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COMMANDER COMPLEX: a new endosomal protein sorting platform

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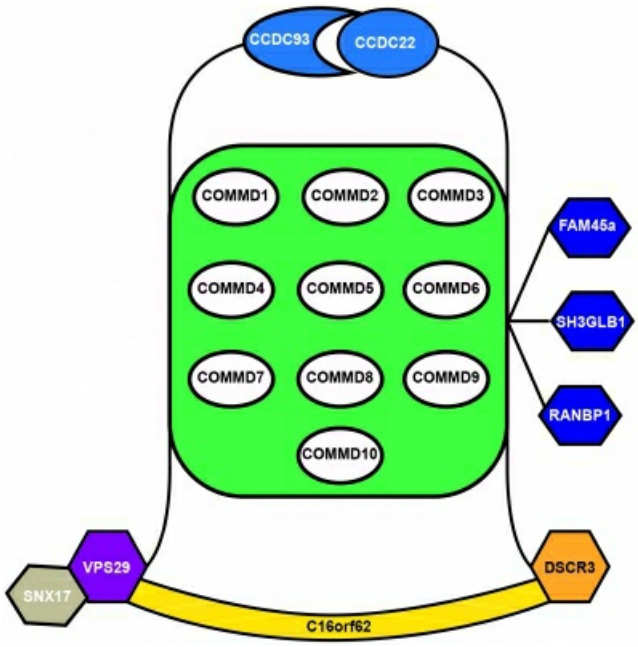
Regulation of correct endo- and exocytic trafficking is central to maintaining cellular homeostasis. Internalised cargo proteins, lipids and nutrients enter intracellular sorting stations called endosomes, and perturbations of endosomal trafficking and lysosomal degradation are implicated in the onset of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and Down Syndrome (DS). Recently an evolutionarily conserved endosomal protein trafficking machinery called the COMMANDER complex was identified (Fig. 1). This large assembly is potentially composed of 18 core subunits, mutations of which have been associated with X-linked intellectual disability, PD and dementia related disorders. Through our systematic and comprehensive analyses of the COMMANDER complex, we have dissected both in-vitro and in-situ protein-protein interactions of all of the various subunits required to form the holo-complex. By employing MultiBac technology and the mammalian human embryonic kidney Expi293FTM system we have identified and reconstituted stable sub-complexes from the COMMANDER complex. Our studies on isolated subunits of this large assembly have begun to unravel the mechanisms of their stable higher order oligomerisation highlighting how the COMMANDER assembly is generated. Endosomal recruitment of trafficking complexes generally occurs through the interaction with membrane lipids (specifically phosphoinositides), Rab small GTPases, guanine nucleotide exchange factors (GEFs) and GTPase-Activating Proteins (GAPs). Our investigations on the ability of subunits of the COMMANDER complex to interact with phosphoinositdes demonstrate that this endosomal-sorting complex potentially localizes to cellular membranes by virtue of COMMANDER-lipid association. Our work is defining key interaction networks required for COMMANDER complex function and now provides a foundation for ongoing high-resolution structural studies.



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