Researchers identify critical gene for brain development, mental retardation (w/ Video)

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In laying down the neural circuitry of the developing brain, billions of neurons must first migrate to their correct destinations and then form complex synaptic connections with their new neighbors.

When the process goes awry, neurodevelopmental disorders such as mental retardation, dyslexia or autism may result. Researchers at the University of North Carolina at Chapel Hill School of Medicine have now discovered that establishing the neural wiring necessary to function normally depends on the ability of neurons to make finger-like projections of their membrane called filopodia.

The finding, published as the cover story of the Sept. 4 issue of the journal *Cell,* indicates that the current notion regarding how cells change shape, migrate or differentiate needs to be revisited.

Scientists have thought that the only way for a cell to morph and move is through the action of the cytoskeleton or the scaffold inside the cell, pushing membrane forward or sucking it in, said senior study investigator Franck Polleux, Ph.D., associate professor of pharmacology at the UNC School of Medicine.

But Polleux's study shows that the brain protein srGAP2 can also impose cell shape by directly bending membranes, forming filopodia as a mean to control the migration and branching of neurons during brain development.

Interestingly, srGAP2 is one of a family of proteins that have been implicated in a severe mental retardation syndrome called the 3p- syndrome. Therefore this research could also yield important insights into the underlying causes of this and other forms of mental retardation.

Polleux and his colleagues began looking at srGAP2 because the gene was almost exclusively "turned on" or expressed during brain development. The brain protein contains a unique combination of domains - small functional chunks of protein sequence that may be common to other proteins as well. The star of these domains is one called the F-BAR domain, one of a handful of similarly termed "BAR domains" that have recently become a hotbed of research.

The UNC researchers were among the first to master a laboratory technique that enabled them to manipulate which genes are turned on or off in neurons, a notoriously difficult cell type.

Working with slices of mouse brain, they used electrical current to introduce pieces of genetic material that would either ramp up or, conversely, knock down the action of the protein's F-BAR domain. They then cultured brain slices in petri dishes allowing researchers to watch how the neurons behaved 'in the wild' in their native environment. When the researchers ramped up the activity of the domain, they saw that the neurons formed the finger-like filopodia which blocked migration by inducing too many branches.

"The textbook notion is that F-BAR proteins fold inward, but here we show it can do the opposite" said Polleux. "This is a completely novel mechanism for producing filopodia."

The researchers then found that when they reduced the expression of this protein, the neurons migrated at a faster rate and branched less. Under a microscope, neurons move like little inchworms. In front, the long thin

cellular protrusion of the neuron extends, pauses, then drags the bulbous cell body behind it, then extends again, and so on.

Polleux says the F-BAR domain of srGAP2 appears to tightly control the amount of branching neurons undergo so they can be more streamlined when they need to migrate, and branch when they need to establish connections with other neurons.

Because disruptions in these critical connections would have detrimental effects on brain development, Polleux will now collaborate with clinicians at UNC to determine whether mutations in the srGAP2 gene are involved in autism or in other forms of mental retardation in addition to the 3p- syndrome. His laboratory is also interested in determining the function of approximately 25 other genes containing F-BAR-like domains, many of which are expressed in the developing brain.

Source: University of North Carolina School of Medicine (news : web)