Human brain development — modeling in bread molds and mice

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Lissencephaly is a severe human neuronal migration defect, characterized by a smooth cerebral surface, mental retardation and seizures. *LIS1* was first gene cloned in an organism important for neuronal migration, as it was deleted or mutated in patients with lissencephaly in a heterozygous fashion. Studies in model organisms, particularly *Aspergillus nidulans*, a bread mold, as well as those in the mouse, have uncovered an evolutionarily conserved pathway that involves LIS1 and cytoplasmic dynein. This pathway codes for proteins in a complex with cytoplasmic dynein and positively regulates its conserved function in nuclear migration. This complex appears to be important for proliferation and neuronal survival as well as neuronal migration. One of the conserved components of this complex, NDEL1, is a phosphoprotein that is a substrate for CDK5 (or CDK2 in fibroblasts) and Aurora A, two mitotic kinases. CDK5-phosphorylated NDEL1 binds to 14-3-3e, which protects it from phosphatase attack. Interestingly, *14-3-3e* is located 1 Mb from LIS1 and is heterozygously deleted with *LIS1* in patients with a severe form of lissencephaly, Miller-Dieker syndrome. Mouse models confirm that *14-3-3e* plays an important role in neuronal migration, and mice that are double heterozygotes for mutations in *Lis1* and *14-3-3e*, display more severe neuronal migration defects. The identification of *LIS1* as the first lissencephaly gene and the first gene required for neuronal migration has revealed the importance of the regulation of cytoplasmic dynein in the control of neuronal migration by modulating nuclear migration in a pathway conserved in virtually all eukaryotes.