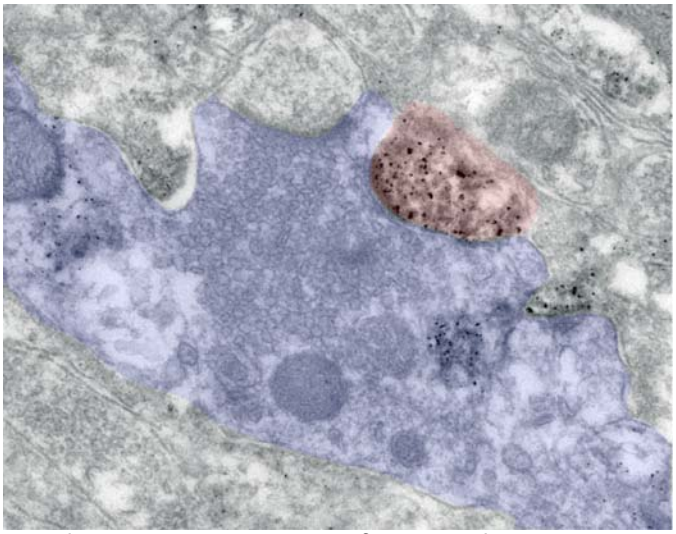
RIKEN Center for Developmental Biology (CDB)
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan

Cold proof: Cadherin-8 in neural circuitry and cold sensation

April 6, 2007 – The classic cadherin family of membrane proteins is best known as essential for its mediation of the cell-cell adhesion that enables multicellular organization, which is primarily achieved through homophilic binding between two identical extracellular domains. The role of these cadherins in the maze of neuronal components that comprises neural circuitry, however, is less clear.

Now, in an article published in *The Journal of Neuroscience*, Sachihiro Suzuki of the Laboratory for Cell Adhesion and Tissue Patterning (Masatoshi Takeichi; Group Director) and his collaborators have demonstrated that one of classic cadherins, cadherin-8 (cad8), is essential for the synaptic transmission of cold sensation, as evidenced by the the finding that cad8 knockout mice (cad8$^{-/-}$) are insensitive to cold stimuli.



Immunoelectron microscopic image of a synapse between an axon of a cad8-expressing sensory neuron (blue) and a dendrite of a cad8-expressing neuron in the dorsal part of the spinal cord (red)

Each classic cadherin subtype is differentially expressed by functionally connected neurons, a property that Suzuki had been studying for some time. In his efforts to develop a better understanding of the potential roles of different subtypes in the nervous system, he generated cadherin-8 (cad8) knockout mice. "We noticed that knocking out cad8 in mice led to the animals raising their tails [see movie below] — a phenotype similar to that observed on morphine administration," says Suzuki. As both the μ-opioid receptor and cad8 are heavily expressed in the dorsal spinal cord, which is important for such somatic sensations as temperature, pain and touch, the group set out to examine cad8's exact role by focusing on neural circuitry in that region of the mouse nervous system.

Suzuki first identified the types of cells that express cad8 as sensory neurons in the DRG, and examined the relationship between cad8-expressing sensory neurons and cad8-expressing DH neurons. They found a significant overlap between cad8 sensory neurons and those expressing TRPM8, a cold and menthol receptor in DRG: most of the cad8-expressing neurons also expressed TRPM8, and vice versa. Electron microscopy showed that synapses were formed between sensory neurons and DH neurons expressing cad8. Next they examined effects of cad8 genetic

Contact: Douglas Sipp sipp@cdb.riken.jp TEL: +81-78-306-3043
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ablation on their connection and found that even in the absence of cad8, synapses still formed. The group also performed electrophysiological analyses to examine the effects of loss of cad8 on functions of the synapses. Although cad8-expressing DH neurons received inputs from menthol activated fibers (that is TRPM8-expressing sensory neurons in the cad8$^{+/-}$ population), originally cad8-expressing DH neurons in cad8$^{-/-}$ did not receive functional input from TRPM8-expressing sensory neurons. Based on these results, the authors concluded that cad8 is not essential for formation of synapses between cad8-expressing sensory neurons and cad8-expressing DH neurons, but is somehow involved in the physiological function of the synapses between them.

[movie]
Tail-raising phenotype of cadherin8-knockout mouse (top); wildtype shown below

Suzuki et al. further observed that a single cad8-expressing sensory neuron expresses nearly 10 classic cadherins, and that β-catenin and αN-catenin, which are binding partners of classic cadherins, were still localized at the originally cad8-localized synapses in cad8$^{-/-}$. They speculated that cell-cell adhesion at the synapses between TRPM8-expressing sensory neurons and their target DH neurons were linked by cadherins other than cad8 in cad8$^{-/-}$. Despite the presence of other cadherin subtypes in the synapse, however, cad8-deficient synapses were functionally abnormal. This suggests that this particular cadherin has a unique physiological function that cannot be replaced by other members of the classic cadherins, indicating that these molecular family members cannot be regarded as being functionally identical.

Suzuki notes that, “cad8 may facilitate synaptic vesicle release at the axon terminals of TRPM8-expressing sensory neurons. In the future, we aim to clarify how cad8 regulates activities of the synapses between TRPM8-expressing neurons and their target neurons in the spinal cord in more detail.”

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