MIF inhibits the formation of misfolded SOD1 amyloid aggregates: Implications for familial ALS

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Abstract

Mutations in superoxide dismutase (SOD1) cause amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease caused by the progressive loss of motor neurons in the brain and spinal cord. It has been suggested that toxicity of mutant SOD1 results from its misfolding, however, it is yet unclear why misfolded SOD1 accumulates specifically within motor neurons. We recently demonstrated that macrophage migration inhibitory factor (MIF)—a multifunctional protein with cytokine/chemokine activity and cytotoxic chaperone-like properties—inhibits the accumulation of misfolded SOD1. Here, we show that MIF inhibits mutant SOD1 nuclear clearance when overexpressed in motor neuron-like NSC-34 cells. In addition, MIF alters the typical SOD1 aggregation pathway in vitro, and, instead, promotes the formation of disordered aggregates, as measured by Thioflavin T (ThT) assay and transmission electron microscopy (TEM) imaging. Moreover, we report that MIF reduces the toxicity of misfolded SOD1 by directly interacting with it, and that the chaperone function and protective effect of MIF in neuronal cultures do not require its intrinsic catalytic activities. Importantly, we report that the locked-trimeric MIF-N105C mutant, which inhibits strongly impaired CD47-mediated cytokine functions, has strong chaperone activity, discretizing, for the first time, these two cellular functions. Altogether, our study implicates MIF as a potential therapeutic candidate in the treatment of ALS.

Results

1. MIF inhibits misfolded SOD1 nuclear export in NSC-34 cells

2. Recombinant MIF specifically suppresses mutant SOD1 amyloid fibril formation in a dose-dependent manner

3. Recombinant MIF alters the morphology of SOD1G85A and SOD1G85A

4. The catalytic activities of MIF and its normal oligomeric states are not necessary for its chaperone activity and its protective effect against mutant SOD1 toxicity in NSC-34 cells

5. The locked-trimeric mutant MIFN105C suppresses amyloid fibril formation of the mutant SOD1

6. MIF inhibition of mutant SOD1 misfolding is independent of its enzymatic activities or its normal oligomeric structure

Conclusion

Our findings suggest that MIF directly interacts with misfolded SOD1 to inhibit its toxic amyloid aggregation by inducing the formation of disordered aggregates with lower toxicity. These findings provide new insights regarding the potential therapeutic role of MIF in suppressing the selective accumulation of misfolded SOD1 in ALS.

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