Familial dysautonomia (FD, OMIM 223900; also known as HSAN III or Riley-Day syndrome) is the most prevalent form of hereditary sensory and autonomic neuropathy (HSAN; Axelrod et al., 1974). Patients suffering from autonomic and sensory nervous system impairment have no available effective treatment and the average age of death is approximately 24 years. FD is a congenital and progressive disease almost exclusively caused by inheritance of a single nucleotide mutation in the splice acceptor site in intron 20 of the ELPL1 (IKBKA) gene. The germline mutation leads to particularly poor transcript splicing in sympathetic and some sensory neurons which in turn leads to a translational frame shift, introduction of a non-sense codon, and premature truncation and degradation of the encoded Elp1 protein (Anderson et al., 2000; Slaugenhaupt et al., 2001). The resulting low level of Elp1 protein in sympathetic and some sensory neurons leads to their death and results in physiologic sympathetic and sensory nervous system dysfunction (Tourtellotte, 2016). Several laboratories have developed transgenic mice to recapitulate major features of the disease to provide experimental tools to better study disease pathophysiology and potential therapy (Hims et al., 2007; Chen et al., 2009; Jackson et al., 2014; Morini et al., 2016), but how Elp1 functions in disease relevant neurons has not been precisely defined until recently.

Elp1 serves as a scaffolding protein essential for stabilizing the heterohexameric (Elp1-6) transcriptional elongator complex (Elongator). Elp3, a constituent of Elongator, serves as the major effector protein within the complex because it facilitates transcriptional elongation by binding to RNA polymerase II and it mediates chromatin remodeling through its histone acetyltransferase activity (Otero et al., 1999). In addition to a role in regulating protein translation, Elongator has been shown to mediate tubulin acetylation where it is proposed to have roles in microtubule function, cytoskeleton organization and cell migration (Close et al., 2006; Creppe et al., 2002). An interesting question related to the mechanism of Elp1 function and the pathogenesis of FD has been "why does the disease preferentially impact a specific subset of neurons when the germline mutation is present in all cells in patients with FD?" While comparatively poor splicing efficiency in sympathetic and sensory neurons relative to other cells may explain why these neurons may have lower Elp1 protein levels compared to other cells, the mechanism by which Elp1 functions to mediate their survival and target tissue innervation has not been clear until recently. Indeed, Elp1 appears to have a new role, not previously described, in regulating retrograde NGF signaling and therefore sympathetic and nociceptive sensory neuron survival (Li et al., 2020). NGF is derived from target tissues innervated by sympathetic and some sensory neurons, and it binds to its cognate receptor tropomyosin-related kinase A (TrkA) on nerve terminals where it initiates a series of signaling events including receptor dimerization, intracellular domain auto-phosphorylation, receptor internalization and retrograde transport to the nucleus of activated receptor-containing "signaling endosomes" that regulate gene transcription essential for neuron differentiation and survival (Kaplan and Mobley, 2020). Since retrograde transport of activated/NGF-bound TrkA receptors requires substantial time to travel through the axon from the target tissues where NGF is secreted, a long-standing quandary in the field has been how TrkA maintains its phosphorylation/activation status during its journey through the axon to the cell body. Tyrosine kinase receptors maintain their phosphorylation state through a dynamic balance between phosphorylation mediated kinase activity and dephosphorylation mediated phosphate activity. TrkA is kept in a dephosphorylated/inactivated state through the activity of several phosphatases, the most well-studied being the Src homology 2 domain-containing protein tyrosine phosphatase 1, Shp1/PTPN6 (Marsh et al., 2003). While Shp1 binds to phosphorylated NGF/TrkA in retrogradely transported signaling endosomes, how it is maintained in a phosphorylated/activated state to induce gene transcription required for differentiation and survival has not been well understood.

The nexus between regulating the phosphorylation status of TrkA during its retrograde journey to the nucleus in neurons and the recently discovered function for Elp1 in maintaining TrkA phosphorylation is where a new story to understand the pathogenesis of FD begins (Figure 1). Mice engineered to lack Elp1 specifically in sympathetic and sensory neurons recapitulate neuron loss and target tissue innervation abnormalities found in FD patients (Jackson et al., 2014). Using sympathetic neurons derived from these mice and a strategy to temporally ablate Elp1 function in them, we found that Elp1 represses the phosphatase activity of Shp1 bound to phosphorylated TrkA in retrogradely transported signaling endosomes. In neurons lacking Elp1, Shp1 phosphatase is hyperactivated and TrkA is precociously dephosphorylated during its retrograde journey to the nucleus, leading to failed activation of down-stream signaling pathways essential for sympathetic neuron differentiation and survival. Accordingly, molecular and pharmacological strategies to inhibit Shp1 phosphatase activity in Elp1-deficient sympathetic neurons are capable of rescuing retrograde sympathetic neuron survival in vitro and in vivo. These results identify a novel function for Elp1 in regulating retrograde NGF signaling in sympathetic neurons and provide a novel explanation for why these neurons die during development in patients with FD (Li et al., 2020).

These recent studies focused on the mechanisms of Elp1 function in sympathetic neurons. However, patients with FD also have profound sensory deficits related to pain and temperature (nociceptive) sensation. Nociceptive neurons also express TrkA receptors and, like sympathetic neurons, their survival requires intact NGF signaling during development. Indeed, mouse models that have been generated to recapitulate human disease by mutating Elp1 in the germline have both sensory and sympathetic nervous system abnormalities, similar to human disease (Jackson et al., 2014). While not yet specifically studied, it is tempting to speculate that Elp1 has a similar function in sensory neurons by regulating retrograde NGF signaling through TrkA receptors and Shp1 phosphatase inhibition to maintain its activation status during retrograde signaling. This recent report linking Elp1 to retrograde NGF/TrkA signaling and to the pathogenesis of FD raises important new questions regarding how Elp1 functions to regulate Shp1 phosphatase activity in the NGF/TrkA/Shp1/Elp1-containing signaling endosomes. New studies to better understand how Elp1 regulates Shp1 phosphatase activity will involve understanding whether they directly interact and if so through which functional domains. Moreover, it will be useful to learn how Elp1 may coordinate SH2 domain interactions on Shp1 to alter its conformation and activity. New insights related to the relevant SH2 domain interacting proteins in the complex may make it possible to develop specific inhibitors targeted to sympathetic neurons since broad pharmacological inhibition of Shp1 phosphatase activity,
as a potential treatment for FD, may be fraught with significant side effects since Shp1 has important functions in immune regulation outside of the nervous system. An important additional question that needs to be addressed is whether the association of Elp1 in this previously unrecognized NGF/TrkA/Shp1 complex contained in signaling endosomes is associated with other members of Elongator where it is best known to serve a scaffolding function to stabilize the multimeric Elongator complex. Potentially, Elp1 exists in other non-Elongator protein complexes where it has distinct function apart from translational regulation mediated by Elongator.

These recent studies showing that Elp1 has an essential role in retrograde NGF signaling may not be surprising considering that other well-established subtypes of HSAN namely, HSAN IV and HSAN V are caused by germline mutations in TrkA and NGF which disrupt normal NGF signaling. In these diseases, there is significant phenotypic overlap with FD that very likely relates to FD that very likely relates to familial dysautonomia. Neural regeneration research 16(9):1795-1796.

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