

A molecule that protects from neuronal disorders

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Many neuronal disorders, including epilepsy, schizophrenia and lissencephaly – a form of mental retardation -, result from abnormal migration of nerve cells during the development of the brain.

Researchers from the Mouse Biology Unit of the European Molecular Biology Laboratory (EMBL) in Italy, have now discovered that a protein that helps organising the cells' skeleton is crucial for preventing such defects.

In the current issue of *Genes & Development* they report that mice lacking the protein show symptoms of lissencephaly brought about by faulty development of the cerebral cortex, the brain's surface layer.

The cerebral cortex is a complex structure with many important functions and a very unique architecture consisting of different cell types arranged in a specific order of layers. During embryonic development the cortical layers are generated by neuronal progenitor cells that migrate long distances before they settle down in a given layer. The spatial organisation in cell layers is essential to cortical functions. When the layer architecture is disturbed, like in the case of lissencephaly where entire layers are missing, the consequences are mental retardation, muscle spasms and seizures. The new study by a team of EMBL researchers reveals that a molecule called n-cofilin can play a key role in the disease.

“We genetically engineered mice that lack n-cofilin and they show the same anatomical defects and symptoms as patients suffering from

lissencephaly,” says Walter Witke, whose team carried out the research. “Their brains miss several cortical layers because neurons do not migrate normally during development.”

The ability of neurons to migrate is largely brought about by the dynamic properties of their skeleton. The skeleton of a cell consists of constantly growing and shrinking filaments that function like strings and struts to give the cell shape and stability. N-cofilin interacts with one kind of filaments, called actin filaments, and helps to disassemble them into their individual building blocks. Interfering with this filament remodeling impairs the cell’s ability to move and thus blocks migration of neurons during cortical development.

N-cofilin also controls the fate of neural stem cells, which are involved in development of the cortex. In its absence more stem cells stop to self-renew and instead start differentiating. This imbalance depletes the pool of neuronal progenitors so that fewer cells can be made to build a complete and functional cortex. The study provides the first proof that proteins affecting actin filament dynamics are involved in neuronal migration disorders.

“This might have implications for humans, too,” says Gian Carlo Bellenchi from Witke’s lab. “Like many other cytoskeletal proteins n-cofilin is conserved between mice and humans and it is likely to play a similar role in the development of the human cortex.”

This makes the gene encoding n-cofilin an interesting candidate that might be mutated in neuronal disorders such as lissencephaly and other forms of mental retardation.

“The mouse model is a powerful tool to further investigate the roles n-cofilin and the actin cytoskeleton play in stem cell physiology and cell migration. Our studies also identified n-cofilin as a potential target

molecule that might allow to interfere with stem cell function in diseases where stem cell division has derailed,” concludes Christine Gurniak from Witke’s group.

Source: European Molecular Biology Laboratory

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