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ORIGINAL PAPER

Methionine in Proteins: It's Not Just for Protein Initiation Anymore

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Abstract
Methionine in proteins is often thought to be a generic hydrophobic residue, functionally replaceable with another hydrophobic residue such as valine or leucine. This is not the case, and the reason is that methionine contains sulfur that confers special properties on methionine. The sulfur can be oxidized, converting methionine to methionine sulfoxide, and ubiquitous methionine sulfoxide reductases can reduce the sulfoxide back to methionine. This redox cycle enables methionine residues to provide a catalytically efficient antioxidant defense by reacting with oxidizing species. The cycle also constitutes a reversible post-translational covalent modification analogous to phosphorylation. As with phosphorylation, enzymatically-mediated oxidation and reduction of specific methionine residues functions as a regulatory process in the cell. Methionine residues also form bonds with aromatic residues that contribute significantly to protein stability. Given these important functions, alteration of the methionine–methionine sulfoxide balance in proteins has been correlated with disease processes, including cardiovascular and neurodegenerative diseases. Methionine isn't just for protein initiation.

Keywords Methionine · Methionine sulfoxide · Methionine sulfoxide reductase · Oxidative defenses · Protein structure · Cellular regulation

Abbreviations

Msr	Methionine sulfoxide reductase
MetO	Methionine sulfoxide
ROS	Reactive oxygen species

Introduction

We are pleased to join the colleagues, students, and admirers of Elias Michaelis in this special issue honoring him. At first glance, a mini-review on the roles of methionine in proteins may seem tenuously connected to his many contributions to neuroscience. Actually, it connects directly through his interest in oxidative stress, one of the important areas in which Dr. Michaelis has advanced our knowledge through his research.

When many of us took our first course in biochemistry, we learned that methionine was one of several hydrophobic residues in proteins and, except for its role in protein initiation, we were taught that these hydrophobic residues were pretty much interchangeable. Such was not the case for the other sulfur-containing residue, cysteine. This important amino acid was recognized as having roles as an antioxidant—especially in the tripeptide glutathione, in protein structure through disulfide bond formation, in catalysis at the active site of several classes of enzymes such as proteases, oxidoreductases, phosphatases, and peroxiredoxins, and in cellular regulation through its reversible oxidation and reduction. Research from many investigators in the last years has revealed that methionine in proteins shares many of these functions [1–8]. The results of these studies make clear that each of the two sulfur-containing amino acids function in antioxidant defense, protein structure, and redox sensing and regulation. Experimental investigation of methionine's roles in those functions thus has a high probability of identifying important cellular mechanisms as well as diseases caused by defects in their function. With the recognition that oxidative defense, protein structure, and cellular regulation are mediated by methionine residues in proteins, it is not surprising that impairment of those functions has also been associated with several disease processes, including neurodegeneration, cancer, and cardiovascular disease. In this article, we provide examples of the expanded role of methionine and

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summarize the mechanisms by which methionine is thought to perform these functions.

Oxidation of Methionine to Methionine Sulfoxide and Reduction Back to Methionine

One of the important properties of both cysteine and methionine residues in proteins is that they are subject to reversible oxidation and reduction, mediated either enzymatically or non-enzymatically. While cysteine is well-recognized for the ease of its oxidation, it is often not appreciated that methionine can be readily oxidized to methionine sulfoxide (MetO) [9, 10]. Indeed, the standard redox potential for the two electron reduction of dimethyl sulfoxide is + 160 mV [11] while that for cystine is + 220 mV [12]. Cysteine is easily oxidized when ionized to its thiolate, but is difficult to oxidize when in the thiol form [13]. However, most cysteine residues, including those in glutathione, have a pK_a around 8.3–8.7 and are not easily oxidized at physiological pH, unless the oxidation is catalyzed by an enzyme. In contrast, oxidation of methionine residues is essentially independent of pH [14]. In vitro, hypochlorous acid (HOCl), a major halogenated oxidant generated by leukocytes, reacts rapidly with methionine at physiological pH [14, 15], but hydrogen peroxide does not, although the rate can be accelerated by the bicarbonate/carbon dioxide present in vivo [16].

MetO is reduced back to methionine by the methionine sulfoxide reductases, thioredoxin-dependent enzymes that are virtually universal among aerobic organisms [17, 18]. Oxidation of methionine to MetO introduces a chiral center at the sulfur atom so there are two epimers of MetO, R-MetO and S-MetO [19]. While an epimerase that interconverts the forms could theoretically exist, none has been found so far. Instead, organisms have two types of methionine sulfoxide reductases (msr). MsrA specifically reduces S-MetO, but not R-MetO. Conversely, msrB reduces R-MetO, but not S-MetO. Recycling by the reductases allows the methionine residue to react again with oxidizing species, creating a system with catalytic efficiency in scavenging reactive species. The reducing power is ultimately provided by NADPH (Fig. 1).

The A class of reductases was described some years ago and has been characterized in considerable detail, especially by Weissbach et al. [20]. The B class of reductases, some of which are selenoproteins in higher animals, was discovered more recently but has also been studied intensively [21, 22]. Mammals have 3 isoforms of the B class, and one of the A class. While there is only one gene for msrA, the enzyme has been reported to be in both the cytoplasm and in mitochondria, although we are re-evaluating the subcellular localization in our laboratory.

The in vivo importance of the reductases is well established, particularly for msrA. Knocking out the enzyme

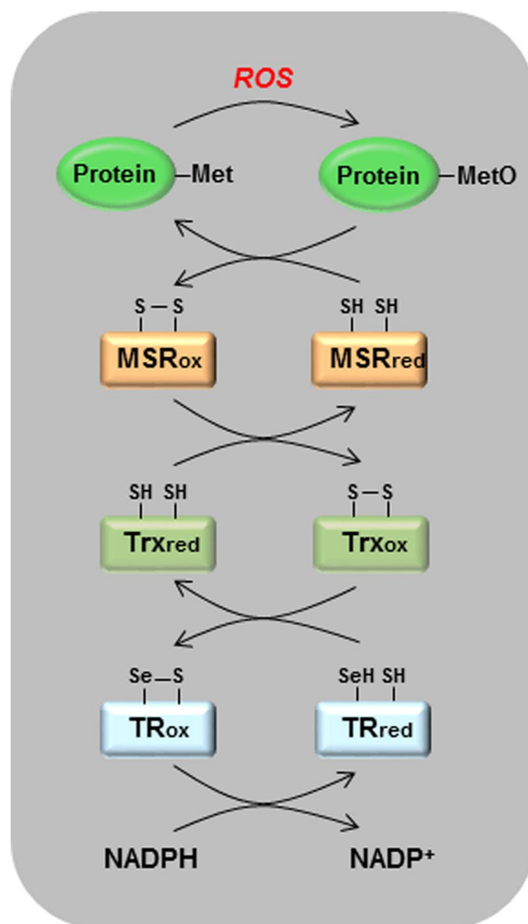

Fig. 1 Scavenging of reactive oxygen species (ROS) by the msr-dependent catalytic cascade. Reduced forms of the proteins carry the subscript "red" and oxidized forms carry "ox". Reading from top to bottom, an ROS is intercepted by a Met residue that is oxidized to MetO. MetO is reduced back to Met by msr, with the formation of a disulfide bond. The oxidized msr is reduced by thioredoxin (Trx), which now carries the disulfide bond. It is reduced by thioredoxin reductase (TR), which in mammals contains a selenocysteine residue that is oxidized, forming a selenocysteine-cysteine bond. This disulfide analogue is then reduced by NADPH. The net result is that ROS is reduced at the expense of NADPH

caused increased susceptibility to oxidative stress in mice [23], yeast [24], and bacteria [25–28]. Conversely, overexpressing msrA conferred increased resistance to oxidative stress in *Drosophila* [29], *Saccharomyces* [30], *Arabidopsis* [31], PC-12 cells [32], human T cells [30], and microglial-mediated neuroinflammation [33]. *Helicobacter pylori*, a causative agent of gastric ulcers and carcinoma, requires msrA for protection against oxidative stress and appears to act through reduction of methionine sulfoxide in the bacterial catalase [28, 34].

Overexpression of bovine msrA in *Drosophila* almost doubled the lifespan of the flies [29], and this impressive result was replicated using *Drosophila* msrA in an

independent laboratory [35]. However, overexpression of msrA in mice does not increase lifespan [36]. Although an initial report with a small number of mice suggested that knocking out msrA caused neurological abnormalities and drastically reduced the lifespan of mice [23], studies with appropriate numbers of animals found no change in lifespan nor neurological abnormalities [36].

Solvent Exposed Methionines as Antioxidants

α-2-Macroglobulin is a physiologically important proteinase inhibitor, often acting at sites of inflammation where reactive oxygen and nitrogen species are at relatively high concentration. It had been thought that α-2-macroglobulin was resistant to oxidative modification, but studies by Weiss and colleagues demonstrated that the protein was consuming oxidizing species, initially without loss of anti-proteinase activity [37]. More detailed studies established that while activity was indeed retained, consumption of oxidant was stoichiometrically accounted for by oxidation of methionine residues to the sulfoxide [38]. With continued exposure to an oxidizing environment, a single tryptophan residue was eventually oxidized with concomitant loss of anti-proteinase activity. These observations led to the proposal that certain methionine residues of α-2-macroglobulin served as antioxidants, protecting the critical tryptophan from damage.

The protecting methionines were presumed to be surface exposed, but no structure of α-2-macroglobulin was then available to determine whether that was the case. We therefore examined the effect of hydrogen peroxide on glutamine synthetase, since the crystal structure for this 12-subunit enzyme was solved by Eisenberg and colleagues [39] and because the active site was known to be susceptible to oxidative inactivation [40]. Exposure of the enzyme to varying concentrations of hydrogen peroxide generated a series of preparations with increasing content of methionine sulfoxide; no other covalent modifications were detected [1]. Eight of the 16 methionine residues could be oxidized without loss of catalytic activity. Mapping of the oxidizable methionine residues revealed that all were surface exposed; conversely, the residues that remained unoxidized were buried. More detailed examination of the topographic distribution of the oxidizable methionine residues was intriguing as these residues were found to line the bay leading from the surface of the enzyme to its active site (Fig. 4 in [1]). In other words, these methionine residues are mustered in a phalanx guarding the active site where they function as macromolecular bodyguards.

The effective concentration of exposed methionines is extremely high near the protein surface, greater than 1 M with certain assumptions [1]. Recognizing the ease of oxidation of methionines already mentioned, surface-exposed methionines constitute a formidable antioxidant defense mechanism, capable of protecting critical residues within the protein as well as other cellular components. Since the methionine sulfoxide reductases can reduce MetO back to methionine, this antioxidant defense gains catalytic efficiency. One of a number of examples of the system's function comes from Stocker and colleagues who established that high density lipoproteins reduce toxic cholesteryl ester hydroperoxides to alcohols, with the concomitant oxidation of two methionine residues to the sulfoxides [41]. This system can function catalytically as shown by Sigalov and Stern, who demonstrated that the oxidized apolipoprotein could be reduced by methionine sulfoxide reductase [42].

As summarized in the introduction, there exists considerable experimental evidence compatible with the proposal that methionines in proteins have an important antioxidant function, analogous to that of cysteine in glutathione. However, all of the studies describe correlations and do not assess causality. Direct experimental testing of the methionine antioxidant hypothesis is difficult in eukaryotic cells, but it has been done with *E. coli* by altering the global content of methionine in the bacterial cellular proteins. It is well established that the selenium analogue of methionine, selenomethionine, can replace methionine in proteins with little or no effect on protein structure and function. It is not so well known that the carbon analogue, norleucine, can also replace methionine, at least in bacteria. This was shown by Cohen and his colleagues in 1959 [43]. Barker and Bruton then demonstrated that norleucine was charged onto both methionyl-tRNA and formylmethionyl-tRNA [44]. After charging with norleucine, the latter undergoes formylation, allowing *N*-formylnorleucine to initiate protein synthesis. When grown in a medium with a high ratio of norleucine to methionine, norleucine substitutes for methionine residues globally. As with selenomethionine substitution, the incorporation of norleucine does not alter the activity of enzymes that have been assayed to date.

The methionine as antioxidant hypothesis was tested by comparing the survival of control and norleucine-substituted cells, with and without oxidative stress. If there were little difference in survival, the hypothesis would be rejected. If there were a difference, the hypothesis would live to face other tests. We were able to replace 40% of the methionine residues in *E. coli* with norleucine [45]. Control and norleucine-grown cells had almost identical growth rates, and neither free methionine nor S-adenosylmethionine levels were altered by growth on norleucine. When left unstressed, both control and norleucine-substituted cells survived equally well in stationary phase for at least 32 h. However, when challenged by exposure to hypochlorite, hydrogen peroxide, or ionizing radiation, the norleucine-substituted cells died more rapidly than the control cells. For example, 10 µM hypochlorite did not kill any control cells while it killed 100% of the norleucine-substituted cells.

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Further support for the methionine as antioxidant hypothesis comes from more recent investigations in several laboratories that establish the surprising ability of eukaryotes, including mammals, to *increase* the content of methionine in their proteins in response to oxidative stress [7, 46]. The mechanism was elucidated by Kim and colleagues [8] who showed that ERK1/2 phosphorylates methionyl-tRNA synthetase in cells experiencing oxidative stress. The phosphorylation renders the synthetase promiscuous, so that it acylates non-methionine tRNAs with methionine, thus increasing the methionine content of proteins during oxidative stress (Fig. 2).

Studies on the evolution of mitochondria and their use of an alternate genetic code also support the proposition that methionine in proteins acts as an antioxidant [2, 47, 48]. Bender and colleagues noted that AUA codes for isoleucine in the nucleus, but it specifies methionine in the mitochondria of animals using the modified code. Looking at a large number of species not using the modified mitochondrial code, they established that the average methionine content in mitochondrially encoded proteins is 2%, which is the same as that for nuclear proteins encoded in those organisms. However, in organisms whose mitochondrial code evolved to specify methionine by AUA, the average mitochondrial methionine content jumped threefold to 6%. Moreover, the additional methionine residues were topographically arranged on the surface of the proteins, nicely positioned to intercept reactive oxygen species generated by mitochondrial respiration [2].

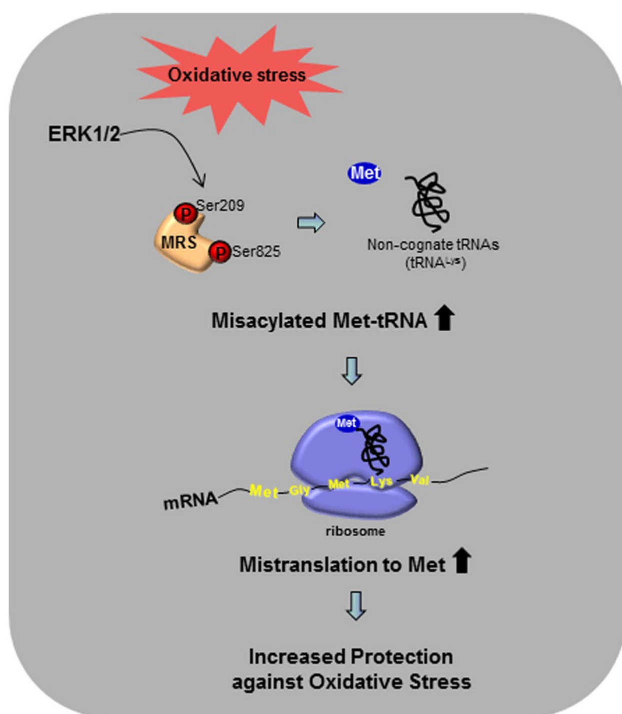

Fig. 2 The mechanism by which oxidative stress increases the methionine content of proteins [8]. In response to oxidative stress, ERK1/2 phosphorylates methionyl tRNA synthetase (MRS). This renders the synthetase promiscuous so that it charges non-cognate tRNAs with Met, as shown here for $tRNA^{Lys}$. In this example, the Lys codon leads to insertion of Met, thus increasing the total methionine content of the protein to provide additional protection against oxidative stress

Cellular Regulation Through Redox Cycling of Methionine Residues

Progress in understanding the physiological and pathological effects of methionine oxidation is severely hampered by the lack of analytical tools for detecting and quantitating MetO content of individual proteins in complex mixtures such as those found in tissue homogenates. The absence of immunochemical or chemical methods for detecting and quantitating MetO is particularly vexing [49, 50].

Just as is the case for phosphoserine and phosphothreonine, no general anti-MetO antibody exists, but one *can* raise sequence specific anti-MetO or anti-methionine antibodies by immunization with a peptide or protein containing MetO or methionine [50, 51]. An antiserum sold by several vendors is claimed to specifically recognize MetO [52]. A number of publications, particularly in the area of neurodegeneration, have reported using it for that purpose [52–63]. Without confirmation by an independent method of analysis, one must be extremely cautious about results from that antiserum [49].

Like phosphorylation, methionine oxidation is a reversible covalent modification. Thus, cyclic oxidation and reduction of methionine residues could function as a regulatory or signaling mechanism [64, 65]. Although oxidation could occur non-enzymatically, the products would then be a mixture of the R and S epimers. Reversal would require coordinated action of msrA and msrB which is not an attractive regulatory mechanism. Enzymatic oxidation would likely be stereospecific and thus require coupling to only one reductase to complete the regulatory cycle.

Despite these limitations, many examples of regulation by methionine oxidation have been published, although in most cases it is unknown whether the oxidation is reversed in vivo by msr. Ciorba et al. reported that the inactivation of a potassium channel by nitric oxide was likely due to oxidation of an essential methionine residue in the channel [66]. Similarly, Sroussi et al. presented evidence that the ability of the calcium-binding proteins to direct leukocyte migration was abolished by oxidation of specific methionine residues [67]. Interestingly, consistent with the notion that methionine oxidation does not invariably link to enzyme inactivation, Erickson and collaborators convincingly identified a calcium-independent pathway for activation of Ca^{2+}/calmodulin-dependent protein kinase that was mediated by

oxidation of specific methionine residue in vitro and in vivo [68]. In yet another example of a MetO “activation” process, oxidation of Met80, an iron ligand in cytochrome c, increases cytoplasmic translocation of the cytochrome as part of a potential defense system against nitrative stress in non-apoptotic cells [69]. Likewise, in plants, hydrogen peroxide-triggered protein phosphorylation can be regulated by oxidation of a specific methionine residue in the substrate recognition site of kinases [70]. Alternatively, methionine oxidation may lead to enhanced function via indirect routes. For example, the blood clotting protein, von Willebrand factor, undergoes HOCl-dependent methionine oxidation that renders the protein resistant to proteolysis by the metalloprotease, ADAMTS123, thereby endowing it with increased activity [71].

The Terman laboratory identified an NADPH oxidoreductase, MICAL, that specifically oxidizes a methionine residue in actin that induces filament severing and decreases actin polymerization [72]. Subsequently that group and Gladyshev’s laboratory demonstrated that the oxidation was stereospecific and generated only the R-MetO [4, 5]. Importantly, the modification was fully reversible by msrB1, a cytosolic msrB. Thus, oxidation of Met44 in actin by MICAL induces de-polymerization of actin and reduction of MetO44 by msrB1 restores the ability to polymerize (Fig. 3).

msrA operating in oxidase mode stereospecifically oxidizes just one of the 9 methionine residues in calmodulin [73]. Met77 is oxidized to S-MetO77. When msrA operates in reductase mode, MetO77 is fully reduced back to

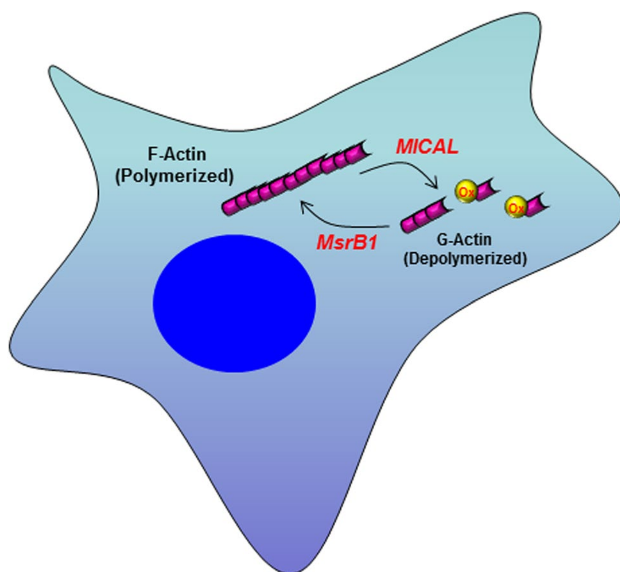

Fig. 3 Redox regulation of actin polymerization by oxidation and reduction of methionine. Met44 of actin is oxidized by the monooxygenase MICAL causing depolymerization. Reduction of MetO44 by msrB1 restores the ability to polymerize

methionine. However, to date, no in vivo targets of calmodulin affected by this oxidation have been identified.

Methionine and Protein Structure

It has long been appreciated that the sulfur atom of methionine is a ligand to the heme in cytochrome c [74]. In myeloperoxidase, the heme is linked to methionine via a sulfonium ionic bond [75, 76]. More recently, a sulfilimine bond (–S=N–), the nitrogen analogue of a sulfoxide (–S=O–), was discovered in type IV collagen [77]. In a mechanism that is conserved from flies to humans, the carboxyl-terminal methionine of one type IV collagen subunit is covalently linked to a lysine of another subunit. Formation of the sulfilimine is catalyzed by a specific peroxidase, termed peroxidasin, that appears to generate the sulfilimine by formation of hypohalous acids as a reactive intermediate [78]. *Drosophila* with mutant peroxidasin fail to generate sulfilimine crosslinks and display disorganized collagen IV networks with associated defects in basement membrane structure [78].

An interaction of methionine residues with nearby aromatic residues was pointed out 30 years ago [79], and crystallographic data suggested that the interaction contributed to protein stability [80]. More recent work of Valley and colleagues established that methionine, like cysteine, has a substantive role in stabilizing protein structure and in protein–protein interactions [3]. While the methionine-aromatic interaction occurs at a greater distance (~ 5–6 Å) than that of a salt bridge (< 4 Å), the energies associated with either interaction are comparable. These bonds are very common in proteins and thus contribute significantly to the stabilization of the native protein structure [3].

Oxidation of methionine to its sulfoxide provides a simple mechanism for an on–off switch for cellular regulation. For example, the binding of lymphotoxin-α to the tumor necrosis factor receptor 1 requires a methionine-aromatic bond between Met120 of lymphotoxin-α and Trp107 of tumor necrosis factor receptor 1 [3]. Oxidation of Met120 prevents binding [81]. Other hydrophobic amino acids are unable to form the bond with aromatic rings, potentially explaining some of the many examples in the literature in which leucine, isoleucine, or valine cannot functionally replace a methionine.

While oxidation may strengthen rather than weaken the methionine-aromatic bond [81], oxidation of a sufficient number of methionine residues is expected to perturb the native structure and expose otherwise normally buried residues, explaining both the association of methionine oxidation with increased surface hydrophobicity of proteins and their increased susceptibility to proteolytic degradation [1, 82]. This effect may be substantial during aging in which progressive increases in the surface hydrophobicity of proteins correlate with an age-related increase in MetO content

[82]. However, in general, the changes in MetO content in aging tissues are rather modest. Thus far, no studies have validated total MetO content as a marker of biological aging.

Methionine Sulfoxide Reductases and Disease

Cardiopulmonary Disease

In humans, a G to A polymorphism in *msrA* is associated with an increased risk of cardiovascular disease [83, 84]. In another genome-wide association study, an A to G intron variant was associated with hypertension, a known risk factor for cardiovascular disease [85]. In apolipoprotein E deficient mice, feeding a high fat "Western diet" causes atherosclerosis and hepatic steatosis. Hepatic overexpression of msrA in those mice reduced the plasma VLDL/LDL levels, hepatic steatosis, and aortic atherosclerosis [86]. As mentioned above, msrA in mammals has been localized to mitochondria and the cytosol. Because mitochondria are a major source of reactive oxygen species, it was hypothesized that overexpression of msrA targeted to the mitochondria would protect against cardiac ischemia-reperfusion while cytosolic msrA would not [87]. Notably, the opposite was found: mitochondrial overexpression of msrA provided no protection while cytosolic overexpression gave substantial protection. Moreover, the cytosolic form required myristoylation to be protective, an observation that is not yet explained mechanistically.

α1-antitrypsin is a member of the serpin family that inhibits serine proteases. The main physiological target of α1-antitrypsin is neutrophil elastase. A genetic deficiency in the synthesis of α1-antitrypsin is associated with the development of emphysema by the third or fourth decade of life, and 15 years earlier if the affected person is a smoker [88]. Deficiency of α1-antitrypsin causes a protease:antiprotease imbalance in which lung elastase damages tissue. Proteolytic injury to the lung is also a feature of diseases such as cystic fibrosis and cigarette-smoking in which serum levels of α1-antitrypsin are normal and therefore should theoretically provide a protective antiprotease [89, 90]. However, the specific activity of the α1-antitrypsin in the lung is decreased in these disorders [90, 91] because inflammation that occurs produces reactive oxygen species that oxidize a surface exposed methionine residue that is required for α1-antitrypsin activity [90, 92, 93]. This mechanism also accounts for the much earlier onset of emphysema in α1-antitrypsin deficient individuals who smoke. Inactivated α1-antitrypsin can be reactivated in vitro by msrA [94], suggesting that increasing the activity of msrA could be therapeutic [95].

Neurodegenerative Disease

Oxidative damage in the brain is a well-established feature of Alzheimer's disease [96], and the activity of msrA is decreased in the brain of Alzheimer's patients [97]. Aβ peptides, particularly $A\beta_{(1-42)}$, are a major component of the senile plaques found in Alzheimer's brains, and oxidative damage is distinctly increased in regions rich in Aβ [98]. Aβ peptides are toxic in a variety of in vivo and in vitro systems [99]. There are no reports of the activity of the msrB isozymes in Alzheimer's disease, although it has been shown that msrB1 interacts with an Aβ peptide [100]. The $A\beta_{(1-42)}$ peptide contains one methionine, at position 35. Butterfield and his colleagues have reported strong evidence supporting their proposal that oxidation of Met35 is required for the toxicity of $A\beta_{(1-42)}$ [101, 102]. For example, substituting norleucine for methionine at position 35 abolishes toxicity. Thus, the decrease in msrA associated with Alzheimer's disease could lead to an increased concentration of MetO-containing $A\beta_{(1-42)}$ that mediates toxicity.

Oxidative stress is also a feature of Parkinson's disease [103]. Lewy bodies, a pathognomonic feature of Parkinson's pathology, are rich in aggregated α-synuclein, and familial mutations in α-synuclein or elevated levels of wild-type α-synuclein cause Parkinson's disease [104]. Dopaminergic cells in rat midbrain cultures were protected from oxidative-stress induced damage by transfection with msrA [105]. α-synuclein contains 4 methionine residues, two of which are particularly susceptible to oxidation that is reversible by msrA [106]. Overexpression of human α-synuclein in *Drosophila* creates a model of Parkinson's disease with loss of dopaminergic neurons and the appearance of locomotor defects [107]. When bovine msrA was overexpressed along with the α-synuclein, the locomotor defects were almost completely suppressed [108].

Cancer

Following up on their studies that associated a deletion on chromosome 8 with metastatic spread of hepatocellular carcinoma, Lei and colleagues identified *msrA* as a candidate metastasis suppressor gene [109]. They then measured the mRNA levels for msrA in 40 human hepatocarcinoma tissue samples, half with metastasis and half without. The mean messenger RNA level was lower in tissue from patients with metastasis. They also transfected a human hepatocarcinoma cell line with msrA and found suppression of colony formation as well as decreased invasion in a 3-D Matrigel assay. There was no effect on cell proliferation itself. These results are consistent with an effect on metastasis but not on cell division itself.

MsrA has also been found to be down regulated in human breast cancer, with the decrease being greater in tumors of

advanced grade [110]. This observation led the investigators to investigate the effect of reducing msrA levels in a human breast cancer cell line, MDA-MB231. They found that knocking down msrA with shRNA caused an increase in cellular reactive oxygen species and oxidative damage to cellular proteins. Further, since msrA levels were decreased, the effects on tissue invasion and 3-dimensional growth were the opposite of those in the hepatocarcinoma study mentioned above—the breast cancer cells exhibited increased invasiveness and increased 3-dimensional growth.

Deafness

Loss of msrB3 causes congenital deafness, as first established by Riazuddin and her colleagues through genetic studies of Pakistani families [111]. These investigators also showed that msrB3 is present in the auditory and vestibular sensory epithelia of the inner ear. Knocking down msrB3 in zebrafish caused apototic death of hair cells in the fish neuromasts, providing a mechanistic basis for deafness [112]. Apototic death of hair cells also occurs during gestation in the msrB3 knockout mouse, causing deafness [113]. Lack of msrB3 may cause a failure of reduction of R-MetO in a specific protein, thus causing the apototic death. Neither the hypothesized protein nor the stereospecific methionine oxidase that generates R-MetO has been identified.

Other Disorders

A genome-wide association study in a Chinese population was carried out to identify single nucleotide polymorphisms (SNPs) associated with schizophrenia [114]. The study demonstrated an association of SNPs in *msrA* with schizophrenia. The same group reported an association of SNPs in *msrA* with bipolar disorder, although the number of subjects in the study was relatively small [115].

A genome-wide association study of French and German populations reported an association of extreme obesity in children and adolescents with a locus at or near the *msrA* gene. The association with central adiposity was confirmed by a meta-analysis of genome-wide associations [116]. Another genome-wide association study found an association of the *msrB3* locus with delayed development of teeth in human infants [117].

Conclusion

Methionine isn't just for protein initiation anymore.

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