CD13 is a Therapeutic Target in Human Liver Cancer Stem Cells

Haraguchi, N.;***Ishii, H.***; Mimori, K.; Tanaka, F.; Ohkuma, M.; ***Kim, H.M.***; ***Akita, H.***; ***Takiuchi, D.***; ***Hatano, H.***; ***Nagano, H.***; Barnard, G.F.; ***Doki,Y.***; ***Mori, M.***
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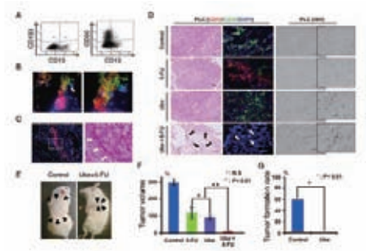
***The Journal of Clinical Investigation,* 120(9),** 3326-3339 (2010)

Cancer stem cells (CSCs) are involved in resistance to chemo-radiation therapy and occurrence of tumor relapse and progression. We demonstrate that CD13+ cells act as potent dormant CSCs in human liver cancer, and thus, suggest a novel approach for treating liver cancer based on CSC concepts. CD13+ cells exhibit a prolonged dye-retaining capacity, highly resist to anti-cancer agents and irradiation. CD13 regulates reactive oxygen species (ROS) scavenger, elicits a reduction in ROS-induced DNA damage after genotoxic chemo-radiation stress, and protects cells from apoptosis. In mouse models, combination with a CD13 inhibitor and free radical inducible chemo-radiation drastically reduced tumor volume and inhibited self-renew activity of CSCs.



Environmental Sex Determination in the Branchiopod Crustacean *Daphnia magna*: Deep Conservation of a *Doublesex* Gene in the Sex-determining Pathway

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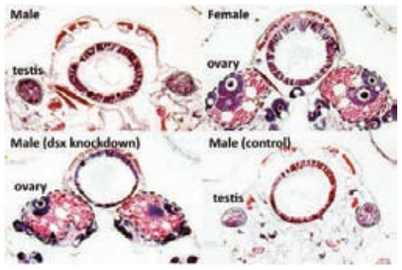
***PLoS Genetics,* 7,** e1001345 (2011)

The authors have found a highly significant connection between the molecular mechanisms underlying genetic and environmental sex determination. Sex determination can be broadly divided into two categories: genetic and environmental. The authors identified a gene responsive for the production of males during environmental sex determination in the crustacean, *Daphnia*. Knocking out the gene in male embryos resulted in the production of female traits and ectopic expression of the gene in female embryos resulted in the production of male traits. The identified gene showed higher similarity to dsx gene, which plays a critical role in controlling sex differentiation in genetic sex determination such as vertebrates.



Enhancement of Odor Avoidance Regulated by Dopamine Signaling in *Caenorhabditis Elegans*

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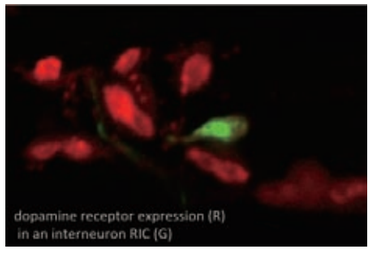
***The Journal of Neuroscience,* 30,**
16365-16375 (2010)

Dopamine regulates locomotion, cognition, emotion and addiction in the mammalian brain. Despite of its significance, molecular basis of dopamine action, especially *in vivo*, remains unclear. We studied dopamine-dependent neural function in the nematode *C. elegans* as a model for genetic analysis of *in vivo* dopamine signaling. We found that odor avoidance behavior of *C. elegans* is enhanced after preexposure to the odor, and that the enhancement requires dopamine signaling via a D2-like dopamine receptor in a pair of interneurons. Moreover, D2-type dopamine receptor antagonists, such as the antipsychotic drug haloperidol, specifically suppressed the enhancement. Thus, our data suggest a new genetic and pharmacological paradigm for neural function regulated by dopamine signaling.



Transition from Positive to Neutral in Mutation Fixation along with Continuing Rising Fitness in Thermal Adaptive Evolution

Kishimoto, T.; ***Iijima, L.***[*2]; Tatsumi, M.; ***Ono, N.***[*1]; Oyake, A.; Hashimoto, T.; Matsuo, M.; Okubo, M.; ***Suzuki, S.***[*1]; Mori, K.; Kashiwagi, A.; ***Furusawa, C.***[*1]; ***Ying, B.W.***[*1]; ***Yomo, T.***[*1,2]
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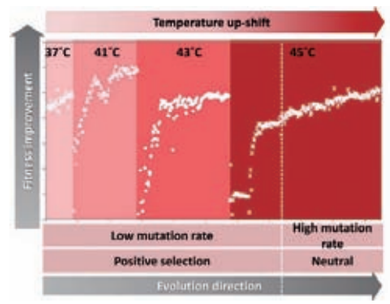
[*2](Graduate School of Frontier Biosciences)

***PLoS Genetics,* 6,** e1001164 (2010)

The paper presents the results of a 2-year evolution experiment in E. coli performed with stepwise increases in temperature. A marked improvement in the upper temperature limit of the endpoint cells was finally achieved. The transition from positive to neutral in mutation fixation on the genome was clearly observed accompanied with increasing fitness, which indicated the independence of the neutrality of mutation fixation and fitness saturation. The neutrality of molecular evolution was clearly observed with the rising fitness of bacterial cells. Such a discrete evolutionary mode occurred in the continuous evolutionary route linking Darwinian adaptive selection with Kimura's neutral evolution.



Pravastatin Induces Placental Growth Factor (PGF) and Ameliorates Preeclampsia in a Mouse Model

Kumasawa, K.[*1,2]; ***Ikawa, M.***[*1]; ***Kidoya, H.***[*1]; ***Hasuwa, H.***[*1]; ***Saito-Fujita, T.***[*1]; ***Morioka, Y.***[*1]; ***Takakura, N.***[*1]; ***Kimura, T.***[*2]; ***Okabe, M.***[*1]
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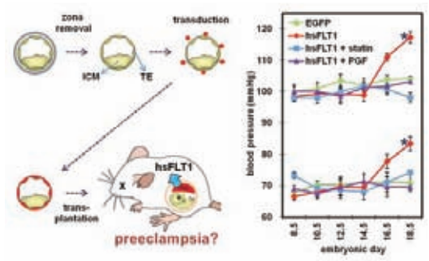
[*2](Graduate School of Medicine)

***Proceedings of National Academy of Sciences of the United States of America,* 108,** 1451-5 (2011)

Preelcampsia affects about 5% of pregnant women and is a major cause of maternal and neonatal morbidity and mortality. Here, we established a unique experimental model using a lentiviral vector-mediated placenta-specific expression of soluble VEGFR1 (sFLT1). The model mice showed hypertension and proteinuria during pregnancy, and the symptoms regressed after parturition. We further showed that pravastatin induced the VEGF-like angiogenic factor, PGF, and ameliorated the symptoms. Our data support the idea that the placenta derived sFLT1 can cause preeclampsia and the statins could be a promising candidate for prevention/amelioration of preeclampsia.



Solution of the Structure of the TNF-TNFR2 Complex

Mukai, Y.[*1]; Nakamura, T.; ***Yoshikawa, M.***[*1]; ***Yoshioka, Y.***[*2]; ***Tsunoda, S.***[*1]; ***Nakagawa, S.***[*1]; ***Yamagata, Y.***; ***Tsutsumi, Y.***[*1]
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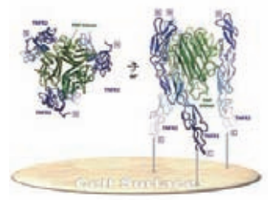
***Science Signaling,* 3,** ra83 (2010)

Tumor necrosis factor (TNF) is an inflammatory cytokine that has important roles in various immune responses, which are mediated through its two receptors, TNFR1 and TNFR2. Antibody based therapy against TNF is used clinically to treat several chronic autoimmune diseases; however, such treatment sometimes results in serious side effects, which are thought to be caused by the blocking of signals from both TNFRs. Therefore, knowledge of the structural basis for the recognition of TNF by each receptor would be invaluable in designing TNFR-selective drugs. Here, we solved the crystal structure of the TNF-TNFR2 complex, which provided insight into the molecular recognition of TNF by TNFR2. Comparison to the known TNFR1 structure highlighted several differences between the ligand binding interfaces of the two receptors. These results may contribute to the design of therapeutics for autoimmune diseases.



Local Microbleeding Facilitates IL-6– and IL-17–Dependent Arthritis in the Absence of Tissue Antigen Recognition by Activated T Cells

Murakmai, M.[*1,2,3]; ***Okuyama, Y.***[*1]; ***Ogura H.***[*1,3]; ***Asano, S.***[*1]; ***Arima, Y.***[*1]; ***Tsuruoka, M.***[*2]; ***Harada, M.***[*1]; ***Kanamoto, M.***[*1]; ***Sawa, Y.***; Iwakura, Y.; Takatsu, K.; ***Kamimura, D.***[*1,2,3]; ***Hirano, T.***[*1,2,3]
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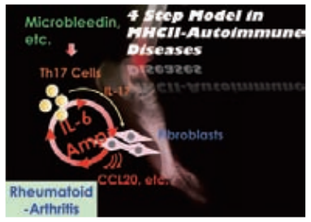
***The Journal of Experimental Medicine,* 208,** 103-114 (2011)

The autoimmune-disease development is believed to be due to a breakdown in CD4+T-cell-tolerance for a tissue-specific-antigen. However, we show initiation of CD4+T-cell-dependent-arthritis in gp130$^{F759/F759}$ mice involves the local accumulation of T$_H$17-cells in the absence of cognate-antigen-recognition. We proposed a Four-Step-Model for MHC-class-II (MHCII)-associated autoimmune-diseases, which have 4-factors followed by a chronic-activation of the IL-17A-triggerred positive-feedback of IL-6-signaling (IL-6-amplifier) in the affected-tissues, (i) activation of CD4+T-cells regardless of the antigen-specificity, (ii) the presence of factors that promote local-accumulation of the T-cells, (iii) transient activation of the IL-6-amplifier in local-tissues by T-cell-cytokines, and (iv) increased sensitivity to the cytokines in these tissues. This model provides a possible explanation for why tissue-specific-antigens recognized by activated CD4+T-cells have not been identified in many MHCII-autoimmune-diseases.



X-ray Crystal Structure of the Light-independent Protochlorophyllide Reductase

Muraki, N.; Nomata, J.; Ebata, K.; Mizoguchi, T.; Shiba, T.; Tamiaki, H. ***Kurisu, G.***; Fujita, Y.
(Institute for Protein Research)

***Nature,* 465,** 110-114 (2010)

The greening ability of photosynthetic organisms is attributed to the role played by protochlorophyllide (Pchlide) oxidoreductase in the formation of the direct precursor of chlorophyll (Chl). Two distinct types of enzymes catalyze the Pchlide reduction: light-dependent and dark-operative type enzymes. Dark-operative Pchlide oxidoreductase (DPOR) is a nitrogenase-like enzyme containing oxygen-sensitive metallocenters. In 2010, we revealed the structural basis of the greening ability of plants in the dark through X-ray crystallographic analysis of the catalytic component of DPOR. The catalytic component of DPOR from the photosynthetic bacterium, *Rhodobacter capsulatus*, was crystallized in its Pchlide-bound and Pchlide-free forms; the structures were resolved to 2.3 and 2.8 Å resolution, respectively.