# Misfolded SOD1 Toxicity in Amyotrophic Lateral Sclerosis

https://neurodegenerationresearch.eu/survey/misfolded-sod1-toxicity-in-amyotrophic-lateral-sclerosis/

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**Contact information of fellow**
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Misfolded SOD1 Toxicity in Amyotrophic Lateral Sclerosis

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**Research Abstract**
Amyotrophic lateral sclerosis (ALS) is a late-onset fatal neurodegenerative disease characterized by the loss of upper and lower motor neurons. The reason for the degeneration of motor neurons in ALS is still unknown. Mitochondria have been implicated as a possible target

for toxicity by several studies reporting a range of dysfunctions and the toxic binding of misfolded SOD1 to mitochondrial targets. However, the mechanism by which mutant SOD1 associates with mitochondria specifically from affected tissues is still unknown. Preliminary data show that a cytosolic factor in unaffected tissues is responsible for preventing the accumulation of misfolded SOD1. This factor was identified as the macrophage migration inhibitory factor (MIF). MIF inhibits the association of mutant SOD1 with mitochondria and accumulation of misfolded SOD1. The hypothesis of this proposal is that MIF is reduced in abundance or inactive as a chaperone within the CNS, leading to increased accumulation of misfolded SOD1 and neurodegeneration. This proposal aims to unambiguously determine how toxicity is caused by misfolded SOD1 accumulation and finally an attempt to rescue these toxic effects in models of ALS will be done. The specific aims are (1) Determination of the tissue specificity of misfolded SOD1 accumulation and mitochondrial association and characterization of MIF activity as a chaperone for misfolded SOD1; (2) Determination of how mitochondrial association of misfolded SOD1 affects mitochondrial function in the spinal cord of mutant SOD1 animals; and (3) Determination of whether increased synthesis or depletion of MIF affects misfolded mutant SOD1 accumulation and pathogenesis in mice. The proposed study has the potential to yield important information about misfolded SOD1 toxicity mechanisms. Moreover, the characterization of MIF as a novel chaperone for misfolded SOD1 opens new avenues for the development of ALS therapies.

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