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Artificial Intelligence
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ABSTRACT

TITLE: SARM1 modulation by HDAC6 inhibition as a neuroprotective strategy in chemotherapy-induced peripheral neuropathy

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TOPICS: Cellular and molecular neuroscience

OBJECTIVES: Chemotherapy-induced peripheral neuropathy (CIPN), affecting up to 70% of cancer patients, is a major dose-limiting toxicity with few treatments available. SARM1, a pro-degenerative enzyme driving axonal loss, is a promising therapeutic target. We investigated how Histone Deacetylase 6 (HDAC6) inhibition, a regulator of microtubule stability, affects SARM1 expression, acetylation, and activity in sensory neurons exposed to Bortezomib, Oxaliplatin, Paclitaxel, and Vincristine.

MATERIALS: Neurotoxicity *in vitro* experiments were performed using cultures of adult mice dorsal root ganglia sensory neurons, an ideal CIPN model due to their direct exposure to chemotherapeutic agents.
DRGs were extracted, processed and ultimately treated.
The treated neurons were then used to perform:

- Viability and neurite elongation analysis
- Immunoblotting anti NMNAT2, SARM1 and acetylated tubulin
- Immunoprecipitation to evaluate SARM1 acetylation and its NADase activity
- Immunofluorescence to evaluate NMNAT2 and SARM1 localization

METHOD: Adult mouse primary sensory neurons were cultured *in vitro* and treated with HDAC6 inhibitors (Ricolinostat, SW-100, Tubastatin A), alone or in combination with chemotherapeutic agents (Bortezomib, Oxaliplatin, Paclitaxel, Vincristine).
After treatment, neuronal viability and neurite length were measured. Western blotting assessed NMNAT2 and SARM1 expression, immunoprecipitation evaluated SARM1 acetylation, NAD^+/NADH quantification assays measured SARM1 activity, and immunofluorescence analyzed SARM1 and NMNAT2 localization.

RESULTS: Ricolinostat demonstrated to have the most neuroprotective effects against Bortezomib and Paclitaxel, whilst Tubastatin had the most promising results against Oxaliplatin. No HDAC6i showed to be neuroprotective against Vincristine. Bortezomib, Oxaliplatin and Paclitaxel reduced NMNAT2 levels, while Vincristine showed no significant effect. More significantly, HDAC6i treatment, alone or combined with chemotherapeutics, increased SARM1 acetylation, potentially contributing to its inhibition and reduced activity. Immunofluorescence analysis revealed no major alterations in SARM1 localization. In contrast, NMNAT2 levels were reduced following chemotherapeutic treatment but were preserved when Ricolinostat was co-administered with the antineoplastic agent.

DISCUSSION: Our results highlight SARM1 as a key mediator of HDAC6i–induced neuroprotection. HDAC6i treatment increased SARM1 acetylation, reduced its activity, and prevented neurotoxicity from Bortezomib, Oxaliplatin, and Paclitaxel. These effects suggest that acetylation-dependent inhibition of SARM1 is central to the protective mechanism. The lack of protection against Vincristine implies that its toxicity may bypass SARM1, emphasizing the pathway's specificity and therapeutic potential in CIPN.

CONCLUSIONS: HDAC6 inhibitors reduce SARM1 activity via increased acetylation, protecting neurons from chemotherapy-induced damage. Targeting SARM1 acetylation may represent a promising strategy against CIPN.