SARM1 Loss of Function Prevents Degeneration of Peripheral and Central Axons

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OBJECTIVE
Degeneration of axons causes disability and progression in chronic and acute diseases of the central, ocular, and peripheral nervous systems such as multiple sclerosis, ALS, glaucoma, and peripheral neuropathies. Although substantial evidence indicates that these disorders are primarily the result of damage to axons, there are currently no therapies to prevent axonal degeneration.

BACKGROUND
SARM1 is the central mediator of a cell-autonomous program of axonal degeneration and loss of function. A variety of genetic, immune, metabolic insults activate SARM1’s enzymatic mechanism that directly leads to dismantling of axons. SARM1 is an attractive target for a novel class of therapeutics for neurological disorders characterized by axonopathy. Disarm is developing two small molecule inhibitors of SARM1, one for central axonopathies, including multiple sclerosis, and one for peripheral axonopathies such as chemotherapy induced peripheral neuropathy.

DESIGN/METHODS
To assess in vivo PK/PD of therapeutic candidates, we established translational models of CNS axonopathies in optic nerve crush, experimental acute encephalomyelitis (EAE), and cuprizone demyelination, and monitored SARM1-dependent biomarkers in wild type and SARM1-f. mutants.

RESULTS
We discovered that cADPR is a proximal biomarker of SARM1 enzymatic activity and also established that plasma neurofilament light chain (NF-L) is a biomarker of SARM1-dependent axonal degeneration. SARM1 genetic deletion prevented cADPR and plasma NF-L increases in an optic nerve crush model of CNS axonal injury. We are evaluating these two biomarkers, together with histological readouts, to assess the ability of SARM1 deletion to protect chronically demyelinated axons in cuprizone and EAE models.

CONCLUSIONS
SARM1 loss of function is a powerful mechanism of axonal protection in CNS axonopathies. Serum NF-L is increasingly being used as a clinical biomarker of neurodegeneration to measure disease progression and efficacy of disease-modifying therapies. cADPR and serum NF-L are SARM1-dependent biomarkers of axonal degeneration useful to monitor efficacy of SARM1 small molecule inhibitors.

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

2. SARM1 Drives Rapid NAD+ Loss Leading to Axonal Dismantling

3. SARM1 Loss of Function Protects Axotomy and Chemical Injury Models in vitro

4. cADPR Generates cADPR in Mouse DRG Neurons After Axotomy

5. NF-L is a Biomarker of Axonal Degeneration in vitro

6. cADPR and NF-L Increase after Peripheral and Central Nerve Injury in vivo

7. cADPR and NF-L Increase after Peripheral and Central Nerve Injury in vivo

cADPR is a proximal biomarker of SARM1 activity. NF-L is a distal biomarker of axonal degeneration.

8. cADPR and NF-L Increases after Axonal Injury are SARM1-Dependent

cADPR changes in SARM1 Heterozygous and KO mutants show gene dosage effect.

9. Evaluation of Axonal Degeneration in Demyelinating Models

Conclusions
- SARM1 genetic deletion protects axons in vitro and in vivo
- cADPR is a proximal biomarker of SARM1 enzymatic activity in vitro and in vivo
- NF-L, a prognostic biomarker of neurodegeneration increasingly used in the clinic, is released in blood following CNS, ocular, and PNS axonal degeneration in a SARM1-dependent manner.
- Disarm is developing small-molecule SARM1 inhibitors as potentially disease-modifying therapeutics for patients with central and peripheral nervous system diseases such as multiple sclerosis and CIPN.