Brain development: How a 'molecular compass' regulates proper cell division

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Researchers at the Institute of Molecular Biotechnology in Vienna have unravelled how a tiny microRNA molecule controls growth and differentiation of brain cells.

It is mind-boggling to imagine how our brain develops from just a handful of cells at the early embryo into a highly convoluted biochemical and bioelectric system comprising more than 100 billion neurons in adults. Scientists at the Institute of Molecular Biotechnology (IMBA) in Vienna have published new research in *EMBO Journal*, in which they reveal how cells are instructed by a small RNA molecule to shape the complex layered structures of developing mouse brains.

When stem cells divide to form new tissues and organs, they have to position their cell division apparatus in a specific orientation to position their daughter cells at sites where they experience different fate cues defining their subsequent function. The newly formed cells may then go on to take a specialised function – in the brain, for example, they can become various types of neurons to generate and transmit electrical impulses – or stay stem cells that will keep dividing to generate more cells. Failure to correctly induce fate decisions leads to multiple developmental brain disorders.

The orientation of dividing cells governs cell fate

Dr Juan Pablo Fededa, a postdoctoral scientist at IMBA and first author

of the study, explains his findings: "Our research focused on understanding what controls the orientation of the mitotic spindles. We already knew that if the spindles are not in the correct orientation, then cells divide irregularly, and in the brain this can lead to neurodevelopmental disorders. We also knew that molecules called microRNAs might be important in this process, but we didn't know exactly how."

From microscopy-based screening to the study of mouse brains

Tiny 'micro-RNA' molecules can interfere with the expression of genes – turning them on, turning them off, or causing them to function differently. Led by principal investigator Dr Daniel Gerlich, Dr Fededa and the IMBA team used cultured cells in a dish to test the function of all micro-RNAs expressed during brain cell division.

Fededa describes the approach: "By visualizing the spindle of the cells with a fluorescent marker in live cells, we observed that a family of six microRNAs called miR-34/449 influenced the spindle orientation during cell division. We then tested whether these micro-RNAs could also influence the orientation of mitotic spindles in developing mouse brains, using methodology established in Jürgen Knoblich's laboratory at IMBA. Indeed, we found that after deletion of miR-34/449 genes, mice developed smaller brains and these contained a larger proportion of stem cells called radial glial cells. This showed us that radial glial cells can grow relatively normally, but suggested that they are unable to further differentiate into more complex cells. We therefore concluded that miR-34/449 microRNAs must be required for normal brain development."

miR-34/449 regulates the orientation of the mitotic

spindle

The scientists at IMBA compared the gene expression patterns in cells with or without miR-34/449 and discovered a difference in the expression of a protein called JAM-A. This protein was interesting, as it was previously shown to have a role in orienting the mitotic spindle in other tissues. By engineering a JAM-A gene version that is insensitive to miR-34/449, the team at IMBA was able to pinpoint its relevance for mitotic spindle orientation. "Our findings show that in developing mouse brains, miR-34/449 regulates JAM-A to ensure the correct orientation of dividing cells and accurate formation of brain layers" concludes Daniel Gerlich. "The current research provides insights into the role of micro-RNAs in brain development, but similar mechanisms might be at place in other organs."

More information: Juan Pablo Fededa et al. MicroRNA-34/449 controls mitotic spindle orientation during mammalian cortex development, *The EMBO Journal* (2016). DOI: 10.15252/embj.201694056

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