Elpl-dependent Shpl Phosphatase Regulation and its Essential Role in Familial Dysautonomia Pathogenesis.

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Familial Dysautonomia (FD; Riley-Day Syndrome; IISAN3) is a rare heritable disease characterized by debilitating sensory and sympathetic neuropathy. It is caused by a germline mutation of the Elpl gene that leads to exon mis-splicing, nonsense-mediated truncation of the Elpl protein and loss of Elpl protein primarily in sympathetic and nociceptive sensory neurons. How Elpl functions in FD disease-vulnerable neurons is very poorly understood.

Using Elpl 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 Elpl 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 Elpl 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 Elpl-deficient neurons normally bind NGF and they normally internalize and activate (phosphorylate) TrkA receptors in response to NGF. However in the absence of Elpl, TrkA receptor phosphorylation, which is essential for activation and downstream signaling, was markedly diminished. Shpl phosphatase, which normally binds to TrkA receptors and terminates signaling by dephosphorylation, was found to be hyperactivated in the absence of Elpl. Shpl hyperactivation results in precocious TrkA receptor dephosphorylation and attenuation of retrograde signaling. Pharmacological treatment with either Shpl phosphatase inhibitors or molecular inhibition of Shpl 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 Shpl phosphatase hyperactivity and precocious attenuation of TrkA signaling. Inhibition of Shpl phosphatase activity may provide a novel therapy for sympathetic neuron loss in FD. Future studies are focused on understanding how Elpl regulates Shpl phosphatase activity and whether it may regulate Shpl phosphatase activity in other signal transduction pathways involved in immune function and oncogenesis.

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