies to strengthen statistical significance are needed, the effect of the GPX1 Pro/Leu variants on the function of this selenoenzyme is substantial; in fact, several studies indicate a lower GPX1 activity in the Pro198Leu variant [98, 104, 105], suggesting that the correlation found between this functional variant and the increased risk of CVD, in particular CAD, might be related to a decreased GPX1 enzyme activity [104, 105].

GPX3 is the major plasma antioxidant enzyme, which controls the vascular tone and the thrombotic properties of the vascular endothelium [106]. A GPX3 deficiency inevitably leads to an impaired catalytic reduction of H_2O_2 and organic hydroperoxides to their corresponding alcohols [107]. Consequently, there is a decreased NO bioavailability [108, 109] that can augment platelet activation and arterial thrombosis [110]. The potential relationship between GPX3 deficiency and platelet-dependent thrombosis was addressed by Jin et al. [107], who developed a mouse model presenting a phenotype resembling that of two brothers with GPX3 deficiency, with arterial thrombosis and stroke syndromes [111]. GPX3 deficiency alters ROS metabolism, resulting in a pro-thrombotic state and vascular dysfunction, and promotes platelet-dependent arterial thrombosis [111].

These results are corroborated by the correlation found between decreased GPX3 activity and arterial thrombosis in humans [112]. Starting from idiopathic childhood stroke patients, whose clinical manifestations and thrombosis were in a familiar GPX3 and NO bioavailability reduction [111, 113], the authors hypothesized that mutation(s) or polymorphism(s) in the plasma GPX3 gene promoter may be responsible for the reduction in enzyme activity and predispose to a thrombotic disorder. Accordingly, in patients with arterial ischemic stroke, a novel GPX3 promoter haplotype reduces the gene expression with consequences typical of the lack of a crucial antithrombotic and antioxidant key enzyme [111, 113]. Of note, mice with embryonic *knockdown* of phospholipid hydroperoxide GPX (GPX4), the main antioxidant enzyme known to directly inhibit lipid peroxidation by reducing phospholipid hydroperoxides and lipoproteins within membranes, exhibit abnormal development

of the heart, lacking the left atrium [114]. Interestingly, in support to the essential role displayed by this enzyme in the development of the cardiac system, Smith et al. [115] identified selective mutations of GPX4 as responsible of Sedaghatian type of spondylometaphyseal chondrodysplasia (SSDM), a neonatal lethal form of spondylometaphyseal dysplasia described as a new autosomal recessive disorder in 1980 [116]. Accordingly, SSDM patients die prematurely by cardio-respiratory failure [117]. In particular, patients present with severe hypotonia and cardiorespiratory problems, most die within days of birth due to respiratory failure and, as showed in an article by Aygun et al. and reference therein [117], several patients presented cardiac conduction defects, complete heart block and different structural cardiac anomalies [38, 115].

While the essential role of TXNRDs and GPXs in the heart development and function is well established, promising results have also been obtained for another selenoprotein, MSRB1 [118]. MSRB1, located in the cytosol and nucleus, reduces the enantiomer R of methionine sulfoxide, R-MetO [119–121]. In 2009, Fomenko et al. [82] found that the *knock-out* of MSRB1 in mice leads to potent oxidative stress in several organs, such as liver and kidney that highly express MSRB1 under physiological conditions, but to a lesser extent in the heart [82].

Glutathione peroxidases and thioredoxin reductases contribute to redox regulation and cardioprotection in cardiovascular disease

The expression of selenoproteins during cardiogenesis, and during/after stressful events, and their antioxidant function, is complex and intriguing. In cardiac adaptation to different stimuli, the evaluation of selenoprotein expression patterns and enzymatic activities under physiological and pathological conditions may provide important information about the role of this enzyme in counteracting cardiac sufferance [19]; above all, a specific role of the selenoproteomic response in protecting the heart against stress-induced damage represents an ambitious goal for basic and translational research.

In this regard, studies by Hoffman et al. [122], provided insights in the expression and the enzymatic activity of key cardioprotective selenoproteins during oxidative stress-dependent cardiac stress. In particular, these authors reported significant increases of mRNA and protein levels of MSRB1 [123], TXNRD1, GPX3 and GPX4 in mouse models of T3- or isoproterenol-induced myocardial hypertrophy. Along with the results described above showing the cardiac abnormalities after genetic disruption of selective selenoproteins, these data suggest a significant induction of the selenoproteome response to cardiac damage, where some selenoproteins seem to be indispensable for cardioprotection in circumstances of oxidative injury.

GPXs and TXNRDs are certainly among those antioxidant enzymes most involved in cardiovascular pathologies [12–14, 124]. The direct role of GPX1 in myocardial I/R, endothelial dysfunction, athero-thrombotic vascular disease, and cardiotoxicity induced by chemotherapeutic agents has been extensively studied in in vitro and in vivo models [125]. Among the many studies related to the cardioprotective potential of GPX1, a work published in *The New England Journal of Medicine* by Blankenberg et al. [126] examined the protective effect of GPX1 against cardiovascular events in a large prospective cohort of patients with coronary artery disease. The authors found that low erythrocyte GPX1 activity [126] identifies patients with coronary artery disease who are at the highest risk for cardiovascular events [126]. These results indicate that the GPX1 activity assay provides a key information for identifying patients who would benefit from preventive antioxidant treatment.

In addition to GPX1, GPX3 (plasmatic isoform of GPX) also affords heart and vasculature protection against oxidative stress in a NO-dependent mechanism, contributing to preserve the platelet function in human arterial thrombosis [125]. Noteworthy a recent study carried out by Pastori et al., provides novel evidence regarding the association between reduced levels of GPX3 and increased risk of cardiovascular events in patients with atrial fibrillation. The authors also found a negative correlation between age and GPX3 levels, proposing the GPX3 decline as a possible mechanism for the enhanced cardiovascular risk in the elder population [127]. Besides, GPX4 protects lipids from oxidative damage during myocardial hypertrophy and I/R injury [125]. Finally, the roles displayed by the Trx and TXNRD system in cardiovascular events have been extensively reviewed, and the crucial participation of these redox-regulating and sensitive enzymes in the control of various cardiac functions is well established.

Cardiovascular effects of the emerging endoplasmic reticulum-resident selenoproteins

Selenoprotein S

An important role is played by the ER-associated SELENOS in cardiac function. SELENOS is also located in the plasma membrane and is involved in the retro-translocation of misfolded proteins from the ER lumen to the cytosol for degradation [128], and thus in cell protection against oxidative stress and inflammation, typical events of the misfolded protein response [129].

SELENOS seems to be particularly linked to inflammatory processes [130, 131]. Variations in the SELENOS gene influence the circulating levels of the inflammatory

cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) [130], and the SELENOS gene expression is activated by inflammatory cytokines [131]. A case-cohort design and time-to-event analysis demonstrated that variation in the SELENOS locus may be associated with specific risk factors for CVD [132].

In 2013, in a large number of European Americans from the family-based Diabetes Heart Study, the association between SELENOS genetic variants and the risk for subclinical CVD and mortality in type 2 diabetes patients was postulated [133]. Considering the link of SELENOS gene variation and inflammatory response, the involvement of this selenoprotein in type 2 diabetes and HF should not be surprising. Accordingly, an association of SELENOS polymorphisms with coronary and carotid calcified plaque, as well as with glycemia and glycated hemoglobin (HbA_{1C}) was observed [133].

A recent study provides evidence about selective alleles of SELENOS gene (i.e. rs34713741T) associated with an increased risk of peripheral arterial disease, while other variants (i.e. rs3877899A) seem to prevent the risk for developing abdominal aortic aneurysm [134]. Of course, all these observations deserve further genetic investigations to better clarify the role of this gene and protein in the pathogenesis of these diseases.

Selenoprotein K

Another ER transmembrane selenoprotein that appears to have multiple biological functions, including cardiac influences, is SELENOK. There is evidence that SELENOK mRNA is highly expressed in human heart and that its overexpression might reduce ROS production protecting cardiomyocytes from oxidative stress-induced by H_2O_2 exposure [135]. In addition, purified human SELENOK has been shown to reduce phospholipid hydroperoxides [136]. SELENOK, through interaction with other protein factors, may participate to the transport of glycosylated misfolded proteins and to the regulation of ER stress in particular cell types, contributing to ER homeostasis [137, 138]. For this reason, the effects observed in cardiomyocytes suggest a potential antioxidant action of SELENOK by regulating ER stress, a key process highly sensitive to oxidative stress.

On the other hand, Verma et al. found that SELENOK is strongly expressed in cells of the immune system, where it exerts an important role for their function and activation [139]. *A knockout* mice model for SELENOK revealed serious impaired activities of immune response activation, including impairment in cell migration, proliferation, and oxidative status, particularly evident for macrophages [139, 140]. It has also been observed that SELENOK deficiency inhibits the uptake of modified low density lipoprotein (LDL), which may lead to foam cell formation in primary macrophages, and inhibits the TNF-α-induced scavenger receptor CD36 surface expression [141]. These results suggest the important role of SELENOK in the expression of CD36 in macrophages during inflammation, thereby contributing to foam cell formation and atherogenesis, significant inflammatory processes also associated with cardiovascular complication [142].

However, the limited number of studies related to SELENOK in the heart, and the lack of in vivo analysis of its cardiac antioxidant potential warrant further studies to decipher its precise cardiovascular implication.

Other endoplasmic reticulum-resident selenoproteins: focus on SELENOT

The results obtained on the cardiac involvement of SELENOS and SELENOK suggest that other ER-resident selenoproteins (SELENOM, SELENON, SELENOT, and SELENOF) could be involved in ER homeostasis in the heart.

As critically reviewed by Pitts and Hoffmann [57], these selenoproteins are involved in calcium flux modulation into and from the ER lumen, in the regulation of protein folding and maturation, and in ER redox homeostasis. Through their antioxidant activity, displayed by a Sec residue in the active site, the ER-resident selenoproteins participate to fundamental biological processes such as proliferation, survival, and apoptosis [57].

Noteworthy, type 2 iodothyronine deiodinase (DIO2), a classical type-1 membrane protein residing on the ER membrane and the main T4-activating enzyme [143, 144], is very sensitive to ER stress [145]. In fact, pharmacologically induced dysregulation of the ER status triggers a rapid loss of DIO2 activity and protein via a posttranscriptional mechanism that leads to a decrease in intracellular T3 production [145].

However, from a cardiovascular point of view, limited results have been obtained so far for this subfamily of selenoproteins (particularly for SELENOM, SELENON, and SELENOF). Since ER stress (in terms of disrupted ER homoeostasis and ER altered functions) is a key process regulating death/survival mechanisms of cardiomyocytes under several types of stressful stimuli [146], the research in this field appears mandatory and may lead to an increase of the potential clinical-therapeutic impact.

Several studies indicate that ER stress is involved in the development and progression of diverse heart diseases, such as cardiac hypertrophy, ischaemic heart diseases and HF [146]. In this context, an emerging selenoprotein able to prevent ER-stress is SELENOT. After the discovery of selenoprotein R (SELENOR), which is currently known as MSRB1 [147], SELENOT was the second selonoprotein identified using a bioinformatic approach [61]. The identification of SELENOT as an up-regulated gene during neuroendocrine

cell differentiation in response to the neurotrophic factor pituitary adenylate cyclase-activating polypeptide (PACAP) [148] paved the way for numerous studies. In this regard, the critical review by Anouar et al. recently updated the findings that have been reported for SELENOT during the last years [61]. SELENOT displays a thioredoxin reductase-like enzymatic activity [79] and associated with the ER membrane; in this subcellular compartment, the protein can interact with other thiol-containing proteins through its Sec active moiety [60, 62, 148]. These features strongly suggest that SELENOT exerts a key redox function by controlling protein processing in the ER, thus contributing to ER homeostasis. In particular, through its thioredoxin-like fold, SELENOT may take part to the thiol redox circuits including thiol-disulfide oxidoreductase reactions and may participate to the regulation of protein folding and maturation [61].

Accordingly, Hamieh et al. reported that SELENOT is required for adaptation to the stressful conditions of high hormone level production in endocrine cells [62]. Indeed, the *knockdown* of the protein in corticotrope cells resulted in an unfolded protein response (UPR), in ER stress and ER altered function, thus identifying SELENOT as an indispensable effector of hormone maturation and secretion [62]. In the cardiac ER, the protein has been identified by immunofluorescence analysis, and co-localizes with calsequestrin-2 during rat cardiogenesis [149]. Our work revealed a strong expression of SELENOT in the cardiac ER at E7 (embryonic day 7) stage of embryogenesis, which decreased at P14 (post-natal day 14) and disappeared in the adult and mature heart. However, in the adult heart exposed ex vivo to 30 min of global, no-flow ischemia, followed by 120 min of reperfusion [myocardial ischemia/reperfusion (I/R) model], SELENOT expression was significantly induced, suggesting a functional re-activation of this protein during an important oxidative burst like that generated by I/R [149]. Therefore, it is very likely that SELENOT is not required for heart function under normal conditions, but its expression can be triggered after exposure to I/R injury. An increased SELENOT expression was also observed in a neurological context after exposure to noxious toxins that are known to induce a potent oxidative stress [79], confirming the importance of this protein in pathological conditions.

Rocca et al. also highlighted an intriguing role for SELENOT in direct cardiomodulation and cardioprotection (2018) [149]. The protective role of SELENOT in the context of myocardial I/R injury was further evaluated through post-conditioning I/R protocols using a SELENOT-derived peptide, PSELT (FQICVSUGYR), that encompasses the active Sec-containing redox motif (CVSU) [149]. PSELT was able to improve the cardiac performance and to reduce the infarct size after I/R insult [149]. These effects were strictly related to the catalytic motif containing the Sec residue, since an analogous peptide lacking this residue did not exert such effects [149]. The mechanism that underlies these effects consist of the activation of protective pro-survival signalling cascades and the inhibition of pro-apoptotic factors [149]. Moreover, PSELT decreased ROS and RNS formation [149], which are known to be strongly implicated in I/R tissue damage [150, 151]. However, it is still unclear if this is a direct or indirect effect of the peptide.

Notably, these findings suggest that SELENOT/PSELT could represent a therapeutic tool able to provide an antioxidant protection in individuals at high risk of coronary heart disease.

As demonstrated by Grumolato et al. [60] and reviewed by Pitts and Hoffmann [57], SELENOT upregulation is dependent on cAMP levels and intracellular calcium flux during differentiation of pheochromocytoma cells in response to PACAP. In addition, these authors found that SELENOT plays an important role, via its redox activity, in maintaining calcium homeostasis and influencing proliferation, survival and apoptosis in neuronal and endocrine cells. SELENOT can modulate calcium signaling likely through a redox mechanism involving thiol groups on calcium channels and pumps [57, 60, 152].

Future studies to improve the knowledge about the mechanism of action exerted by SELENOT in an ischemic heart may allow a better understanding of a novel adaptive pathway by which cardiomyocytes could combat the calcium overload in the ischemic heart disease.

A comprehensive picture of the intracellular signaling involved in the selenoproteins action in cardiomyocytes is represented in Fig. 1.

Role of selenoprotein W

SELENOW is a 85–88 amino acid protein first identified in sheep suffering from selenium deficiency [153]. Its selenocysteine residue is located in the N-terminal portion of a relatively short functional domain [153] and different studies demonstrated a tissue-specific distribution of the protein [154]. Indeed, in sheep and primates SELENOW is highly expressed in the muscle, heart and brain [154]; on the contrary, in cardiac tissues from rodents the levels are very low [154]. SELENOW protein levels correlated with its mRNA levels but not with tissue selenium concentrations [155]. SELENOW is known to play a key antioxidative role in many cell types [156–158]. Interestingly, an alteration of SELENOW levels is able to influence the mRNA expression of other selenoproteins, maybe depending on the amount of ROS [159]. In a study performed by Yang et al. [160] on chicken embryo myocardial cells, SELENOW was sensitive to Se levels mediating, supposedly, its protective effects. Recently, it was found that a reduced Trx expression inhibits

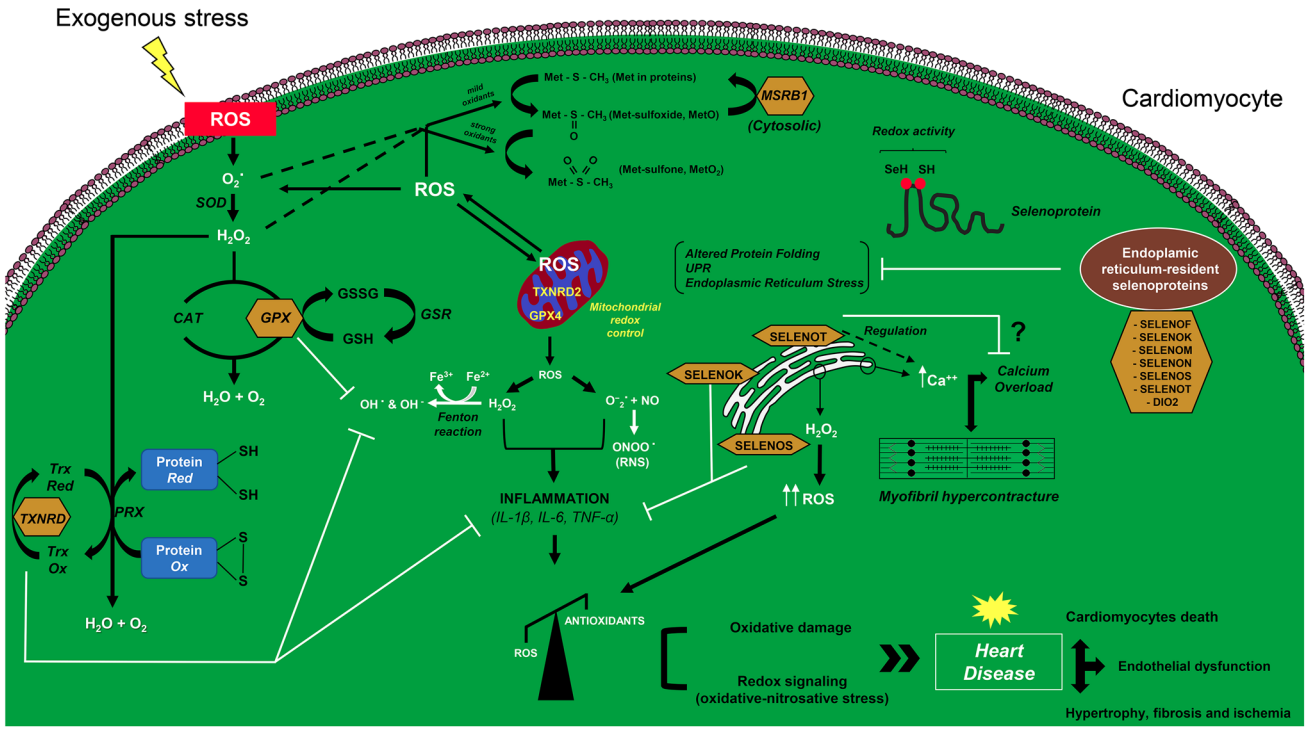

Fig. 1 Proposed model for the action of selenoproteins in cardiomyocytes, focusing on the redox state control in both cytosolic and mitochondrial compartments. The mechanism of action of the well-characterized selenoproteins thioredoxin reductase (TXNRD), glutathione peroxidase (GPX) and methionine sulfoxide reductase B1 (MSRB1) is illustrated. The mechanism of action of the emerging endoplasmic reticulum-resident selenoproteins in the heart, based on previous studies, is postulated. Selenoproteins are indicated with a yellow box. *CAT* catalase, *DIO2* iodothyronine deiodinase type 2, *GPX4* mitochondrial isoform of glutathione peroxidase, *GSH* glutathione, *GSSG* glutathione disulphide, *GSR* glutathione-disulfide reductase, H_2O_2 hydrogen peroxide, *IL-1β* interleukin-1β, *IL-6* interleukin-6, *Met* methionine, *MSRB1* methionine sulfoxide reductase B1, *NO* nitric oxide, $O_2^{\cdot}$ superoxide radical, *OH* hydroxyl radical, *OH* hydroxide ion, $ONOO^-$ peroxynitrite, *PRX* peroxiredoxin, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *SELENOF* selenoprotein F, *SELENOK* selenoprotein K, *SELENOM* selenoprotein M, *SELENON* selenoprotein N, *SELENOS* selenoprotein S, *SELENOT* selenoprotein T, *SOD* superoxide dismutase, *TNF-α* tumor necrosis factor-α, Trx_{Ox} oxidized thioredoxin, Trx_{Red} reduced thioredoxin, *TXNRD2* mitochondrial isoform of thioredoxin reductase, *UPR* unfolded protein response

SELENOW in chicken cardiomyocytes demonstrating a close mutual relationship between these two systems [161].

Selenoproteins as biomarkers in cardiovascular diseases

Currently, a molecule is considered to be a biomarker if it represents a distinctive indicator of a biological process or condition [162]. A link between CVD and selenoproteins can be straightforwardly postulated since a relative Se deficiency is detected in different cardiac pathologies [163]. For example, the Se deficiency observed in patients with chronic HF [164] could be responsible of the inactivation of the selenoprotein enzymes TXNRD and GPXs [26]. Conversely, the cardiovascular protective effects of Se supplementation in populations with low serum levels have been widely discussed [165].

Owing to their properties, selenoproteins could represent good markers for cardiovascular pathologies related to oxidative stress. This is the case for preeclampsia [166], a condition characterized by high blood pressure in pregnancy that represents a leading cause of maternal and perinatal mortality and morbidity [167, 168]. Presumably, preeclampsia results from a reduced placental perfusion that increases ROS levels that, in turn, induce oxidative stress and endothelial cell dysfunction, resulting in hypertension and in the typical manifestations of preeclampsia [169]. Under normal conditions, the antioxidant selenoprotein GPX works by limiting these effects, but in preeclamptic women reduced plasma levels of Se [170, 171] and of plasma and placental GPX levels can be detected [166] and may represent useful biomarkers in this contest.

Oxidative stress has a well-known effect also in cerebrovascular events, such as stroke [172]. Reduced serum levels of SELENOP can be found in patients who underwent a stroke and are associated with a higher risk to

Table 1 Selenoproteins in cardiovascular diseases

Selenoprotein	Localization	Biological function	Cardiovascular implication
TXNRD1	Cytosol, nucleus [14].	Oxidoreductase activity; antioxidant defense [21].	knockout associated with embryonic lethal phenotypes; associated with hypertrophy and oxidative stress in response to pressure overload; implication in cardiovascular diseases [19, 73, 124].
TXNRD2	Mitochondria [14].	Oxidoreductase activity; antioxidant defense [75].	Involvement in hematopoiesis, heart development and heart function; congestive heart failure and postnatal death (*knockout-model)*; dilated congestive cardiomyopathy (*human*); metabolic and contractile dysfunction [73, 75, 87, 88, 91].
GPX1	Ubiquitous, cytosol [14].	Oxidoreductase and perodoxidase activities; antioxidant defense [14].	Susceptibility to oxidative stress and viral myocarditis; acceleration of cardiac hypertrophy and dysfunction; increased risk of developing congenital cardiac malformation; structural abnormalities in vascular and cardiac tissues; modest increased risk of coronary artery disease; susceptibility to coronary-arteriosclerosis; protection against cardiovascular pathologies [92–94, 97, 98, 100, 122, 126].
GPX3	Plasma [14].	Oxidoreductase and perodoxidase activities; antioxidant defense [14].	Decreased NO bioavailability; platelet activation and arterial thrombosis; stroke syndromes; control of the tone and the thrombotic properties of the vascular endothelium [14, 106, 110–112].
GPX4	Ubiquitous [14].	Oxidoreductase and perodoxidase activities; antioxidant defense [14].	knockout associated with embryonic lethal phenotypes; abnormal cardiac development; lack of the left atrium [73, 114].
MSRB1	Cytosol and nucleus [119].	Oxidoreductase activity; antioxidant defense [14].	Contribution to the redox control in several organs, but to a lesser extent in the heart [119].
SELENOS	Endoplasmic reticulum; plasma membrane [128].	Retro-translocation of misfolded proteins; antioxidant defense; endoplasmic reticulum stress response [128].	Association with specific risk factors for cardiovascular diseases; risk for subclinical cardiovascular diseases and mortality in type 2 diabetes; coronary and carotid calcified plaque; risk of peripheral arterial disease [132–134].
SELENOK	Endoplasmic reticulum [135].	Antioxidant defense; regulation of endoplasmic reticulum stress [135–138].	Association with impaired activities of immune response activation; atherogenesis; inflammation in cardiovascular diseases [139, 142].
SELENOP	Plasma [14].	Se transport; antioxidant defense [175].	Correlation with metabolic syndrome and cardiovascular disease [176, 177].
SELENOT	Endoplasmic reticulum [60].	Antioxidant defense; intracellular Ca^{2+} regulation; regulation of endoplasmic reticulum stress [60, 62, 79].	knockout associated with embryonic lethal phenotypes; increased expression in the cardiac embryogenesis; sensor of myocardial ischemia damage [79, 80, 149].
SELENOW	Cytosol [52].	Antioxidant defense [153].	Myocardial oxidative damage [159].

develop this severe pathology [173]. This finding could be ascribed to the fact that SELENOP is the main Se supplier to the brain [174], and its decreased levels could reduce the protection against ROS through the Se-dependent antioxidant enzymes, leading to increased stroke risk [175]. A recent study assessed the plasma levels of SELENOP also in patients with metabolic syndrome accompanied by a history of CVD [176], and demonstrated that a decrease in circulating SELENOP levels also occurs in patients with documented CVD [176].

Thus, available data showing the potential use of selonoproteins as clinical biomarkers in cardiovascular dysfunction need to be further substantiated, but they already represent a promising starting point for translational medicine.

In addition, very recently, SELENOP plasma levels have been associated to acute MI, more precisely to its

related inflammatory response and mortality in patients with cardiogenic shock [177]. In this pathological condition SELENOP levels increase in a significative manner and correlate with C-reactive protein levels, an inflammatory marker, suggesting its diagnostic potential in this context [177].

In Table 1 is reported a schematic representation of the major implications of selenoproteins in cardiovascular diseases.

Conclusions

Oxidative stress, due to increased ROS production or reduced ROS detoxification, is one of the leading causes of the onset and the progression of cardiovascular diseases. Potent endogenous antioxidant systems, such as selenoproteins, represent a fundamental defense mechanism able to counteract the detrimental effects of these noxious agents. Recent studies of the ER-resident selonoproteins, in particular SELENOT and its derivative peptide PSELT, pave the way for a possible therapeutic application in the ischemic heart, as post-conditioning agents. Further studies are needed to better clarify and describe the clinical potential of selenoproteins both as drugs and biomarkers, but the existing information already indicates that they represent promising factors in this field.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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