Endogenous Non-retroviral RNA Virus Elements in Mammalian Genomes

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Nature, **463**, 84-87 (2010)

This paper shows the first evidence for endogenization of non-retroviral RNA virus in mammalian species. We discovered the elements homologous to the nucleoprotein (N) gene of bornavirus, a non-segmented, negative strand RNA virus, in the genomes of several mammals including humans, non-human primates, rodents and elephants. We also demonstrated that N mRNA of a current bornavirus, Borna disease virus (BDV), is reverse-transcribed and integrated into the genome DNA of persistently infected cells, although BDV does not encode reverse transcriptase gene. Our findings provide novel insights not only into generation of endogenous

elements of RNA viruses but also into a role of bornavirus as a source of genetic novelty in its host.

Brownian Search-and-catch Mechanism for Myosin-VI Steps

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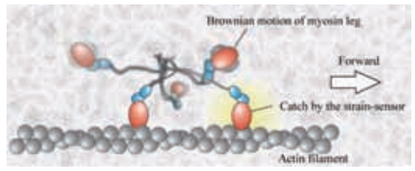
Nature Chemical Biology, **5**, 403-405 (2009)



Myosin-VI is a two-legged cargo transporter that "walks" along an actin filament in cells. During walking motion, myosin leg undergoes Brownian motion, resulting in a "drunkenly walking". A key question is how the Brownian leg searches for and catches the forward actin target. Here, we developed a rapid (micro-second) mechanical manipulation technique using optical tweezers and applied force to the single Brownian leg. We found the strongly catch in the forward actin is accelerated by the mechanical strain. We propose the strain-dependent asymmetric catch mechanism is the origin of the rectification of the Brownian motion and would be useful for efficient and adaptable walking in the cell.

Protein Kinase G Dynamically Modulates TASK1-Mediated Leak K^+ Currents in Cholinergic Neurons of the Basal Forebrain

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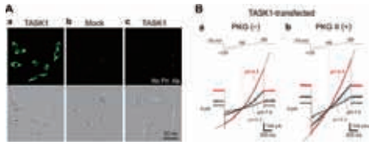
The Journal of Neuroscience, **30**, 5677-5689 (2010)



Leak K^+ conductance generated by TASK1/3 channels is crucial for neuronal excitability. However, endogenous neuromodulators activating TASK channels remained unknown. We demonstrated that PKG activation and inhibition respectively up- and down-regulates TASK1 channels heterologously expressed in PKG-loaded HEK293 cells at physiological pH, by shifting the pH-sensitivity of TASK1 channels in the acidic and basic directions, respectively. In the cholinergic basal forebrain (BF) neurons, similar modulations of TASK1-like pH-sensitivity of leak K^+ currents were caused by PKG. It is strongly suggested that PKG activation and inhibition dynamically modulate TASK1 currents at physiological pH by bidirectionally changing K_d values for protonation of extracellular pH-sensors of TASK1 channels in cholinergic BF neurons.

Protocadherin-α family is required for serotonergic projections to appropriately innervate target brain areas.

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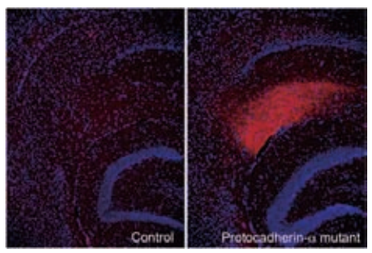
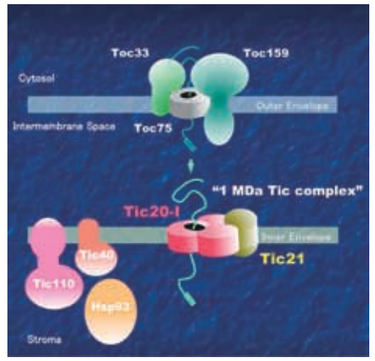
The Journal of Neuroscience, **29**, 9137-9147 (2009)

Serotonergic neurons play a pivotal role in psychiatric disorders such as depression. Serotonergic neurons in the brainstem project their axons to every region of the brain. However, this molecular mechanism had been almost unknown. We found that protocadherin-α genes, encoding transmembrane proteins, were strongly expressed in serotonergic neurons, and that in protocadherin-α mutant mice serotonergic axons were abnormally clumped in the areas proximal to the final target brain areas such as the hippocampus (see the figure). This result demonstrates that protocadherin-α proteins regulate the distribution of serotonergic axon terminals.





A 1-Megadalton Translocation Complex Containing Tic20 and Tic21 Mediates Chloroplast Protein Import at the Inner Envelope Membrane

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The Plant Cell, **21**, 1781-1797 (2009)

Nuclear-encoded chloroplast proteins are synthesized in the cytosol and posttranslationally imported across the double envelope membranes of chloroplasts. The chloroplastic outer and inner envelope membranes contain multisubunit machinery for the import of preproteins, termed the Toc and the Tic complexes, respectively. This work describes the identification of a 1-MDa translocation complex as a novel intermediate during general protein translocation across the inner membrane of chloroplasts. Tic20 and Tic21 are involved in the 1-MDa complex, whereas Tic110, the most characterized component of the protein translocon at the inner membrane, exists as a distinct entity from the 1-MDa complex.

A Transposon-based Chromosomal Engineering Method to Survey a Large *Cis*-regulatory Landscape in Mice.

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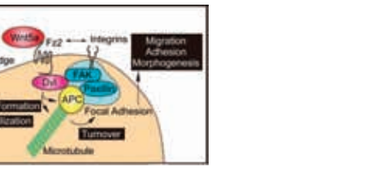
Nature Genetics, **41**, 946-952 (2009)

The widespread existence of large *cis*-regulatory regions is a remarkable feature of mammalian genomes and potentially involved in the etiology of human genomic disorders. Characterization of such regions, however, has been hampered by the limited availability of tools for manipulating large genomic regions in model animals. Here we propose a novel experimental approach using targeted integration of the Sleeping Beauty transposon into the mouse genome. The "local hopping" capability of the transposon allowed scanning of the surrounding genomic region with a reporter gene cassette, revealing the location and territory of enhancer actions along the chromosome.



Binding of APC And Dishevelled Mediates Wnt5a-Regulated Focal Adhesion Dynamics in Migrating Cells

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The EMBO Journal, **29**, 1192-1204 (2010)

Wnt5a is a representative ligand that activates the Wnt/β-catenin-independent pathway, resulting in the regulation of cell adhesion, migration, and polarity, but its molecular mechanism is not clear. This report showed that Dishevelled (Dvl) binds to adenomatous polyposis coli gene product (APC) and that this binding is enhanced by Wnt5a. Dvl co-localized with APC at the leading edge of migrating cells and both proteins associated with focal adhesion components. Frizzled2 (Fz2), a Wnt5a receptor, was present with Wnt5a at the leading edge and interacted with integrins. These results suggest that the binding of APC to Dvl is involved in Wnt5a-dependent focal adhesion turnover and migration.

Defined factors induce reprogramming of gastrointestinal cancer cells

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Proceedings of National Academy of Sciences of the United States of America, **107**, 40-45 (2010)

We assessed the effects of the induction of immature status-related genes and showed the introduction of induced pluripotent stem cells with retroviral-mediated methods in gastrointestinal cancer cells. The pluripotency was represented in the induced cells, and the induced pluripotent cancer (iPC) cells were remarkably distinct from parental cancer cells. To determine the differentiation ability, iPC cells were grown in differentiation- stimulating culture condition. These cultured cells, termed post-iPC cells, showed slow proliferation and were sensitized to chemotherapy and differentiation-inducing reagents *in vitro*. *In vivo* analysis showed that tumorigenesis was reduced. These results demonstrated the novel cancer treatment in addition to the conventional therapy, and the exploitation of drug producing strategy towards future clinical applications.