How Rett Syndrome mutation targets the brain

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Researchers have pinpointed why mutations that cause Rett Syndrome (RTT)--among the leading causes of mental retardation in females--specifically target the brain rather than other body tissues. They said their findings yield important insight into the origin and course of the disease.

RTT has been especially puzzling because girls with the disorder develop normally through the first 6 to 18 months of life. But then they lose motor skills and speech, their heads cease normal growth, and they begin to show irregular breathing, obsessive hand-wringing, and autistic behaviors.

Researchers had traced the RTT's cause to mutations in the gene for methyl-CpG-binding protein 2 (MeCP2)--a protein found in tissues throughout the body that regulates many target genes by repressing their activity. The gene for MeCP2 is found on the X chromosome, which is why females, with two X chromosomes, are far more likely to suffer from RTT than are males.

In their new studies, reported in the October 19, 2006, issue of the journal *Neuron*, published by Cell Press, Michael Greenberg and colleagues tackled a central mystery of the disorder: why mutations in the MeCP2 gene specifically produce neural pathology. They also sought to understand why the pathology of RTT does not appear until well into infant development.

In experiments with rats and mice, the researchers identified a particular site, called S421, on the MeCP2 protein that is the trigger site for activating MeCP2 during its normal function. MeCP2 is activated by a process called phosphorylation, in response to neuronal activity, as when the brain receives sensory experience, they found. Without such activation, as occurs when MeCP2 is "crippled" by a mutation affecting S421, the protein does not function properly.

Particularly significant was the researchers' finding that MeCP2 is selectively phosphorylated at the S421 site only in the brain. This specificity explains why mutations affecting that site target brain development, they said.

The researchers' experiments showed that mutating the MeCP2 gene specifically at the S421 site disrupts normal growth of interconnections, called dendrites, among neurons. Such growth is necessary for the brain to wire itself normally in response to experience. Dendrites are the structures that form one side of the contacts, called synapses, among neurons.

"In this study, we identify an important missing link in the synaptic hypothesis of RTT by identifying S421 as a major site of activity-dependent modification on MeCP2 that is required for the maturation of neuronal connectivity, thereby providing a potential mechanism by which experience-dependent stimuli might regulate MeCP2 function," concluded the researchers.

They wrote that "These findings suggest a key role for the activity-dependent regulation of MeCP2 in the maturation of neuronal connectivity and provide a new framework for understanding how mutations in MeCP2 lead to the deregulation of these processes in RTT."

Source: Cell Press