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DCX, a new mediator of the JNK pathway

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In the development of the mammalian brain, neurons migrate long distances to form the complex laminar structures of the cerebral cortex. The molecular mechanisms involved in the initiation of neuronal cell movement, guidance of migration, and recognition of final position, are not well understood. Phosphorylation, which dynamically modulates protein activity, is a fine way to control these events. The study of neuronal migration disorders as lissencephaly can help to elucidate the genes and pathways involved. Lissencephaly occurs in individuals with mutations in either the autosomal *LIS1* or the X-linked *doublecortin (DCX)* genes. Both of these gene products are microtubule associated proteins. Our recent data demonstrates the involvement of the c-Jun N-terminal kinase (JNK) signaling pathway in controlling neuronal migration via its action on DCX. DCX is a JNK substrate and interacts with JIP (JNK interacting protein). The localization of this signaling module in the developing brain suggests its functionality in migrating neurons. The localization of DCX at neurite tips is determined by its interaction with JIP and by the interaction of the later with kinesin. DCX is phosphorylated by JNK in growth cones. DCX mutated in sites phosphorylated by JNK affected neurite outgrowth, and the velocity and relative pause time of migrating neurons. We hypothesize that during neuronal migration there is a need to regulate molecular motors that are working in the cell in opposite directions; kinesin a plus-end directed molecular motor versus dynein a minus-end directed molecular motor.

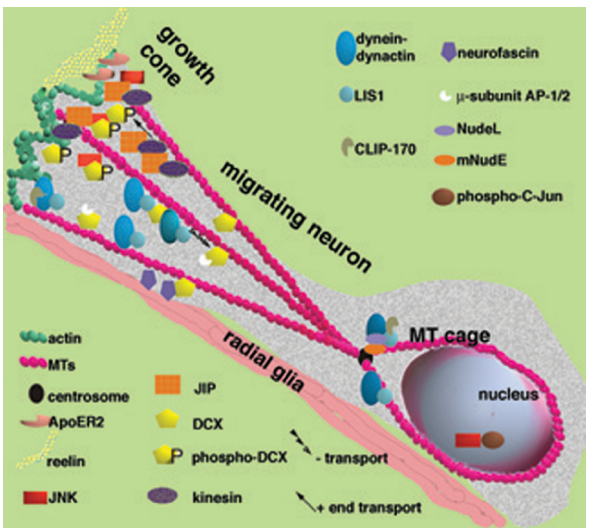

Fig. 1 A model of a neuron migrating along radial glia. *The migrating neuron has an elongated structure with a growth cone. There is more p-DCX located in the growth cone where it interacts with JNK, and JIP. JIP is mobilized there by kinesin. JIP interacts also with ApoER2 that binds to the extracellular matrix protein reelin, and to kinesin that is a plus-end directed motor. DCX also interacts with the membranal protein neurofascin, and with the m-subunits of the AP-1/2 complexes. At the MT plus-end tips we can also find CLIP-170, that recruits LIS1, and the dynein-dynactin complex. The dynein-dynactin retrograde motor is recruited to MTs with LIS1 and DCX followed by enhanced activity of this motor. Nucleokinesis is assisted by the activity of the dynein motor that is associated with the MT cage and the centrosome (there also mNudE and NudeL can be found). Within the nucleus the transcription factor c-Jun is phosphorylated by JNK. The activity of JNK may thereby indirectly regulate the differential activities of kinesin and dynein.*

Selected Publications

Reiner, O.,Carrozo, R., Shen, Y., Whenert, M., Faustinella, F., Dobyns, W.B., Caskey, C. T. and Ledbetter, D.H. (1993) Isolation of a Miller-Dieker lissencephaly gene containing G protein ß-subunit-like repeats. *Nature* 364, 717-721.

Sapir, T., Elbaum, M., Reiner, O. (1997) The Lissencephaly 1 (LIS1) Gene Product Interacts With Tubulin and Reduces Microtubule Catastrophe Events. *EMBO J* 16, 6977-6984.

Horesh, D., Sapir, T., Francis, F., Caspi, M., Grayer Wolf, S., Elbaum, M., Chelly, J. and Reiner, O. (1999) Doublecortin, a stabilizer of microtubules. *Hum Mol Genet* 8, 1599-1610.

Sapir, T., Horesh, D., Caspi, M., Atlas, R., Burgess, H.A., Grayer Wolf, S., Francis, F., Chelly, J., Elbaum, M., Pietrokovski, S., and Reiner, O. (2000) Doublecortin Mutations Cluster in Evolutionary Conserved Functional Domains. *Hum Mol Genet* 5, 703-712.

Caspi, M., Atlas, R., Kantor, A., Sapir, T. and Reiner, O. (2000) Interaction between LIS1 and Doublecortin, two Lissencephaly gene products. *Hum Mol Genet* 9, 2205-2213.

Shmueli, O., Gdalyahu, A., Sorokina, K., Nevo, E., Avivi, A., and Reiner, O. (2001) DCX in PC12 Cells: Downregulation of CREB -mediated Transcription. *Hum Mol Genet* 10, 1061-1070.

Cahana, A., Escamez, T., Nowakowski, R.S., Hayes, N.L., Giacobini, M., von Holst, A., Shmueli, O., Sapir, T., McConnell, S., Wurst, W., Martinez, S., and Reiner, O. (2001) Targeted mutagenesis of *Lis1* disrupts cortical development and LIS1 homodimerization. *Proc Natl Acad Sci U S A* 98, 6429-6434.

Burgess, H.A. and Reiner, O. (2001) Cleavage of Doublecortin-like Kinase by Calpain Releases an Active Kinase Fragment from a Microtubule Binding Domain *JBC* 276,36397-403.

Coquelle, F.M., Caspi, M., Cordelières, F.P., Dompierre, J.P., Dujardin, D.L., Martin, P., Hoogenraad, C.C., Akhmanova, A., Galjart, N., De Mey, J.R. and Reiner, O. (2002) LIS1: CLIP-170's Key to the Dynein/Dynactin Pathway. *MCB* 22, 3089–3102.

Burgess, H.A. and Reiner, O. (2002) Alternative Splice Variants of Doublecortin-like Kinase are Differentially Expressed and have Different Kinase Activities *JBC* 277,17696–17705.

Caspi, M., Coquelle, F.M., Koifman, C., Levy, T., Arai, H., Aoki, J. De Mey, J.R., and Reiner, O. (2003) LIS1 Missense Mutations: Variable Phenotypes Result from Unpredictable Alterations in Biochemical and Cellular Properties. *JBC* 278, 38740-38748.

Gdalyahu, A., Ghosh, I., Levy, T., Sapir, T., Sapoznik, S., Fishler, Y., Azoulai, D., and Reiner, O. (2004) DCX, a New Mediator of the JNK Pathway. *EMBO J* 3, 823- 832.

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