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Review

Genetic regulation of longevity and age-associated diseases through the methionine sulfoxide reductase system☆,☆☆

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ABSTRACT

Methionine sulfoxide reductase enzymes are a protective system against biological oxidative stress in aerobic organisms. Modifications to this antioxidant system have been shown to impact the lifespan of several model system organisms. In humans, methionine oxidation of critical proteins and deficiencies in the methionine sulfoxide reductase system have been linked to age-related diseases, including cancer and neurodegenerative disease. Substrates for methionine sulfoxide reductases have been reviewed multiple times, and are still an active area of discovery. In contrast, less is known about the genetic regulation of methionine sulfoxide reductases. In this review, we discuss studies on the genetic regulation of the methionine sulfoxide reductase system with relevance to longevity and age-related diseases. A better understanding of genetic regulation for methionine sulfoxide reductases may lead to new therapeutic approaches for age-related diseases in the future.

1. Introduction

Biological oxidative stress is characterized by elevated free radicals and reactive oxygen species (ROS) in cells and tissues, which is generally accompanied by a reduced cellular antioxidant capacity [1–3]. A network of endogenous antioxidant systems are conserved among many species, including the major systems of glutathione and thioredoxin, and further antioxidants such as superoxide dismutases and catalases. The methionine sulfoxide reductase (Msr) enzymes are a unique group of antioxidants that can reduce the methionine sulfoxides of proteins, and also scavenge free radicals as general cellular antioxidants [4,5].

Cell and tissue ROS are often generated as a byproduct of metabolism in healthy cells, and can be further generated through apoptotic mechanisms and exogenous agents such as chemotherapy drugs [6,7]. These ROS can directly oxidize amino acids, and surface-exposed sulfur atoms of methionine are readily oxidized to methionine sulfoxide. These resulting methionine sulfoxides are posttranslational modifications that can be reversed by Msr enzymes. Moreover, Msr expression levels decrease with age in mammals [8], which can vary by organ [9], and may indicate a role of the Msr system in longevity and age-related disease [8,10–14]. Consequently, the accumulation of methionine sulfoxide has been proposed as a biomarker of biological aging [15].

Oxidation of the sulfur in the methionine thioether side chain results in an *S* or *R* sulfoxide diastereomer [16]. The *S* and *R* methionine sulfoxides in proteins are reduced by the discrete enzymes of methionine sulfoxide reductase A (MsrA) and B (MsrB), respectively. MsrA can also reduce free methionine-*S*-sulfoxide, which can contribute to cellular free radical scavenging and may promote availability of reduced-form methionine as a methyl donor for epigenetic DNA methylation. No mammalian enzymes have been found to reduce free methionine-*R*-sulfoxide, but enzymes such as fRmsr in unicellular microbes can perform this function [17,18]. In humans, MsrA has nuclear/cytoplasmic and mitochondrial isoforms generated from the *MSRA* gene. MsrA contains cysteine residues that are critical for the oxidoreductase activity, and form an intraprotein cysteine disulfide bond during substrate reduction. MsrA is reactivated by the thioredoxin system, and there is also evidence for activation by glutaredoxins [19]. There are three distinct human *MSRB* genes, *MSRB1/SELR/SELX*, *MSRB2/SEPX1/CBS-1*, and *MSRB3*. MsrB1 is a selenoprotein that is primarily localized to the nuclear and cytoplasmic cellular fractions, where MsrB2 and MsrB3 are associated with mitochondria (MsrB3 also has an alternative splice variant that is targeted to the endoplasmic reticulum [20]). The Msr

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system varies in other species, but all aerobic organisms have at least some type of an Msr enzyme.

Based on the physiological and pathophysiological relevance of the Msr system, understanding the regulation of Msr enzymes may lead to new therapeutic approaches [4]. There are limited reports for activators of Msr enzymes, and no reported small molecule inhibitors for Msr expression (to our knowledge). Multiple studies have reported that resveratrol can increase the expression of MsrA [21,22], which promotes this expression through the Sirt1-FOXO3a pathway [23]. Retinoic acid can also stimulate receptor binding to the *MSRA* promoter region [24]. Natural extracts such as quercetin and bambangan fruit cause increased expression of both MsrA and glutathione reductase [25]. Weissbach and colleagues recently reported compounds derived from natural products that activate human and bovine MsrA and MsrB, which are structurally related to fusaricidins [26]. Lipochroman-6, ultraviolet A irradiation, and ultraviolet B irradiation may also stimulate Msr expression and activity, which has been shown in keratinocytes [16,27,28]. However, there is a lack of information on the molecular mechanism for most of these Msr-promoting compounds and extracts. Moreover, the expression and activity of Msr enzymes can be modified by the cell environment, such as in hypoxic and hyperoxic conditions [29]. According to a study with chickens, increased methionine supplementation in the diet can also increase *MSRA* gene expression under heat stress conditions [30]. Moreover, mice fed on a diet lacking selenium display a loss of *MsrB1* mRNA and corresponding MSRB1 selenoprotein expression [31].

There is currently limited information the genetic regulation of the Msr system, and a dearth of information on the epigenetic regulation of Msr enzymes. The first reported search for nuclear proteins regulating the *msrA* gene was in a yeast model [32]. It was found that the calcium phospholipid-binding protein, a homologue of elongation factor-1γ, bound the *msrA* promoter region and enhanced *msrA* expression. A few years later, the transcription start site for the human *MSRA* gene was identified [33], followed by mapping promoters and identifying a retinoic acid response element for *MSRA*. De Luca et al. reported multiple Sp1 binding sites in the *MSRB1* promoter, and also provided evidence for epigenetic regulation of *MSRB1* [34]. In this review, we discuss reports on the genetic regulation of Msr enzymes and potential associations with longevity and age-related disease.

2. Genetic regulation of the Msr system for microbes and insects

The first Msr enzyme discovered was msrA in *Escherichia coli* [35]. The initial evidence that msrA protects cells against oxidative damage was also shown in *E. coli*, and later supported by numerous reports of this phenomenon in other model systems including the *MsrA* knockout mouse [1,36–39]. The addition of exogenous ROS or modifying aerobic conditions are commonly used as models of aging [13,32,40], which results in oxidized protein accumulation that has been previously shown as a hallmark of cellular aging [41,42]. In contrast to exogenous stressors, eliminating Msr enzymes in eukaryotic cells without additional stress also has an effect on yeast lifespan.

Prior to the knowledge of any other Msr genetic regulators, we discovered that the calcium-phospholipid-binding protein bound a 39-bp sequence of the yeast MsrA promoter region, and found eliminating this promoter impacted the ability of yeast cells to express MsrA [32]. Interestingly, knocking out MsrB in yeast only had a limited effect on lifespan, which knocking out MsrA had a significant lifespan effect and a double knockout of MsrA and MsrB had the largest lifespan-decreasing effect [40]. Even in the absence of exogenous ROS, MsrA knockout yeast models have shown to accumulate ROS-induced protein carbonyls, which are irreversible posttranslational modifications [37]. Consequently, it has been proposed that the Msr system contributes to free radical scavenging even at normal oxidative conditions, by direct enzyme oxidation or reducing readily oxidized substrates, which is in addition to the role of Msr for reducing critical and signal-associated methionine sulfoxides in substrates [4,43].

The msrA and msrB enzymes have also been shown as a defense system and vulnerability in bacterial species. Thus, it is no surprise that these enzymes can be upregulated in stress conditions. For example, *Staphylococcus aureus* have elevated *msr* expression after sunlight exposure, which also varies based on the oxygen level in the environment [44]. *Streptococcus gordonii* express high levels of *msrA* in biofilms, which helps maintain normal adhesion and biofilm function in response to exogenous oxidants [45]. In contrast, the RyhB small RNA binds *msrB* mRNA in *E. coli* to reduce msrB levels as a response to changes in cellular iron levels [46].

In *Drosophila*, MsrA overexpression increased resistance to paraquat-induced oxidative stress, and prolonged lifespan and fertility under normal conditions [47]. A recent study also showed ectopic expression of yeast fRMsr, an enzyme not found in *Drosophila* that reduces free methionine-*R*-sulfoxide, can extend lifespan in a methionine nutrient-dependent manner [48].

3. Genetic regulation of the Msr system and Msr-dependent longevity in mammals

MsrA is widely expressed throughout mammalian tissues [49], and highly expressed in the liver and kidneys [36]. The human mitochondrial MsrA protein (referred to as MsrA1) is 235 amino acids and the MsrA targeted to the nucleus and cytoplasm is 192 amino acids (referred to as MsrA2) [20,50]. An enzymatically inactive 195-amino acid MsrA3 protein has also been reported [20]. These proteins are

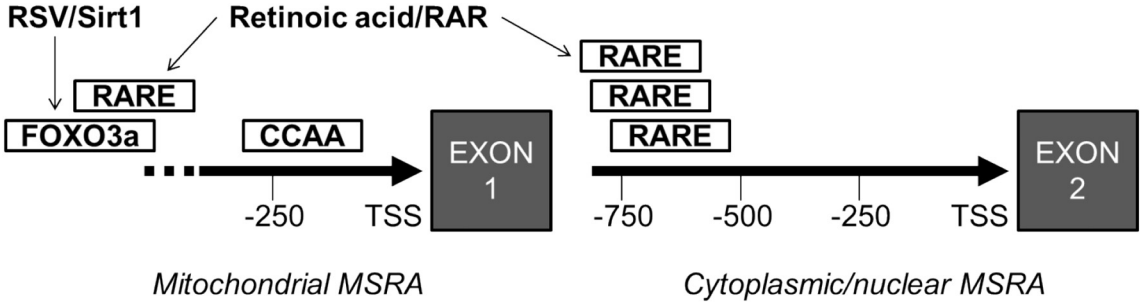

Fig. 1. Schematic representation of reported characterization studies for the human *MSRA* gene. The mitochondrial *MSRA* transcript contains exon 1, with the transcription start site (TSS) 59 bp upstream, skipping exon 2 and splicing to exon 3. The cytoplasmic/nuclear *MSRA* transcript has a distinct promoter region and transcription starts near exon 2. FOXO3a is translocated to the nucleus by resveratrol (RSV)/Sirt1 signaling, and directly binds the mitochondrial *MSRA* promoter region between −1408 to −50 bp. Both promoter regions respond to retinoic acid through retinoic acid receptors (RAR), although the RAR element (RARE) locations have only been reported for the cytoplasmic/nuclear MSRA transcript (−690 to −683, −684 to −675, −655 to −645). A negative regulatory CCAA box approximately 200 bp upstream from the TSS has also been reported to impact expression of the mitochondrial *MSRA* transcript. Upstream *dashes* in promoter 1 region indicate the precise location of RARE and the FOXO3 binding site were not reported.

generated from the same *MSRA* gene, differing by promoter regions and alternative splicing (Fig. 1). The mitochondrial *MSRA* transcript starts 59 bp upstream from exon 1, and exon 1 splices to exon 3 with exon 2 omitted [50,51]. The cytoplasmic/nuclear *MSRA* transcript begins at a separate transcription start site near exon 2. The transcription start sites are 41 kb apart, which supports that expression of these splice variants are controlled by two different promoter regions. Pascual et al. reported retinoic acid response elements for both *MSRA* promoter 1 and promoter 2, corresponding respectively to exon 1 and exon 2, and an increase of *MSRA* transcription from retinoic acid stimulation [24]. Also, Minniti et al. found FOXO3a binds to the promoter 1 region (using human *MSRA* in HEK cells, with further evidence in *Caenorhabditis elegans* studies) [23], and this finding was supported by resveratrol-stimulated Sirt1 activation of FOXO3a to increase MsrA in human neuronal SH-SY5Y cells. Other putative response elements for *MSRA* have been identified, including three retinoic acid receptor elements for promoter 2, but these have not been confirmed [51]. De Luca et al. identified a CCAA box negative regulatory region approximately 200 bp upstream of the first *MSRA* transcription site, which was associated with decreased MsrA in MCF7 breast cancer cells [33]. The same group further discovered multiple Sp1 binding sites in the *MSRB1* promoter region, which is 169 base pairs upstream from the corresponding *MSRB1* transcription start site [34]. These binding sites were confirmed by mutation analyses in the promoter region and chromatin immunoprecipitation assays. The *MsrA* knockout mouse also has decreased *MsrB* mRNA and MsrB protein levels compared to wildtype counterpart mice, which is suggestive of MsrA having a regulatory role in *MsrB* expression [31].

MSRA expression decreases with age, which has been shown in rat organs where *MsrA* expression is typically high (liver, kidneys, brain) [8,9,14]. Methionine oxidation in rat brain calmodulin has also been used as a biomarker for aging [52]. However, *MsrA* expression in livers of older mice has been reported to remain relatively unchanged, but *MSRB1* expression decreased with age [53]. Senescent human fibroblasts have decreased expression for both *MSRA* and *MSRB2* when compared to young cells [10]. The *MsrA* knockout mouse has a shorter lifespan and exhibits enhanced sensitivity to oxidative stress when compared to control mice [36]. *MsrA* knockdown in a mouse fibroblast cell model was demonstrated to inhibit cell proliferation, which also promoted acetylation of tumor suppressor p53 and activated p21 transcription promoting cell cycle arrest, although ectopic *MsrA* expression in this cell model was not found to have cell proliferation effects [54]. It was recently reported that elevated MsrA2 expression can reduce the rate of age-related death in mice, but overexpression of mitochondrial MsrA1 did not have a similar effect [55]. Methionine oxidation can be a biomarker of aging in model systems, along with other aging biomarkers such including clusterin/apolipoprotein J expression, protein glycosylation/glycation, and protein carbonyl accumulation [15].Outside of cell line models, there is limited data to support the human aging association with decreased Msr expression. It was reported that human skin collagen has an age-related increased methionine sulfoxide accumulation, although Msr expression was not evaluated [56].

Environmental and cellular stress can enhance the expression of Msr enzymes. This has been shown with low doses of hydrogen peroxide in human lung fibroblasts and monkey retinal pigment epithelial cells [10,57]. Moreover, MsrA expression increases in an inflammatory response to microglial activation in rats [58]. In contrast, we have shown that caloric restriction, which can alleviate some effects of oxidative stress, can attenuate age-related phenotypes such as locomotion in the *MsrA* knockout mouse [59].

Very little has been reported on the epigenetic regulation of the Msr system. Arrest defective 1 is an acetylation enzyme that has been demonstrated to regulate MsrA, but it is not known if this regulation is at the posttranscriptional level or *via* lysine acetylation at the post-translational level [60]. *MSRB1* expression was increased using the 5-aza-2′-deoxycytidine demethylating agent in the highly metastatic MDA-MB231 breast cancer cell line, which has lower basal *MSRB1* expression than the low metastatic MCF7 breast cancer cell line [34]. This evidence was further supported by demonstrating the *MSRB1* promoter region was hypermethylated in MDA-MB231 cells compared to the same region in MCF7 cells, suggesting epigenetic modifications contribute to differences in *MSRB1* expression in these model systems, and that regulation of the Msr system may be associated with cancer progression.

4. Regulation of the Msr system in age-associated disease

The physiological aging process, both at the organ/organism level and the cellular level, is associated with free radicals and a decreased antioxidant capacity [4,61]. The aging process is not a disease; however, age is generally the most prominent risk factor for several diverse age-associated diseases. Ergo, age-associated diseases generally involve abnormal redox conditions. Nervous tissues can be particularly sensitive to oxidative stress [41]. Moreover, Msr expression and activity in tissues can decrease with age [9,14,36,53], such as *MsrA* expression in brain tissue of older rats [8]. Oxidative stress is also a frequent phenotype of cancer cells [62,63]. Furthermore, increased antioxidant expression often correlates with resistance to systemic chemotherapies [2,64–67], and MsrA has been demonstrated to protect kidneys against cisplatin-induced methionine oxidation and cytotoxicity [68]. Additionally, reactive oxygen species can promote tumorigenesis and cancer promotion pathways [6,69,70]. The Msr system is associated with neurodegenerative disease and cancer as a general scavenging antioxidant system and through specific substrates of the Msr enzymes. For example, the *MsrA* knockout mouse accumulates carbonyl-modified proteins under oxidative stress conditions [36]. In separate studies, it was also found that these mice have abnormal dopamine regulation and locomotor activity, which may be attributed to methionine oxidation in dopamine receptor signaling [11,59,71–73].

Oxidative stress is a factor implicated in several neurodegenerative diseases such as Alzheimer disease [74]. Expression of MsrA protein is decreased in the brains of Alzheimer patients, although mRNA analysis demonstrated that the genetic expression of *MSRA* is similar to control brains without this diagnosis [75]. The presence of proteins with methionine sulfoxide enhances Msr activity, as shown by the amyloid beta-methionine sulfoxide-35 protein [76]. The presence of oxidized protein likely induces expression of antioxidants, but molecular mechanisms were not evaluated in this study. Moreover, lack of MsrA enhances the stability of α-synuclein and slows the degradation of this protein [13,77], although it is not known if Msr expression is decreased in Parkinson disease.

Astragaloside IV has been reported to increase MsrA expression in PC12 cells through the Sirt1-FOXO3 signaling pathways, which can rescue mitochondrial dysfunction from 1-methyl-4-phenylpyridinium exposure that reduces MsrA expression [78]. Resveratrol can increase *SIRT1* expression [79], and also increase *MSRA* expression that has been shown to enhance resistance of neuroblastoma cells to neurotoxins [80]. Punicalagin, an antioxidant from pomegranate extract, has also been found to upregulate *MSRA* expression in neuroblastoma cells. *MSRA* expression can be inhibited by the microRNA miR-193b, where it was reported to function as a tumor suppressor in liposarcoma [81].

MsrA and MsrB have been implicated in the characteristics of cancer cell line models and cancer progression. Leukemia and lymphoma cell lines were reported to lack detectable expression of *MSRA* [82]. *MSRA* mRNA was found to be decreased in metastatic hepatocellular carcinoma compared to nonmetastatic liver cancer in clinical samples, suggesting MsrA may be a metastasis suppressor, and *in vitro* overexpression of *MSRA* prevented cell line migration in permeable membrane assays [83]. Expression of *MSRA* mRNA is downregulated in several breast cancer tissue clinical samples and these levels are further decreased in advanced tumor grades of breast cancer [84]. *MSRA*

knockdown in the metastatic MDA-MB231 breast cancer cell line increased cell proliferation and degradation of the extracellular matrix in cell culture and xenograft models, which resulted in upregulation of vascular endothelial growth factor and activation of the phosphoinositide 3-kinase pathway. As previously mentioned, epigenetic regulation may decrease *MSRB1* expression in the MDA-MB231 cell line [34]. In contrast to reports of *MSRA* knockdown increasing cancer cell line proliferation, *MSRB1* knockdown in osteosarcoma U2OS cells decreased cell proliferation in cell culture and xenograft models, and further modified the mitogen-activated protein kinase pathway by disrupting the phosphorylation of the key proteins erk, MEK, and p53 [85]. *MSRB3* knockdown in breast cancer MCF7, lung cancer A549, and liver cancer SKHep1 human cell lines reduced cell proliferation, while overexpression of *MSRB3* stimulated cell proliferation in these cancer cells [86]. The same group later reported that *MSRB3* knockdown induces cancer cell apoptosis through endoplasmic reticulum stress-dependent pathways [87]. The seemingly contradictory evidence for Msr associations to different cancer types suggests both further undiscovered complexity and a need for more studies on the role of Msr enzymes in various cancer types.

Only a very limited number of studies correlated Msr expression to cancer types in clinical samples [83,84], while most studies relied on *in vitro* evidence from cell lines. Using the cBioPortal web tool [88,89], we searched The Cancer Genome Atlas database and report here the top three cancer types with the highest expression for each *MSR* transcript from clinical samples (Fig. 2). In this analysis, *MSRA*, *MSRB1*, and *MSRB2* are highly expressed in liver cancers, and *MSRB1* and *MSRB2* are highly expressed in papillary renal cancer. Since the Msr expression is already relatively high in the liver and kidney organs for healthy individuals, it may not be surprising that the *MSR* transcripts are often upregulated in these cancers, but further investigation is required to understand the impact of this expression. Using multiple cancer genomic databases, Morel et al. recently found expression of *ZEB1* and *MSRB3* mRNA were correlated in primary breast cancers, which was also demonstrated in several breast cancer cell lines [90]. ZEB1 was confirmed to bind to the human *MSRB3* promoter region and induce transcription in mammary epithelial cells, which also decreased when cells were depleted of ZEB1. The increases in ZEB1 and MsrB3 promoted the intrinsic susceptibility for stem cells to undergo malignant transformation, however, these expression levels were inversely correlated with chromosomal instability in breast cancer cell lines and primary triple negative breast cancer clinical samples. These results highlight the complexity of the Msr system in tumorigenesis, where malignant transformation can occur in cellular conditions with high Msr in addition to the previously characterized pathway of early-stage genomic instability for many neoplasms [91,92].

There is growing evidence that Msr enzymes are also important in cardiovascular disease. It was shown ectopic MsrA expression can protect the heart from ischemia-reperfusion injury, although this protection requires myristoylation that suggests MsrA may be more efficient in the presence of a hydrophobic substrate [93]. Msr activity also has been found to be decreased in the ischemia-reperfusion environment, although genetic regulation of Msr was not particularly implicated and Msr activity partially recovers over longer periods of reperfusion [94]. Resveratrol has been found to upregulate MsrA expression and decrease ROS in electrically stimulated neonatal rat cardiomyocytes [22]. Furthermore, the myocardial cells in the *MsrA* knockout mouse are more susceptible to mitochondrial damage under stimulated stress conditions [95]. *MsrB1* mRNA and protein expression were also increased under cardiac stress conditions in a mouse model of myocardial hypertrophy [96].

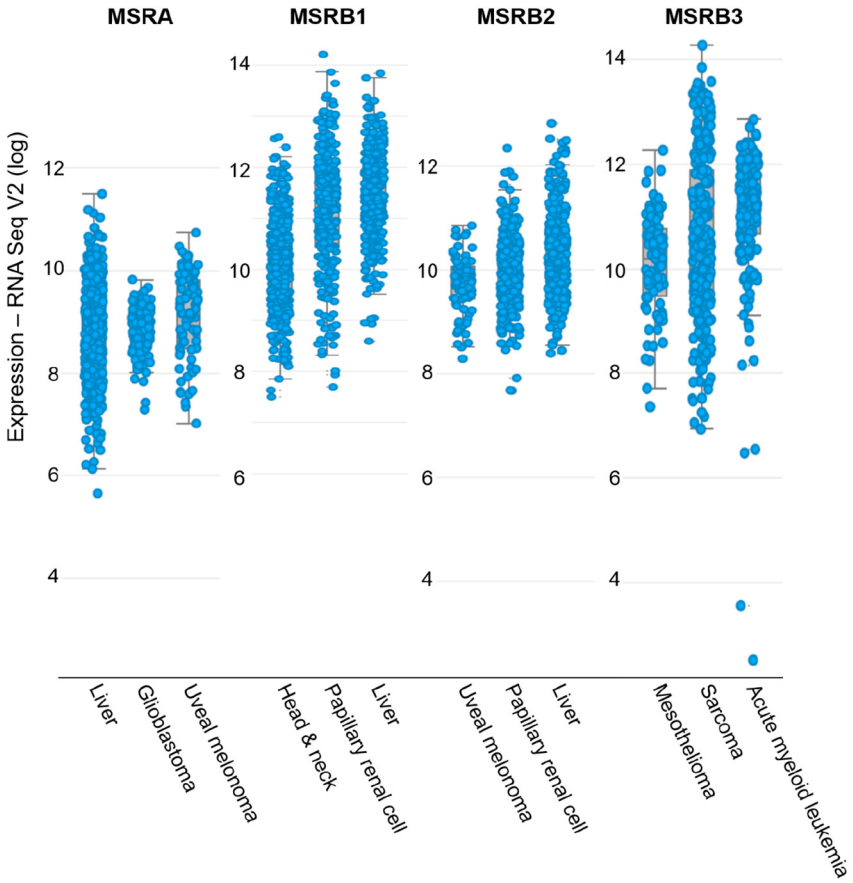

Fig. 2. Cancer types with the highest human *MSR* mRNA expression. Of 30 TCGA cancer datasets, the top three datasets based on the highest median expression are presented for each respective *MSR* gene. Blue dots represent each sample. Data are RNA Seq V2 values from TCGA Research Network with graphs generated by cBioPortal software with the size of each graph adjusted for similar vertical scales.

5. Conclusions

Manipulation of the Msr system may lead to new treatment approaches in diseases such as neurodegenerative disease and cancer, although information on the genetic regulation of Msr enzymes is limited. Hawkes et al. found several putative regulatory regions in *MSRA1* and *MSRA2* [51], although currently the only confirmed enhancer regions are the retinoic acid response elements for both the *MSRA* promoter 1 and promoter 2 that respond to retinoic acid stimulation [24]. An antioxidant response element was one of the putative regulatory regions reported for the *MSRA1* promoter, which may associate MsrA with nuclear factor-like 2 (Nrf2) regulation [51]. The Nrf2 transcription factor regulates the expression of many antioxidant proteins, including thioredoxin. MsrA can inhibit Nrf2 activation, which may be a regulatory loop, and MsrB3 deficiency also stimulates Nrf2 activation [97]. It has been further reported in vascular smooth muscle cells that Keap1 binding to Nrf2, which inactivates Nrf2, is diminished in the absence of oxidative stress conditions [98]. MsrA regulation of thioredoxin has also been implicated in protecting hepatocytes against acetaminophen-induced toxicity, although association with Nrf2 activation was not investigated [99].

Single nucleotide polymorphisms and copy number alterations in *MSRA* have been associated with multiple diseases. In Chinese populations, *MSRA* polymorphisms correlated with a risk of rheumatoid arthritis, coronary artery disease, schizophrenia, and bipolar disorder [100–103]. MsrA was found to have a high number of polymorphisms in acute coronary syndrome blood samples, and was categorized as a “suspicious biomarker candidate” [104], although this is likely far from the high threshold of being a primary diagnostic marker [105]. In oral cancers, *MSRA* was reported to be one of the most frequently lost genes (21%) among copy number alterations in chromosome 8 [106].

Methionine is an essential amino acid, and complete depletion would be lethal. Methionine restriction has been found to extend the lifespan in fruit flies and *mice* [107,108], which may be dependent on growth hormones [109]. Methionine supplementation in excess may promote cancer growth as the methyl donor for DNA methylation [110,111]. In contrast, it was shown that *S*-adenosylmethionine (derived from methionine and ATP) treatment can promote methylation of proto-oncogenes in prostate cancer cells [112]. Unbound methionine can be readily oxidized similar to exposed methionine residues in a protein, and human MsrA can reduce the unbound methionine-*S*-sulfoxide but there is no known human enzyme for reduction of unbound methionine-*R*-sulfoxide [17]. Whether methionine regulation (*via* diet or Msr targeting) has therapeutic benefit for human aging and age-related diseases remains an open question.

Aside from the studies in this review, there is a general lack of knowledge for molecular mechanisms of genetic and epigenetic Msr regulation. Thus, this review is intended to promote further research in this field and shed light on specific areas for study. The role of Msr in cancer is one of the least understood fields, and this may highlight the complexity of tumorigenesis and disease progression, as well as differences in cancer types and pathways. Moreover, except when mentioned most of these studies lack clinical data correlation to model systems. Future studies should associate human samples of aging and age-related disease with Msr expression. To date, these correlation analyses are mainly limited to specific cancers and Alzheimer disease [75,90]. Perhaps more knowledge regarding the role of Msr enzymes in human longevity would provide a better understanding for the role of Msr in age-associated disease. Then, genetic activators like resveratrol and undiscovered small molecule inhibitors of Msr may have clinical implications in addressing the age-related factors of age-associated disease.

In general, increased antioxidants can prevent neurodegeneration and also alter the characteristics of cancer cells, especially in cancer cells treated with systemic chemotherapy. Consequently, finding both new positive or negative regulators of the Msr system may have clinical implications with therapeutic benefit. Understanding the genetic regulation of the Msr system may prove to be crucial in the discovery of these potential therapies.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgements

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