

Public Abstract

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Title:MOLECULAR MECHANISMS OF RADIAL AXONAL GROWTH: INSIGHTS FROM ANALYSIS OF NEUROFILAMENT GENE-TARGETED MICE

For the nervous system to send signals rapidly, axons must undergo growth that expands their diameter. This process is known as radial growth and is dependent upon insulating myelin that wraps around the axon and the expression of proteins known as neurofilaments within the axon. Neurofilaments are the most abundant cytoskeletal proteins composed of neurofilament light (NF-L), medium (NF-M) and heavy (NF-H) subunits. It was not fully understood how neurofilament subunits mediate the radial growth of axons. To investigate, I analyzed mice in which neurofilament proteins have been deleted or altered through gene replacement. I also analyzed neurofilaments across mammals through DNA sequencing in order to identify variations that may suggest how neurofilaments function in radial growth of axons. Analysis of NF-H gene deleted mice suggested that axons grow radially in distal regions of axons prior to proximal axon regions due to delayed expression of NF-H. NF-H expression was developmentally delayed to allow distal axon segments prior to proximal segments which may have been beneficial for long-term maintenance of axonal diameter. DNA sequencing analysis of the NF-M across mammals suggested that the length of NF-M determined the magnitude that axons grow radially. As a direct test, I increased the length of NF-M in mice through gene replacement. Expanding NF-M length resulted in mice with larger diameter axons yet myelin thickness did not increase around the axons, suggesting that myelin lacked plasticity to compensate for changes in the growth of the axon. Variation of the NF-M length across mammals may have been an evolutionary mechanism to adjust the magnitude of radial growth of axons.