A CLN6-CRMP2-KLC4 complex regulates anterograde, ER-derived vesicle trafficking in cortical neurites

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Cargo transportation along the microtubule network of the axon is crucial for neuronal development, plasticity, and homeostasis. For neuronal differentiation and maintenance, building blocks, such as neurotransmitters, organelles, transmembrane receptors, and membrane components must be anterogradely transported to the distal ends of axons. Here we expand on a novel complex that regulates vesicular transport in axons: CLN6, an ER-associated protein implicated in Batten disease with relatively unknown function; ¬CRMP2, a tubulin- binding protein which is vital in regulation neurite microtubule dynamics; and KLC4, a transport motor protein. Using BioID, a protein interactome screening system that exploits a promiscuous biotin ligase BirA, it was revealed that CLN6 has extensive interactions with intracellular transport proteins including vesicular transport and sorting interactors. We find that CLN6 not only co-localizes with CRMP2 and KLC4 along the axon but also with COPII at ER exit sites present in the cell body and distal processes. This CCK complex aids in the anterograde transport of ER-derived vesicles, allowing for proper neurite outgrowth and arborization. The CCK complex is unable to form in the absence of CLN6 which ultimately leads to reduced vesicular transport and curbed neurite outgrowth. Treatment with lanthionine ketamine ester, a CRMP2 modulating compound, partially restores deficits in a CLN6 deficient mouse model, but does not ameliorate neuroinflammation. Collectively, these results support a novel role for CLN6 in axonal transport and provide new insights into the neurocentric nature of CLN6 disease.