FORUM REVIEW ARTICLE

Regulation of CuZnSOD and Its Redox Signaling Potential: Implications for Amyotrophic Lateral Sclerosis

Michael J. Hitchler¹ and Frederick E. Domann²

Abstract

Significance: Molecular oxygen is a Janus-faced electron acceptor for biological systems, serving as a reductant for respiration, or as the genesis for oxygen-derived free radicals that damage macromolecules. Superoxide is well known to perturb nonheme iron proteins, including Fe/S proteins such as aconitase and succinate dehydrogenase, as well as other enzymes containing labile iron such as the prolyl hydroxylase domain-containing family of enzymes; whereas hydrogen peroxide is more specific for two-electron reactions with thiols on glutathione, glutaredoxin, thioredoxin, and the peroxiredoxins. **Recent Advances:** Over the past two decades, familial cases of amyotrophic lateral sclerosis (ALS) have been shown to have an association with commonly altered superoxide dismutase 1 (SOD1) activity, expression, and protein structure. This has led to speculation that an altered redox balance may have a role in creating the ALS phenotype. **Critical Issues:** While SOD1 alterations in familial ALS are manifold, they generally create perturbations in the flux of electrons. The nexus of SOD1 between one- and two-electron signaling processes places it at a key signaling regulatory checkpoint for governing cellular responses to physiological and environmental cues. **Future Directions:** The manner in which ALS-associated mutations adjust SOD1's role in controlling the flow of electrons between one- and two-electron signaling processes remains obscure. Here, we discuss the ways in which SOD1 mutations influence the form and function of copper zinc SOD, the consequences of these alterations on free radical biology, and how these alterations might influence cell signaling during the onset of ALS. *Antioxid. Redox Signal.* 20, 1590–1598.

Introduction

THIS DISCOVERY OF oxygen containing free radicals in biological materials by Townsend, Commoner, and Pake in the 1950s raised several questions about their existence (10). Life in oxygen affords cells with a suitable reductant substrate with which to facilitate numerous biological reactions, including oxidative phosphorylation, cell signaling, and mounting an immune response. The addition of one electron to oxygen generates superoxide anion ($O_2^{\bullet-}$), which is made as either a product or byproduct. As a product, superoxide is generated by endogenous oxidases with a multitude of biological objectives ranging from cellular defense to redox signaling pathways. Superoxide becomes a byproduct during the incomplete reduction of oxygen during oxidative phosphorylation in the mitochondria. In both roles, $O_2^{\bullet-}$ has been speculated to influence diverse biological events, including

cancer, aging, neurodegenerative disorders, and development. When the first superoxide dismutase (SOD) was discovered by McCord and Fridovich in the 1960s, the understanding of the function of $O_2^{\bullet-}$ in biology became more complex (36). Superoxide is generally labeled as a toxic species with SODs labeled as their “detoxifiers.” However, a more sophisticated perspective of superoxide can be held if we designate these enzymes as modifiers of superoxide function by regulating the flux of superoxide, rather than prescribing to them the diminutive role of free radical scavengers. Eukaryotic compartmentalization allows superoxide to exist in varying steady state levels within the same cell. Mammalian cells have three identified SODs: manganese superoxide dismutase (MnSOD), extracellular superoxide dismutase (ECSOD), and copper zinc superoxide dismutase (CuZnSOD), the last which will be the subject of this review. Alterations to the activities of these enzymes can have varying

¹Department of Radiation Oncology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California.

²Free Radical and Radiation Biology Program, Department of Radiation Oncology, The University of Iowa, Iowa City, Iowa.

effects on the superoxide's function and be the etiology of numerous pathologies.

CuZnSOD, or SOD1, is a soluble protein that catalyzes the dismutation of superoxide in numerous subcellular compartments (52, 73). SOD1 was originally designated erythrocyuprein, a copper storage protein with no known enzymatic activity. Since the discovery of SOD1's superoxide dismutase activity by McCord and Fridovich, several human conditions and pathologies have been associated with alterations in its function. SOD1 alterations have been shown to be associated with aging, cancer, and amyotrophic lateral sclerosis (ALS). ALS is a motor neuron disease that generally exhibits adult onset. Originally, it was suggested that roughly 20% percent of ALS cases are associated with mutations in SOD1 (58). Today, this estimate has been refined to ~7% of ALS patients having SOD1 mutations (1). This realization has greatly increased our understanding of ALS, and the mechanisms that might be responsible for its manifestation. In this review, we will specifically address the ways in which alterations can influence the form and function of CuZnSOD, the consequences of these alterations on free radical biology, and how these alterations might influence cell signaling during the onset of ALS.

SOD1 Gene

The gene encoding human CuZnSOD, *SOD1*, resides on chromosome 21q22.1 of the human genome. SOD1's association with multiple disease phenotypes has led to extensive characterization of the transcription factors that bind this region. The gene is ubiquitously expressed at a relatively high level in human tissues, an attribute that is facilitated by these generic transcriptional regulatory elements. The *SOD1* gene contains numerous genetic features that are conserved across several eukaryotic species, and suggest they are required for the gene's function. A proximal promoter containing a TATA box, GC-rich region, and a CCAAT motif mediates basal expression of SOD1. Bona fide binding sites for activator protein 1 (AP-1), specificity protein 1 (SP-1), and early growth response 1 (EGR-1) are within the CG-rich domain of the proximal promoter (27) (Fig. 1). These elements are common to eukaryotic genes, and they are likely the mechanical factors that are responsible for driving SOD1's universal expression in all tissues and cell types.

SOD1 transcription can also be induced following numerous abiotic and biotic stimuli *via* the activation of other accessory cis-regulatory elements. These enhancer-like elements in SOD1 are located upstream from its transcriptional start site. Again, SOD1's association with human disease has led to the thorough characterization of these DNA elements (Fig. 1). A majority of inducible SOD1 expression is facilitated by the binding of nuclear factor kappa B (NFκB), nuclear factor (erythroid-derived 2)-like 2 (NRF2), aryl hydrocarbon receptor/aryl hydrocarbon receptor nuclear translocator (AHR/ARNT), and CAATT enhancer binding proteins (C/EBP) transcription factors to enhancer regions of SOD1 (38, 40, 47). For example, NFκB binding the human SOD1 promoter increases after exposure to cytokines, oxidative stress, and hydrogen peroxide (H₂O₂) (32, 40). Likewise, cellular stress leads to the swift localization of NRF2 to the nucleus to increase the expression of genes such as SOD1. Similar mechanisms lead to the transcriptional activation of SOD1 by increasing the

FIG. 1. Molecular genetic structure of the 5'-regulatory region of the human SOD1 gene that encodes CuZnSOD. Numerous cis-regulatory elements for common transcription factors are present in this region, some experimentally documented to be functional and others remaining as uncharacterized "putative" response elements. SOD1, superoxide dismutase 1; CuZnSOD, copper zinc superoxide dismutase.

binding of AHR/ARNT and C/EBP at the proximal promoter. As a part of the encyclopedia of DNA elements (ENCODE) project, several histone modifications have been mapped to the entire genome of numerous cell lines using Chromatin immunoprecipitation sequencing (ChIP-Seq). The confluence of these efforts provides a qualitative view of the "epigenetic landscape" of SOD1 in model cell lines (Fig. 2). The presence of H3K4me₃, and H3K9ac at a gene's basal promoter, as well as H3K36me₃ within its coding region, are hallmarks of a gene that is actively expressed (54, 60). Both these histone modifications are present at SOD1 in numerous cell lines (Fig. 2). Likewise, the cis-elements of SOD1 bound by NFκB, NRF2, AHR/ARNT, and C/EBP are enriched with H3K4me₂ modified histones, a modification that is synonymous with enhancers (48, 57). Combined, SOD1's transcriptional regulatory elements not only govern its basal expression in all tissues, but also mobilize increased levels of CuZnSOD activity in response to pro-oxidants, toxins, and cytokines. While these studies suggest that SOD1 expression may be altered following some exogenous stimuli, it should also be noted that the production of a fully formed, active CuZnSOD dimer formation by post-translational processing may facilitate another means by which dismutase activity can be altered in cells.

ALS-Associated Changes in Expression

Thus far, studies testing an association between SOD1 gene activity and the development of ALS have produced mixed results. An early study noted that of SOD1 mRNA levels in the motor, neurons of sporadic and familial cases were not significantly different from those exhibited by normal controls; however, decreased expression was observed in atrophic neurons (43). These reports have been confirmed by others looking at expression profile of several genes in ALS (64). Conversely, others have suggested that SOD1 expression might be higher in ALS patients (11, 19). This duplicity regarding SOD1 expression in ALS is confusing, and it is mostly likely confounded by the complex pathology of the disease, or attributable to disease-associated mutations in SOD1.

FIG. 2. ChIP-Seq tracks from the ENCODE project showing the localization of various modified histone markers along the human SOD1 gene. The gene possesses an epigenetic landscape that is consistent with a constitutively expressed gene in all cell and tissue types. ENCODE, encyclopedia of DNA elements.

Recently, a 50 bp deletion in the SOD1 promoter was identified in individuals with sporadic ALS of Italian decent. However, these changes were shown to have no effect on SOD1 transcription (39). Epigenetic repression is another possibility leading to altered gene expression. While this mechanism has not been completely explored, SOD1 is probably not a target for epigenetic silencing by cytosine methylation in ALS (44). Decreasing the expression of SOD1 has also been explored as a therapeutic avenue to reduce SOD1 expression in ALS. Compounds that inhibit SOD1 transcription in model cell lines have been identified, and may serve as the basis for developing clinically viable strategies for ALS aimed at decreasing SOD1 expression (66).

CuZnSOD Protein

Manufacturing a functional CuZnSOD dimer requires a process that includes several concerted steps: disulfide bond formation, protein folding, metal ion loading, and dimer formation. Each monomer is 153 amino acids, and it weighs ~19 kDa. An SOD1 homodimer consists of two catalytically active nondisulfide linked subunits; however, creating and maintaining the structure of each monomer utilizes intramolecular disulfides (5). Fully formed monomers contain a disulfide bond between Cys 57 and Cys 146, but may use

other cysteines to obtain proper folding (9, 67). Loss of the disulfide bridge results in a catalytically dead version of CuZnSOD.

The loading of Cu(II) and Zn(II) ions is another critical step in forming active SOD1. Both metals are coordinated in the active site of the enzyme by several histidine residues. In humans, the active site metal ions are held in place by His46, 48, 60, 63, 71, and 120 (Fig. 3). The layout and structure of the SOD1 active site is distinct from the other mammalian SODs, MnSOD, and EcSOD (41). The nature of active site most likely bestows SOD1 with unique activities unobserved in the other SODs. The addition of copper to SOD1 is assisted by the protein copper chaperone for SOD1 (CCS). CCS contains unique structural motifs that create a binding site to stabilize the structure of a nascent SOD1 monomer to facilitate the integration of copper into the enzyme (17, 20). Interactions with CCS facilitate SOD1 folding, metal ion chelation, and disulfide formation to create an active protein (28). This mechanism is reliant on a stable structure of CCS, which is oxidatively sensitive (20).

SOD1 processing may also be involved in directing its subcellular localization. SOD1 is most abundant in the cytosol; however, it has also been observed in endosomes, and the mitochondrial intermembrane space (24, 52) (Fig. 4). During mitochondrial import, SOD1 is imported as an immature, catalytically inactive form into the intermembrane space. Once there, it is processed by CCS into the active form, becoming trapped in the mitochondria (24, 30). This mechanism allows SOD1 to be targeted to the intermembrane space even without a canonical mitochondrial targeting sequence. Stress signals may also influence the subcellular localization of SOD1. Increased stress can trigger events that lead to the import of SOD1 from the cytoplasm and into the nucleus (73).

SOD1 Catalytic Mechanism and ALS

Similar to other mammalian SODs, SOD1 utilizes a ping-pong mechanism that requires two successive loadings of $O_2^{\bullet -}$. The step-by-step mechanism for human SOD1 is shown in Figure 5. In this mechanism, the metals in the catalytic core of SOD1 withdraw an electron from the first superoxide, then mask the negative charge by redistributing it, which favors the attraction of a second $O_2^{\bullet -}$ molecule. SOD1 also exhibits a low level of intrinsic peroxidase activity. This activity of SOD1 is unique among mammalian SODs (Fig. 6). Specific

FIG. 3. Primary amino-acid sequence of the product of the human SOD1 gene, the human CuZnSOD protein. Asterisks mark histidine amino-acid residues that are responsible for chelating the Cu and Zn ions in the holoenzyme. Y mark the amino-acid residues that are commonly mutated in familial ALS. ALS, amyotrophic lateral sclerosis.

FIG. 4. Sub-cellular localization of CuZnSOD protein. Typically considered a cytosolic protein, evidence indicates that approximately 10% of CuZnSOD resides in the mitochondrial intermembrane space with the presumptive function of scavenging superoxide leaked from the back side of the coenzyme Q cycle in complex III of the electron transport chain. In addition, under conditions of significant oxidative stress, CuZnSOD can re-localize to the nucleus of cells. Although its function in the nucleus is less clear, it may re-localize there to maintain nuclear redox buffering capacity and keep nuclear Zn finger transcription factors and other DNA binding proteins in a properly reduced state for optimal responses to oxidant stress.

conditions appear to favor this activity, such as H_2O_2 and superoxide concentration.

SOD1 Mutations Influence Its Activity in ALS

The association between SOD1 mutations that affect enzyme activity and ALS has garnered much attention beginning with the initial report of Rosen *et al.* describing the linkage between the two (51). Thus far, SOD1 mutations associated with ALS have been identified in the promoter, untranslated regions, exons, and introns. To date, ~150 mutations scattered across the coding region of SOD1 have been identified as associated with ALS. In North America, the most abundant mutation is the A4V mutant. This mutation is associated with aggressive forms of familial ALS, with a median survival time of 1.2 year compared with other mutations with a survival of 2.5 year after onset (50). Other familial mutations such as H46R and G93 present a less severe phenotype and exhibit longer survival times after disease onset (58).

The identification of ALS-associated mutations in familial cases has ushered in the development of mouse genetic models that attempt to emulate the ALS phenotype. Several SOD1 mutant transgenic mouse models corresponding to human mutations have been created and characterized in an attempt to gain insights into the etiology of ALS, the principal of which are A4V, H46R, H48Q, and G93A (23, 46). These enzymes vary in the amount of SOD activity they exhibit *in vitro*. Some forms display no detectable SOD activity, while others appear to process superoxide that is similar to

FIG. 5. Enzymatic mechanism for the activity of CuZnSOD. The enzyme works through a so-called ping pong mechanism in which the first reacting superoxide reduces the holoenzyme Cu at the active site, depositing an electron and leaving as molecular oxygen. The second reacting superoxide then accepts an electron from the reduced Cu to become hydrogen peroxide (HOOH) and leaving the Cu oxidized and ready to accept another electron, thus completing the cycle.

FIG. 6. Several reactions can be catalyzed by CuZnSOD. In addition to the canonical SOD reaction (*top panel*), CuZnSOD also has a peroxidase activity (*middle panel*) as well as a nitrosylation activity (*bottom panel*).

wild-type CuZnSOD. Furthermore, unlike these transgenic lines, SOD1 knockout mice do not develop an ALS phenotype (56). This suggests that mutant forms of SOD1 exhibit a gain of function that is responsible for the manifestation of the ALS phenotype. Both the expression level of mutant SOD1 and the genetic background of mice transgenic cell lines appear to influence the severity of disease and the time at which ALS symptoms are exhibited (12, 55). Even with this caveat, a great deal has been learned about ALS disease pathology. Some of the mutations, such as the aggregation mutation AV4, do not create the ALS phenotype in transgenic systems, even though protein aggregation is present (16). Several elegant *in vitro* and *in vivo* studies using these genetic models have rendered some insights into the various mechanisms by which mutant SOD1 may be responsible for ALS. The power of these model systems has allowed investigators to determine whether a broad spectrum of items may influence ALS symptoms, including diet, overexpression of other neuronal proteins, altered signaling cascades, and antioxidant status (7, 29, 31, 42).

Several groups have suggested that increased peroxidase activity in the SOD1 mutants may be responsible for creating

the ALS phenotype (6). As mentioned earlier, mutant forms of SOD1 vary in their relative amounts of SOD activity. Apart from their normal SOD activity, some SOD1 mutant gain-of-function variants have an increased propensity to utilize their peroxidase activity (Fig. 6). Indeed, the aggressive A4V mutant shows the highest affinity for H₂O₂ and increased ability to produce H₂O₂. Increased peroxidase activity is observed in mouse models that are synonymous with the human AV4, H48Q, and G93A mutations (34, 49). The outcomes from this activity are manifold. In some cases, peroxidase activity can generate superoxide from H₂O₂, and a hydroxyl radical that modifies the imidazole ring of histidine, which irreversibly inactivates the enzyme (33, 34). If cellular conditions favor it, H₂O₂ can react with carbonate to form peroxymonocarbonate, which can also be processed by the enzyme to create the carbonate radical (4, 37, 70).

Another unique mechanism exists by which SOD1 processes ONOO⁻, leading to the nitration of tyrosine residues in several key cellular proteins (2, 21). In ALS, increased tyrosine nitration has been detected in familial and sporadic cases alike, suggesting that tyrosine nitration might play a role in the etiology of the disease (59). Tyrosine nitration of proteins in motor neurons, such as neurofilament light chain, alters their structure and function, which ultimately leads to death of the motor neuron (15). Wild-type- and ALS-associated mutant forms of SOD1 are capable of nitration activity; however, some evidence suggests that metal chelation mutants lacking zinc create profound increases in tyrosine nitration (14, 18). However, not all ALS-associated mutations exhibit increased levels of the aberrant activities, suggesting that their role may lie beyond the free radicals or ROS they discharge into the cellular milieu.

Another clue to the role that mutant SOD1 might play in ALS is exhibited by enzymes that gain functions other than peroxidase activity. Defects in protein folding, processing, and three-dimensional structure may contribute to the ALS phenotype. Displaced or ill-coordinated metal ions within an SOD1 monomer are a common theme in ALS-associated mutations. Disrupting the histidines that coordinate Zn²⁺ ion can alter enzyme function and its redox state (35). SOD1 mutations can impair the processing of the enzyme, which gives rise to the other possibilities outlined in Figure 7. Enzymes deficient in copper, zinc, or intra-monomer disulfides can lead to protein aggregation and have been associated with

FIG. 7. Several possible molecular mechanisms mediating mutant CuZnSOD cellular toxicity in familial ALS. There are many different and distinct mutations associated with this disease, which suggests that multiple mechanisms of toxicity are possible.

ALS. Similarly, defective CCS may create a comparable response. In this scenario, the mis-folded or metal ion-deficient monomers form insoluble protein inclusion bodies. These mis-folded proteins can be created by a plethora of SOD1 mutants. Most notable among these mutants are Cys 57 and 146; however, mutations in surrounding amino acids can have a similar outcome. Recently, whole exome sequencing has identified mutations at these codons (67).

Mutations that result in altered zinc coordination can also lead to mis-folded proteins and end up creating SOD1 aggregates. Likewise, mis-coordination of Cu^{+2} can also influence protein-folding activity, and lead to the formation of aggregates (45). In the case of copper, aggregates can be formed by dysfunction with CCS, or by mutating amino acids that are responsible for copper binding in SOD1. These immature forms of SOD1 can have far-reaching effects in cells. If CCS is dysfunctional in the mitochondria, mis-folded proteins can accumulate here, and create mitochondrial stress (13). ALS-associated mutations in SOD1 can alter the interaction between CCS and immature monomer (26, 53).

Disrupting the disulfide bridges of SOD1 is the most common mechanism leading to protein aggregation in ALS, and numerous studies have established alterations in disulfide formation as important in the pathology of ALS. Numerous ALS-associated SOD1 mutants exhibit altered biophysical properties that are traceable to disrupted disulfide linkages (25). Disulfides may also be responsible for the formation of SOD1 aggregates. Using cell free assays, Wang and colleagues demonstrated that intermolecular disulfides could form between SOD1 monomers (62). Here again, a role for CCS may exist in the pathology of ALS. CCS interacts with immature SOD1 monomers *via* disulfide bridges. If these cysteines are reduced, the two proteins cannot interact (8). SOD1 is also a target for post-translational modification by glutathionylation at phosphorylation. The addition of these modifications may disrupt the structure of SOD1, and lead to protein instability (65).

SOD1's Role in ALS Pathology

Elucidating a linkage between SOD1 and ALS has been a relatively straightforward process, while understanding the nature of this relationship has proved more difficult. Alterations of SOD1 may influence the development of ALS in several ways. Mis-folded and incomplete processed CuZn-SOD proteins may serve as cellular cues. The accumulation of unfolded proteins in aggregates initializes endoplasmic reticulum (ER) stress signaling pathways. Exacerbating the unfolded protein response hastens ALS progression (63). Others have suggested that chronic activation of ER stress by mis-folded SOD1 can possibly lead to cell death in ALS, and cite that mutations in proteins involved in stress signaling can also cause the disease (61).

SOD1 Mutations May Influence Redox Signaling in ALS

Another way in which altered SOD1 may be causal in the development of ALS is by disrupting redox signaling pathways. If we conceptualize superoxide as a signaling molecule rather than just a reactive species, we can construct a signal transduction pathway in which superoxide influences one electron signaling through compounds such as glutathione (Fig. 8). The conversion of superoxide to H_2O_2 by SOD1 cre-

FIG. 8. CuZnSOD resides at a critical junction between one-electron and two-electron signaling pathways that elicit different cellular response programs. One-electron-sensitive labile iron pools reside in proteins such as Fe/S cluster proteins, including ACO, “cytosolic aconitase” or IRP, and SDH, and in other non-heme iron-containing enzymes such as those in the JmjC and TET family. Two-electron signaling pathways mediated *via* SOD1’s product H_2O_2 include thioredoxin, glutaredoxin, and the peroxiredoxins along with their respective cofactors. Fe/S, iron-sulfur; ACO, aconitase; IRP, iron-response protein; SDH, succinate dehydrogenase.

ates new possibilities for signaling. Here, classic paradigms of cell stress such as peroxiredoxin and thioredoxin can be activated, and influenced, by the steady-state levels of reactive oxygen and exert an influence on a cell’s phenotype by altering gene expression (22). How might this influence ALS? Cells harboring a wild-type SOD1 maintain a balance of different reactive oxygen species that is consistent with fully functional signaling pathways. McCord and Fridovich aptly demonstrated that changes in SOD1 alter superoxide levels (36). Likewise, others have described the altered level of superoxide in cells harboring mutated SOD1 (72). We speculate that ALS-associated changes in SOD1 would upset a cell’s reactive oxygen species balance by altering the steady-state level of superoxide. In turn, this would alter the aforementioned pathways and serve as one avenue to create the phenotype of ALS. This scenario can be created by alterations in SOD1 expression, or the creation of dysfunctional enzyme complexes with incomplete or unique activities (33, 41). Furthermore, “gain-of-function” SOD1 mutants with identical dismutase activity may harbor altered peroxidase activity compared with wild-type counterparts. This would create another means to modify the redox status of the cellular milieu (68, 69). Both mechanisms would impact cellular function by manipulating cell signaling, and put SOD1 as a central player on a signal transduction stage.

Could perturbations in the flux of superoxide and H_2O_2 have a role in ALS? To date, the underpinnings of free radical flux on cell signaling are not yet fully defined and may serve as an avenue to pursue the role of SOD1 in the etiology of ALS. Studies related to hypoxia have shown that altering free

radical flux influences signal transduction pathways that are reliant on H_2O_2 in brains of developing animals (3). Likewise, the ER stress mechanism mentioned earlier may influence this signaling in a similar manner, inducing neuronal apoptosis (71). Studies aimed at investigating the effect that altered free radical flux in ALS has on paradigms of signal transduction may further support a linkage between SOD1 and this disease.

Conclusions

CuZnSOD plays a central role not only in detoxifying damaging superoxide in the cytosol and mitochondrial intermembrane space, but also by acting as a transistor to convert one electron signaling to two electron signaling. Too much or too little CuZnSOD activity can lead to aberrant cellular signaling and maintenance of homeostasis around a nonequilibrium steady state. In addition, mutant forms of CuZnSOD with potentially altered signaling properties have emerged as candidate disease genes in humans. This is particularly true in the case of familial ALS, but a deep understanding of the enigmatic connection between SOD1 and ALS remains obscure. The central question is: By what mechanism does SOD1's gain-of-function mutations influence the manifestation of the ALS phenotype? Fundamental discoveries suggest that H_2O_2 , superoxide, protein processing, and aberrant enzyme activities might be strings connecting SOD1 with ALS. Perhaps ALS could be a disease with a free radical pathology that is supported by an undercarriage of aberrant cell signaling.

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Address correspondence to:

Dr. Frederick E. Domann

Free Radical and Radiation Biology Program

Department of Radiation Oncology

The University of Iowa

B180 Medical Laboratories

Iowa City, IA 52242

E-mail: frederick-domann@uiowa.edu

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Abbreviations Used

ACO = aconitase
 AHR = aryl hydrocarbon receptor
 ALS = amyotrophic lateral sclerosis
 AP-1 = activator protein 1
 ARNT = aryl hydrocarbon receptor nuclear translocator
 C/EBP = CAATT enhancer binding proteins
 CCS = copper chaperone for SOD1
 CuZnSOD = copper zinc superoxide dismutase
 Cys = cysteine
 ECSOD = extracellular superoxide dismutase
 EGR-1 = early growth response 1
 ENCODE = encyclopedia of DNA elements
 Fe/S = iron-sulfur cluster
 H3K36me3 = histone H3 Lysine 36 tri-methyl
 H3K4me2 = histone H3 Lysine 4 di-methyl
 H3K4me3 = histone H3 Lysine 4 tri-methyl
 H3K9ac = histone H3 Lysine 9 acetylated
 His = histidine
 IRP = iron-response protein
 MnSOD = manganese superoxide dismutase
 NFkB = nuclear factor kappa B
 NRF2 = nuclear factor (erythroid-derived 2)-like 2
 ONOO = peroxynitrite
 SDH = succinate dehydrogenase
 SOD = superoxide dismutase
 SOD1 = superoxide dismutase 1
 SP-1 = specificity protein 1