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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a selective loss of motor neurons. Mutations in superoxide dismutase 1 (SOD1) cause motor neuron death in familial ALS (FALS), suggesting that mutant SOD1 has a toxic effect on motor neurons. However, the question of how the toxic function is gained has not been answered. In this study, we have shown that the mutant SOD1s linked to FALS, but not wild-type SOD1, aggregated in association with the endoplasmic reticulum (ER) and induced ER stress in the cDNA-transfected COS7 cells. These cells showed an aberrant intracellular localization of mitochondria and microtubules, which might lead to a functional disturbance of the cells. Motor neurons of the spinal cord in transgenic mice with a FALS-linked mutant SOD1 also showed a marked increase of GRP78/BiP, an ER-resident chaperone, just before the onset of motor symptoms. These data suggest that ER stress is involved in the pathogenesis of FALS with an SOD1 mutation.

Key word: superoxide dismutase 1, amyotrophic lateral sclerosis, endoplasmic reticulum stress