The APCs of nerve cell function

June 16 2008

Rapid information processing in the nervous system requires synapses, specialized contact sites between nerve cells and their targets. One particular synapse type, cholinergic, uses the chemical transmitter acetylcholine to communicate between nerve cells. Cholinergic synapses are essential for normal learning and memory, arousal, attention, and all autonomic (involuntary) nervous system functions. Malfunction of cholinergic synapses is implicated in Alzheimer's disease, age-related hearing loss, autonomic neuropathies, and certain forms of epilepsy and schizophrenia. Despite the importance of cholinergic synapses for cognitive and autonomic functions, little is known about the mechanisms that direct their assembly during development.

In a new study published in the June 2008 issue of *Molecular and Cellular Neuroscience*, researchers at Tufts University School of Medicine (TUSM), uncover mechanisms that direct cholinergic synapse assembly between neurons in vivo.

"We have identified the protein adenomatous polyposis coli (APC) as a key organizer of a multi-protein complex that is required for assembly of neuronal cholinergic synapses" says corresponding author Michele H. Jacob, PhD, professor of neuroscience at TUSM and member of the neuroscience program faculty of the Sackler School of Graduate Biomedical Sciences.

"APC is expressed in all cell types and has multiple functions and binding partners. It is best known for its role in colorectal cancer. Our work defines a novel role for APC in neurons. We show that APC brings

together several proteins at the synapse and coordinates their functions in directing the surface membrane delivery and stable retention of nicotinic acetylcholine receptors at the synapse."

"A single nerve cell synthesizes multiple different neurotransmitter receptor types. The nerve cell must target each of them to distinct synaptic sites that oppose incoming nerve cell contacts that release the correct transmitter to activate that receptor type. Matching of receptor and transmitter types is critical for proper function," states Madelaine Rosenberg, PhD, first author and research associate in the department of neuroscience at TUSM.

Rosenberg says that APC and its associated proteins play a key role in accomplishing this task at cholinergic synapses. The authors report that APC interacts with and positions the microtubule plus-end binding protein EB1 and thereby directs the delivery of acetylcholine receptors to restricted surface membrane regions. APC and EB1 interact with other proteins, cytoskeletal regulators and adapter proteins, which together stabilize the scaffold at the synapse and link acetylcholine receptors to APC at the complex. This study identifies several novel components of neuronal nicotinic cholinergic synapses.

Jacob and colleagues showed that blocking APC function led to dramatic and specific decreases in acetylcholine receptor levels at synapses. They showed this by using molecular techniques to manipulate APC protein interactions during synapse formation. "We study an in vivo model system to gain insights into mechanisms that likely direct synapse assembly and function in the human nervous system," Jacob explains. She further suggests that their data "support the emerging concept that APC is a central organizer of a core multi-protein complex that directs the assembly of excitatory, but not inhibitory, synapses in the vertebrate nervous system.

The importance of APC's neural role is highlighted by reports that loss of function gene mutations correlate with mental retardation, schizophrenia, and autism spectrum disorders." Jacob notes, "By identifying the synapse organizing role of APC and its associated proteins, our findings bring us closer to understanding disorders of cognition and neurological function on a molecular level."

Source: Tufts University