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Elp1-dependent Shp1 Phosphatase Regulation and its Essential Role in Familial Dysautonomia Pathogenesis.

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Familial Dysautonomia (FD; Riley-Day Syndrome; HSAN3) is a rare heritable disease characterized by debilitating sensory and sympathetic neuropathy. It is caused by a germline mutation of the Elp1 gene that leads to exon mis-splicing, nonsense-mediated truncation of the Elp1 protein and loss of Elp1 protein primarily in sympathetic and nociceptive sensory neurons. How Elp1 functions in FD disease-vulnerable neurons is very poorly understood.

Using Elp1 conditional knockout mice that we generated to recapitulate the molecular and physiologic phenotypes associated with human FD, we identified abnormalities in sympathetic neurons that explain the pathophysiologic basis for disease. Sympathetic neurons isolated from Elp1 conditional knockout mice have abnormalities in nerve growth factor signaling which is essential for their survival. NGF is normally acquired from peripheral tissues by innervating axons and NGF retrograde signal transduction to the neuron cell body is essential for their normal survival and differentiation. We found that sympathetic neurons lacking Elp1 have abnormalities in retrograde NGF signaling and as a consequence they have impaired survival and differentiation in response to NGF. After binding to NGF, the terminal axon TrkA (NTRK1) receptors are internalized and phosphorylated to activate downstream signaling pathways essential for sympathetic neuron survival and differentiation. We found that Elp1-deficient neurons normally bind NGF and they normally internalize and activate (phosphorylate) TrkA receptors in response to NGF. However in the absence of Elp1, TrkA receptor phosphorylation, which is essential for activation and downstream signaling, was markedly diminished. Shp1 phosphatase, which normally binds to TrkA receptors and terminates signaling by dephosphorylation, was found to be hyperactivated in the absence of Elp1. Shp1 hyperactivation results in precocious TrkA receptor dephosphorylation and attenuation of retrograde signaling. Pharmacological treatment with either Shp1 phosphatase inhibitors or molecular inhibition of Shp1 phosphatase activity resulted in complete rescue of TrkA dephosphorylation and restoration of normal NGF-dependent retrograde neuron survival.

These results demonstrate that sympathetic neuron death in patients with FD is due to loss for normal retrograde NGF signaling mediated by Shp1 phosphatase hyperactivity and precocious attenuation of TrkA signaling. Inhibition of Shp1 phosphatase activity may provide a novel therapy for sympathetic neuron loss in FD. Future studies are focused on understanding how Elp1 regulates Shp1 phosphatase activity and whether it may regulate Shp1 phosphatase activity in other signal transduction pathways involved in immune function and oncogenesis.

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