Xiao-Juan Zhu et al., J Neurol Disord 2018, Volume 6
DOI: 10.4172/2329-6895-C4-034



# DCC-mediated Dab1 phosphorylation participates in the multipolar-to-bipolar transition of migrating neurons

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Newborn neurons undergo inside-out migration to their final destinations during neocortical development. Reelin-induced tyrosine phosphorylation of disabled 1 (Dab1) is a critical mechanism controlling cortical neuron migration. However, in reelin null mice, Dab1 tyrosine phosphorylation decreased, but not eliminated, suggesting that Reelin-independent tyrosine phosphorylation of Dab1 may occur. The roles remain unclear. Here, we report that deleted in colorectal carcinoma (DCC) interacts with disavled1 (Dab1) specifically. Based on the endogenous DCC and Dab1 expression in the developing neocortex, we demonstrate that DCC physically interacts with Dab1 both *in vitro* and in cortical neurons, and this interaction depends on the P3 domain of DCC and the PTB domain of Dab1. Netrin 1, a DCC ligand, binding to the DCC induces Dab1 phosphorylation at Y220 and Y232 through it has no detectably enhancing the DCC-Dab1 interaction. Interestingly, knockdown of DCC or truncation of its P3 domain dramatically delays neuronal migration and impairs the multipolar-to-bipolar transition of migrating neurons, as well as migration of newborn neurons toward to the CP, indicating that DCC is required for the proper neuronal migration, particularly for the multipolar-to-bipolar transition. Furthermore, the presence and proper phosphorylation of DCC at tyrosine 1420 is critical for neuronal migration. Notably, the migration delay and morphological transition defects are rescued by the expression of a phospho-mimetic Dab1 or a constitutively active form of Fyn proto-oncogene (Fyn), a member of the Src-family tyrosine kinases that effectively induces Dab1 phosphorylation, suggesting that Dab1 is the downstream effector of DCC during neuronal migration. Collectively, these findings illustrate a DCC-Dab1 interaction that ensures proper neuronal migration during neocortical development. Thus, our finding reveals a cross - talk between reelin and netrin 1 signaling pathways via DCC-Dab1 interaction to illustrate a previously undefined DCC-Dab1 signaling pathway that regulates neuronal migration during neocortical development.

## Recent Publications

1. Zhang J, Zhu X et al (2018) DCC-mediated Dab1 phosphorylation participates in the multipolar-to-bipolar transition of migrating neurons. Cell Reports 22:3598-3611.
2. Guo Y, Zhu X et al (2017) Gβ2 regulates the multipolar-bipolar transition of newborn neurons in the developing neocortex. Cerebral Cortex 27(6)3414-3426.
3. Sheikh M, Malik Y, Yu H, Zhu X et al (2017) Epigenetic regulation of Dpp6 expression by Dnmt3b and its novel role in the inhibition of RA induced neuronal differentiation of P19 Cells. PLOS One 8 (2):E55826-1-12.
4. Lai M, Zhu X et al (2015) Myosin 10 regulates neuronal radial migration through interacting with N-cadherin. Frontiers in Cellular Neuroscience 9:326.
5. Jv X, Zhu X et al (2014) Both myosin-10 isoforms are required for radial neuronal migration in the developing cerebral cortex. Cerebral Cortex 24:1259-1268.

## Biography

Xiao-Juan Zhu has completed her PhD in Cell Biology from Northeast Normal University, Changchun, China and; Post-doctorate degree from Medical College of Georgia, Augusta, GA, USA. Her research interest includes "Understanding genetic, molecular and cellular basis of brain development". She is also interested in how the dendritic spines stabilize mature, and how changes in their activities may lead to rapid remodeling of dendritic spines, as well as the defective regulation in dendritic spines that associated with human neuropsychiatric disorders, including autism spectrum. She is using primary culture neuron and genetic modified mice models to study these questions.

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