

P005 COMMD1 as a novel regulator of SOD1 activity and aggregation in amyotrophic lateral sclerosis
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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by selective degradation of motor neurons in the spinal cord and brain stem. Approximately 20% of the familial ALS cases is caused by dominant mutations in the Cu/Zn superoxide dismutase (*SOD1*) gene, which is involved in the detoxification of free radicals. Mutant *SOD1* proteins are prone to form aggregates in the spinal cord. A role of redox-active metals in the etiology and progression of ALS has been proposed, however, the molecular mechanisms of *SOD1* aggregation and the role of metals in this process are not well understood.

Recently, we identified a previously unknown interaction between *SOD1* and *COMMD1*. *COMMD1* was identified as the gene mutated in copper toxicosis in Bedlington terriers, a copper-overload disorder. The interaction was strictly copper-dependent and required the presence of CCS, the copper chaperone for *SOD1*. Overexpression of *COMMD1* markedly reduced the formation of active *SOD1* dimers. Interestingly, *COMMD1* displayed a more pronounced binding to a series of fALS-associated *SOD1* mutants (G93A, G85R, G37R, A4V and I113T) compared to WT *SOD1*. In the presence of excess copper, *COMMD1* profoundly promoted the aggregation of several mutants. Together, these data suggest that *COMMD1* regulates *SOD1* activity under normal conditions and represents a general promoter of mutant *SOD1* aggregation in ALS. This work possibly offers novel avenues to ameliorate the severe neurodegeneration associated with this disease.