Disabled-1 Functions as a Dynamic Switch Regulating Reelin Receptor Endocytic Machinery

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During development of the mammalian cerebral cortex, post-mitotic neurons migrate radially from the ventricular zone to the cortical plate where they settle and differentiate. This neuronal migration is highly regulated to ensure normal brain development. Reelin, a secreted protein synthesized and released in the cerebral cortex largely by Cajal–Retzius cells in the marginal zone, is known to regulate the ultimate positioning of cortical neurons during brain development. Lack of the Reelin protein produces a reeler phenotype, with the affected animals exhibiting a wobbly gait and anatomically exhibiting a disorganized cerebral cortex, cerebellum and hippocampus. Reelin signals to migratory neurons and glia through the lipoprotein receptors ApoER2 and VLDLR, and requires an intracellular adaptor protein Disabled-1 (Dab-1), which is critically phosphorylated by the Src Family of tyrosine Kinases (SFKs) upon Reelin stimulation. While some of the events subsequent to Dab1 tyrosine phosphorylation have been worked out, relatively little is known. In this study, we look at the interaction of Dab-1 with its C-terminal binding protein CIN85 (Cbl interacting protein of 85 kDa). We show that Dab-1 negatively regulates CIN85 phosphorylation and also inhibits the interaction of CIN85 with its SH3 binding protein Cbl, but not its C-terminal binding protein CapZ. Cbl and CIN85 are known regulators of clathrin-mediated receptor endocytosis, and Dab-1 is known to inhibit internalization and endocytosis of Reelin receptors. We propose a model whereby Dab1 functions as a Reelin-dependent dynamic switch to recruit and regulate the Reelin receptor enodyctic machinery.