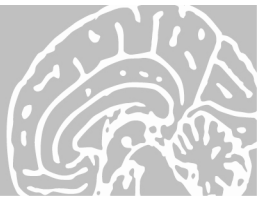
Mechanisms of distal axon degeneration and neuroprotection in peripheral neuropathies



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Abstract: Distal axonal degeneration seen in many peripheral neuropathies share common molecular pathways with Wallerian degeneration. The key molecules that play a role in Wallerian degeneration such as expression of *Wlds* gene and genetic deletion of *Sarm1* also prevent slow axonal degeneration seen in several models of peripheral neuropathy, including chemotherapy-induced peripheral neuropathies (CIPN). Since these pathways point to a common final pathway of axon degeneration, regardless of the underlying molecular mechanisms of a specific disease, one can potentially identify neuroprotective compounds through a phenotypic drug screening strategy. Using such a strategy we identified ethoxyquin as a compound that prevented axon degeneration in various models of CIPN and showed that it binds to Hsp90 and inhibit binding of one of its client proteins, SF3B2. Ethoxyquin and its novel derivatives are potential neuroprotective drugs to treat CIPN.