THE INVOLVEMENT OF KINESIN-1 ADAPTOR, FEZ1, ON MOTOR NEURON DEVELOPMENT

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Neurons are the most polarized cells in the body with a small cell body and long neuronal processes. Thus, neurons rely heavily on anterograde transport mechanisms for delivery of newly synthesized proteins and organelles to the synapses. Delivery of synaptic cargoes is required both for the formation and maintenance of synapses by ensuring replenishment of synaptic vesicles and sustained synaptic function. Failure in anterograde transport machinery, hence, has repercussions on neurodevelopment.

Fasciculation and elongation protein zeta-1 (FEZ1), an adaptor for kinesin-1-mediated axonal transport, is involved in synaptic trafficking. FEZ1 plays the dual role of regulating kinesin-1 activation as well as acting as a molecular bridge between kinesin-1 and a specific subset of its cargoes. Loss of FEZ1 has been associated with perturbed axonal trafficking and consequent neurodevelopmental defects including axo-dendritic specification and synapse formation. Evidence presented mainly in invertebrates (*C. elegans* and *Drosophila*) show the importance of FEZ1 in the development of invertebrate PNS. However, there is a dearth of studies on the role of FEZ1 in the mammalian PNS. Nonetheless, abundance of FEZ1 protein in rodent spinal cord and FEZ1 mRNA in human spinal cord indicate a role FEZ1 for in the mammalian PNS. Furthermore, motor deficits were observed in patients with Jacobsen syndrome, a chromosomal deletion disease involving a loss of *FEZ1*. Indisputably, these evidence provide a strong basis for investigation of the role of FEZ1 in human motor neuron.

Using hESC-derived human motor neurons (hMNs), we observed a developmentally regulated increase in FEZ1 expression across hMN development and maturation. Deleting *FEZ1* resulted in impaired axo-dendritic development, possibly mediated by dysregulated trafficking. Through electrophysiological studies, FEZ1 knockout (FKO) hMNs were further shown to exhibit functional deficits including reduced outward currents in DIV14 hMNs and reduced frequency of action potential firing in DIV21 hMNs. Collectively, this study highlights the importance of FEZ1 in motor neuron development and potentially contributes to further our understanding of developmental pathologies of human motor neuron disorders.

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