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The selenoprotein methionine sulfoxide reductase B1 (MSRB1)

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25 **Abstract**

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

41

42 **Highlights**

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

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

45 MSRB1 protects against oxidative stress but few targets are known

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

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

48

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

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

76 toward the reduction of Met-*S*-O [3,24,25]. At that time, such strict stereospecificity was unexpected for
77 an enzyme that was supposed to act in "antioxidant defense". These results, and others such as the
78 demonstration that leukocytes preferentially reduce Met-*R*-O [26] suggested that other enzymes might
79 exist having an opposite stereospecificity to MSRA. Indeed, such an enzyme, now known as MSRB,
80 was discovered in mammals and bacteria by several labs. One such enzyme that could reduce Met-*R*-O
81 was found in *E. coli* [27]. Although it did not share sequence or structural characteristics with MSRA
82 [28], it was shown that it is also a thiol-oxidoreductase [29,30]. In mammals, bioinformatic approaches
83 initially revealed a selenoprotein of unknown function called SELR or SELX [31,32]. Subsequent
84 comparative genomics analyses and biochemical characterization demonstrated that it is a Met-*R*-O
85 reductase, and this protein was renamed as MSRB1 [33,34]. This enzyme is the subject of this review.
86 In addition to the role of MetO reduction in proteins, it has been shown that MSRA and MSRB have
87 important functions in cellular metabolism. Numerous studies showed the involvement of MSRs in the
88 protection of cells from oxidative stress, supporting repair of oxidized proteins, and serving a role of
89 scavenger of oxidant molecules due to cyclic oxidation and reduction of Met [35]. The roles of protein
90 Met oxidation and of MSRAs and MSRBs in various organisms have been reviewed recently [29,35–
91 38].

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

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

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

115 Genes encoding selenocysteine-containing MSRA have been identified in all major kingdoms
116 except archaea (**Table 1**), but they are usually restricted to a very few organisms in each kingdom
117 [19,53,54]. On the contrary, selenocysteine-containing MSRBs are strictly restricted to the animal
118 lineage (**Table 1**) but are present throughout the lineage with few exceptions like insects and nematodes
119 [55]. We also note animals from the Porifera phylum (sponge) having both selenocysteine-containing
120 MSRA and MSRB [55], and the occurrence of an MSRB with five selenocysteines in the sea anemone
121 *Metridium senile* (Cnidaria), among which four are not involved in catalysis but probably in metal
122 binding [56]. The human MSR system is composed of one gene encoding an MSRA and three genes
123 encoding MSRBs, including MSRB1, the only selenoprotein MSR. The same set of genes is present in
124 mice and very likely all other mammals [57–59].

125

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

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

129 transcript, the SECIS element is located 479 base pairs from the end of the coding sequence and 536
130 base pairs away from the UGA codon encoding Sec, located in exon III (**Figure 1**). The produced protein
131 of 116 amino acids localizes to the cytosol and nucleus [6,58]. In comparison with other human MSRBs
132 (i.e., MSRB2 and MSRB3), MSRB1 is the smallest, mostly because of the shorter N-terminal sequence
133 and the lack of signal peptides (**Figure 2A**). This is a general feature, as selenoprotein MSRBs from
134 other organisms are shorter than their Cys containing counterparts [62,63]. Like most known MSRBs,
135 human MSRB1 possesses four Cys organized in two Cys-X-X-Cys motifs and involved in the
136 coordination of a zinc atom. This metal ion plays a structural role and is not involved in catalysis [64,65]
137 (**Figure 2B**). The catalytic selenocysteine is in position 95, and site-directed mutagenesis approaches
138 demonstrated that the presence of Sec instead of a Cys, provides a strong catalytic advantage [66] (**Table**
139 **2**). Indeed, it was shown that when the catalytic Sec of MSRB1 was mutated to Cys, the enzyme specific
140 activity decreased 85-fold, whereas the replacement of the catalytic Cys of MSRB2 or MSRB3 by a Sec
141 increased the activity 173- and 126-fold, respectively [66] (**Table 2**). Substitution of the catalytic Cys
142 conserved in most MSRBs by Sec in MSRB1 is accompanied by the replacement of other key residues:
143 in positions 3, 77, 81 and 97, wherein Thr, His, Val/Ile and Asn, conserved in Cys-containing MSRBs
144 are substituted with Phe, Gly, Glu and Phe in MSRB1 (**Figure 2A & C**). Reinsertion of conserved
145 residues in MSRB1 by site-directed mutagenesis was shown to be detrimental for its activity but
146 increased the activity of its Cys mutant [66]. Structures of MSRB1 proteins from human (unpublished)
147 or mouse [62] have been solved (**Figure 2B**). These proteins have similar structures, with an overall β-
148 fold consisting of two antiparallel β-sheets and a highly flexible N-terminal region (**Figure 2B**). This
149 last feature is necessary for the MSRB1 activity and its regeneration by the thioredoxin system. Indeed,
150 after substrate binding and MetO reduction by the catalytic Sec95, a selenenic acid is formed, and is
151 subsequently reduced by the formation of a selenylsulfide bridge with the resolving Cys4. This bond is
152 then reduced by the thioredoxin system to release a reduced MSRB1 [66,67].

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

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

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

171

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

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

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

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

194

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

196 As for most MSRs, the reductase activity of MSRB1 towards free MetO and MetO present in
197 molecules mimicking MetO protein residues has been clearly established, but information about the
198 proteins oxidized in cells and known to be physiological substrates of this MSR is extremely limited.
199 One of the only examples was the Mg^{2+} channel TRPM6 (for *transient receptor potential melastatin*
200 *type 6*) found in renal and intestinal epithelial cells, which was shown to be inactivated by H_2O_2 and to
201 interact with MSRB1 [80]. The co-expression of MSRB1 with TRPM6 in HEK293 cells strongly
202 reduced the effect of H_2O_2, suggesting that oxidized TRPM6 might be a substrate of MSRB1 *in vivo*
203 [80]. However, the view that MSRs were “antioxidant” enzymes only changed when it was demonstrated
204 that two Met residues on actin can be oxidized enzymatically *in vivo* and become substrate of MSRB in
205 *D. melanogaster* [81], and of MSRB1 in mammals [6]. The cytoskeleton protein actin, conserved in
206 eukaryotes, exists as free monomer named G-actin (‘Globular’) or as part of a linear polymeric
207 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 Ca^{2+}/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

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

244

245 **6. Physiological roles of MSRB1 and association with pathological conditions**

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

250 One of the first pieces of evidence for the role of MSRB1 in the protection against oxidative damage
251 was obtained with *MSRB1*$^{-/-}$ mice, for which kidney and liver tissues presented increased levels of
252 protein MetO, protein carbonylation, oxidized glutathione, malondialdehyde and decrease in the levels
253 of free and protein thiols [69]. The elevation in the levels of these oxidative stress markers was more
254 pronounced when mice were administered acetaminophen, an oxidant-generating drug [97]. By
255 knocking-down *MSRB1* in human lens epithelial cells, it was shown that MSRB1 participates in the
256 prevention of cataract formation by protecting against oxidative stress-induced apoptosis after treatment
257 with *tert*-butyl hydroperoxide [98] or peroxynitrite [99,100], or in the context of diabetes [101,102]. The
258 lack of MSRB1, or any other MSR, resulted in increased oxidative stress-induced cell death [98].
259 Consistent results were obtained with human hepatocytes LO2, in which the knockdown of *MSRB1*
260 resulted in elevated H_2O_2-induced apoptosis [103].

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

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

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

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

299 Interestingly, despite the potential involvement of MSRB1 in several physiological processes,
300 *MSRB1*$^{-/-}$ mice do not present strong phenotypic alteration [69]. This might be due to potential
301 functional redundancy with other Msr. As a matter of comparison, we propose an assessment of the data
302 obtained on individual *MSR* mutated mice, the *MSRA*$^{-/-}$/*MSRB1*$^{-/-}$ double mutant, as well as mice
303 lacking all 4 MSRs (**Table 3**). *MSRA*-deleted mice were the first created and currently the most
304 characterized. They are more susceptible to oxidative stress and lipopolysaccharide challenge
305 [8,115,116] and exhibit higher kidney damage following ischemia-reperfusion [117] or cisplatin
306 treatment [118]. Similarly to *MSRB1*$^{-/-}$ mice, liver damage is exacerbated in *MSRA*$^{-/-}$ mice following
307 acetaminophen treatment [119]. Ischemia-reperfusion induced higher brain damage [120], fibrosis was
308 increased following ureteral obstruction [121] and common carotid artery ligation induced neointimal
309 hyperplasia [122]. Contradictory results were obtained on the lifespan of *MSRA*$^{-/-}$ mice, with the first
310 study showing a decrease in lifespan [123] and the second showing no difference with wildtype mice
311 [115]. MSRA knockout mice were also shown to suffer cataract [124], progressive hearing loss [125],
312 brain pathologies, decreased complex task learning capabilities and abnormal behavior [126,127] (**Table**
313 **3**).

314 To evaluate whether a potential redundancy might explain the mild phenotype of *MSRB1*$^{-/-}$ and 315 *MSRA*$^{-/-}$ mice, double KO mice were created [128]. They do not show growth retardation compared to 316 wild-type or single mutant mice. Feeding with a Met restricted diet retarded the growth of weanling 317 mice, and the retardation was higher in the double mutant, but no effect was observed in single knockout 318 MSR mice [128]. These data indicated that MSRs are involved in the assimilation of Met from food, 319 wherein external conditions can induce Met oxidation, and highlighted a potential redundancy of MSRA 320 and MSRB1 function, even if they target opposing diastereomers of MetO. However, these double KO 321 mice did not show any strong phenotype, suggesting a potential redundancy of function with the other 322 MSRBs [115,128] (**Table 3**).

323 Mice genetically deprived of MSRB2 or MSRB3 have also been created [129,130] (**Table 3**). 324 *MSRB2* knockout mice were shown to suffer the depletion of platelets which was associated with the 325 increase of oxidant molecules levels in these cells [130]. Their use helped to understand that in human 326 patients suffering diabetes mellitus, *MSRB2* expression is increased and leads to increased platelet 327 mitophagy, whereas in patients with Parkinson's disease, *MSRB2* expression is reduced and associated 328 with reduced mitophagy [130]. In these processes, MSRB2 is released from the matrix of leaking 329 mitochondria and reduces MetO in Parkin protein, inducing mitophagy through ubiquitination and 330 interaction with the microtubule-associated protein light-chain 3 [130]. The *MSRB3*$^{-/-}$ mice were found 331 to be profoundly deaf, most likely due to degeneration of the stereociliary bundles and subsequent loss 332 of hair cells due to apoptotic cell death [129]. However, this effect was not shown to be correlated with 333 an increase in protein oxidation in the inner ear [129].

334 Finally, quadruple *MSRA*$^{-/-}$/*MSRB1*$^{-/-}$/*MSRB2*$^{-/-}$/*MSRB3*$^{-/-}$ mutant mice were created and shown 335 to lack any MSR activity [131]. However, their characterization revealed an unexpected phenotype: they 336 were found to be more resistant to cardiac ischemia-reperfusion injury and killing upon treatment with 337 superoxide-generating paraquat [131]. In other words, genetic ablation of all MSRs rendered the mice 338 more resistant to oxidative stress. A viability test of embryonic fibroblasts derived from the quadruple 339 mutant revealed that these cells were not affected by paraquat, hydrogen peroxide or chromium 340 treatments, compared to embryonic fibroblasts from wildtype mice. Only the treatment with cadmium

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

350

351 **7. Conclusion and outlooks**

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

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

371 Since the discovery of actin as the substrate of MICAL enzymes, two other substrates have been
372 proposed, the actin-related protein 3B (ARP3B), whose Met293 is oxidized by MICAL2 [132] and
373 CaMKII, oxidized on Met308 by MICAL1 [94]. This puts in light the fact that Met oxidation by MICAL
374 enzymes may affect various proteins, including yet to be discovered and, knowing the strict
375 stereospecificity of MICALs to form *R*-diastereomers, MSRB1 and other MSRBs, could have important
376 functions in regulating the oxidation state of Met in these unidentified proteins. These two recently
377 identified oxidized proteins also bring to light two potential "hubs" of Met oxidation in animals: actin
378 and actin-related proteins as well as the CaMKII and calmodulin. ARP3B belongs to the ARP2/3
379 complex which catalyzes filamentation of actin and drives lamellipodia formation and cell protrusion,
380 MICAL1 and MICAL2 would thus oxidize both actin and ARP3B to depolymerize the filament, and
381 MSRB1 would reverse these oxidations [6,132]. CaMKII has also been shown to be potentially oxidized
382 on 3 Met residues: Met281 and Met282 by oxidants in a process reversible by MSRA [8] and the
383 Met308, oxidized by MICAL1 and potentially reduced by MSRB1 [94]. Interestingly, the oxidation of
384 these Met was shown to exert different effects on the CaMKII activity [8,94] (**Figure 5**). Moreover,
385 calmodulin, which binds and regulates CaMKII activity, is also potentially oxidized on Met and reduced
386 by MSRs [4,133–135]. As calmodulin binding to CaMKII involves Met of both partners (**Figure 5**), it
387 would be interesting to evaluate the oxidation states in physiological conditions in wildtype and MSR-
388 deficient cells or mice. This would be particularly relevant in nervous system cells, where CaMKII
389 phosphorylation, a Ca^{2+}/Calmodulin dependent process, was shown to be reduced in *MSRB1*$^{-/-}$ mice
390 [95].

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

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

406 Finally, our knowledge of MSRB1 functions, functions of other MSRs, and the role of Met
407 oxidation in general lags behind other post-translational modifications because of the lack of easily
408 usable tools to identify MetO-containing proteins. Recently, the use of heavy hydrogen peroxide
409 ($H_2{}^{18}O_2$) allowed to avoid nonspecific oxidation in proteomics and map Met oxidation, identifying
410 proteins with Met highly sensitive to oxidation in several bacterial and mammalian proteomes [139–
411 142]. Furthermore, the recently developed oxaziridine probes specifically binding Met in a reactivity-
412 dependent fashion [143,144] have been used to show that pyruvate kinase M2 can be activated by
413 oxidation of its Met239 in pancreatic tumor metastasis, and that MSRA could reduce it and act as a
414 suppressor of pancreatic ductal adenocarcinoma [145]. We think that the use of these recently developed
415 (chemo)proteomic methods, based on heavy hydrogen peroxide ($H_2{}^{18}O_2$) or on oxaziridine probes
416 targeting reactive Met would be very useful in identifying targets of MSRB1 and other MSRs. Moreover,
417 the use of genetically-encoded fluorescent biosensors able to detect the levels of Met oxidation *in vivo*
418 [146–149] should help to understand the roles of this post-translational modification and of the MSRs
419 in many physiological contexts.

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434 L.T., B.C.L and V.N.G conceived the review content. L.T. drafted the manuscript and prepared the
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437

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959 **Tables**

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

Organisms	MSRA Catalytic res.		MSRB Catalytic res.		fRMSR	MSRP	Other molybdo MSR
	Cys	Sec[1]	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]

961 [1] Selenoprotein MSRAs are extremely rare.[2] With few exceptions, selenoprotein MSRBs are found
962 throughout the animal lineage.[3] Although the presence of sulfite oxidase and dimethyl sulfoxide oxidase
963 molybdoenzymes in archaeal genomes has been clearly established [52], to our knowledge, none have
964 been tested for their ability to reduce free or protein-based MetO.
965
966
967
968 **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	

969 Data are from Kim and Gladyshev, 2005 [66]

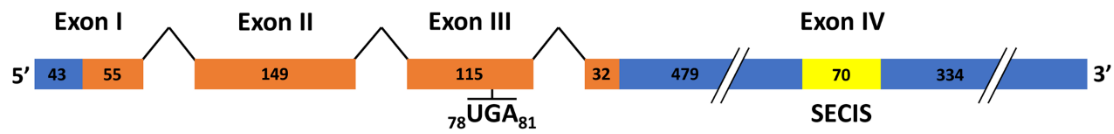
970

Table 3. Phenotypes of *MSR* KO mice.

	MSRA$^{-/-}$	*MSRB1*$^{-/-}$	*MSRB2*$^{-/-}$	*MSRB3*$^{-/-}$	*MSRA*$^{-/-}$/*MSRB1*$^{-/-}$	*MSRA*$^{-/-}$/*MSRB1*$^{-/-}$ /*MSRB2*$^{-/-}$/*MSRB3*$^{-/-}$
Oxidative stress susceptibility and markers	- Sensitivity to paraquat, to 100% O_2 [115,123] - Increased protein carbonylation [123] - Increased beta-amyloid aggregate[1] [112] - Sensitivity to cisplatin [118] - Lethal susceptibility to chronic oxidative stress and lipopolysaccharide challenge [8,116]	In liver and kidney [69]: - Increased protein MetO - Increased protein carbonylation - Increased oxidized glutathione - Reduced free and protein thiols - Increased malondialdehyde - MSRA activity decreased [69]	In platelets [130]: - Increased oxidant molecules	In the inner ear [129]: - No increase in protein MetO - No increase in protein carbonylation		- More resistant to paraquat [131] - More resistant to cardiac ischemia-reperfusion [131] - Sensitivity to cadmium [131]
Growth, lifespan and metabolism	- Decreased lifespan [123] - Normal lifespan [115] - Exacerbated insulin resistance caused by high fat feeding [150]	- Normal growth [69] - Normal lifespan [69] - No increase in high-fat diet-induced insulin resistance [151]			- 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	- Tip-toe walking [123] - Decreased complex task learning capabilities [126] - Progressive hearing loss and sensitivity to acoustic trauma [125]	- Decreased spatial learning and memory abilities [95]		- Deafness [129]		- Deafness [131]
Tissues and organ injuries	- 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 O_2 induced cataract [124]	- 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]	- Decreased platelets [130]			

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

Figures



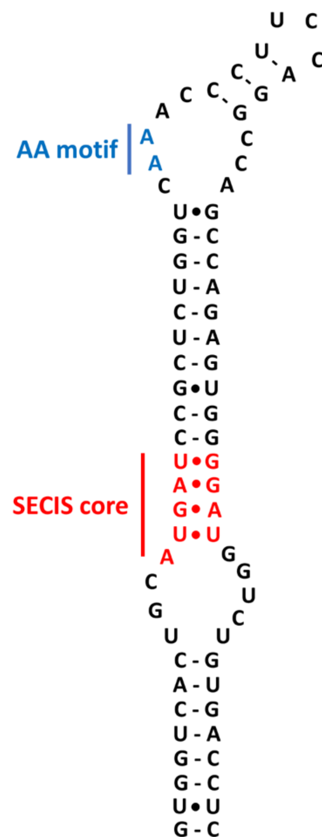


Figure 1. Schematic representation of *MSRB1* gene and its type-II SECIS element. (**A**) *MSRB1* gene. *Blue* and *orange* boxes represent UTRs, and exons, respectively. Numbers in the boxes correspond to their size in base pairs. The SECIS element is represented by a *yellow* box, with its size in base pairs. (**B**) The MSRB1 SECIS element. The AA motif and the SECIS core, necessary for Sec insertion recognition machinery, are in *blue* and *red*, respectively. Adapted from [31,60,152].

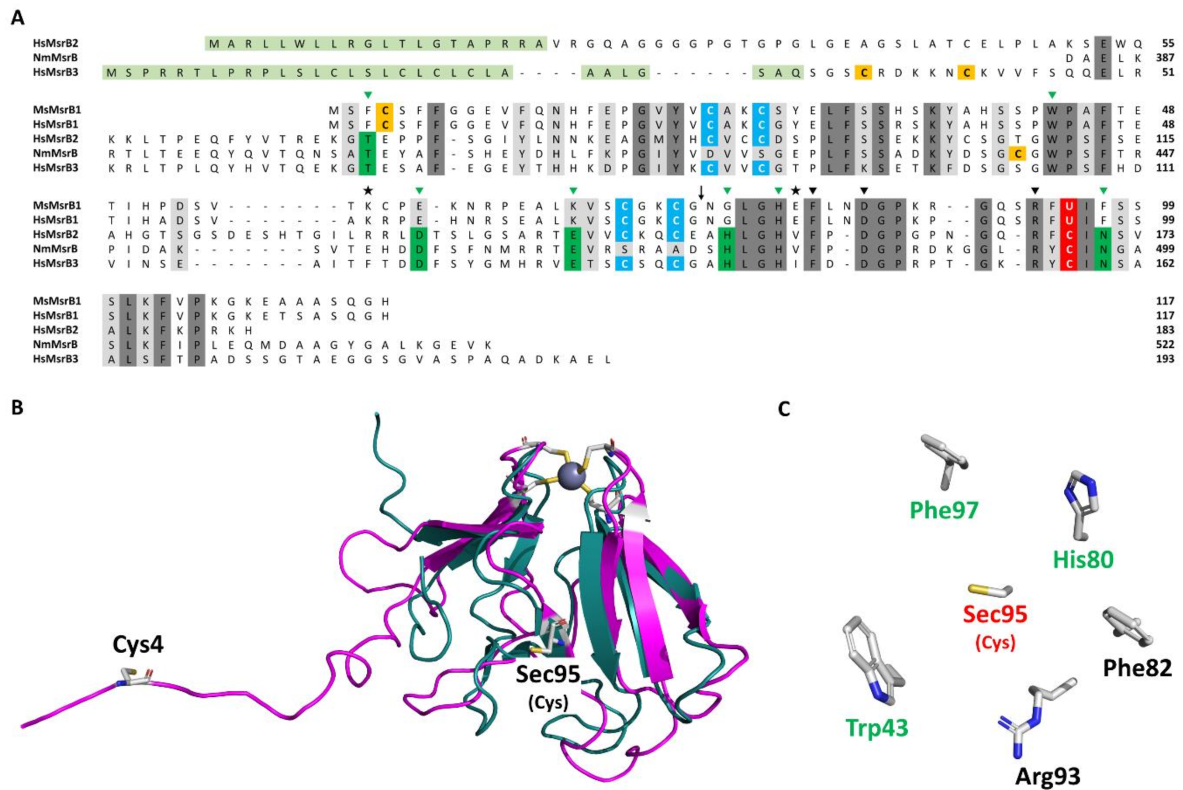


Figure 2. MSRB1 sequence and structure. Protein sequence alignment of human and mouse Sec-MSRB1s with human and *N. meningitidis* Cys-MSRBs. Identical and similar amino acids are in *dark* and *light grey* backgrounds, respectively. Sequences in *green* background correspond to targeting peptides. Resolving 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/).

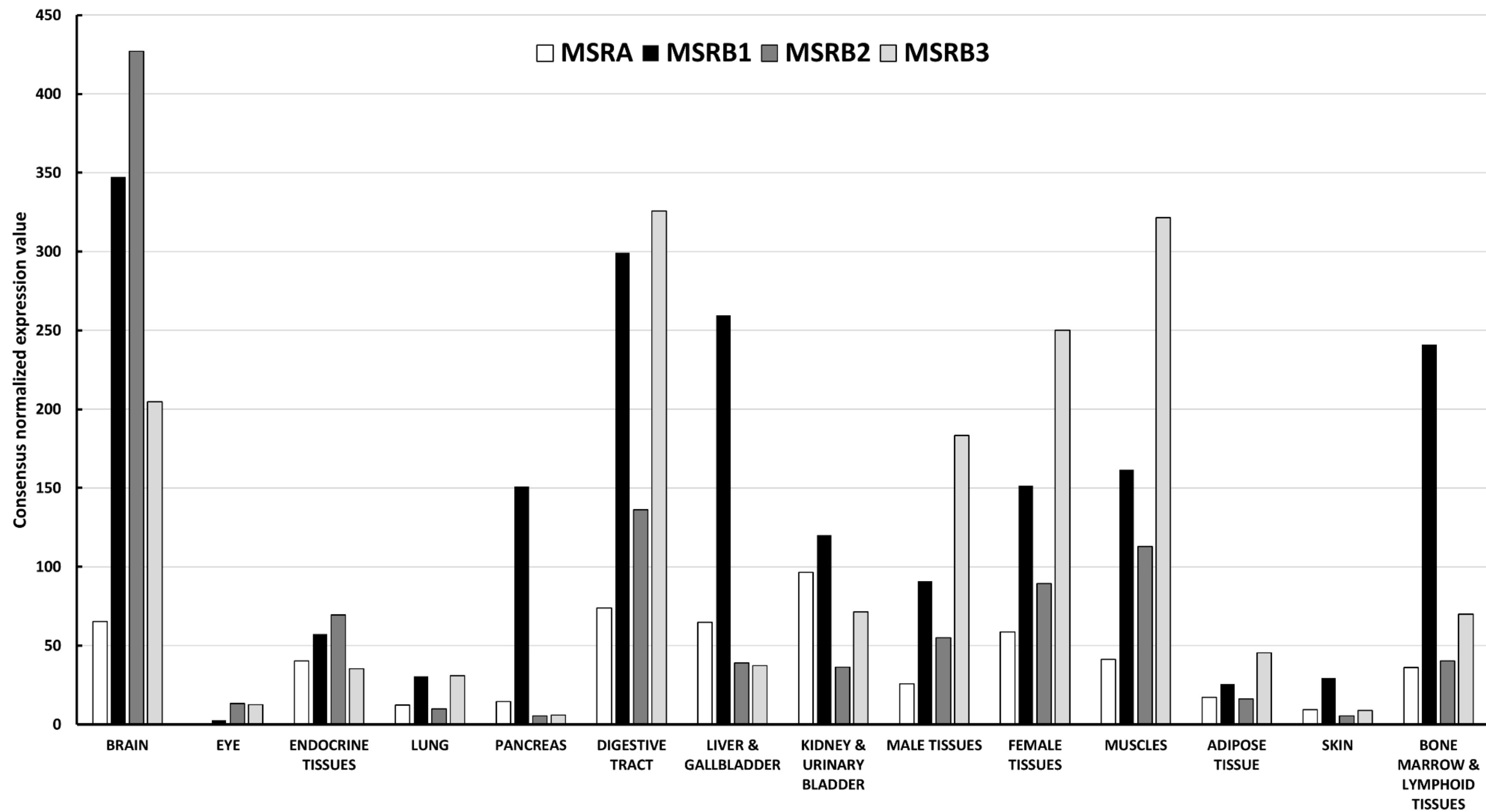


Figure 3. Expression levels of MSRs genes in main human tissues. Data of transcript abundances were retrieved from the Human Protein Atlas https://www.proteinatlas.org and are presented with '*consensus normalized expression values*' from several RNAseq analyses [70].

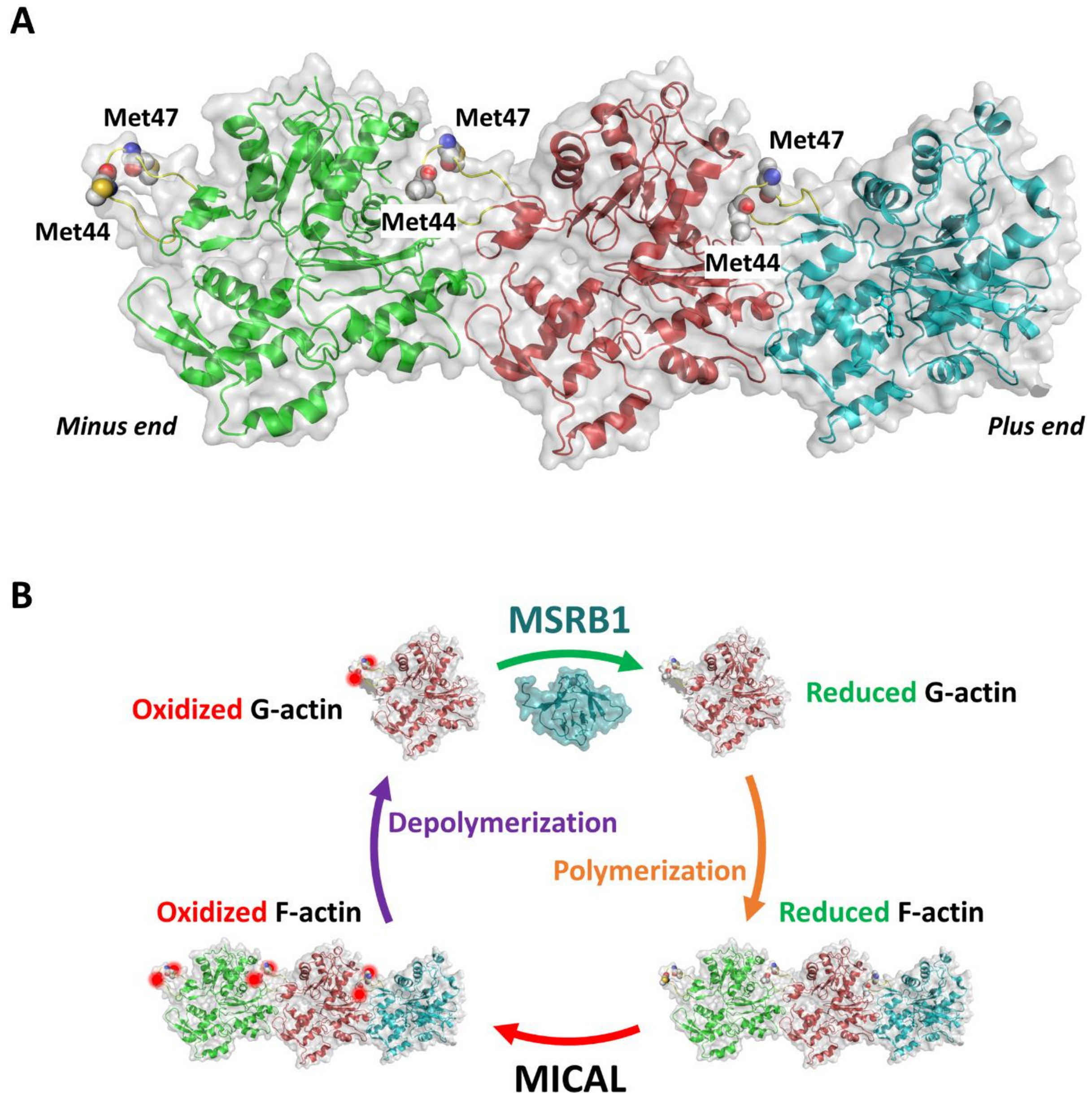


Figure 4. Regulation of actin by MICAL-dependent oxidation and MSRB1-dependent reduction of its Met residues. (**A**) The position of Met44 and Met47 in F-actin filament. Three monomers of actin in the filament are shown in *grey*, *red* and *cyan* from the minus end to plus end, respectively. The D-loop 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 MSRB1. MSRB1 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/).

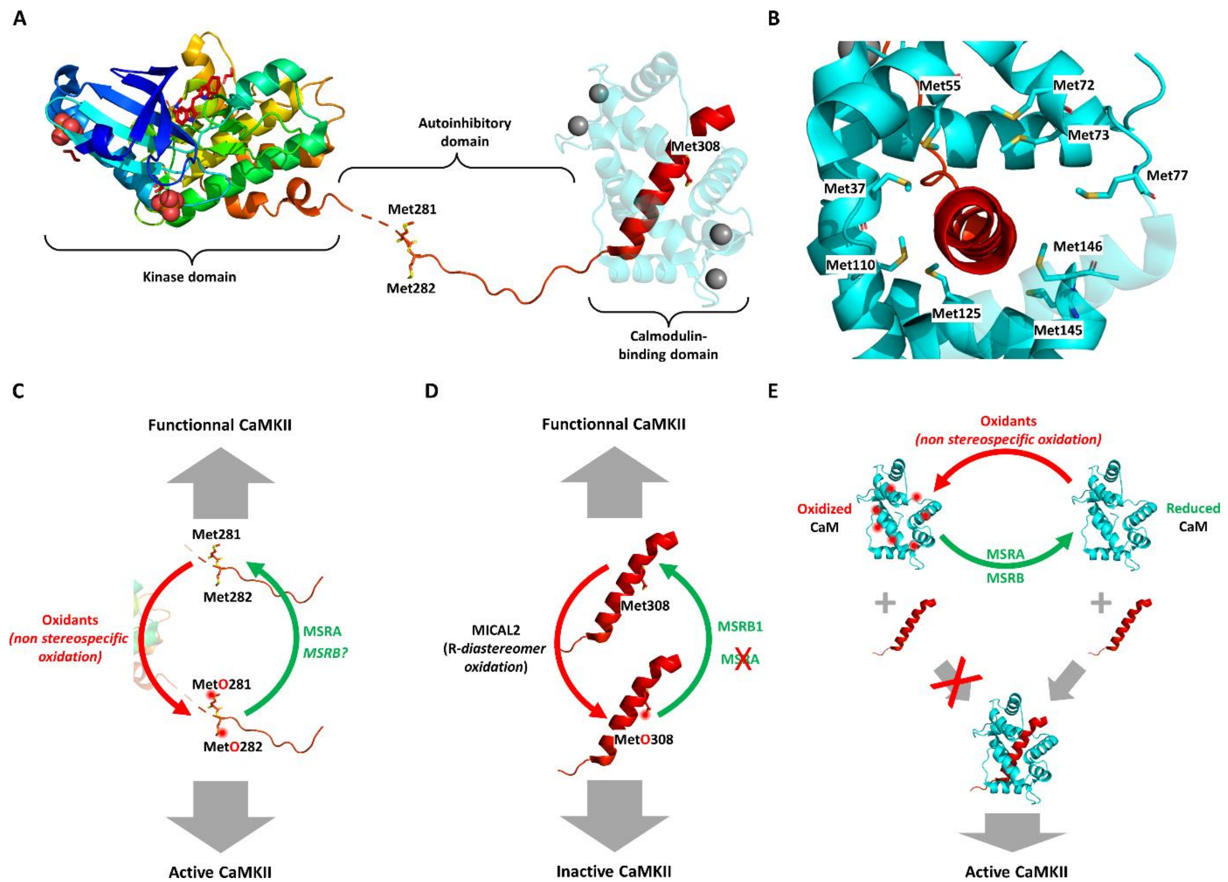


Figure 5. Regulation of CaMKII and calmodulin through oxidation and reduction of Met. (**A**) Structure of human CaMKII and the positions of Met281, Met282 and Met308. CaMKII with its kinase, autoinhibitory and calmodulin-binding domains is shown in *rainbow* color. Met are shown as sticks. Calmodulin 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 prevents 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/).