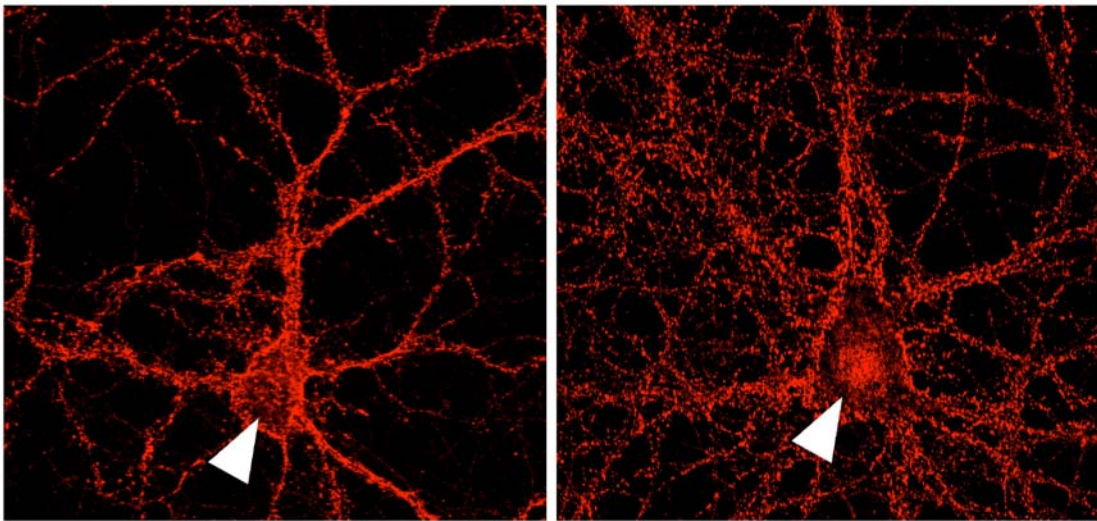


Catenin cleft: Calpain-mediated cleavage of β -catenin in novel signaling pathway

February 19, 2007 – The molecule β -catenin famously plays a dual role as a binding partner of the classic cadherin machinery in cell-cell adhesion, and as a critical component in the Wnt signaling pathway, which features in so many developmental and differentiative processes. New work from the Laboratory for Cell Adhesion and Tissue Patterning (Masatoshi Takeichi; Group Director) now suggests that this same protein participates in a hitherto unreported signaling pathway in the nervous system. This study, performed by Kentaro Abe, a Ph. D. candidate at the Kyoto University Graduate School of Biostudies, revealed that post-synaptic activation of the NMDA receptor triggers a novel pathway in which β -catenin is cleaved by the enzyme calpain before entering the nucleus to initiate gene transcription.



In cultured hippocampal neurons, β -catenin could be found only at synapses (left) but, after stimulation with glutamate (right), β -catenin signal was also observed in the nucleus (indicated with arrowhead).

“The study actually began when I was looking into possible interactions between neuronal activity and cadherin adhesion,” says Abe. “But what I found was when I treated neurons in culture with an agent that activates the NMDA receptor, truncated fragments of β -catenin began appearing in the cells.” This sparked a search for a mechanism by which the full-length catenin could be cut into smaller lengths, which ultimately led to the identification of calpain, a proteolytic enzyme known for its roles in cell cycle progression and apoptosis.

Abe found that after NMDA-R activation, calpain cleaves the N-terminus of the β -catenin protein, protecting it from degradation within the cytoplasm. Ordinarily, full-length β -catenin is phosphorylated by the kinase GSK3 β , marking it for ubiquitination and digestion in the proteasome. Activation of the Wnt pathway protects against this degradation, allowing β -catenin to make its way into the nucleus, associate with the transcription factor Tcf/Lef, and activate the transcription of various genes. Interestingly, β -catenin cleaved by calpain is also safeguarded from destruction in the cytoplasm and thus able to reach the nucleus and engage transcription. “While the evidence is not yet conclusive, it appears possible that calpain even cleaves β -catenin that is bound to cadherin, which, if it

proves to be true, would set up a link between neuronal activity and a loosening of the adhesion between cells at the synapse,” notes Abe.

Additional tests confirmed that this cleavage of β -catenin could be blocked by the administration of a calpain inhibitor, and its effects on Tcf-dependent gene transcription could be mimicked by the transfection of β -catenin fragments of the same length. Abe next turned to the question of what genes might be activated by this pathway, and on analyzing transcripts amplified by RT-PCR, finding that *Fos/1*, a gene also activated by the canonical Wnt pathway, was upregulated after NMDA-R stimulation by glutamate (which leads to calpain activation). Again, this effect was blocked by calpain inhibition and duplicated in experiments using exogenous β -catenin fragments, strongly indicating that a novel pathway in which NMDA-R induces calpain to cleave β -catenin was being used to initiate the transcription of genes in hippocampal neurons.

Looking ahead, Abe says, “For the next step, I’d like to try to work out what role this transcriptional activity plays in nervous system functions such as memory and learning. And, of course, a possible scenario in which neuronal activation sets off interactions between cellular adhesion and transcriptional pathways remains intriguing.”