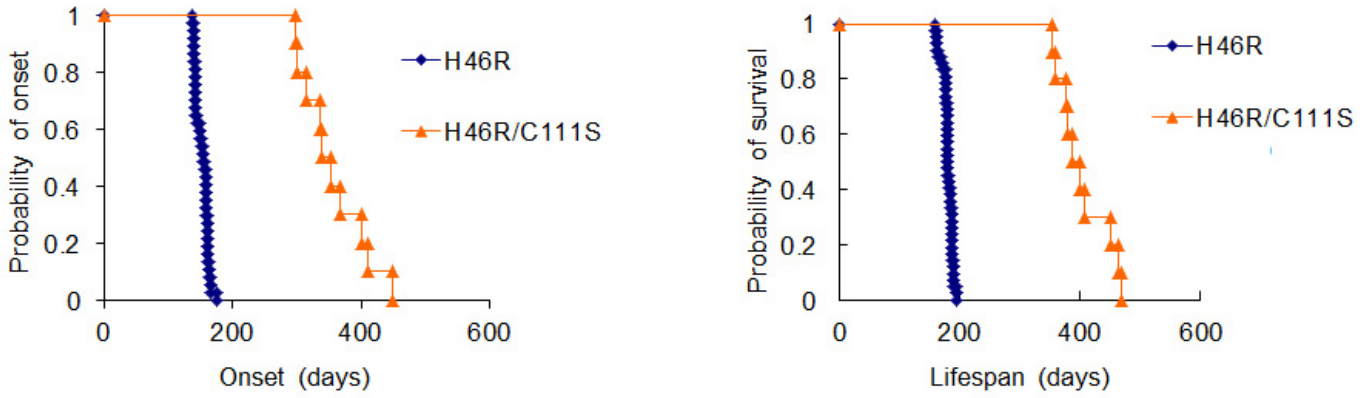
A cysteine residue is a key commander of SOD1-related neuronal toxicity in ALS

Amyotrophic lateral sclerosis (ALS; a.k.a. Lou Gehrig's disease) is a life-threatening disease of motor neurons that gradually affects muscle strength of the whole body. The disease occurs familially in some cases, and 25 to 30% of the familial cases are caused by mutations of the Cu, Zn-superoxide dismutase (SOD1) gene.

In the pathogenic mechanism of ALS caused by the SOD1 gene mutation, mutant SOD1 protein produced from the gene is supposed to take an abnormal structure, which is different from that of wild-type SOD1 protein (i.e., misfolding), and thereby forms aggregates to generate abnormal deposits that exerts toxicity in neuronal cells.



We previously proved using cultured cells, that the 111th amino acid cysteine residue (Cys111) is susceptible to oxidative modification in mutant SOD1 compared to wild-type SOD1, which causes misfolding of the mutant protein to potentiate its toxicity in neuronal cells (Watanabe S et al. Free Radic Biol Med 42, 1534-1542, 2007, Kishigami et al. Free Radic Biol Med 48, 945-952, 2010). Therefore, we examined whether Cys111 of mutant SOD1 is critical for toxicity of the protein to develop ALS phenotype using model mice of the disease in this study.

First, we generated mice expressing human SOD1 where ALS-linked mutation is introduced with substitution of histidine to arginine at 46 (H46R SOD1 mice). The H46R SOD1 mice start to show motor symptoms at about 5 months. Then the mice show progressing paralysis to end their life at the age of about 6 months. Next we generated mice expressing SOD1 where Cys111 was replaced with a serine residue in addition to H46R mutation (H46R/C111S SOD1 mice). We found that it took about 12 months for the H46R/C111S SOD1 mice to develop motor symptoms. Furthermore, their survival was also extended up to 14 months of age as shown in the figure. The oxidation of SOD1 Cys111, misfolding and aggregation of SOD1 was detected, and the number of motor neurons was decreased in the spinal cord of H46R SOD1 mice at the symptomatic stage. On the other hand, at the same age of H46R/C111S SOD1 mice, no misfolding or aggregation of SOD1

was seen, reflecting that motor neurons were preserved in the spinal cord. Our study clearly showed for the first time that Cys111 of SOD1 plays an important role for the pathogenesis of ALS by mutant SOD1, and inhibition of the oxidation of Cys111 can be a promising strategy to develop a novel therapeutics of the disease.

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