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The selenoprotein methionine sulfoxide reductase B1 (MSRB1)

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Abstract

Methionine (Met) can be oxidized to methionine sulfoxide (MetO), which exist as *R*- and *S*- diastereomers. Present in all three domains of life, methionine sulfoxide reductases (MSR) are the enzymes that reduce MetO back to Met. Most characterized among them are MSRA and MSRB, which are strictly stereospecific for the *S*- and *R*-diastereomers of MetO, respectively. While the majority of MSRs use a catalytic Cys to reduce their substrates, some employ selenocysteine. This is the case of mammalian MSRB1, which was initially discovered as selenoprotein SELR or SELX and later was found to exhibit an MSRB activity. Genomic analyses demonstrated its occurrence in most animal lineages, and biochemical and structural analyses uncovered its catalytic mechanism. The use of transgenic mice and mammalian cell culture revealed its physiological importance in the protection against oxidative stress, maintenance of neuronal cells, cognition, cancer cell proliferation, and the immune response. Coincident with the discovery of Met oxidizing MICAL enzymes, recent findings of MSRB1 regulating the innate immunity response through reversible stereospecific Met-*R*-oxidation of cytoskeletal actin opened up new avenues for biological importance of MSRB1 and its role in disease. In this review, we discuss the current state of research on MSRB1, compare it with other animal Msrs, and offer a perspective on further understanding of biological functions of this selenoprotein.

Highlights

Met residues can be oxidized to Met sulfoxide and reduced by methionine sulfoxide reductases (MSR)

The selenoprotein MSRB1 is present in animals and its expression regulated by dietary selenium

MSRB1 protects against oxidative stress but few targets are known

MSRB1 regulates actin polymerization in a cycle of Met oxidation/reduction with MICALs enzymes

CaMKII and CaM oxidation and reduction by MSRB1 may protect cardiac and nervous cells

1. Oxidation of methionine and the discovery of methionine sulfoxide reductases

Oxidants such as hydrogen peroxide (H_2O_2) or hypochlorous acid (HOCl), formed by cellular metabolism or coming from the environment, play a key role in the metabolism of organisms by oxidizing proteins and regulating their functions in physiological and pathological contexts [1]. Methionine, either as a free amino acid or as an amino acid residue in proteins, can be oxidized by the addition of an oxygen atom to the side chain sulfur, producing a methionine sulfoxide. (MetO). This oxidation generates a stereogenic sulfur center yielding two diastereomers, *R* and *S*, of MetO (i.e., Met-*R*-O and Met-*S*-O) [2]. A racemic mixture is formed upon oxidation of the free amino acid, whereas oxidation of Met residues in polypeptides may favor formation of one diastereomer or the other, as was shown for calmodulin, which preferentially forms Met-*R*-O [3]. In proteins, Met oxidation can have several consequences, ranging from molecular damage to fine-tuned regulation of protein function. It can participate in the regulation of protein-protein interactions, either by preventing intermolecular binding [4] or homomultimer formation [5,6], or by inducing protein aggregation as demonstrated for α -synuclein [7]. There are also data indicating that oxidation of critical Met residues can alter enzyme activity, either negatively or positively [8–11]. Met can also act as an antioxidant, either in proteins, where it can be oxidized to protect other residues from deleterious oxidation, as shown for glutamine synthetase [12], or at the cellular level, where it acts as a scavenger of oxidant molecules [13]. All these functions are essential for cellular metabolism, suggesting that Met oxidation is a posttranslational modification that is as important as cysteine modification, particularly because it is enzymatically reversible. Indeed, MetO, free or in proteins, can be reduced back to Met by oxidoreductases called methionine sulfoxide reductases (MSR). One of the earliest pieces of evidence for the enzymatic reduction of MetO was obtained from *Escherichia coli* extracts [14], and since then several enzymes capable of reducing MetO, either free or embedded in proteins have been discovered [15]. The first discovered enzyme was MSRA, isolated from *E. coli* in 1981 [16] and cloned in 1992 [17]. MSRA-coding genes were found in almost all prokaryotes and eukaryotes [18–21]. Initial biochemical characterization of MSRA demonstrated that it is a thiol-based oxidoreductase, i.e., the enzyme uses cysteines as redox active residues to reduce the MetO [22,23], and that it shows strict stereospecificity

toward the reduction of Met-S-O [3,24,25]. At that time, such strict stereospecificity was unexpected for an enzyme that was supposed to act in "antioxidant defense". These results, and others such as the demonstration that leukocytes preferentially reduce Met-R-O [26] suggested that other enzymes might exist having an opposite stereospecificity to MSRA. Indeed, such an enzyme, now known as MSRB, was discovered in mammals and bacteria by several labs. One such enzyme that could reduce Met-R-O was found in *E. coli* [27]. Although it did not share sequence or structural characteristics with MSRA [28], it was shown that it is also a thiol-oxidoreductase [29,30]. In mammals, bioinformatic approaches initially revealed a selenoprotein of unknown function called SELR or SELX [31,32]. Subsequent comparative genomics analyses and biochemical characterization demonstrated that it is a Met-R-O reductase, and this protein was renamed as MSRB1 [33,34]. This enzyme is the subject of this review. In addition to the role of MetO reduction in proteins, it has been shown that MSRA and MSRB have important functions in cellular metabolism. Numerous studies showed the involvement of MSRs in the protection of cells from oxidative stress, supporting repair of oxidized proteins, and serving a role of scavenger of oxidant molecules due to cyclic oxidation and reduction of Met [35]. The roles of protein Met oxidation and of MSRAs and MSRBS in various organisms have been reviewed recently [29,35–38].

Other enzymes with the capacity to reduce MetO were found, principally in bacteria. In 2007, free-methionine-*R*-sulfoxide reductase (*fRMSR*), also called MSRC, was isolated and characterized, and shown to reduce only the free form of Met-R-O [39]. It is a thiol-oxidoreductase unrelated to MSRA or MSRB [40–42]. *fRMSR* may have an antioxidant function by maintaining the pool of Met available for protein synthesis and the production of sulfur-containing metabolites [42,43]. Bacterial molybdoenzymes of the dimethyl sulfoxide reductase family have been known for their ability to reduce free MetO *in vitro*, but for some of them, the data indicated the ability to maintain the pool of free MetO reduced *in vivo* [44,45] or showed a potential role in the reduction of MetO residues [46,47]. Finally, another bacterial molybdoenzyme related to the sulfite oxidase family has been brought to light. Called MSRP, with P standing for its 'periplasmic' subcellular localization, this enzyme can reduce both free MetO and protein-based MetO in a broad spectrum of substrates without any stereospecificity [48–50].

2. Distribution of MSRs across the tree of life: selenocysteine-containing MSRB1 is only present in animals

Nowadays, we know five types of MSRs distributed across the tree of life, among which some MSRA and MSRBs are selenocysteine-containing enzymes (**Table 1**). The genes coding for MSRA or MSRB are present in almost all organisms. They are absent only in some strictly anaerobic prokaryotes and eukaryotes, extremophiles and obligatory intracellular parasites, which are organisms very likely protected from direct oxidative pressure [18,19,21]. Most organisms have several *MSR* genes, usually one for each type, but this number can increase significantly, particularly in plants, e.g., 5 *MSRA* and 9 *MSRB* genes in *Arabidopsis thaliana* [18–21]. In addition, some bacteria encode a bifunctional MSRA/MSRB fusion [18,51]. The gene coding for *fRMSR* is present in bacteria, some unicellular eukaryotes and throughout the kingdom of fungi [19,42], whereas molybdenum-containing enzymes with MSR activity have only been found in bacteria [49,52] (**Table 1**).

Genes encoding selenocysteine-containing MSRA have been identified in all major kingdoms except archaea (**Table 1**), but they are usually restricted to a very few organisms in each kingdom [19,53,54]. On the contrary, selenocysteine-containing MSRBs are strictly restricted to the animal lineage (**Table 1**) but are present throughout the lineage with few exceptions like insects and nematodes [55]. We also note animals from the Porifera phylum (sponge) having both selenocysteine-containing MSRA and MSRB [55], and the occurrence of an MSRB with five selenocysteines in the sea anemone *Metridium senile* (Cnidaria), among which four are not involved in catalysis but probably in metal binding [56]. The human MSR system is composed of one gene encoding an MSRA and three genes encoding MSRBs, including MSRB1, the only selenoprotein MSR. The same set of genes is present in mice and very likely all other mammals [57–59].

3. Characteristics of the human *MSRB1* gene, the encoded protein and its enzymatic activity

The human *MSRB1* gene is located in the p arm extremity of chromosome 16 (p13.3) and contains four exons and a type II SECIS element of 70 base pairs (**Figure 1**) [31,60,61]. In the produced

transcript, the SECIS element is located 479 base pairs from the end of the coding sequence and 536 base pairs away from the UGA codon encoding Sec, located in exon III (**Figure 1**). The produced protein of 116 amino acids localizes to the cytosol and nucleus [6,58]. In comparison with other human MSRBs (i.e., MSRB2 and MSRB3), MSRB1 is the smallest, mostly because of the shorter N-terminal sequence and the lack of signal peptides (**Figure 2A**). This is a general feature, as selenoprotein MSRBs from other organisms are shorter than their Cys containing counterparts [62,63]. Like most known MSRBs, human MSRB1 possesses four Cys organized in two Cys-X-X-Cys motifs and involved in the coordination of a zinc atom. This metal ion plays a structural role and is not involved in catalysis [64,65] (**Figure 2B**). The catalytic selenocysteine is in position 95, and site-directed mutagenesis approaches demonstrated that the presence of Sec instead of a Cys, provides a strong catalytic advantage [66] (**Table 2**). Indeed, it was shown that when the catalytic Sec of MSRB1 was mutated to Cys, the enzyme specific activity decreased 85-fold, whereas the replacement of the catalytic Cys of MSRB2 or MSRB3 by a Sec increased the activity 173- and 126-fold, respectively [66] (**Table 2**). Substitution of the catalytic Cys conserved in most MSRBs by Sec in MSRB1 is accompanied by the replacement of other key residues: in positions 3, 77, 81 and 97, wherein Thr, His, Val/Ile and Asn, conserved in Cys-containing MSRBs are substituted with Phe, Gly, Glu and Phe in MSRB1 (**Figure 2A & C**). Reinsertion of conserved residues in MSRB1 by site-directed mutagenesis was shown to be detrimental for its activity but increased the activity of its Cys mutant [66]. Structures of MSRB1 proteins from human (unpublished) or mouse [62] have been solved (**Figure 2B**). These proteins have similar structures, with an overall β -fold consisting of two antiparallel β -sheets and a highly flexible N-terminal region (**Figure 2B**). This last feature is necessary for the MSRB1 activity and its regeneration by the thioredoxin system. Indeed, after substrate binding and MetO reduction by the catalytic Sec95, a selenenic acid is formed, and is subsequently reduced by the formation of a selenylsulfide bridge with the resolving Cys4. This bond is then reduced by the thioredoxin system to release a reduced MSRB1 [66,67].

Determination of the structure of mouse MSRB1 by NMR and comparison with the known mechanism of Cys-containing MSRBs of *Neisseria meningitidis* and *N. gonorrhoeae* bacteria offered insight into the function of key amino acids involved in catalysis. In *N. meningitidis* MSRB, Phe482,

Asp484 and Arg493 (*N. meningitidis* MSRB numbering) were found to be necessary for activation of the catalytic Cys495 (**Figure 2A, black triangles & Figure 2C**) whereas Thr403, Trp442, Asp457, Glu466, His477, His480 and Asn497 were shown to be involved in stabilization of the transition state and of the polarized form of the sulfoxide function of the substrate [28,68] (**Figure 2A, green triangles & Figure 2C**). The residues conserved in MSRB1 (i.e., Trp43, His80, Phe82, Asp85 and Arg93) might play a similar function. Glu81, unique to selenoprotein MSRB1s, forms a salt bridge with Lys57 and is important for MSRB1 activity (**Figure 2A, black stars**) [62,66]. Phe97 plays also critical roles for MSRB1 activity by favoring the movement of its N-terminal part by hydrophobic interactions with three other Phe residues (Phe3, Phe6 and Phe7), present in the vicinity of the resolving Cys4, in order to stabilize enzyme/substrate interactions and promote the formation of the intramolecular selenylsulfide bond after product release [62,66].

Finally, a short form of MSRB1 of ~5 kDa corresponding to the C-terminal part of the protein starting from Asn76, was found in several mouse tissues and in human cell lines [69]. This shorter version might be produced by protein cleavage [69], and while it contains Sec95, it lacks the zinc-binding motif and the resolving Cys raising the question of its role *in vivo* [69].

4. Expression of human *MSRB1* and comparison with other MSR coding genes

Human *MSR* genes are expressed in most tissues, as demonstrated in the global expression study ‘Human Protein Atlas’ [70] (**Figure 3**). The *MSRB1* transcript is highly abundant in the brain, the digestive tract, the liver and the bone marrow. Of note, *MSRB1* transcript is largely more abundant than the other *MSR* genes in the pancreas, the liver, the bone marrow and lymphoid tissues, and to a lesser extent, in the skin (**Figure 3**). *MSRA* coding gene is highly expressed in kidney, digestive tracts, brain, liver, and female tissues. *MSRB2* is the most abundantly expressed in the brain, and it is also highly expressed in the digestive tract, muscles, and female tissues (**Figure 3**). The gene coding for MSRB3 has a similar expression profile as *MSRB2* and it is the most abundant of all *MSRs* in the digestive tract, the muscles, and the male and female tissues (**Figure 3**). These data are consistent with those found on

dedicated analyses of *MSR* genes expression [71–74], and similar expression profiles were found in mouse tissues [75].

Expression of the *MSRB1* gene has been proposed to be regulated by the Sp1 transcription factor and by DNA methylation in human cells [76]. The active MSRB1 enzyme has been shown to be located primarily in the liver, where it is responsible for most of the MetO reduction activity [77]. As a selenoprotein, the expression and the activity of MSRB1 was found to be dependent on bioavailability of the dietary selenium in mice [77,78]. MSRB1 expression decrease with selenium deficiency and can increase with supplementation of dietary selenium up to 0.4 ppm, resulting in an increase in total MSRB activity [77,78]. The effect of dietary selenium on MSRB1 expression is influenced by the host microbiome, which, through its own use, affects selenium availability for the host [79]. Moreover, MSRB1 expression decreases with age but is not affected by caloric restriction, independently of dietary selenium [77].

5. Functional regulation by reversible Met oxidation and reduction by MSRB1

As for most MSRs, the reductase activity of MSRB1 towards free MetO and MetO present in molecules mimicking MetO protein residues has been clearly established, but information about the proteins oxidized in cells and known to be physiological substrates of this MSR is extremely limited. One of the only examples was the Mg^{2+} channel TRPM6 (for *transient receptor potential melastatin type 6*) found in renal and intestinal epithelial cells, which was shown to be inactivated by H_2O_2 and to interact with MSRB1 [80]. The co-expression of MSRB1 with TRPM6 in HEK293 cells strongly reduced the effect of H_2O_2 , suggesting that oxidized TRPM6 might be a substrate of MSRB1 *in vivo* [80]. However, the view that MSRs were “antioxidant” enzymes only changed when it was demonstrated that two Met residues on actin can be oxidized enzymatically *in vivo* and become substrate of MSRB in *D. melanogaster* [81], and of MSRB1 in mammals [6]. The cytoskeleton protein actin, conserved in eukaryotes, exists as free monomer named G-actin (‘Globular’) or as part of a linear polymeric microfilament called F-actin (‘Filamentous’) [82]. The polymerization/depolymerization process is

necessary for numerous cellular functions such as cell motility, cell division and cytokinesis, organelle movement or muscle cell contraction, and involves several proteins, like Formin or Cofilin, regulating microfilaments assembly and disassembly, in an ATP-dependent or -independent processes (for review see [83,84]). Actin polymerization has also been shown to be regulated by redox reactions and oxidative posttranslational modifications [85]. Particularly, it has been demonstrated that flavin monooxygenases of the MICAL (‘*Molecule Interacting with CasL*’) family can stereospecifically convert actin’s Met44 and Met47 (*Drosophila melanogaster* cytoskeleton actin numbering) into Met-R-O [6,86,87]. These two Met are located in the D-loop of actin, in the contact zone of two monomers in the F-actin filament (**Figure 4A**). They are widely conserved in eukaryotes, especially Met44, and their oxidation induces depolymerization of F-actin [6,86–88]. Structural analysis showed that depolymerization is partially due to a twist of the actin D-loop induced by the reorientation of Met44 after oxidation and the formation of a new hydrogen bond between the oxidized sulfur of Met47 and the hydroxyl of Thr351 [89]. Moreover, actin oxidation favors F-actin filament disassembly by removing the protection against the action of Cofilin, a disassembly factor [90]. It has been shown that actin oxidation by MICAL is reversible by the action of MSRBs (**Figure 4B**). Reversible oxidation of both actin’s Met residues has been shown to be involved in hair development, muscle organization and axon guidance in *D. melanogaster* and in cytokinesis in human cells [81,91]. In particular, the role of MSRB1 in antagonizing the effect of MICAL on actin in macrophages has been demonstrated [6]. The response of macrophages to pathogens or associated molecules like lipopolysaccharides (LPS) requires the reorganization of actin cytoskeleton to produce filopodia and lamellipodia, involved in phagocytosis and cell migration, respectively [92,93]. It has been shown that there is a strong increase in the amount of MSRB1 protein and MSRB activity in LPS-treated macrophages, and that MSRB1 colocalizes with actin in lamellipodia of LPS-stimulated macrophages. Moreover, the increase of filopodia numbers observed in wild-type macrophages treated with LPS was lost in *MSRB1*^{-/-} macrophages [6].

Recently, it has been proposed that the MICAL1/MSRB1 couple regulates Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) activity in the heart by controlling the redox state of its M308 [94]. Oxidation of M308 in CaMKII, catalyzed by MICAL1, decreases calmodulin binding and kinase

activity, which prevents cardiac arrhythmias and decreased fight-or-flight response in mice and protects human pluripotent stem cell–derived cardiomyocytes with catecholaminergic polymorphic ventricular tachycardia but it strongly impairs heart function in fly [94]. Of note, regardless of the role of MICAL1 in oxidation of M308 in CaMKII, the effect of MSRB1 on the reduction of oxidized M308 was evaluated *in vitro* only [94]. However, this work echoes the data obtained in mouse, wherein it has been shown that the inactivation of *MSRB1* gene correlated with the decrease in CaMKII phosphorylation [95]. The direct interaction of MSRB1 with CaMKII was evidenced by yeast-two hybrid assays [96]. Overall, the data suggest that, as it has been shown for MSRA [8], CaMKII could be oxidized and become a substrate for MSRB1 *in vivo*.

6. Physiological roles of MSRB1 and association with pathological conditions

The roles of MSRB1 in animal physiology have been evaluated mainly by genetic approaches in both cells and whole animals (mice). Collectively, these studies revealed that MSRB1 participates in i) the protection against oxidative stress, ii) cancer cell proliferation, iii) the immune response, and iv) maintenance of cells of the nervous system and in cognition.

One of the first pieces of evidence for the role of MSRB1 in the protection against oxidative damage was obtained with *MSRB1*^{−/−} mice, for which kidney and liver tissues presented increased levels of protein MetO, protein carbonylation, oxidized glutathione, malondialdehyde and decrease in the levels of free and protein thiols [69]. The elevation in the levels of these oxidative stress markers was more pronounced when mice were administered acetaminophen, an oxidant-generating drug [97]. By knocking-down *MSRB1* in human lens epithelial cells, it was shown that MSRB1 participates in the prevention of cataract formation by protecting against oxidative stress-induced apoptosis after treatment with *tert*-butyl hydroperoxide [98] or peroxynitrite [99,100], or in the context of diabetes [101,102]. The lack of MSRB1, or any other MSR, resulted in increased oxidative stress-induced cell death [98]. Consistent results were obtained with human hepatocytes LO2, in which the knockdown of *MSRB1* resulted in elevated H₂O₂-induced apoptosis [103].

MSRB1 was also shown to promote proliferation and invasion of cancer cells. Indeed, *MSRB1* knockdown inhibited migration and division of human bone osteosarcoma epithelial (u2os) cells [104] and hepatocellular carcinoma cells [105]. In these models, the decrease in *MSRB1* expression correlated with the decrease in phosphorylation of ERK, MEK, and p53 proteins of the mitogen-activated protein kinase pathway [104,105]. Moreover, *MSRB1* knockdown inhibited tumor growth in xenograft tumorigenicity models [104,105]. In colorectal cancer cells, a similar effect was observed and proposed to involve the GSK-3 β / β -catenin signaling pathway [106].

Recent evidence also suggests a role of MSRB1 in the immune response. *MSRB1* mRNA, protein and activity levels were very high in mouse macrophages stimulated by LPS treatment [6,75]. Whereas a role of MSRB1 in the detection and triggering of intracellular signaling in response to LPS was excluded, the induction of anti-inflammatory cytokine genes *Il10* and *Il1rn* was greatly reduced in LPS-treated *MSRB1*^{-/-} macrophages [75]. On the contrary, the expression of pro-inflammatory *Il12a* and *Il12b* genes was enhanced in the absence of MSRB1 [75]. These results indicated an anti-inflammatory role for MSRB1, which was also consistent with a greater skin sensibility of *MSRB1*^{-/-} mice to irritating treatment, compared to wild-type or *MSRA*^{-/-} mice [75]. In dendritic cells, it was shown that genetic ablation of MSRB1 compromised upregulation of the expression of cluster of differentiation (CD) 80 and CD86, and of the major histocompatibility complex class II in response to LPS [107]. MSRB1 was shown to regulate phosphorylation of the signal transducer and activator of transcription-6 (STAT6), to potentiate the LPS-induced Interleukin-12 production by dendritic cells and to drive T-helper 1 differentiation after immunization [107]. In the proposed model, LPS induced the production of ROS in dendritic cells, leading to Met oxidation on STAT6 and its inactivation. MSRB1 would reduce these MetO residues, maintaining STAT6 function [107].

MSRB1 was also shown to be involved in the maintenance of nervous cells and cognition in mice. *MSRB1* KO mice exhibited impaired spatial learning and memory abilities [95]. This was correlated to astrogliosis and astrocyte migration, to the disruption of long-term synaptic plasticity in hippocampus and decreased CaMKII phosphorylation [95]. Moreover, MSRB1 was shown to interact with the Clusterin chaperone through its Zn-binding domain, and this binding increased MSRB1 activity [108].

Clusterin (apolipoprotein J) is a chaperone participating in protein folding of secreted proteins and was shown to diminish β -amyloid peptide aggregation in an Alzheimer's disease model [109]. Interestingly, a direct interaction of MSRB1 with the β -amyloid peptide has also been demonstrated [110]. Moreover, lower MSRB1 activity was detected in neutrophils of Alzheimer's disease patients [111]. Together, these data suggest that MSRB1 may participate in the prevention of β -amyloid peptide oxidation and reduction of neuronal toxicity, similarly to what was proposed for MSRA [112,113]. Finally, *MSRB1* mRNA was found to be more abundant in lymphoblastoid cells of schizophrenia patients in comparison to their healthy monozygotic twin, indicating a potential link of MSRB1 with mental disorders [114]. Altogether, these data suggest that MSRB1 participates in the neuroprotection through several mechanisms, which are related to CaMKII or β -amyloid peptide via a direct and indirect protection against protein aggregation.

Interestingly, despite the potential involvement of MSRB1 in several physiological processes, *MSRB1*^{-/-} mice do not present strong phenotypic alteration [69]. This might be due to potential functional redundancy with other Msr. As a matter of comparison, we propose an assessment of the data obtained on individual *MSR* mutated mice, the *MSRA*^{-/-}/*MSRB1*^{-/-} double mutant, as well as mice lacking all 4 MSRs (**Table 3**). *MSRA*-deleted mice were the first created and currently the most characterized. They are more susceptible to oxidative stress and lipopolysaccharide challenge [8,115,116] and exhibit higher kidney damage following ischemia-reperfusion [117] or cisplatin treatment [118]. Similarly to *MSRB1*^{-/-} mice, liver damage is exacerbated in *MSRA*^{-/-} mice following acetaminophen treatment [119]. Ischemia-reperfusion induced higher brain damage [120], fibrosis was increased following ureteral obstruction [121] and common carotid artery ligation induced neointimal hyperplasia [122]. Contradictory results were obtained on the lifespan of *MSRA*^{-/-} mice, with the first study showing a decrease in lifespan [123] and the second showing no difference with wildtype mice [115]. *MSRA* knockout mice were also shown to suffer cataract [124], progressive hearing loss [125], brain pathologies, decreased complex task learning capabilities and abnormal behavior [126,127] (**Table 3**).

To evaluate whether a potential redundancy might explain the mild phenotype of *MSRB1*^{-/-} and *MSRA*^{-/-} mice, double KO mice were created [128]. They do not show growth retardation compared to wild-type or single mutant mice. Feeding with a Met restricted diet retarded the growth of weanling mice, and the retardation was higher in the double mutant, but no effect was observed in single knockout MSR mice [128]. These data indicated that MSRs are involved in the assimilation of Met from food, wherein external conditions can induce Met oxidation, and highlighted a potential redundancy of MSRA and MSRB1 function, even if they target opposing diastereomers of MetO. However, these double KO mice did not show any strong phenotype, suggesting a potential redundancy of function with the other MSRBs [115,128] (**Table 3**).

Mice genetically deprived of MSRB2 or MSRB3 have also been created [129,130] (**Table 3**). *MSRB2* knockout mice were shown to suffer the depletion of platelets which was associated with the increase of oxidant molecules levels in these cells [130]. Their use helped to understand that in human patients suffering diabetes mellitus, *MSRB2* expression is increased and leads to increased platelet mitophagy, whereas in patients with Parkinson's disease, *MSRB2* expression is reduced and associated with reduced mitophagy [130]. In these processes, MSRB2 is released from the matrix of leaking mitochondria and reduces MetO in Parkin protein, inducing mitophagy through ubiquitination and interaction with the microtubule-associated protein light-chain 3 [130]. The *MSRB3*^{-/-} mice were found to be profoundly deaf, most likely due to degeneration of the stereociliary bundles and subsequent loss of hair cells due to apoptotic cell death [129]. However, this effect was not shown to be correlated with an increase in protein oxidation in the inner ear [129].

Finally, quadruple *MSRA*^{-/-}/*MSRB1*^{-/-}/*MSRB2*^{-/-}/*MSRB3*^{-/-} mutant mice were created and shown to lack any MSR activity [131]. However, their characterization revealed an unexpected phenotype: they were found to be more resistant to cardiac ischemia-reperfusion injury and killing upon treatment with superoxide-generating paraquat [131]. In other words, genetic ablation of all MSRs rendered the mice more resistant to oxidative stress. A viability test of embryonic fibroblasts derived from the quadruple mutant revealed that these cells were not affected by paraquat, hydrogen peroxide or chromium treatments, compared to embryonic fibroblasts from wildtype mice. Only the treatment with cadmium

showed a decrease in viability of embryonic fibroblast from the quadruple mutant [131]. In the absence of treatment, the mice grew like wildtype animals, but they were deaf, very likely because of the lack of *MSRB3*, and potentially *MSRA*. Cardiac and muscular performance were not affected upon dobutamine test (mimicking effort test), and it was observed that cardio-protection in the quadruple mutant mice without preconditioning was similar to that observed in wildtype mice after preconditioning, indicating a potential link with signaling response to oxidant molecules [131]. However, the search of signaling pathway allowed only to exclude the involvement of the antioxidant response transcription factor NRF2 and pro-survival kinase AKT [131]. Mechanisms rendering the quadruple mutant mice more resistant to oxidative stress remain to be elucidated.

7. Conclusion and outlooks

Since its discovery in the late 1990's, important knowledge was acquired about selenoprotein MSRB1. In parallel to the characterization of other MSRs in animals and other organisms, it was shown that the use of selenocysteine in MSRB was restricted to animals [55] and provides a strong catalytic advantage over Cys [66]. This specificity renders the expression and activity of MSRB1 dependent on selenium availability in the diet [77]. This enzyme participates in the protection of proteins from oxidative stress, mainly in the liver and kidney [69,97]. The use of genetically modified mice and cells revealed the roles of MSRB1 in the protection against oxidative stress, in cancer cell proliferation, in the protection of the nervous system and in the immune response. However, in most cases, molecular mechanisms remained unclear because the identity of proteins oxidized at their Met and reduced by MSRB1 are largely unknown. A similar statement can be made for most MSRs, in general. Actually, MSRB1 is one of rare MSRs for which a substrate is known and has been validated *in vivo*: this substrate is actin, and the discovery of the importance of Met oxidation in actin depolymerization was a milestone in redox research. The fact that oxidation of critical Met in actin is catalyzed by enzymes (MICALs), and that MSRs, notably MSRB1, reverse their oxidation state, has changed the long-time view of Met oxidation as a representation of "damage". These discoveries showed that the reversible formation of MetO is a redox post-translational modification able to regulate protein functions and biological

processes, similarly to phosphorylation of serine, threonine and tyrosine, or the oxidation of cysteines. It also shows that MSRs in general, and MSRB1 in particular, should not be considered only as "antioxidants" or "protein repair enzymes", but also as redox regulators.

Since the discovery of actin as the substrate of MICAL enzymes, two other substrates have been proposed, the actin-related protein 3B (ARP3B), whose Met293 is oxidized by MICAL2 [132] and CaMKII, oxidized on Met308 by MICAL1 [94]. This puts in light the fact that Met oxidation by MICAL enzymes may affect various proteins, including yet to be discovered and, knowing the strict stereospecificity of MICALs to form *R*-diastereomers, MSRB1 and other MSRBs, could have important functions in regulating the oxidation state of Met in these unidentified proteins. These two recently identified oxidized proteins also bring to light two potential "hubs" of Met oxidation in animals: actin and actin-related proteins as well as the CaMKII and calmodulin. ARP3B belongs to the ARP2/3 complex which catalyzes filamentation of actin and drives lamellipodia formation and cell protrusion, MICAL1 and MICAL2 would thus oxidize both actin and ARP3B to depolymerize the filament, and MSRB1 would reverse these oxidations [6,132]. CaMKII has also been shown to be potentially oxidized on 3 Met residues: Met281 and Met282 by oxidants in a process reversible by MSRA [8] and the Met308, oxidized by MICAL1 and potentially reduced by MSRB1 [94]. Interestingly, the oxidation of these Met was shown to exert different effects on the CaMKII activity [8,94] (**Figure 5**). Moreover, calmodulin, which binds and regulates CaMKII activity, is also potentially oxidized on Met and reduced by MSRs [4,133–135]. As calmodulin binding to CaMKII involves Met of both partners (**Figure 5**), it would be interesting to evaluate the oxidation states in physiological conditions in wildtype and MSR-deficient cells or mice. This would be particularly relevant in nervous system cells, where CaMKII phosphorylation, a Ca^{2+} /Calmodulin dependent process, was shown to be reduced in *MSRB1*^{-/-} mice [95].

Our analysis of many articles cited in this review put also in light a lack of biochemical characterization of proteins oxidized by oxidants or enzymes and their reduction by MSR. In other words, several papers bring data involving genetic analyses but do not show that particular MSRs actually reduce proposed targets. This is the case for CaMKII, for which an increase in Met281 and

Met282 oxidation was observed in some tissues of *MSRA*^{-/-} mice [8,136], but to our knowledge, a biochemical demonstration that MSRA, or any other MSR, actually reduces these oxidized Met in CaMKII, has not been shown. As shown for other proteins [50,135,137,138], Met oxidation by oxidants is rarely completely stereospecific and these Met281 and Met282 could be oxidized as *R*-diastereomers, potentially raising the question of the role of MSRB1 in the regulation of their redox state (**Figure 5**). Of note, oxidation of Met308 to the *R*-diastereomer by MICAL1 was shown to be reduced by MSRB1 only, as expected [94]. A similar observation can be made for ARP3B oxidation by MICAL2, which was proposed based on genetic and colocalization data, but not demonstrated biochemically [132]. We think that it is very important to bring clear biochemical evidence of oxidation and reduction in parallel with genetic data to validate proteins as specific substrates of Met oxidases and MSRs to avoid potential misinterpretation.

Finally, our knowledge of MSRB1 functions, functions of other MSRs, and the role of Met oxidation in general lags behind other post-translational modifications because of the lack of easily usable tools to identify MetO-containing proteins. Recently, the use of heavy hydrogen peroxide ($\text{H}_2^{18}\text{O}_2$) allowed to avoid nonspecific oxidation in proteomics and map Met oxidation, identifying proteins with Met highly sensitive to oxidation in several bacterial and mammalian proteomes [139–142]. Furthermore, the recently developed oxaziridine probes specifically binding Met in a reactivity-dependent fashion [143,144] have been used to show that pyruvate kinase M2 can be activated by oxidation of its Met239 in pancreatic tumor metastasis, and that MSRA could reduce it and act as a suppressor of pancreatic ductal adenocarcinoma [145]. We think that the use of these recently developed (chemo)proteomic methods, based on heavy hydrogen peroxide ($\text{H}_2^{18}\text{O}_2$) or on oxaziridine probes targeting reactive Met would be very useful in identifying targets of MSRB1 and other MSRs. Moreover, the use of genetically-encoded fluorescent biosensors able to detect the levels of Met oxidation *in vivo* [146–149] should help to understand the roles of this post-translational modification and of the MSRs in many physiological contexts.

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Author contributions

L.T., B.C.L and V.N.G conceived the review content. L.T. drafted the manuscript and prepared the figures and tables. L.T., A. K., H.Y.K., B. M., B.C.L. and V.N.G. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1. Distribution of MSRs in the main kingdoms of life.

Organisms	MSRA		MSRB		fRMSR	MSRP	Other molybdo MSR
	Catalytic res. Cys	Sec ¹	Catalytic res. Cys	Sec			
Animals	Yes	Yes	Yes	Yes ²	No	No	No
Fungi	Yes	Yes	Yes	No	Yes	No	No
Plants	Yes	Yes	Yes	No	No	No	No
Bacteria	Yes	Yes	Yes	No	Yes	Yes	Yes
Archaea	Yes	No	Yes	No	No	? ³	? ³

¹ Selenoprotein MSRA are extremely rare.² With few exceptions, selenoprotein MSRBs are found throughout the animal lineage.³ Although the presence of sulfite oxidase and dimethyl sulfoxide oxidase molybdoenzymes in archaeal genomes has been clearly established [52], to our knowledge, none have been tested for their ability to reduce free or protein-based MetO.

Table 2. Specific activities of Sec- and Cys-containing human MSRBs.

	Specific activity (nmol.min ⁻¹ .mg protein ⁻¹)	Increase in the activity of Sec vs Cys
MSRB1 Wt (Sec)	170 ± 26	85
MSRB1 U95C	2 ± 1	
MSRB2 C169U	692 ± 124	173
MSRB2 Wt (Cys)	4 ± 2	
MSRB3 C158U	5158 ± 565	126
MSRB3 Wt (Cys)	41 ± 13	

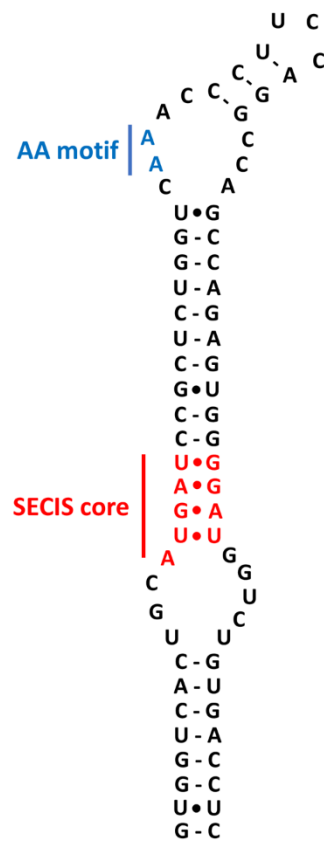
Data are from Kim and Gladyshev, 2005 [66]

Table 3. Phenotypes of *MSR* KO mice.

	<i>MSRA</i> ^{-/-}	<i>MSRB1</i> ^{-/-}	<i>MSRB2</i> ^{-/-}	<i>MSRB3</i> ^{-/-}	<i>MSRA</i> ^{-/-} / <i>MSRB1</i> ^{-/-}	<i>MSRA</i> ^{-/-} / <i>MSRB1</i> ^{-/-} / <i>MSRB2</i> ^{-/-} / <i>MSRB3</i> ^{-/-}
Oxidative stress susceptibility and markers	<ul style="list-style-type: none"> - Sensitivity to paraquat, to 100% O₂ [115,123] - Increased protein carbonylation [123] - Increased beta-amyloid aggregate¹ [112] - Sensitivity to cisplatin [118] - Lethal susceptibility to chronic oxidative stress and lipopolysaccharide challenge [8,116] 	In liver and kidney [69]: <ul style="list-style-type: none"> - Increased protein MetO - Increased protein carbonylation - Increased oxidized glutathione - Reduced free and protein thiols - Increased malondialdehyde - MSRA activity decreased [69] 	In platelets [130]: <ul style="list-style-type: none"> - Increased oxidant molecules 	In the inner ear [129]: <ul style="list-style-type: none"> - No increase in protein MetO - No increase in protein carbonylation 		<ul style="list-style-type: none"> - More resistant to paraquat [131] - More resistant to cardiac ischemia-reperfusion [131] - Sensitivity to cadmium [131]
Growth, lifespan and metabolism	<ul style="list-style-type: none"> - Decreased lifespan [123] - Normal lifespan [115] - Exacerbated insulin resistance caused by high fat feeding [150] 	<ul style="list-style-type: none"> - Normal growth [69] - Normal lifespan [69] - No increase in high-fat diet-induced insulin resistance [151] 			<ul style="list-style-type: none"> - Normal growth [128] - Retarded growth on low Met diet [128] - No change in plasma Met, S-adenosylmethionine or S-adenosylhomocysteine concentration [128] 	Normal growth [131]
Senses, behavior, and locomotion alteration	<ul style="list-style-type: none"> - Tip-toe walking [123] - Decreased complex task learning capabilities [126] - Progressive hearing loss and sensitivity to acoustic trauma [125] 	<ul style="list-style-type: none"> - Decreased spatial learning and memory abilities [95] 		- Deafness [129]		- Deafness [131]
Tissues and organ injuries	<ul style="list-style-type: none"> - Kidney damage and brain damage following ischemia-reperfusion [117,120] - Kidney fibrosis in ureteral obstruction [121] - Liver damage by acetaminophen [119] - Susceptibility to cardiomegaly [8] - Neurodegeneration in brain hippocampus [127] - Arterial neointimal hyperplasia following injury to the common carotid artery [122] - Hyperbaric O₂ induced cataract [124] 	<ul style="list-style-type: none"> - Liver damage by acetaminophen [97] - Astrogliosis in brain [95] - Reduced production of anti-inflammatory cytokines in macrophages treated by LPS [75] - Greater severity of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin inflammation [75] 	<ul style="list-style-type: none"> - Decreased platelets [130] 			

¹ When *MSRA* gene is inactivated in an Alzheimer's disease (AD) model mice

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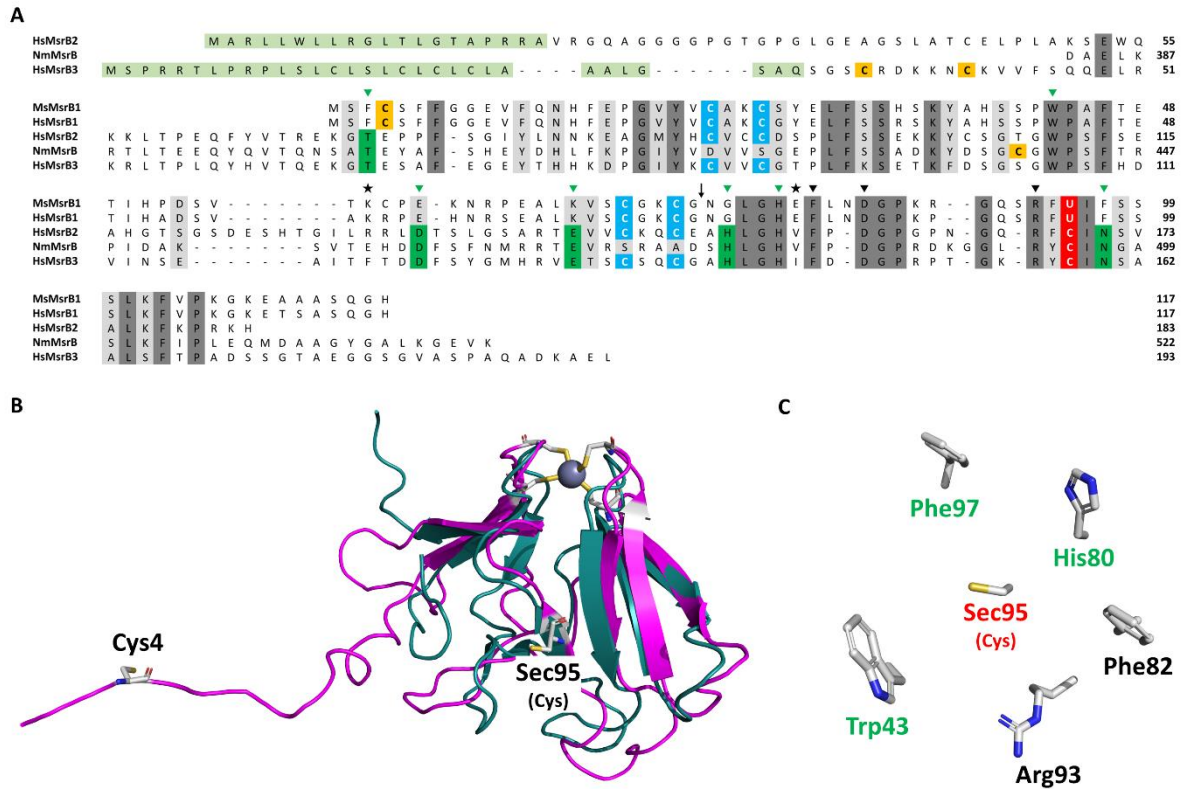


Figure 2. MSRB1 sequence and structure. Protein sequence alignment of human and mouse Sec-MSRB1s with human and *N. meningitidis* Cys-MSRBs. Identical and similar amino acids are in *dark* and *light grey* backgrounds, respectively. Sequences in *green* background correspond to targeting peptides. Resolving Cys, zinc-binding Cys and catalytic Sec/Cys are in *yellow*, *blue* and *red* backgrounds, respectively. *Green* and *black* triangles indicate residues involved in stabilization of sulfoxide and the transition state, and residues necessary for catalytic Cys/Sec activation, respectively. *Black* stars indicate residues involved in salt bridge and the *dark arrow* highlights a probable cleavage site yielding the short form of MSRB1. *HsMSRB1*, *Homo sapiens* MSRB1 (Uniprot #Q9NZV6); *HsMSRB2*, *Homo sapiens* MSRB2 (Uniprot #Q9Y3D2); *HsMSRB3*, *Homo sapiens* MSRB3 (Uniprot #Q8IXL7); *MmMSRB1*, *Mus musculus* MSRB1 (Uniprot #Q9JLC3); *NmMSRB*, *N. meningitidis* MSRB domain of the PILB protein (Uniprot #Q9JWM8). **(B)** Superposition of human and mouse Sec-MSRB1 structures. Human MSRB1 (PDB #3MAO) and mouse MSRB1 (PDB #2KV1) structures, in *dark cyan* and *magenta*, respectively, are superimposed. Resolving Cys, zinc-binding Cys, and catalytic Sec95 (mutated to Cys) are represented as sticks. **(C)** 3D representation of the mouse MSRB1 active site. Residues of mouse MSRB1 are represented by sticks and the colors of the labels correspond to those of the triangles indicating their roles in **(A)**. The protein sequences alignment has been made with

ClustalOmega (<https://www.ebi.ac.uk/Tools/msa/clustalo/>) and represented with Microsoft Excel 365.

Representation of proteins structures was made using PyMol 2.3.2 (<https://pymol.org/2/>).

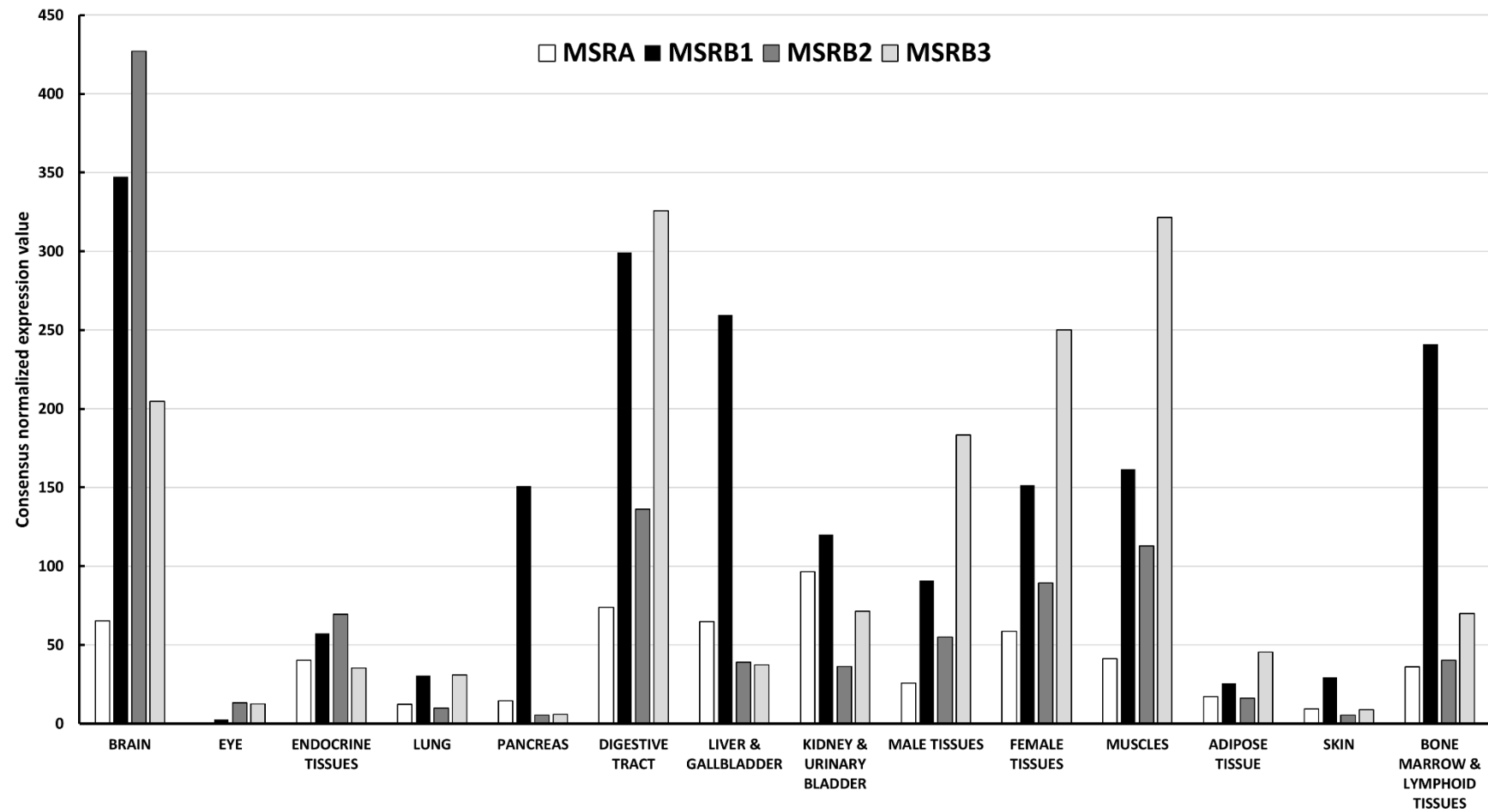


Figure 3. Expression levels of MSRs genes in main human tissues. Data of transcript abundances were retrieved from the Human Protein Atlas <https://www.proteinatlas.org> and are presented with ‘*consensus normalized expression values*’ from several RNAseq analyses [70].

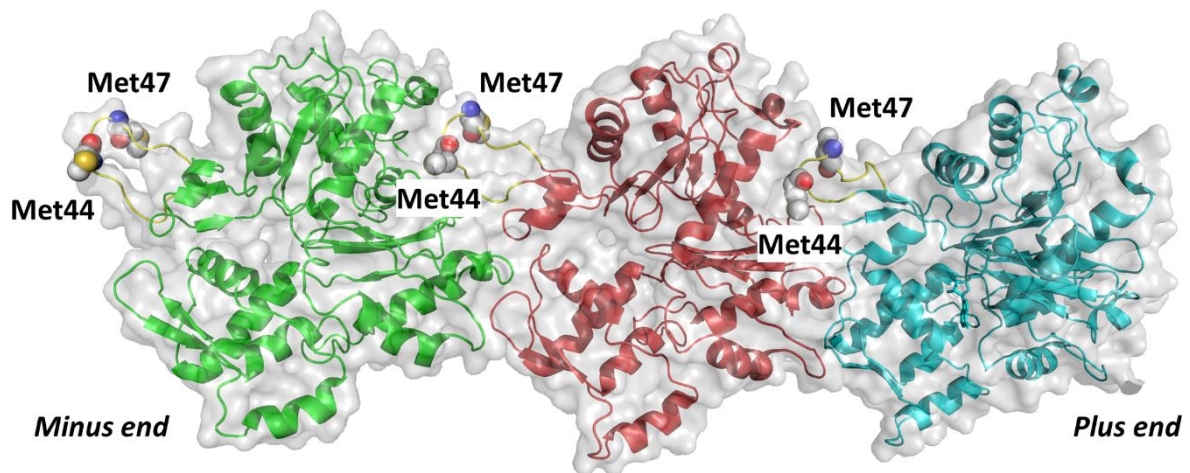
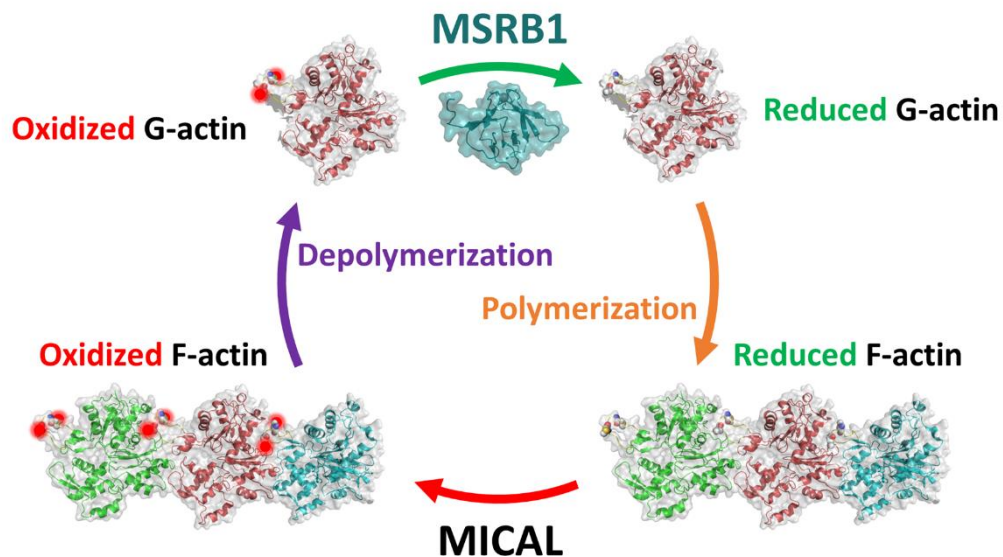
A**B**

Figure 4. Regulation of actin by MICAL-dependent oxidation and MSR1-dependent reduction of its Met residues. (A) The position of Met44 and Met47 in F-actin filament. Three monomers of actin in the filament are shown in *grey*, *red* and *cyan* from the minus end to plus end, respectively. The D-loop is shown in *yellow* and Met44 and Met47 are shown as spheres. (B) Regulation of actin polymerization by cyclic oxidation and reduction by MICALs and MSR1. MSR1 reduces the monomer of G-actin formed after depolymerization of F-actin following oxidation by MICAL. Structure representations were based on *Mus musculus* actin structure (PDB# 3J8A) [153]. Representation of proteins structures was made using PyMol 2.3.2 (<https://pymol.org/2/>).

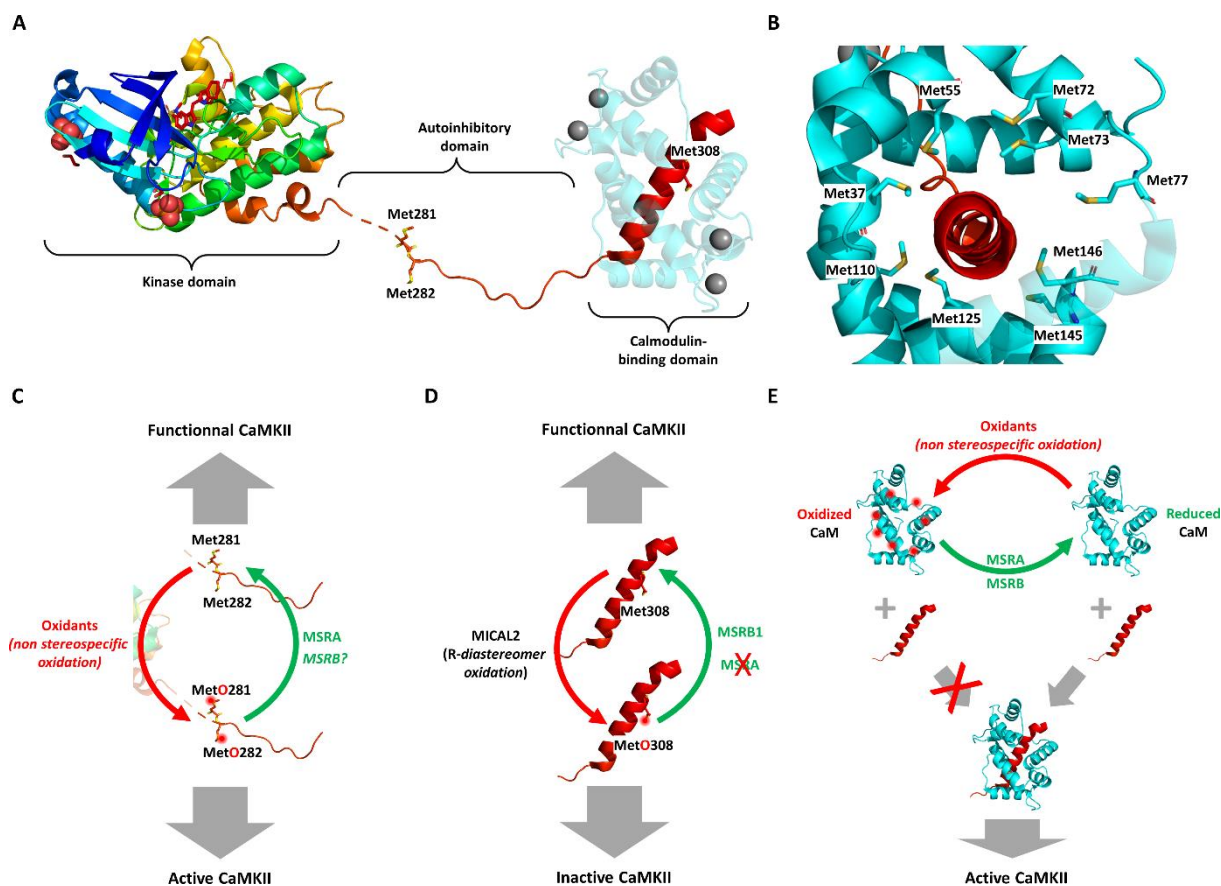


Figure 5. Regulation of CaMKII and calmodulin through oxidation and reduction of Met. (A)

Structure of human CaMKII and the positions of Met281, Met282 and Met308. CaMKII with its kinase, autoinhibitory and calmodulin-binding domains is shown in *rainbow* color. Met are shown as sticks. Calmodulin and calcium atoms are shown in *cyan* in the transparent mode, and as *grey* spheres, respectively. **(B)** Detailed view of the 8 Met of calmodulin surrounding the CaMKII calmodulin-binding domain. Calmodulin and CaMKII calmodulin-binding domain are shown in *cyan* and *red*, respectively. For clarity, residues 78 to 93 of calmodulin were made transparent. **(C)** Oxidation of Met281 and Met282 by small molecule oxidants activates CaMKII [8]. The process is potentially reversible by MSRA, but since the oxidation is most likely not stereospecific, the role for MSRB should possibly be considered too. **(D)** Stereospecific oxidation of CaMKII Met308 by MICAL2 prevents its activation, in a process reversible by MSRB1, but not MSRA [94]. **(E)** Considering the position of calmodulin Met around the CaMKII calmodulin-binding domain, their oxidation by oxidants might prevent its ability to bind and activate CaMKII. Potential reduction by MSRA and MSRB might restore the calmodulin capacity to bind CaMKII. Structure representations are based on human CaMKII and calmodulin

complex structure (PDB# [2WEL](#)) [154]. Representation of protein structures was made using PyMol 2.3.2 (<https://pymol.org/2/>).