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SOD1 in neurotoxicity and its controversial roles in *SOD1* mutation-negative ALS

Yuki Hayashi, Kengo Homma, Hidenori Ichijo*

Laboratory of Cell Signaling, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a serious neurodegenerative disorder that is characterized by the selective death of motor neurons. While the fundamental cause of the disorder is still unclear, the first identified risk gene, *Cu,Zn superoxide dismutase* (*SOD1*), has led to the proposal of several mechanisms that are relevant to its pathogenesis. These include excitotoxicity, oxidative stress, ER stress, mitochondrial dysfunction, axonal transport disruption, prion-like propagation, and non-cell autonomous toxicity of neuroglia. Recent evidence suggests that the toxicity of the misfolded wild-type SOD1 ($SOD1^{WT}$) is involved in the pathogenesis of sporadic cases. Yet to what extent SOD1 contributes to neurotoxicity in ALS cases generally is unknown. This review discusses the toxic mechanisms of mutant SOD1 ($SOD1^{mut}$) and misfolded $SOD1^{WT}$ in the context of ALS as well as the potential implication of these mechanisms in *SOD1* mutation-negative ALS.

Contents

* Corresponding author.
E-mail address: ichijo@mol.f.u-tokyo.ac.jp (H. Ichijo).

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is one of the most common neuromuscular diseases worldwide. Ever since the disease was named by neurobiologist and physician Jean-Martin Charcot in 1874, ALS has been a grave health threat due to its relentless progression (Oliveira and Pereira, 2009). Most ALS cases appear in mid-life and provoke a selective loss of upper and lower motor neurons, which eventually results in death by respiratory failure. However, only a few methods or ideas have been applied to combat ALS in the century since it was first described. Additionally, its etiologic study has been relatively slow. Only recently has a broader understanding of the cause of ALS begun to quickly emerge.

In 1993, the identification of the *SOD1* gene encoding Cu,Zn superoxide dismutase as a primary cause of ALS accelerated ALS research (Rosen et al., 1993). Now, more than 180 mutations have been associated with ALS and almost all of these mutations are inherited in an autosomal dominant manner (Abel et al., 2012; http://alsod.iop.kcl.ac.uk/). Approximately 10% of all cases are familial, of which *SOD1* is estimated to account for 20% (Fig. 1). Loss or gain of dismutase activity was initially assumed to be the mechanism of *SOD1* mutation toxicity. Regarding this point, an early study demonstrated that clinical severity did not correlate with SOD1 dismutase activity (Cleveland et al., 1995). Moreover, transgenic mice that overexpressed the ALS-linked SOD1 G93A mutant exhibited ALS-like phenotypes, while SOD1 deficient mice did not (Gurney et al., 1994; Reaume et al., 1996). Together, these reports support a gain of toxic function mechanism of $SOD1^{mut}$.

In recent years, ALS research has experienced a paradigm shift. The identification of mutations in a pair of RNA/DNA binding proteins, *TAR DNA-binding protein 43* (*TDP-43*) and *fused in sarcoma* (*FUS*), implicated RNA toxicity in ALS, because their principal physiological functions include RNA processing, such as splicing, transport, and translation (Sreedharan et al., 2008; Kwiatkowski et al., 2009; Vance et al., 2009). Furthermore, a newly identified hexanucleotide repeat expansion in *chromosome 9 open reading frame 72* (*C9ORF72*) displaced *SOD1* as the most frequent causative gene of ALS because *C9ORF72* accounts for approximately 38% of familial ALS (FALS) cases (DeJesus-Hernandez et al., 2011; Renton et al., 2011).

Although the broad understanding of ALS has been significantly transformed by these new insights regarding the genetics of ALS, intensive research of SOD1 for 20 years has significantly contributed to the understanding of ALS. Here, we discuss several mechanisms by which SOD1 exerts its toxicity and the possibility of its implications in SALS and *SOD1* mutation-negative FALS.

2. Molecular mechanism of SOD1 toxicity in ALS pathogenesis

Several groups have reported the mutation-induced conformational changes of SOD1 as the cause of SOD1 toxicity. A conformation-specific antibody, named mutant SOD1-specific antibody clone 785 (MS785), revealed that most SOD1 mutants share a common conformational property. The $SOD1^{mut}$, but not the $SOD1^{WT}$, contains an exposed N-terminal short region, which provokes endoplasmic reticulum (ER) stress by targeting an ER resident protein, Derlin-1 (Fujisawa et al., 2012). Another study reported that $SOD1^{mut}$ has an increased propensity to expose its hydrophobic surfaces when compared to $SOD1^{WT}$ and that the varying hydrophobicity across $SOD1^{mut}$ correlates with aggregation propensity (Münch and Bertolotti, 2010). These reports indicate that suppressing the conformational alterations and/or masking the exposed surfaces of $SOD1^{mut}$ would be beneficial to attenuate toxicity by soluble or aggregated mutant SOD1 species. Activity such as this in intracellular molecular milieu can be attributed to the chaperon system, whose disruption results in cytotoxicity.

In fact, several chaperons have been implicated in the pathogenesis of ALS, including protein disulfide isomerase (PDI). This chaperone catalyzes the thiol-disulfide exchange, thereby facilitating proper disulfide bond formation. Although its role in the pathogenesis of ALS is controversial, the role of PDI in early disease stage is assumed to be protective against aggregate formation (Jaronen et al., 2014). This is supported by a report in which the pharmacological inhibition of PDI catalytic activity resulted in an increased level of SOD1 aggregates (Atkin et al., 2006). Nevertheless, PDI becomes inactivated by S-nitrosylation with disease progression, which leads to an increase in SOD1 aggregation (Chen et al., 2013; Jeon et al., 2014). Another

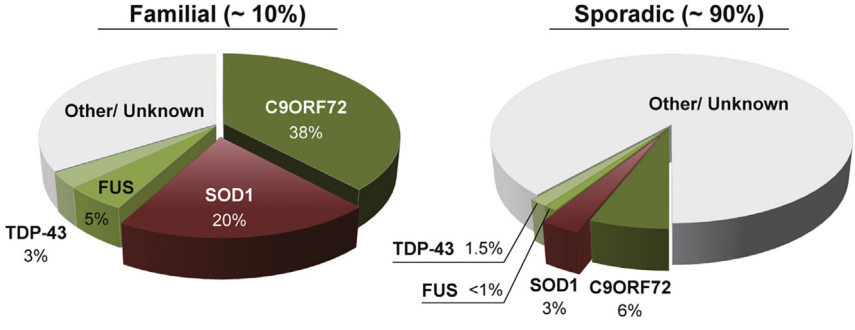

Fig. 1. Major responsible genes for familial and sporadic ALS. As the second most frequent genetic cause for ALS, *SOD1* accounts for approximately 20% of familial and 3% of sporadic cases. The frequency rates of each genetic mutation are described on the authorities of Andersen (2006), Majounie et al. (2012), and Lattante et al. (2013).

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