RGMa Modulates T Cell Responses And Is Involved in Autoimmune Encephalomyelitis

Muramatsu, R.[*1]; Kubo, T.; Mori, M.; ***Nakamura, Y.***[*1]; ***Fujita, Y.***[*1]; Akutsu, T.; ***Okuno, T.***[*2]; Taniguchi, J.; ***Kumanogoh, A.***[*2]; Yoshida, M.; Mochizuki, H.; Kuwabara, S.; ***Yamashita, T.***[*1]
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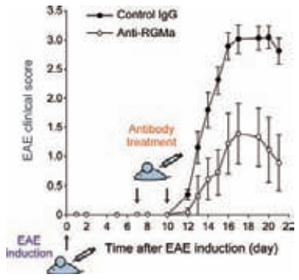
Nature Medicine, **17,** 488-494 (2011)

Murine experimental autoimmune encephalomyelitis (EAE) is a widely accepted model for studying the clinical and pathological features of multiple sclerosis (MS). Onset of EAE is characterized by T cell activation controlled by antigen presenting cells, i.e. dendritic cells (DCs). Here, we show that repulsive guidance molecule a (RGMa), expressed in DCs, activates CD4 T cells. RGMa-stimulated CD4 T cells exhibited intracellular adhesion molecule -1 (ICAM-1) by a mechanism dependent on Rap1 activation. Treatment with anti-RGMa antibodies reduced invasion of inflammatory mononuclear cells and prevented progression of EAE. These findings suggest that RGMa may be a promising molecular target for treating MS.



Recovery of Motoneuron and Locomotor Function After Spinal Cord Injury Depends on Constitutive Activity in 5-HT2C Receptors

Murray, KC.; ***Nakae, A.***; Stephens, MJ.; Rank, M.; D'Amico, J.; Harvey, PJ.; Li, X.; Harris, RLW.; Ballou, EW.; Anelli, R.; Heckman, CJ.; ***Mashimo, T.***; Vavrek, R.; Sanelli, L.; Gorassini, MA.; Bennett, DJ.; Fouad, K.
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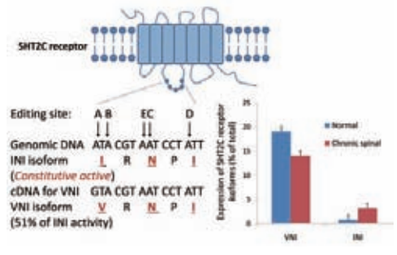
Nature Medicine, **16(6),** 694-701(2010)

Muscle paralysis after spinal cord injury is partly caused by a loss of brainstem-derived serotonin (5-HT), which maintains motoneuron excitability by regulating persistent calcium currents. We find that changes in posttranscriptional editing of 5-HT2C receptor mRNA lead to increased expression of isoforms that are constitutively active without 5-HT. Such receptor activity restores large persistent calcium currents without 5-HT. This helps motoneurons recover their ability to produce sustained muscle contractions. However, without regulation from the brain, these sustained contractions can also cause muscle spasms. By blocking constitutively active 5-HT2C receptors, we may provide a new rationale for antispastic drug therapy.



AMPK Controls the Speed of Microtubule Polymerization and Directional Cell Migration via CLIP-170 Phosphorylation

Nakano, A.; ***Kato, H.***; Watanabe, T.; Min, K.; Yamazaki, S.; ***Asano, Y.***; Seguchi, O.; ***Higo, S.***; ***Shintani, Y.***; Asanuma, H.; Asakura, M.; ***Minamino, T.***; Kaibuchi, K.; Mochizuki, N.; Kitakaze, M.; ***Takashima, S.***
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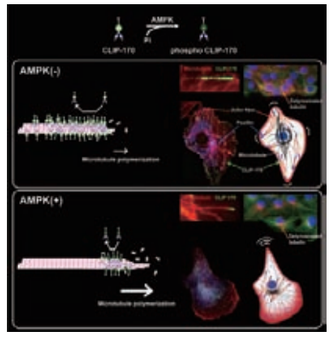
Nature Cell Biology, **12(6),** 583-590 (2010)

AMPK is a stress response kinase which is activated by ATP consuming cellular conditions and have pivotal roles in establishment of cellular polarity. Its molecular mechanism, however, has been unknown. We purified and identified the AMPK substrate CLIP-170 and revealed the physiological importance in cell polarity by AMPK-CLIP170 singling. This report shows that inhibition of AMPK leads to prolonged and enhanced accumulation of CLIP-170 at microtubule tips and impaired microtubule dynamics, resulting disturbance of cell polarity and directional cell migration. These data clarified the novel stress response via the regulation of microtubule polymerization against energy consuming cellular conditions.



Crystal Structure of *Legionella* DotD: Insights into the Relationship between Type IVB and Type II/III Secretion Systems.

Nakano, N.[*1]; ***Kubori, T.***[*1,2]; ***Kinoshita, M.***[*2]; ***Imada, K.***[*2]; ***Nagai, H.***[*1]
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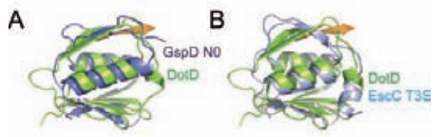
PLoS Pathogens, **6(10),** e1001129 (2010)

The Dot/Icm type IVB secretion system is a membrane-associated transporter complex used by the bacterial pathogen *Legionella pneumophila*. More than 200 bacterial proteins are delivered into host cytoplasm via this system, modulating host cellular functions to establish a replicative niche within host cells. Here we report the crystal structure of DotD, an outer membrane lipoprotein of the core complex. The C-terminal domain of DotD is remarkably similar to the N-terminal subdomains of secretins, the integral outer membrane proteins that form substrate conduits for the bacterial type II and type III secretion systems (GspD and EscC, respectively). This finding uncovers an intriguing link between distinct bacterial secretion systems.



▲From Nakano,N: et al. (2010) Crystal Structure of *Legionella* DotD: Insights into the Relationship between Type IVB and Type II/III Secretion Systems. ***PLoS Pathog*** 6(10):e1001129. doi:10.1371/journal.ppat.1001129

Switch between Large Hand-Over-Hand and Small Inchworm-like Steps in Myosin VI

Nishikawa, S.; Arimoto, I.; Ikezaki, K.; Sugawa, M.; Ueno, H.; ***Komori, T.***[*1,2]; ***Iwane, A. H.***[*1,2]; ***Yanagida, T.***[*1,3]
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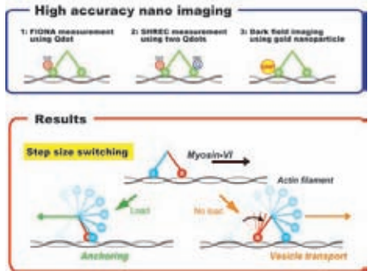
Cell, **142,** 879-888 (2010)

Unlike other molecular motors, myosin VI has much larger and broadly distributed step sizes than those predicted from its structure. Here, this discrepancy was consistently elucidated by highly sensitive single molecule imaging technique. The large step sizes and its variability were attributed to an extended rigid lever arm and two distinct tilt angles which causes newly found large and small step size. The large steps are consistent with the previously reported hand-over-hand mechanism, while the small steps follow inchworm-like mechanism. Switching between these two mechanisms with ADP-dependent manner grants strain-sensitivity to fulfill multiple cellular tasks including vesicle transport and membrane anchoring of myosin VI.

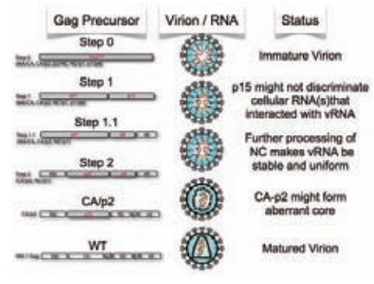


The Relationship between HIV-1 Genome RNA Dimerization, Virion Maturation and Infectivity.

Ohishi, M.; Nakano, T.; ***Sakuragi, S.***; ***Shioda, T.***; Sano, K.; and ***Sakuragi, J.***
(Research Institute for Microbial Diseases)

Nucleic Acids Research**, 39,** 3404-3417 (2011)

We have constructed HIV-1 Gag cleavage site mutants to enable the steady state observation of virion maturation steps, and precisely study Gag processing, RNA dimerization, virion morphology and infectivity. Within the virion maturation process, the RNA dimer stabilization begins during the primary cleavage (p2-NC) of Pr55 Gag and the ensuing cleavages are required for the completion of dimerization. Interestingly, although the endogenous virion RT activity was fully acquired at the initial step of maturation, the following process was necessary for viral DNA production in infected cell, suggesting the maturation of viral RNA/protein plays critical role for viral infectivity other than RT process.



Streptolysin S Contributes to Group A Streptococcal Translocation across Epithelilal Barrier

Sumitomo, T.[*1]; ***Nakata, M.***[*1]; ***Higashino, M.***[*1]; ***Jin, Y.***[*2]; ***Terao, Y.***[*1]; ***Fujinaga, Y.***[*2]; ***Kawabata, S.***[*1]
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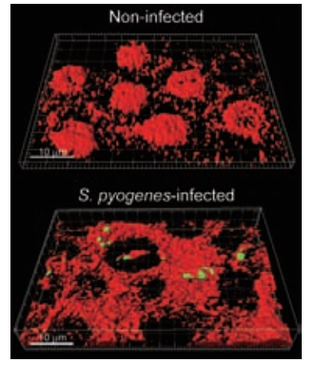
The Journal of Biological Chemistry, **286,** 2750-2761 (2011)

Streptococcus pyogenes is an important human pathogen that causes a range of invasive infections. In this paper, we found that streptolysin S (SLS) is a crucial bacterial factor for *S. pyogenes* translocation across the epithelial barrier, which is followed by degradation of intercellular junctions. Furthermore, we demonstrated that epithelial calpain plays a critical role in the cleavage of intercellular junctions. Interestingly, following *S. pyogenes* infection, calpain was recruited to the plasma membrane along with E-cadherin. Our findings indicate a potential function of SLS that facilitates *S. pyogenes* invasion into deeper tissues via degradation of epithelial intercellular junctions in concert with the host cysteine protease calpain.

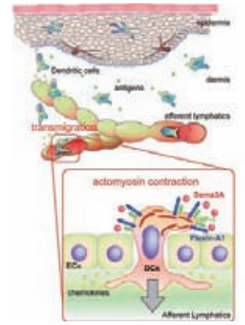


Semaphorins Guide the Entry of Dendritic Cells into the Lymphatics by Activating Myosin II.

Takamatsu, H.[*1]; ***Takegahara, N.***[*1]; ***Nakagawa, Y.***[*1,2]; Tomura, M.; Taniguchi, M.; Friedel, RH.; Rayburn, H.; Tessier-Lavigne, M.; Yoshida, Y.; ***Okuno, T.***[*1,2]; ***Mizui, M.***[*1]; ***Kang, S.***[*1]; ***Nojima, S.***[*1,2]; Tsujimura, T.; ***Nakatsuji, Y.***[*2]; ***Katayama, I.***[*2]; ***Toyofuku, T.***[*1]; ***Kikutani, H.***[*1]; ***Kumanogoh, A.***[*1]
[*1](Immunology Frontier Research Center)
[*2](Graduate School of Medicine)

Nature Immunology **11,** 594-600 (2010)

Recirculation of leukocytes is essential for proper immune responses. However, the molecular mechanisms that regulate leukocyte entry into the lymphatics remain unclear. In this paper, we determined that plexin-A1, a primary receptor component for semaphorins, is crucially involved in the entry of dendritic cells (DCs) into the lymphatics. During DC entry into the lymphatics, Sema3A produced by lymphatic endothelial cells is required for DC transmigration by promoting actomyosin contraction at the trailing edge of migrating DCs. These findings not only demonstrate that semaphorin-signals are involved in DC trafficking but also provide a novel mechanism that induces actomyosin contraction as these cells pass through narrow gaps.



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