disarm THERAPEUTICS

Development of SARM1 Inhibitors to Treat Peripheral Neuropathies

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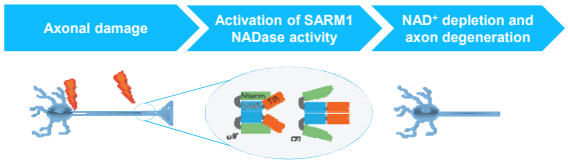
A variety of environmental and genetic insults to peripheral nerves leads to acute injury or chronic disease, examples of which are chemotherapy-induced peripheral neuropathies (CIPN), diabetic peripheral neuropathy (DPN), and chronic genetic disorders such as Charcot-Marie Tooth. Despite ample evidence for axonal degeneration as the driver of disease progression, there are no therapies that specifically target axonal degeneration.

SARM1 has been identified as the central mediator of a cell-autonomous program of axonal degeneration and loss of function. In animal models of CIPN and DPN, SARM1 genetic deletion has shown robust axonal protection and preservation of neural function, thus confirming that SARM1 is an attractive target for development of a novel class of therapeutics for these disorders. Disarm is developing inhibitors of SARM1 to reproduce the SARM1 -/- axonal protective phenotype.

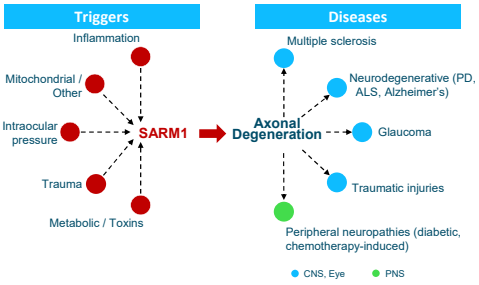
Neurofilament light chain (NF-L) is an axonal-specific cytoskeletal protein that is released as axons degenerate. It is increasingly being used as a clinical blood biomarker of central and peripheral neurodegeneration to measure disease progression and disease-modifying therapy effectiveness. We determined that NF-L is released after traumatic and chemically-induced axonal injuries in vitro and in vivo, and its release is SARM1-dependent.

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



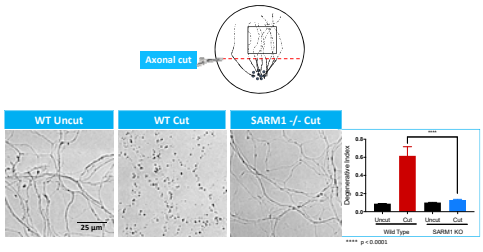
- Multiple acute and chronic triggers
- Upon activation, SARM1 TIR domains dimerize that leads to rapid depletion of NAD⁺
- NAD⁺ depletion leads to a precipitous bioenergetic crisis and resulting AxD

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



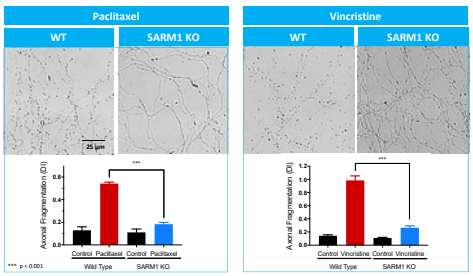
3. SARM1 Deletion Protects in Axotomy Model in vitro

Axonal fragmentation assay in primary mouse DRG neurons

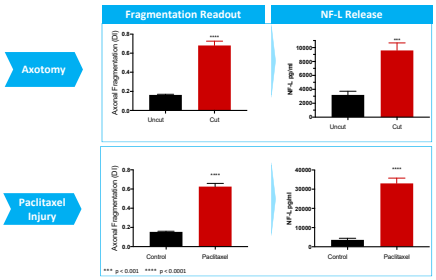


4. SARM1 Deletion Protects in CIPN Models in vitro

Paclitaxel and vincristine cause a SARM1-dependent axonal injury in primary mouse DRG neurons

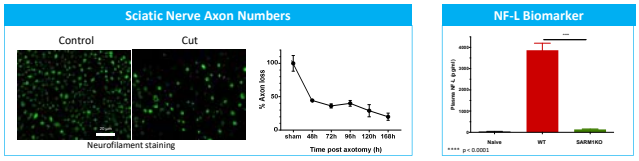


5. Axonal Injury Causes NF-L Release in vitro



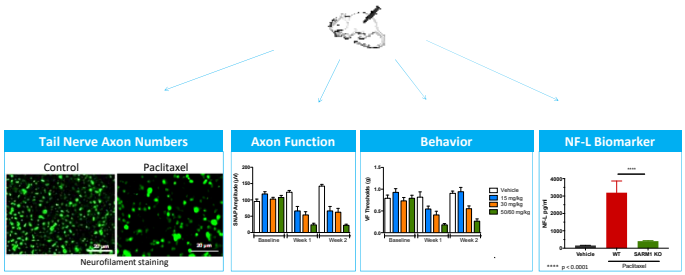
6. SARM1 Deletion Prevents Increase of Plasma NF-L after Axotomy in vivo

Sciatic nerve transection model in mice



7. SARM1 Deletion Prevents Increase of Plasma NF-L in CIPN Model

Paclitaxel-induced peripheral neuropathy in mice



Conclusions

- SARM1 genetic deletion protects axons from traumatic and chemical nerve injuries
- In vitro and in vivo release of NF-L, an increasingly used clinical biomarker of axonal degeneration, is SARM1-dependent
- Disarm is developing SARM1 inhibitors to treat peripheral neuropathies and CNS axonopathies