SARM1 Deletion Protects Axons in a Model of Inflammatory Demyelination
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Background: Axonal degeneration causes disease progression and accumulation of disability in multiple sclerosis (MS) and other neurodegenerative disorders. SARM1 is the central driver of an evolutionarily conserved program of axonal degeneration triggered by inflammatory, mechanical, metabolic, or chemical insults to the axon. SARM1 contains an intrinsic NADase enzymatic activity essential for its pro-degenerative functions, making it a compelling therapeutic target to treat neurodegeneration characterized by axonopathy in MS. We have previously shown that SARM1-dependent axonal degeneration in traumatic nerve injuries can be assessed by measuring plasma levels of neurofilament light chain (NF-L), an axonal cytoskeletal protein released when axons degenerate and a well-established clinical biomarker of disability in MS.

Objectives: Assess axonal protection and therapeutic potential of SARM1 inhibition in inflammatory demyelination.

Methods: SARM1−/− and WT C57BL/6J mice, were subjected to experimental autoimmune encephalomyelitis (EAE) using MOG35-55 peptide. Disease scores were assessed daily, and plasma NF-L levels were measured at various timepoints to assess axonal injury using the SIMOA platform. Spinal cord samples were processed for histological analysis of axonal structure and myelination.

Results: We determined plasma NF-L changes in EAE, a model of inflammatory demyelination characterized by axonal loss. In WT mice plasma NF-L began to rise concomitantly with onset of clinical symptoms, increased ~ 500% by peak of disease, and remained elevated for at least a week before beginning to decline. SARM1 genetic deletion reduced this increase in plasma NF-L by 76% at peak and 85% a week after peak disease. Reduction of NF-L increase was gene-dosage dependent. The peak of clinical symptoms was indistinguishable between WT, SARM1+/−, and SARM1−/− mice, demonstrating that the inflammatory response was not affected by SARM1 genetic deletion in this model where disability is primarily driven by inflammation. Correlates between plasma NF-L and axonal damage are being established by histological analysis.

Conclusions: SARM1 genetic deletion strongly protects axons in an inflammatory demyelinating environment in the CNS and supports the potential of SARM1 inhibition as an axonal protective therapy in MS. Disarm is developing small-molecule SARM1 inhibitors for central axonopathies, including multiple sclerosis and for a number of peripheral and ocular axonopathies.

1. SARM1 Drives Rapid NAD Loss Leading to a Bioenergetic Crisis and Axonal Degeneration

2. SARM1 - The Central Driver of Axonal Degeneration in Neurological Diseases

3. SARM1 Loss of Function Robustly Mitigates Rise in Plasma NF-L in a Gene Dosage-Dependent Manner in EAE

4. SARM1 KO, SARM1 HET, and WT Have Similar Disease Time Course in EAE

5. SARM1 KO Reduces Demyelination in EAE

Conclusions

- Plasma NF-L increases dramatically in EAE in both mouse and rat
- SARM1 genetic deletion prevents increase in plasma NF-L likely by protecting axons from inflammatory milieu
- Reduction of NF-L increase was gene-dosage dependent
- Disease onset, peak clinical scores, and disease time course were not affected in SARM1 heterozygous and SARM1 KO mice, suggesting that SARM1 genetic deletion does not interfere with early inflammation-driven processes
- SARM1 genetic deletion prevents secondary demyelination by protecting axons
- SARM1 inhibition represents a novel therapeutic approach to prevent axonal degeneration in MS and other CNS axonopathies