Lissencephaly, molecular elucidation of a human brain malformation

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Lissencephaly is a severe human brain malformation. The one in 30,000 children that are born with this devastating condition do not reach measurable developmental stages, suffer from recurrent seizures and their brains lack most of the normal convolutions. Careful examination of the lissencephalic cerebral cortex reveals abnormal cortical organization. In humans, lissencephaly has been shown to be caused by mutations in either the genes for Doublecortin (DCX) which is X-linked or LIS1.

LIS1 and Microtubule Regulation
Understanding why mutations in LIS1 result in a severe brain malformation has proven to be a difficult task. LIS1 is a member of the WD (tryptophan-aspartic acid) repeat family of proteins. A hallmark of this family is their involvement in multiple protein-protein interactions, LIS1 is not an exception and it interacts with a large number of proteins. LIS1-protein interactions may be grouped conceptually into two classes: evolutionary conserved and relatively new interactions. Much has been learnt from the interactions that have been conserved throughout evolution connecting LIS1 with microtubule regulation and dynein motor regulation (Fig. 1).

There are several LIS1 interactions that are not conserved in evolution but may still be important in structure formation of the human brain. We have detected an interaction between LIS1 and Doublecortin (DCX). Mutations in doublecortin, an X-linked gene, result in lissencephaly. The phenotypic presentation of the patients is very similar. However, while the frontal brain is more affected in patients with mutated doublecortin, LIS1 mutations affects mainly the parietal and occipital cortex. The product of the doublecortin gene associates with and stabilizes microtubules. We have identified the tubulin binding domain of DCX and found it to be an evolutionary conserved repeat. Our results suggest that LIS1 and DCX are coexpressed, interact and can function in the same protein complex in the developing brain. Although the exact mode of action of the two proteins may differ, we raise the possibility of a crosstalk between them. In addition, we are studying an autosomal DCX-related gene DCLK. The expression of this gene is highly similar to that of

Sapir, T., Elbaum, understanding of LIS1 role in the developing cortex. Functions that are sensitive to LIS1 dosage, thus promoting our first demonstration of the in vivo role of LIS1 as a subunit of platelet-activating factor acetylhydrolase (PAF-AH) is elevated in the embryos, thus a deletion of the first coding exon 1. The deletion resulted in a shorter protein (sLIS1) that initiates from the second methionine. The deletion resulted in a shorter protein (sLIS1) that initiates from the second methionine. Homozygotes are early lethal, although heterozygotes are viable and fertile. Some aspects of corticogenesis are abnormal in the heterozygotes especially in the caudal part of the brain where the expression of Lis1 is higher (Fig. 2).

Formation of the brain structure is a complex process that requires the coordinated function of multiple genes. LIS1 is one of the genes that have a principal role in brain development since hemizygote mutations in LIS1 result in a severe brain malformation known as lissencephaly ("smooth brain"). We have recently generated a mouse model for this disease by a targeted mutation of the first coding exon 1. The deletion resulted in a shorter protein (sLIS1) that initiates from the second methionine. Homozygotes are early lethal, although heterozygotes are viable and fertile. Some aspects of corticogenesis are abnormal in the heterozygotes especially in the caudal part of the brain where the expression of Lis1 is higher (Fig. 2).

Biochemically, the mutant protein is not capable of dimerization, and enzymatic activity of platelet-activating factor acetylhydrolase (PAF-AH) is elevated in the embryos, thus a first demonstration of the in vivo role of LIS1 as a subunit of this enzyme. This mutation allows us to determine a hierarchy of functions that are sensitive to LIS1 dosage, thus promoting our understanding of LIS1 role in the developing cortex.

Selected Publications


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DCX and it is likely to participate in brain structure formation.

A. Whole mount RNT in situ hybridization in E12.5 embryo using Lis 1 probe. Note the dorsal to ventral and caudal to rostral decreasing gradient in Lis 1 expression. B. General scheme indicating the most affected regions in color: occipital and parietal cortex (ocCx), lateral amygdala (1A) and the claustrum (C1). Regions that are not affected include the olfactory bulb (OB) and the neocortex (NCOX). C. General scheme of LIS1 and sLIS1 protein interactions. LIS1 is predominantly a dimer and is found in association with microtubules, as homodimers in the cytoplasm and these homodimers are found interacting with PAF-AH catalytic subunits in the cytoplasm. LIS1 can interact with 1 dimers, with 2 dimers or with 1/2 heterodimers. sLIS1 can interact with microtubules, but not with PAF-AH subunits, nor can interact with LIS1.

LIS1 was initially found to be a regulatory subunit of platelet-activating factor acetylhydrolase (PAF-AH) Ib. A homolog for the catalytic subunit in Drosophila was identified. However, it lacks both enzymatic activity and the ability to interact with LIS1. Interestingly, a Drosophila LIS1 homolog does interact with mammalian PAF-AH catalytic subunits suggesting that the interaction with this enzyme is a relatively recent event in evolution. Is PAF-AH important for brain development? In order to elucidate this matter we are investigating brain development in mice mutated in the catalytic subunits in collaboration with other labs.

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