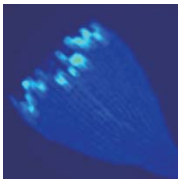
Selected Press Releases from NIBB in 2017

■ 27 January

Discovery of a plant stem cell inducing factor having a similar structure to an animal stem cell inducing factor



The moss *Physcomitrella patens* Cold-Shock Domain Protein 1 (PpCSP1) regulates reprogramming of differentiated leaf cells to chloronema apical stem cells and shares conserved domains with the induced pluripotent stem cell factor Lin28 in mammals. PpCSP1 accumulates in the reprogramming cells and is maintained throughout the reprogramming process and in the resultant stem cells. Genetic manipulation experiments demonstrated a positive role of PpCSP1 in reprogramming, which is similar to the function of mammalian Lin28 (see p. 45).

Li, C., Sako, Y., Imai, A., Nishiyama, T., Thompson, K., Kubo, M., Hiwatashi, Y., Kabeya, Y., Karlson, D., Wu, S.-H., Ishikawa, M., Murata, T., Benfey, P.N., Sato, Y., Tamada, Y., and Hasebe, M. (2017). A Lin28 homolog reprograms differentiated cells to stem cells in the moss *Physcomitrella patens*. Nat. Commun. 8, 14242.

■ 7 February

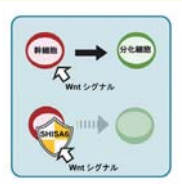
Genome of the pitcher plant Cephalotus reveals genetic changes associated with carnivory

To investigate the molecular bases of carnivory, our research group sequenced the genome of the heterophyllous pitcher plant *Cephalotus follicularis*, in which they succeeded in regulating the developmental switch between carnivorous and non-carnivorous leaves. Transcriptome comparison of the two leaf types and gene repertoire analysis identified genetic changes associated with prey attraction, capture, digestion and nutrient absorption. These results imply constraints on the available routes to evolve plant carnivory (see p. 45).

Fukushima, K., Fang, X., et al. (2017). Genome of the pitcher plant *Cephalotus* reveals genetic changes associated with carnivory. Nat. Ecol. Evol. 1, 0059.

■ 10 February

A mechanism regulating self-renewal and differentiation of sperm stem cells -how stem cells are protected from differentiation-promoting signals

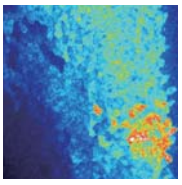


In the seminiferous tubules of mouse testes, a population of GFRα1-positive spermatogonia harbors stem cell functionality. The research group showed that activation of Wnt/β-catenin signaling promotes sperm differentiation and reduces the GFRα1^{+} cell pool. They further discovered that SHISA6, characterized as a cell-autonomous Wnt inhibitor, confers GFRα1^{+} cells resistance to the Wnt/β-catenin signaling. The difference in the effect of Wnt signaling caused by the presence or absence of SHISA6 can produce both self-renewing stem cells or differentiating cells in the uniform tissue environment (see p. 35).

Tokue, M., Ikami, K., Mizuno, S., Takagi, C., Miyagi, A., Takada, R., Noda, C., Kitadate, Y., Hara, K., Mizuguchi, H., Sato, T., Taketo, M.M., Sugiyama, F., Ogawa, T., Kobayashi, S., Ueno, N., Takahashi, S., Takeda, S., and Yoshida, S. SHISA6 confers resistance to differentiation-promoting Wnt/β-catenin signaling in mouse spermatogenic stem cells. Stem Cell Reports, 8, 561-575, 2017.

■ 7 March

Fluctuation in the concentration of calcium ions contributes to neural tube shape formation

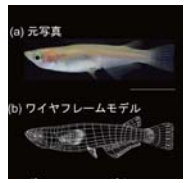


Our research group showed that during the process of neural tube formation a transient increase in the concentration of calcium ions in cells causes morphological changes and is essential for neural tube formation. The group observed the cell population during neural tube formation in *Xenopus laevis* embryos using the fluorescent protein GECO, an intracellular Ca^{2+} concentration indicator. They found that the pattern of the fluctuation in intracellular calcium ion concentration in the cell population is complex. Local and transient rises in intracellular calcium ion concentrations have been found to cause cell deformation and contribute to the formation of the neural tube (see p. 26).

Suzuki, M., Sato, M., Koyama, H., Hara, Y., Hayashi, K., Yasue, N., Imamura, H., Fujimori, T., Nagai, T., Campbell, RE., and Ueno, N. (2017). Distinct intracellular Ca^{2+} dynamics regulate apical constriction and differentially contribute to neural tube closure. Development 144, 1307-1316.

■ 12 April

Three-dimensional computer graphic animation for studying social approach behavior in medaka fish

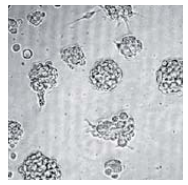


Our research group studied social approach behavior in medaka fish using three-dimensional computer graphic (3DCG) animations. 3DCG virtual fish lacking any combinations of four features (color, shape, locomotion, and body motion) of real medaka fish were created and presented to live fish using a computer display. Medaka fish presented with virtual fish with four normal features spent a long time in proximity to the display, whereas time spent near the display was decreased with other virtual fish lacking any of the four features. The results suggested that the naturalness of visual cues contributes to the induction of social approach behavior (see p. 44).

Nakayasu, T., Yasugi, M., Shiraishi, S., Uchida, S., and Watanabe, E. (2017). Three-dimensional computer graphic animations for studying social approach behaviour in medaka fish: Effects of systematic manipulation of morphological and motion cues. PLoS ONE 12, e0175059.

■ 17 July

Identification of PTPRZ as a drug target for cancer stem cells in glioblastoma



Glioblastoma is the most malignant brain tumor with high mortality. Cancer stem cells are thought to be crucial for tumor initiation and its recurrence after the standard therapy with radiation and temozolomide (TMZ) treatment. An NIBB research group showed that protein tyrosine phosphatase receptor type Z (PTPRZ) is requisite for the maintenance of stem cell properties and tumorigenicity in glioblastoma cells. The research group discovered NAZ2329, an allosteric inhibitor of PTPRZ, in collaboration with a pharmaceutical company. NAZ2329 efficiently suppressed stem cell-like properties of glioblastoma cells in culture, and tumor growth in C6 glioblastoma xenografts. Notably, tumor growth was inhibited more effectively by co-treatment with NAZ2329 and TMZ than by the individual treatments. Thus, pharmacological inhibition of PTPRZ activity is a promising strategy for the treatment of malignant gliomas (see p. 38).

Fujikawa, A., Sugawara, H., Tanaka, T., Matsumoto, M., Kuboyama, K., Suzuki, R., Tanga, N., Ogata, A., Masumura, M., and Noda, M. (2017). Targeting PTPRZ inhibits stem cell-like properties and tumorigenicity in glioblastoma cells. Sci. Rep. 7, 5609.

■ 4 September

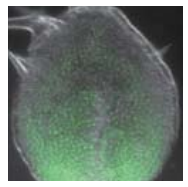
Discovery of dynamic seasonal changes in color perception ~The small fish “medaka” shows large differences in color perception in summer and winter~

Our research group found that color perception of Medaka, a small fish inhabiting rice fields and streams, varies greatly according to seasonal changes. Medaka in the summer conditions were strongly attracted to virtual medaka which showed nuptial coloration, but medaka in the winter conditions were not. It further became clear that expression of opsins, the proteins responsible for the first step in vision, and genes related to signal transduction pathways downstream of opsins are markedly reduced in winter conditions, whereas expression of these genes rises by shifting to summer conditions. This phenomenon of seasonal change in color perception may be a phenomenon widely preserved in various animals (see p. 67).

Shimmura, T., Nakayama, T., Shinomiya, A., Fukamachi, S., Yasugi, M., Watanabe, E., Shimo, T., Senga, T., Nishimura, T., Tanaka, M., Kamei, Y., Naruse, K., and Yoshimura, T. (2017). Dynamic plasticity in phototransduction regulates seasonal changes in color perception. Nat. Comm. 8, 412.

■ 6 September

Building a morphogen gradient by simple diffusion in a growing plant leaf

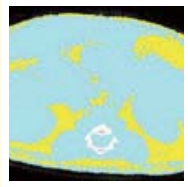


Our research group showed that a transcriptional co-activator ANGUSTIFOLIA3 (AN3) forms a signaling gradient along the leaf proximal-to-distal axis to determine cell-proliferation domain. They demonstrated that pure diffusion in a growing tissue is sufficient to explain the AN3 gradient formation. This work provides evidence that the diffusion-based model of morphogen is viable in developmental patterning of multicellular organisms (see p. 29).

Kawade, K., Tanimoto, H., Horiguchi, G., and Tsukaya, H. (2017). Spatially different tissue-scale diffusivity shapes ANGUSTIFOlIA3 gradient in growing leaves. Biophys. J. 113, 1109-1120.

■ 14 September

Identification of PTPRJ as a regulator of leptin signaling and obesity

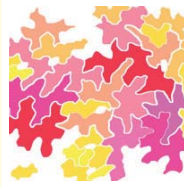


Leptin, an adipocyte-derived hormone, strongly inhibits food intake by acting on the hypothalamus, a part of the mid brain, and plays a crucial role in the body weight control. Circulating leptin levels are closely correlated with the degree of adiposity. An NIBB research group demonstrated that protein tyrosine phosphatase receptor type J (PTPRJ) negatively regulates leptin signaling by inhibiting the activation of leptin receptor-associated JAK2, through the dephosphorylation of Y813 and Y868 in JAK2 autophosphorylation sites. Diet-induced obesity and the leptin treatment both up-regulated PTPRJ expression in the hypothalamus, while the overexpression of PTPRJ induced leptin resistance. Thus, the induction of PTPRJ is a factor contributing to the development of leptin resistance, and the inhibition of PTPRJ may be a potential strategy for improving obesity (see p. 38).

Shintani, T., Higashi, S., Suzuki, R., Takeuchi, Y., Ikaga, R., Yamazaki, T., Kobayashi, K., and Noda, M. (2017). PTPRJ inhibits leptin signaling, and induction of PTPRJ in the hypothalamus is a cause of the development of leptin resistance. Sci. Rep. 7, 11627.

■ 20 September

Rolling dice for cell size specification in plant leaf epidermis

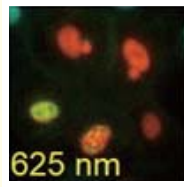


Because size distribution often shows a characteristically skewed pattern in a tissue, there may be some stochastic option for determining cell size. Our research group discovered that endoreduplication, which promotes cellular enlargement in the epidermal tissue of *Arabidopsis thaliana*, occurs randomly as a Poisson process throughout cellular maturation. These results link the probabilistic property of endoreduplication dynamics to cell size distribution, providing a theoretical background to explain how size heterogeneity is established within a leaf (see p. 73).

Kawade, K., and Tsukaya, H. (2017). Probing the stochastic property of endoreduplication in cell size determination of *Arabidopsis thaliana* leaf epidermal tissue. PLoS ONE 12, e0185050.

■ 24 October

Efficient synthesis of a photosynthetic pigment in mammalian cells for Optogenetics

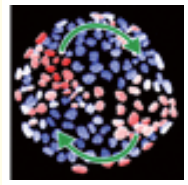


The “Optogenetic” method of controlling the position of proteins in cells using light is becoming widely employed as an important method to understand intracellular signal transduction. The Phytochrome B (PhyB)-PIF system made way to the use of red light / near infrared light, which have low toxicity and good tissue penetrance. However in the case of animal cells the cyanobacterial photosynthetic pigment phycocyanobilin (PCB) must be added from outside, and this step greatly hindered the use of the PhyB-PIF system. NIBB researchers have now succeeded in synthesizing PCB in animal cells directly by introducing four genes encoding cyanobacterial enzymes related to PCB synthesis. In addition, the group succeeded in increasing the amount of PCB synthesis through disruption of the gene that encodes an enzyme called biliverdin reductase A, which is involved in the metabolism of PCB (see p. 15).

Uda, Y., Goto, Y., Oda, S., Kohchi, T., Matsuda, M., and Aoki, K. An efficient synthesis of phycocyanobilin in mammalian cells for optogenetic control of cell signaling. Proc. Natl. Acad. Sci. USA 2017 Oct 24. doi:10.1073/pnas.1707190114

■ 7 November

Discovery of a mechanism for determining the direction of collective cell migration



A group at NIBB have found that when the activity of a molecule called ERK MAP kinase is propagated to neighboring cells, the cells migrate in the opposite direction of ERK propagation. In cells cultured on a circular micro-patterned glass base dish, a spontaneous rotational wave of ERK activity was observed and the cells rotated in the opposite direction. Furthermore, by artificially creating waves of ERK activity by optogenetic techniques, the research group succeeded in making cells move collectively (see p. 15).

Aoki, K., Kondo, Y., Naoki, H., Hiratsuka, T., Itoh, R.E., and Matsuda, M. Propagating wave of ERK activation orients collective cell migration. Develop. Cell 2017 Nov 6. doi:10.1016/j.devcel.2017.10.016

■ 21 November

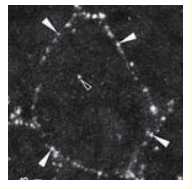
mRNA localization regulatory factor RNG105/caprin1 is essential for long-term memory formation

Researchers at NIBB have revealed that the function of RNG105 (aka Caprin1) is essential for the formation of long-term memory. Mice who have lost RNG105 in the cerebrum and hippocampus can form short-term memories of several minutes, but the long-term memory, developed over several days to one week, does not form in these mice. They also found that RNG105-regulated mRNA localization to dendrites is involved in the correct placement of AMPA receptors in synapses, which are known to be important for memory retention (see p. 23).

Nakayama, K., Ohashi, R., Shinoda, Y., Yamazaki, M., Abe, M., Fujikawa, A., Shigenobu, S., Futatsugi, A., Noda, M., Mikoshiba, K., Furuichi, T., Sakimura, K., and Shiina, N. (2017). RNG105/caprin1, an RNA granule protein for dendritic mRNA localization, is essential for long-term memory formation. eLife 6, e29677.

■ 7 December

Two types of heparan sulfate clusters may constitute a cellular platform for the distribution and signaling of Wnt8, a morphogen molecule

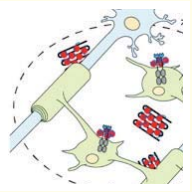


Wnt proteins direct embryonic patterning, but the regulatory basis of their distribution and signal reception remain unclear. Our research group showed that endogenous Wnt8 protein is distributed in a graded manner in *Xenopus* embryo and accumulated on the cell surface in a punctate manner in association with "N-sulfo-rich heparan sulfate (HS)," not with "N-acetyl-rich HS". These two types of HS clusters may constitute a cellular platform for the distribution and signaling of Wnt8 (see p. 29).

Mii, Y., Yamamoto, T., Takada, R., Mizumoto, S., Matsuyama, M., Yamada, S., Takada, S., and Taira, M. (2017). Roles of two types of heparan sulfate clusters in Wnt distribution and signalling in *Xenopus*. Nat. Comm. 8, 1973.

■ 8 December

Protamine neutralizes CSPG-mediated inhibition of oligodendrocyte differentiation



Remyelination is a critical repair process in demyelinating diseases such as multiple sclerosis (MS). Damage to the central nervous system (CNS) results in a glial reaction, leading to the formation of a glial scar enriched with chondroitin sulfate proteoglycans (CSPGs). CSPGs also accumulate as constituents of demyelinating plaques in MS lesions, which inhibit the migration and differentiation of oligodendrocyte precursor cells and remyelination. An NIBB research group found that a polycationic peptide, protamine (PRM) neutralized the inhibitory activity of aggrecan, a representative extracellular matrix CSPG molecule, and that PRM functioned as an inhibitory ligand mimetic of protein tyrosine phosphatase receptor type Z (PTPRZ), a membrane-spanning CSPG predominantly expressed in oligodendrocyte precursor cells. The intranasal administration of PRM accelerated myelination in the developing mouse brain, and its intracerebro-ventricular administration stimulated remyelination after cuprizone-induced demyelination. These results indicate that PRM has CSPG-neutralizing activity, thereby promoting oligodendrocyte differentiation under developmental and morbid conditions (see p. 38).

Kuboyama, K., Tanga, N., Suzuki, R., Fujikawa, A., and Noda, M. (2017). Protamine neutralizes chondroitin sulfate proteoglycan-mediated inhibition of oligodendrocyte differentiation. PLoS ONE 12, e0189164.