

Superoxide Dismutase Type 1 and Redox Signaling

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The traditional view of Cu/Zn superoxide dismutase type 1 (SOD1) focuses on its role in managing reactive oxygen species (ROS) by converting superoxide radicals to peroxide as means of preventing oxidative damage to neurons and other cells (Deng et al., 1993). This naturally raised the specter of oxidative damage as a pathogenic mechanism in ALS, a view that continues to receive support (Barber et al., 2010). However, many mutant forms of SOD1 that produce ALS have significant normal enzymatic activity, which raises questions about the role of SOD1 activity in pathogenesis.

Although the abundance of SOD1 in many tissues argued for an important role in controlling reactive oxygen species, SOD1 knockout mice are viable and the phenotype is remarkably mild, with no evidence of motor neuron disease (Turner & Talbot, 2008). The SOD1 knockout did shorten lifespan of mice modestly, but knockouts of five other antioxidant enzymes had no effect on lifespan and overexpression of SOD1 did not extend lifespan (Perez et al., 2009). Moreover, expression of human mutant SOD1 in a mouse with normal SOD1 background still produces motor neuron disease, primarily affecting lower motor neurons in mouse with pathology very similar to human cases of ALS (Kato, 2008). Curiously, although mutant SOD1 is expressed widely in neuronal and nonneuronal tissues for both human cases of familial ALS and many mouse transgenic lines, the primary pathological consequence is motor neuron disease. Regardless, antioxidant therapeutic strategies have failed to significantly alter the course of the disease in humans.

Recent advances in our understanding of the complex biology of SOD1, oxygen and redox signaling pathways argue for a reconsideration of the cellular function of SOD1. Studies in

the last decade have revealed additional roles for SOD1, which may be underappreciated. Specifically, redox-dependent signal transduction may be responsible for signaling through some cytokine and growth factor receptors associated with lipid rafts or endoplasmic reticulum/endosomes (see Ch. 7), like interleukin-1 β (IL1) and tumor necrosis factor α (TNF), as well as platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and angiotensin II (angII) (Oakley et al., 2009). These redox-active endosomes appear to involve SOD1, NADPH oxidase, peroxiredoxins and chloride channels, as well as more familiar signaling elements like Rac1, NF- κ B and tyrosine kinase/phosphatases pathways (Fukai et al., 2011; Oakley et al., 2009).

Signaling through redox-dependent pathways requires endocytosis for activation, where the production of ROS can be compartmentalized effectively. SOD1 appears to be recruited to endosomal surfaces with redox-mediated receptors (Fukai et al., 2011), where it produces H₂O₂ that can activate downstream effectors like Rac1 (Ch. 21) and NF- κ B, or may inactivate protein tyrosine phosphatases (Ch. 26). Interestingly, SOD1 has been shown to bind Rac1 directly and to inhibit its activity (Harraz et al., 2008). Many of these pathways are shared with or involved in inflammatory signaling (Ch. 34).

Under normal circumstances, these redox-dependent pathways are limited and highly regulated. Less is known about changes in this aspect of SOD1 functionality with familial ALS-linked mutations, although some mutant SOD1s were found to have reduced binding to Rac1 (Harraz et al., 2008). Questions remain about how the 140+ different mutations can all produce the same disease, but recent studies begin to provide insights. Several groups have generated antibodies that recognize a conformation shared by most and perhaps all familial ALS-linked mutant SOD1 (Urushitani et al., 2007). Remarkably, one of these antibodies also recognizes

oxidized forms of wild type SOD1 as well as a conformation of wild-type SOD1 detectable in many cases of sporadic ALS, suggesting that it might recognize a conformation common to all pathogenic forms of SOD1 (Bosco et al., 2010). Such studies support the idea that SOD1 might have a role to play in both familial and sporadic ALS (Kabashi et al., 2007). Significantly, all pathogenic forms of SOD1 examined activated a MAP kinase pathway (see Ch. 25) and inhibited fast axonal transport (Bosco et al., 2010). A better understanding of the normal functions of SOD1 may thus explain the pathogenic gain of function associated with SOD1 in ALS.

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