Mechanisms of SOD1 Aggregation in ALS

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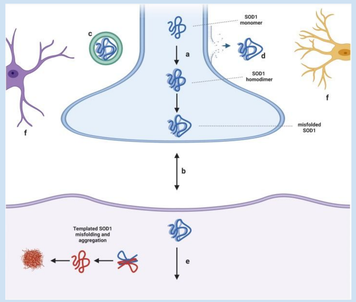
INTRODUCTION

- Amyotrophic lateral sclerosis (ALS) is a disease that causes progressive degeneration of motor neurons, limiting physical abilities and shortens life expectancy
- Believed to follow *prion hypothesis* that posits that the propagation of misfolded SOD1 proteins and SOD1 aggregates is key cause of ALS
- SOD1 gene converts superoxide radicals into hydrogen peroxide and oxygen to reduce oxidative stress in motor neurons
- Protein aggregation is hallmark of ALS, where clumps of mutant or misfolded SOD1 accumulate in motor neurons and disrupt their ability to transmit signals from CNS to muscles
- Tofersen is currently only FDA-approved treatment for SOD1-ALS.
- This study conducts a literature-based content analysis to synthesize research on SOD1 aggregation in ALS, its toxicity, cellular propagation, and therapeutic implications.

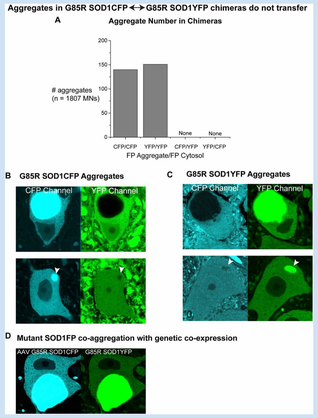
DATA AND FINDINGS

Figure 1



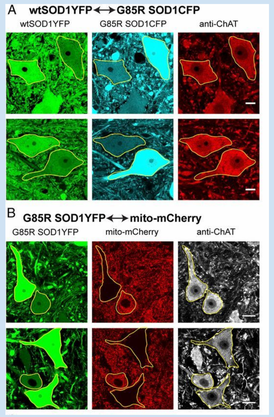
Note. (a) Mutant SOD1 misfolds and forms aggregates, which spread between neurons through anterograde and retrograde synaptic transfer (b), exosome-mediated transfer ©, or macropinocytosis after leaving dead cells (d). Misfolded SOD1 can trigger wild type SOD1 to misfold and aggregate. Astrocytes (yellow), a type of glial cells that regulate axonal growth and support, and microglia (purple), a type of glial cells that regulate the maintenance of neuron network, can release SOD1 aggregates (f). Copyright 2023 by Arnold et al.

Figure 2



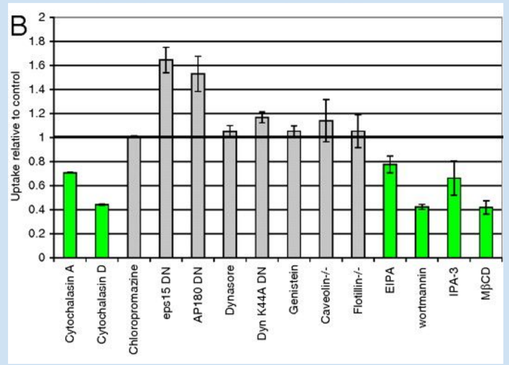
Note. 3 G85R SOD1CFP↔G85R SOD1YFP chimeric mice were experimented on to assess intercellular aggregate transfer in motor neurons. Using fluorescence imaging, G85R SOD1CFP aggregates were only found in the CFP channels, and G85R SOD1YFP aggregates were only found in the YFP channels of cells. The fluorescence of both G85R SOD1 proteins indicate aggregate presence in both of them. Copyright 2017 by Thomas et al.

Figure 3



Note. The transfer of SOD1 wild type gene strain wtSOD1YFP is shown to be possible as seen with G8fR SOD1 CFP-expressing cells displaying YFP fluorescence indicative of wtSOD1YFP being transferred. No symptoms or detectable cell loss are produced by wtSOD1YFP in the parent strain. Copyright 2017 by Thomas et al.

Figure 4



Note. fALS-causing SOD1 mutant H46R was treated with 5-N-ethyl-N-isopropyl-amiloride (EIPA), wortmannin (a phosphoinositide 3-kinase inhibitor), and a *P21-activated kinase inhibitor* (IPA-3) significantly reduced the uptake of aggregates. Additionally, the cholesterol-depleting agent methyl-β-cyclodextrin (MβCD), which disrupts lipid rafts, caused a significant decrease in aggregate entry. Highlighted in green are the conditions that inhibit macropinocytosis. Copyright 2011 by Münch et al.

IMPLICATIONS AND NEXT STEPS

- Inhibiting macropinocytosis reduces SOD1 uptake, suggesting a potential therapeutic strategy to prevent motor neuron damage.
- Role of non-neuronal cells like astrocytes and microglia in ALS pathology expand the scope of future therapeutic targets
- Next steps
  - Further study on soluble SOD1 aggregates, their structure, toxicity, and role in disease progression
  - Investigate transport and compartmentalization of mutant SOD1 in motor neurons
  - Identify molecular interactions and sites where aggregates initiate toxicity

RESEARCH METHODOLOGIES

- Content analysis inquiry approach, meaning and relationship of words, texts, and concepts of existing research journals analyzed to form inferences and piece together messages within the texts
  - Selected journal findings discussing mutant SOD1 neurotoxicity contributors, purpose of protein aggregation in ALS, aggregation propagation mechanisms
  - Qualitative and quantitative data collection from existing research journal findings
    - Diagrams illustrating potential SOD1 aggregation propagation mechanisms
    - Numerical graphs regarding spread of misfolded SOD1 and SOD1 aggregates
  - Data sources
    - Peer-reviewed journals: PubMed, ScienceDirect, Frontiers, PNAS, Nature, etc.
    - Biological pathway and protein-protein interaction databases: STRING, KEGG PATHWAY

CONCLUSIONS AND ANALYSIS

- Mutant SOD1 aggregates spread in a prion-like manner, inducing misfolding of native SOD1 in recipient cells
- SOD1 aggregates propagate between neurons via synaptic transport (anterograde/retrograde), exosomes, exocytosis, leaving dying cell for release, and macropinocytosis and endocytosis for uptake
- Astrocytes and microglia uptake and release SOD1 aggregates
- Chimeric mice expressing different SOD1 mutations show that only soluble SOD1 species, not insoluble aggregates, are transferred between motor neurons
- The transfer of non-toxic wtSOD1YFP to mutant-expressing cells demonstrates that SOD1 propagation does not rely on cell death or toxicity
- Inhibiting macropinocytosis with drugs like EIPA, wortmannin, and IPA-3 reduces SOD1 uptake, confirming it as a therapeutic target to block aggregate entry

ACKNOWLEDGEMENTS / REFERENCES

***Special thanks to my AAR teacher Mr. Lupoli for helping make this project possible.

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