cADPR and NF-L are SARM1-Dependent Biomarkers of Axonal Structure and Function that Enable Therapeutic Discovery and Clinical Translation

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Axonal degeneration is an early and ongoing event that causes disability and disease progression in many neurodegenerative disorders of the central, peripheral, and oculomotor nervous systems, including multiple sclerosis, ALS, peripheral neuropathies, and glaucoma. SARM1 is the central driver of an evolutionarily conserved program of axonal degeneration downstream of inflammatory, metabolic, toxic, 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.

Characterization of SARM1 NADase activity in an in vitro biochemical assay showed that the main product of NAD turnover is adenosine diphosphate ribose (ADPR). Here we show that, unexpectedly, in injured neurons the main product of SARM1 NADase activity is the cyclic form of ADPR (cADPR).

We demonstrated, in vitro and in vivo, that cADPR is present at low levels in intact WT neurons and increases in response to axonal injury with a time course that precedes axonal fragmentation. We also established that neurofilament light chain (NF-L), an axonal-specific cytoskeletal protein released when axons degenerate and an emerging clinical biomarker of axonal degeneration in many neurodegenerative disorders, is a blood biomarker of axonal damage in vivo in a PNS model of sciatic nerve axonotmesis (SNA) and a CNS model of optic nerve crush (ONC).

In SNA and ONC models, SARM1/− and SARM1/− mutant mice exhibited reductions in nerve cADPR and blood NF-L levels as compared to wild-type mice that were consistent with a SARM1 gene-dosage effect. SARM1-dependent cADPR levels correlated with blood NF-L levels in vivo in both axonal injury models. In addition, we have demonstrated SARM1-dependent gene-dosage effects on blood NF-L levels and preservation of axonal function as measured by sensory nerve conduction velocities in a paclitaxel model of chemotherapy-induced peripheral neuropathy. Altogether, these results indicate that cADPR is a proximal biomarker of SARM1 activity that can be used in conjunction with NF-L, a clinically accessible downstream biomarker of axonal degeneration, to assess SARM1-dependent axonal degenerative responses. The availability of SARM1-dependent biomarkers of axonal degeneration enables rapid translation of SARM1 inhibitor therapeutics from discovery to the clinic.

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

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

3. SARM1 NADase Generates ADPR in vitro

4. SARM1 NADase Generates cADPR in Mouse DRG Neurons After Axotomy

5. cADPR Production Precedes Axonal Fragmentation After Axonal Injury

6. cADPR is the Main Metabolite of NAD⁺ Turnover After Axonal Injury in vivo

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

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

9. SARM1 Gene-Dosage Effect on Plasma NF-L, Reflects Protection of Axonal Function in vivo in a Paclitaxel Model of CIPN

Conclusions
- SARM1 NADase generates cADPR in neurons 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
- SARM1 shows gene-dosage effects on cADPR and NF-L in CNS and PNS injuries
- SARM1 gene-dosage effect on biomarkers is indicative of SARM1 effects on axonal structure and function in a model of CIPN in vivo
- 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