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Editorial

Methionine Sulfoxide Reductase System in Health and Disease

Jackob Moskovitz*

Department of Pharmacology and Toxicology, University of Kansas, USA

***Corresponding author:** Jackob Moskovitz, Department of Pharmacology and Toxicology, School of Pharmacy, University of Kansas, 66045, USA

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Editorial

Methionine (Met) is highly susceptible to oxidation *in vivo*, particularly under conditions of oxidative stress that are exacerbated at older age. Oxidation of Met to methionine sulfoxide (MetO)is reversible and the reverse reaction is catalyzed by the methionine sulfoxidereductase (Msr) system, comprising methionine *S*-sulfoxidereductase (MsrA) and methionine *R*-sulfoxidereductase (MsrB), which reduce the *S* and *R* enantiomers of the sulfoxide group, respectively [1,2]. Thus, unlike other consequences of oxidative damage, such as protein carbonylation or nitration, Met oxidation to MetO is reversible and the Msr system provides an efficient protection against oxidative stress by scavenging reactive oxygen species through the recycling of Met [2]. Nonetheless, under consistent oxidative stress conditions, a combination between a compromised Msr system and elevated protein oxidation levels may lead to changes in protein structure and dysfunction of sulfoxidized proteins. All or some of these abnormalities may eventually lead to a permanent cell damage , disease, and death [2]. In recent years, more evidence have emerged supporting the importance of the Msr system in the development of oxidative-stress associated diseases of the brain (e.g. neurodegenerative diseases and disorders), cystic fibrosis (CF), and hearing loss [3-10]. In most of these diseases, reduction of MetO residues by the Msr system has shown to have a protective effect against oxidative damage and related diseases. An exception to this trend is the association between lower MsrA activity and lower chances of developing CF in individuals and in CF mouse models carrying the CF-linked genetic mutations [3]. Accordingly, identifying a specific inhibitor to MsrA activity may prompt the use of this inhibitoras a potential therapy treatment to children having CF. The physiological role of MetO is yet to be completely determined. So far, methionine oxidation has been shown to be involved in controlling protein phosphorylation [11-13], as well as yet to be discovered signal transduction pathway/s leading to an enhanced expression of Msr proteins [14]. In contrast, lack of Msr enzymes causes cells to be more vulnerable to oxidative stress and posttranslational modifications [15-23]. Given the protective role of the Msr system against oxidative damage, induction of Msr activity seems to be beneficiary to support cell survival. For example, over expression of MsrA (by genetic manipulation)in yeast and human cell cultures has been shown to protect these cells from enhanced MetO accumulations while increasing their survival rates under oxidative stress conditions [24]. In addition, several compounds have demonstrated an ability to induce Msr activity in neuronal cell cultures [25]. This observation supports the identification and development of novel compounds that may serve as therapy treatments against neurodegenerative diseases. Another possible approach to reduce the toxic effects of accumulated MetO-proteins is by enhancing their clearance from an organism. Supportive evidence for the importance of the Msr system in protein degradation is demonstrated by the fact that lack of MsrA contributes to the resistant of proteins to degradation. This phenomenon may be explained by the possible interference of MetO residues to phosphorylation-linked degradation processes. For example, over expression of α-synuclein in *msrA*null mutant yeast cells inhibits its phosphorylation and degradation in comparison with wild-type (WT) yeast cells [11]. Accordingly, under degenerative disease conditions (like in the case of neurodegenerative diseases) removal of oxidized proteins from brain may be beneficiary to halt the progression of the disease. One approach that has been used to achieve this goal was carried out by immunization of mice models of Alzheimer's disease (AD) with a MetO-rich protein antigen. Apparently, this treatment reduced mouse brain plaque burden in the hippocampal region of the treated mice compared with non-treated mice [14]. It is speculated that the resulting anti-MetO antibodies [14], produced through this antigen immunization, interacted with MetO-proteins (including MetO-beta amyloid protein) and cleared them from brain (presumably through enhancing these proteins' degradation). The overall importance of the Msr system to promote survival under physiological and enhanced oxidative stress conditions has been manifested in several organisms, from prokaryotes to eukaryotes including mammals. So far, methionine oxidation has been shown to affect many proteins' activities [2]. In mammals, examples of proteins in which their MetO can be also reduced by the Msr system include: the potassium channel of the brain [26], an isoform of the inhibitory protein B [27-29], calmodulin [30,31], calcium/calmodulin-dependent protein kinase II [32], and D2-dopamine receptor [10]. Examples of such proteins in lower eukaryotes (not mammals) include: transcription regulator for head box O (FOXO) in fruit fly [33], and prion-like protein (Sup35) in yeast [34]. These findings suggest a key role for MsrA in regulating MetO reduction in proteins, including major survival regulator transcription factors like FOXO [33]. Genomic analysis of brain of *Msr*A knockout mouse revealed that lack of the *MsrA*gene in mouse causes a strong and significant up regulation of genes that are involved in redox homeostasis and transcription regulation [35]. These data strongly suggest that MetO formation and reduction by the Msr system play a major role in the cellular adaptation to oxidative stress conditions, which is mediated by expression regulation of specific transcription factors. However, up-to-date not much is known about the signaling events that are leading to the transcriptional regulation

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of the Msr proteins themselves. It is suggested that a compounds that can mimic MetO or alternatively contain methyl sulfoxide group can cause an up regulation of at least the MsrA protein [25]. At least in yeast, the MsrA up regulation process may involve thioredoxin and a homologue of elongation factor 1 gamma factor [36,37]. More research is required to identify the components that participated in the Msr signal transduction pathway in order to expand the current understanding of the Msr system. Furthermore, development of specific compounds that can affect signaling molecules of the Msr system will enable the application of novel Msr-based therapeutic approaches.

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