NAIST® Research Highlights

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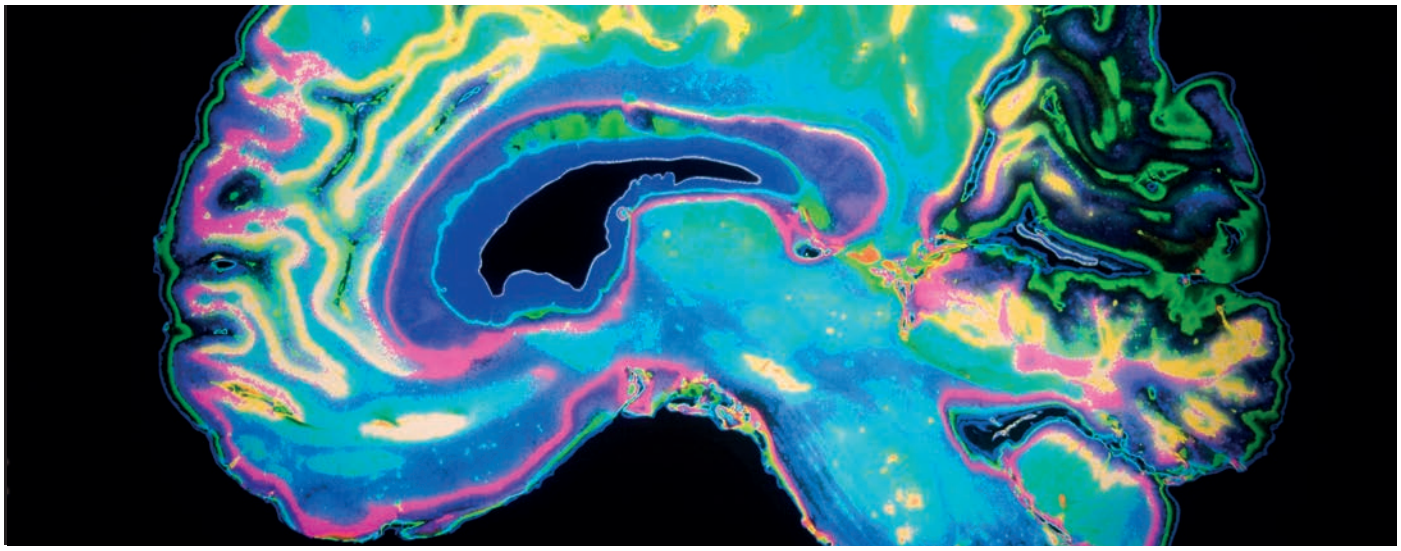

A healthy brain, like this one, has many folds and grooves. A discovery by NAIST researchers could help treat lissencephaly, during which these features fail to develop.

Embryology

Protein does double duty in cell migration

Doublecortin protein has two different roles in controlling how the brain develops

As the fetal brain develops, young brain cells known as neuronal progenitor cells need to migrate from where they are formed to their final home in the cerebral cortex. When that fails to happen, the brain's folds and wrinkles don't develop properly; a condition known as 'smooth brain', or lissencephaly, which leads to developmental delays, seizures and respiratory problems.

> **"Dual and coordinated regulation of two cytoskeleton systems by one molecule was a very exciting finding."**

A number of different proteins and signalling molecules are involved in controlling that migration, and a team of researchers at Japan's NAIST has mapped one pathway that controls when and how the cells get moving.

Within that pathway, they found a surprise: a protein called Doublecortin (DCX) has two different functions when it comes time for the cell's internal scaffolding — the cytoskeleton — to begin moving the cells along on their journey.

"Dual and coordinated regulation of two cytoskeleton systems by one molecule was a very exciting finding," says Hiroshi Itoh, a molecular biologist at NAIST who led the work.

Cellular migration is triggered when a signalling molecule called pituitary adenylyl cyclase-activating peptide (PACAP) binds to a receptor that spans the membrane of the neuronal progenitor cell. That receptor, part of an important class of proteins called G-protein coupled receptors, induces the activation of protein kinase A (PKA) in the cell. PKA then changes the behaviour of DCX, by adding a phosphate group to one particular area of the protein.

Up until this point, DCX has been holding the cell rigid by bundling one part of the cytoskeleton, the microtubules, together. But once it is phosphorylated by PKA, DCX releases the microtubules and switches its attention to another part of that scaffolding, a protein called actin. It induces the actin to form long filaments that push against the cell membrane from the inside and, freed from the stabilising effect of the microtubules, the cell begins to move towards its final home in the developing brain.

The discovery could help with the treatment of lissencephaly by allowing doctors to treat a fetus with drugs that promote proper migration of neuronal progenitor cells if genetic testing reveals a mutation in the phosphorylation site on DCX, says Itoh.

Itoh's team is now investigating how another protein kinase, called CDK5, might be involved. CDK5 is known to regulate neuronal cell migration and, like PKA, also phosphorylates DCX, but at a different point on the protein. They are analysing the relationship between these two different versions of phosphorylated DCX in controlling cell migration.

Reference

1. Toriyama, M., Mizuno, N., Fukami, T., Iguchi, T., Toriyama, M. *et al. The Journal of Biological Chemistry* **287,** 12691-12702 (2012).

More information about the group's research can be found at the Molecular Signal Transduction webpage:
http://bsw3.naist.jp/eng/courses/courses202.html