

## Adaptation to G93A superoxide dismutase 1 in a motor neuron cell line model of amyotrophic lateral sclerosis: The role of glutathione

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Motor neuron degeneration in amyotrophic lateral sclerosis involves oxidative damage. Glutathione (GSH) is critical as an antioxidant and a redox modulator. We used a motor neuronal cell line (NSC-34) to investigate whether wild-type and familial amyotrophic lateral sclerosis-linked G93A mutant Cu,Zn superoxide dismutase (wt/G93ASOD1) modified the GSH pool and glutamate cysteine ligase (GCL), the rate-limiting enzyme for GSH synthesis. We studied the effect of various G93ASOD1 levels and exposure times. Mutant Cu,Zn superoxide dismutase induced an adaptive process involving the upregulation of GSH synthesis, even at very low expression levels. However, cells with a high level of G93ASOD1 cultured for 10 weeks showed GSH depletion and a decrease in expression of the modulatory subunit of GCL. These cells also had lower levels of GSH and GCL activity was not induced after treatment with the pro-oxidant *tert*-butylhydroquinone. Cells with a low level of G93ASOD1 maintained higher GSH levels and GCL activity, showing that the exposure time and the level of the mutant protein modulate GSH synthesis. We conclude that failure of the regulation of the GSH pathway caused by G93ASOD1 may contribute to motor neuron vulnerability and we identify this pathway as a target for therapeutic intervention.

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