RIKEN RESEARCH

AUGUST 2011
VOLUME 6 NUMBER 8

The genetic link in bone disease

HIGHLIGHT OF THE MONTH

Biology: Unraveling genomic changes in the brain

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Biology

Unraveling genomic changes in the brain

Differences in the chemical modification of DNA within neurons from different individuals may hint at new ways of understanding the roots of mental illness

Scientists have known for some time that individual organisms are far more than the sum of their gene sequences. So-called epigenetic variations encompass a diverse array of chemical modifications to DNA that leave the core nucleotide sequence unchanged, but can nevertheless exert powerful effects on gene expression behavior.

A modification commonly associated with the silencing of gene activity in mammals, for example, is the enzyme-mediated attachment of a methyl group onto a cytosine base within a 'CpG dinucleotide', a segment of chromosomal DNA in which cytosine is immediately followed by guanine. Different genes are subject to such methylation in particular tissues, but methylation can also differ markedly in the same tissues between individuals, with potentially profound functional consequences.

According to Tadafumi Kato of the RIKEN Brain Science Institute in Wako, abnormalities in DNA methylation within the brain could even play a role in a variety of neuropsychiatric conditions, such as bipolar disorder. "Mental disorders are the result of gene–environment interaction," he explains, "and DNA methylation may be affected by early environmental effects."

As a first step toward testing this hypothesis, Kato's group teamed up with The University of Tokyo researcher Kazuya Iwamoto, along with colleagues in Japan and the United States, to survey genome-wide methylation in the brains of different individuals[1]. For their analysis, they examined postmortem tissue from the prefrontal cortex of the cerebrum (Fig. 1), a region of the brain with a leading role in decision-making behavior.

Figure 1: The prefrontal cortex is at the front of the cerebrum (in red) of the brain.

The nature of neurons

Kato and colleagues used the neuron-specific protein NeuN as a marker for separating out actual neurons from the larger population of glial cells (Fig. 2), which play a vital part in supporting neuronal function. "If we extracted DNA from the bulk cerebral cortex, the DNA methylation data would mainly reflect the glial cells," says Kato. "Thus, we need to separate out the neurons from the brain."

This approach enabled the researchers to perform a direct comparison of the two cell classes. Indeed, their initial assessment confirmed that the methylation profile of the NeuN-negative (glial) cells displayed a significantly greater degree of similarity to that of bulk cortical samples relative to the NeuN-positive (neuronal) subpopulation. In general, bulk cortical preparations and glial cell fractions also exhibited notably higher levels of overall genomic methylation in comparison to neuronal fractions.

Kato, Iwamoto and colleagues used a platform known as a 'tiling array' to precisely map the positions of these methylation sites within the genome. Based on these data, they were able to compile collections of methylated regions (MRs) that were specifically neuronal, non-neuronal or common to both cell populations. Many of the MRs were located within promoters,

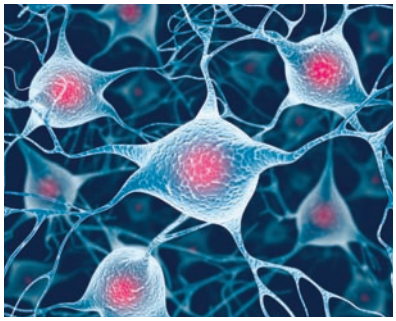


Figure 2: Neurons separated from the brain were profiled for methylation, which can vary greatly between individuals.

which are stretches of DNA that directly control the activity of nearby genes. The researchers also identified hundreds of genes that display similar patterns of epigenetic modification within each of the three categories. Intriguingly, they noted that promoters that were specifically methylated within the glial population regulate a number of established neuronal genes, encoding factors associated with ion transport and neurotransmitter signaling.

In a prior study, the researchers had investigated overall gene expression within the brain, identifying patterns of transcriptional regulation that enabled them to cluster various genes into discreet functional 'modules'[2]. Kato and colleagues used these findings to determine whether any of these modules were particularly enriched among any of the subsets of methylated genes.

Several of the genes that appeared to be specifically methylated, and therefore silenced, among non-neuronal cells belonged to a module associated with mitochondrial function. The activity of these organelles is known to be considerably enriched in neurons. Conversely, the researchers found evidence that silencing among neuronal populations appears to affect genes associated with the function of astrocytes, a glial subpopulation.

Defining our differences

In a comparison of the distribution of MRs between different individuals, Kato and colleagues were surprised to find a very high level of variability in neuronal methylation from person to person. For any given sample, the proportion of unique MRs was significantly higher in genetic material from neuronal cells relative to non-neuronal cells, while the proportion of shared MRs was significantly lower. These results were subsequently mirrored in an independent assessment of 24 additional brain tissue samples.

"Our brain function is continuously changing, and we all have different brain functional status relative to each other, so it seems reasonable that DNA methylation status is more flexible in neurons than in glial cells," says Kato. "However, we did not anticipate this finding before starting our project."

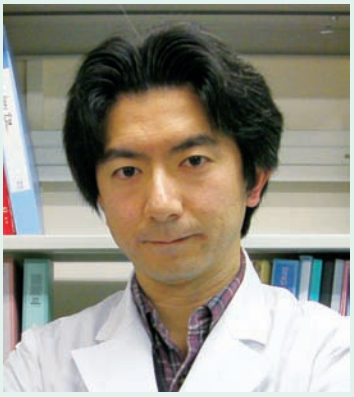
The researchers note that this remains a broad survey of genomic modification, especially for an organ as complex as the brain. The cortex alone contains numerous subtypes of neurons, each of which may manifest its own particular profile of methylation; likewise, relative populations of different neuronal types could differ significantly from person to person. In addition, the method applied in this study is not suitable for tracking every instance of methylation; for example, it is incapable of detecting hydroxymethyl cytosine nucleotides, although such modifications are believed to be widespread in both mouse and human brains.

Nevertheless, the researchers' work represents one of the most detailed epigenetic analyses of the brain to date, and the resulting data have encouraged Kato and his colleagues to dig deeper in an effort to untangle potential links between variable methylation and mental health. "We are now studying the DNA methylation status of neuronal nuclei in the post-mortem brains of patients with bipolar disorder and schizophrenia," says Kato.

1. Iwamoto, K., Bundo, M., Ueda, J., Oldham, M.C., Ukai, W., Hashimoto, E., Saito, T., Geschwind, D.H. & Kato, T. Neurons show distinctive DNA methylatinon profile and higher interindividual variations compared with non-neurons. *Genome Research* **21**, 688–696 (2011).
2. Oldham, M.C., Konopka, G., Iwamoto, K., Langfelder, P., Kato, T., Horvath, S. & Geschwind, D.H. Functional organization of the transcriptome in human brain. *Nature Neuroscience* **11**, 1271–1282 (2008).

ABOUT THE RESEARCHERS

Tadafumi Kato was born in Tokyo, Japan, in 1963. He graduated from the Faculty of Medicine, The University of Tokyo, in 1988. After residency training at The University of Tokyo Hospital, he obtained his PhD in 1995 from Shiga University of Medical Science. After working as a lecturer at the Department of Neuropsychiatry, The University of Tokyo, he was appointed as a team leader at the RIKEN Brain Science Institute in 2001. His research focuses on the neurobiology of bipolar disorder.



Kazuya Iwamoto was born in Wakayama, Japan, in 1974. He graduated from Tokyo University of Agriculture and Technology, in 1996, and obtained his PhD in 2001 from The University of Tokyo. He then joined Kato's lab at the RIKEN Brain Science Institute as a special postdoctoral researcher. In 2010, he moved to the Department of Molecular Psychiatry, The University of Tokyo, as an associate professor. His research focuses on revealing the genomic and epigenomic variations in the brains of patients with psychiatric diseases such as mood disorders, autism and schizophrenia.

Tuning in to noisy interference

Noise reduction in advanced computing circuits comes a step closer thanks to measurements of the noise spectrum affecting superconducting circuits

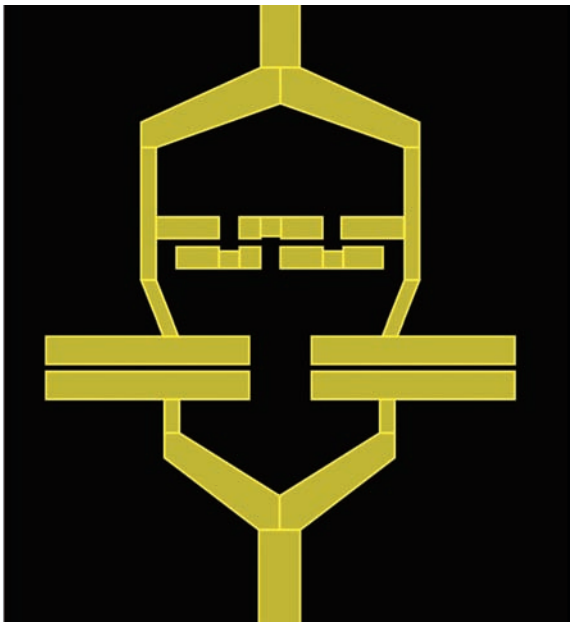


Figure 1: Layout of the superconducting flux qubit, which consists of several aluminum circuits. The key elements are the three 'islands' of metal in the top half of the image, across which the superconducting current flows. Magnetic pulses applied to the qubit control its quantum states.

Establishing a detailed knowledge of the noise properties of superconducting systems is an important step towards the development of quantum computers, which will enable new types of computing. However, the signals of these systems' tiny electronic components, such as transistors on a chip, are so small that ambient noise creates interference. This problem is compounded by the delicate nature of the technology's quantum physical states, which are also susceptible to noise. Now, an international research team has successfully measured the noise spectrum of a superconducting circuit[1]—called a superconducting flux qubit—that is widely investigated for its potential in quantum computing applications.

Precise measurements of the environmental noise affecting superconducting flux qubits are important, according to team leader Jaw-Shen Tsai from the RIKEN Advanced Science Institute in Wako. "They may give us crucial information about the microscopic origin of the noise source, about which we have no solid understanding at all," he says.

The superconducting flux qubit studied by the researchers is a circuit consisting of several junctions, and is a key technology in quantum computing because it can be integrated into a chip (Fig. 1). The first hurdle cleared by the researchers was keeping the qubit stable, and therefore viable, long enough to complete the measurement of the frequency spectrum of the noise that would occur in a quantum computer. They achieved this by applying a series of magnetic pulses that effectively replenished the qubit's quantum state. The net effect of the magnetic pulses was to suppress detrimental contributions from low-frequency noise, as the pulses affect only the quantum states and not the noise.

Suppression of the low-frequency noise extended the lifetime of the quantum information in the qubit by almost an order of magnitude, and enabled the measurement of noise intensity in the system across three orders of magnitude in frequency from 0.2 to 20 MHz. This new-found knowledge on the noise spectrum will be valuable in developing strategies to counter such noise. "If we understand the nature of the noise, we may be able to reduce it considerably," Tsai explains.

Moreover, the team's strategy of extending qubit lifetimes to measure the noise spectrum is not limited to the study of quantum computing circuits; it could also be applied to other systems that operate under similar conditions. Medical imaging and sensing devices, for example, which often operate at the limits of signal resolution, could benefit from this noise reduction strategy. ■

1. Bylander, J., Gustavsson, S., Yan, F., Yoshihara, F., Harrabi, K. Fitch, G., Cory, D.G., Nakamura, Y., Tsai, J.-S. & Oliver, W.D. Noise spectroscopy through dynamical decoupling with a superconducting flux qubit. *Nature Physics* **7**, 565–570 (2011).

Hunting the unseen

Sighting a theoretical exotic particle may become possible thanks to recently developed mathematical simulations

A better knowledge about the composition of sub-atomic particles such as protons and neutrons has sparked conjecture about, as yet, unseen particles. A tool based on theoretical calculations that could aid the search for these particles has been developed by a team of researchers in Japan called the HAL QCD Collaboration[1].

At its most fundamental level, matter consists of particles known as quarks. Particle physicists refer to the six different types as 'flavors': up, down, charm, strange, top and bottom. The protons and neutrons found in the nucleus of an atom are examples of a class of particle called baryons: particles consisting of three quarks. Two baryons bound together are called dibaryons, but only one dibaryon has been found to date: a bound proton and neutron that has three up quarks and three down quarks in total.

Models that reveal the potential physical properties of dibaryons, such as their mass and binding energy, are crucial if more of these particles are to be discovered in the future. To this end, the collaboration, including Tetsuo Hatsuda from the RIKEN Nishina Center for Accelerator-Based Science in Wako, developed simulations that shed new light on one promising candidate: the *H* dibaryon, which comprises two up, two down and two strange quarks (Fig. 1).

The dynamics of quarks are described by an intricate theory known as quantum chromodynamics (QCD). The simulations, however, become increasingly difficult when more particles need to be included: dibaryons with six quarks are particularly testing. Hatsuda and his colleagues used an approach known as lattice QCD in which time and space are considered as a grid of discrete points. They simplified the calculation by assuming that all quarks have the same mass, but the strange quark is actually heavier than the up and down quarks. "We know from previous theoretical studies that the binding energy should be at its largest in the equal mass case," says Hatsuda. "If we had not found a bound state in the equal mass case, there would be no hope that the bound state exists in the realistic unequal mass case."

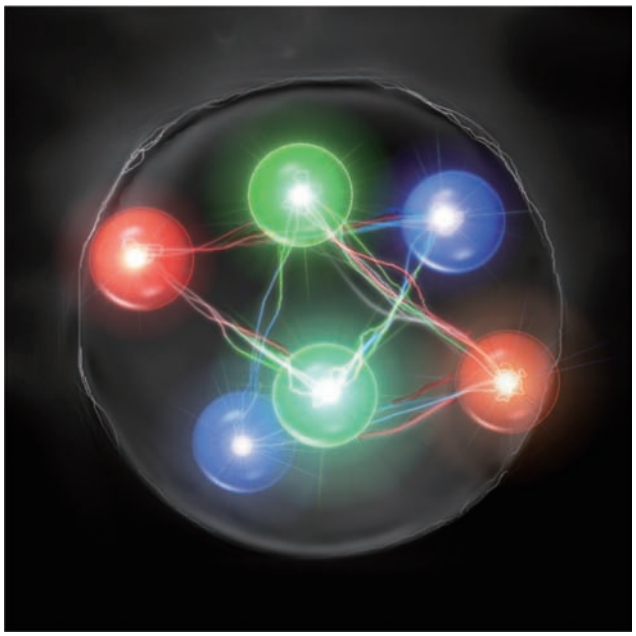


Figure 1: An artistic impression of a bound *H* dibaryon, a theoretical particle consisting of two up, two down and two strange quarks.

The results from the collaboration's simulations showed that the total energy of the dibaryon is less than the combined energy of two separate baryons, which verifies that *H* dibaryons are energetically stable. "We next hope to find the precise binding energy for unequal quark masses, which represents one of the major challenges in numerical QCD simulations," Hatsuda adds. ■

1. Inoue, T., Ishii, N., Aoki, S., Doi, T., Hatsuda, T., Ikeda, Y., Murano, K., Nemura, H. & Sasaki, K. Bound *H* dibaryon in flavor SU(3) limit of lattice QCD. *Physical Review Letters* **106**, 162002 (2011).

Detecting an unexpected delay at ultrafast speed

High-speed laser measurements reveal new insights into rearrangements of light-driven chemical structures with implications for solar-energy conversion and opto-electric devices

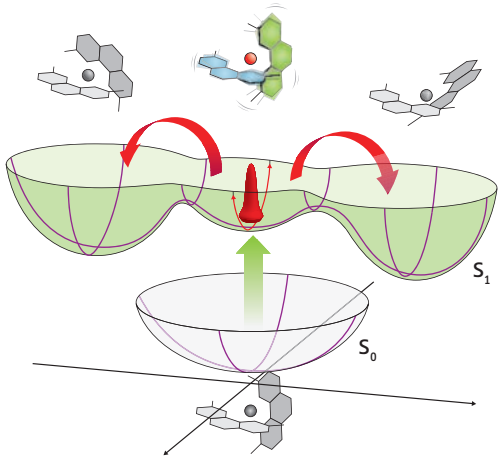


Figure 1: When copper dimethylphenanthroline absorbs a photon (bottom), it transitions from a ground state (S_0) to an electronically excited (S_1) state that causes the molecular structure to flatten. Ultrafast laser spectroscopy has revealed that the molecule coherently vibrates for a short time (upper center) before distorting.

Molecules that suddenly transform into new structures when stimulated by photons or electrons play key roles in many chemical and biological processes. Recently, chemists have discovered that adding transition metals such as copper to photo-responsive organic ligands produces materials with high solar conversion efficiencies, owing to the metal's ready supply of light-activated electrons. But despite the interest in these substances for opto-electronic devices, their inner workings remain mostly inscrutable because the charge-transfer dynamics happen too quickly for detection by typical instruments.

Tahei Tahara and colleagues from the RIKEN Advanced Science Institute, Wako, have spearheaded development of ultrafast laser spectroscopy that can capture these high-speed reactions by taking 'snapshots' of photochemical transformations with quadrillionths-of-a-second (10^{-15} s) accuracy. Now, an unprecedented finding by the research team—a picosecond (10^{-12} s) time delay during a theoretically instantaneous distortion—is set to overturn current thinking about light-driven rearrangements in transition metal complexes[1].

Copper dimethylphenanthroline (Fig. 1) is a compound containing two propeller-shaped wings, made out of thin aromatic sheets. Chemists regularly use it to explore photo-induced structural changes. In its unexcited state, the complex's wings are oriented perpendicular to each other. But when illuminated at a specific wavelength, the copper ion absorbs a photon and transfers an electron to the sheets—an action that flattens the structure by disrupting critical copper—phenanthroline bonds.

The exact flattening mechanism, however, has been controversial because copper electrons can be photo-excited in two different ways: through an easily accessible high-energy state called S_2, or a harder-to-spot, low-energy transition called the S_1 state. Tahara and colleagues tracked the extremely fast relaxation process from both states and found that S_1 electrons provoked the flattening. This finding will allow researchers to eventually squeeze as much efficiency as possible from these devices.

When the team examined how the molecule behaved in the S_1 excited state, they saw unexpected oscillations in the absorption signals during its picosecond-long lifetime. According to Tahara, these signals are unmistakable evidence that the excited complex vibrates coherently in place and waits a short while before distorting.

Because this result contradicts traditional understandings of transition metal processes—atomic movements were theorized to immediately follow excitation to S_1-type electronic states—it may spark revolutionary changes in how chemists conceive and control photo-initiated reactions. "This is a fundamental and deep issue," says Tahara.

By expanding this technique to other poorly understood metal complexes, the team hopes to produce 'textbook-type' results that can guide future development of these remarkable materials. ■

1. Iwamura, M., Watanabe, H., Ishii, K., Takeuchi, S. & Tahara, T. Coherent nuclear dynamics in ultrafast photoinduced structural change of bis(diimine)copper(I) complex. *Journal of the American Chemical Society* **133**, 7728–7736 (2011).

Silence of the genes

As in other multicellular organisms, plants have evolved mechanisms to maintain genome stability and integrity

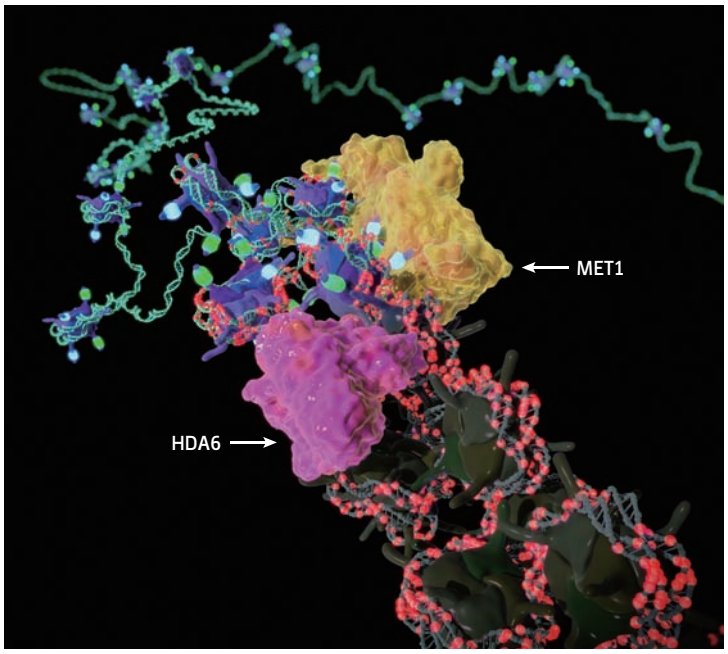


Figure 1: In *Arabidopsis* chromatin, the enzymes HDA6 and MET1 convert epigenetic information to make it 'silent'.

A molecular mechanism by which gene silencing is regulated at the genome-wide level in plants has been uncovered by a research team led by Motoaki Seki of the RIKEN Plant Science Center, Yokohama[1]. The researchers propose that a similar mechanism may also help to protect plant genomes from the potentially harmful effects of DNA elements, such as transposons, or 'jumping genes'. "If left unhindered, transposable elements can cause havoc in the genome, for example by inserting themselves into essential genes," says Seki.

The DNA of eukaryotes—organisms with nucleated cells—is packaged in a complex structure called chromatin within chromosomes. Chromatin also contains DNA-binding proteins called histones. When in its open conformation, known as euchromatin, the DNA is accessible to transcription factors, allowing gene expression to proceed. However, when in its highly condensed form—heterochromatin—gene expression is silenced.

The transition from euchromatin to heterochromatin requires chemical modification of both DNA and histones. These so-called epigenetic changes involve the methylation of DNA by enzymes called DNA methyltransferases, and the elimination of epigenetic marks on histones by other enzymes called histone deacetylases. In addition to silencing gene expression, heterochromatin formation may protect against the potentially damaging effects of transposons by blocking their replication.

Seki and his colleagues studied the regulation of heterochromatin formation in *Arabidopsis thaliana*, a small flowering related to the mustard plant. "*Arabidopsis* is a widely used model species for studying epigenetic changes in plants," explains Seki.

Uniquely in plants, DNA methylation resulting in heterochromatin formation is triggered by small RNA molecules. This process is known as RNA-directed DNA methylation, and involves the DNA methyltransferase MET1 and the histone deacetylase HDA6 (Fig. 1). However, the overall role of HDA6 in heterochromatin formation remained unclear.

By comparing the RNA transcript profiles of normal and mutant plants lacking functional HDA6, the researchers identified 157 target genes spread across the *Arabidopsis* genome. In some target genes in the mutant plants they found that DNA methylation was completely lost, allowing these genes to be expressed. They also found that the target specificity of HDA6 was unexpectedly much greater than that of MET1.

"Our findings suggest that HDA6 recruits MET1 to specific target genes, allowing it to regulate gene silencing on a genome-wide scale," says Seki.

In addition to this general role, the researchers propose that HDA6 may regulate transposon silencing through heterochromatin formation in plant gametes. They also express the hope that their research will help illuminate related processes in humans. ■

1. To, T.K., Kim, J.-M., Matsui, A., Kurihara, Y., Morosawa, T., Ishida, J., Tanaka, M., Endo, T., Kakutani, T., Toyoda, T., *et al*. *Arabidopsis* HDA6 regulates locus-directed heterochromatin silencing in cooperation with MET1. *PLoS Genetics* **7**, e1002055 (2011).

Read, delete and grow

Plants switch off growth signals by targeting 'used' receptor molecules for destruction

Figure 1: After six weeks of growth, bri1-5 mutant *Arabidopsis* plants (left) are developmentally stunted. By comparison, plants with the *sbi* and *bri1-5* mutations together grow as well as wild-type plants (middle), and plants with *sbi* mutations alone exhibit even more uninhibited growth.

Plants coordinate growth using hormones called brassinosteroids (BR), and defects in the associated signaling pathway can result in profoundly stunted development. For example, researchers have identified numerous mutations within the gene encoding the BR receptor, *BRI1*, which yield plants with a dwarf phenotype.

The *bri1-5* mutation does not directly disrupt receptor function, but nevertheless inhibits growth of thale cress, *Arabidopsis thaliana*, plants by somehow accelerating the rate of receptor degradation. The discovery of an additional mutation that fully counteracts this effect has now revealed valuable insights into how plants manage to keep a tight rein on growth signals[1].

When Guang Wu and Joanne Chory of the Salk Institute for Biological Studies, USA, identified this enigmatic *sbi1* mutant (Fig. 1), they partnered with Yuji Kamiya, a biologist at the RIKEN Plant Science Center in Yokohama. "We wanted to know the reason why plants recover from the dwarf phenotype," says Kamiya, "and so Wu visited my laboratory to study the mechanism of the *BRI1* gene."

An initial series of experiments provided strong evidence that the *sbi1* mutant disrupts the function of a negative regulator of *BRI1*, which appears to act on the receptor after it has been activated by binding BR. The researchers were subsequently able to uncover the affected *SBI1* gene, which encodes a member of the leucine carboxylmethyltransferase (LCMT) enzyme family.

LCMTs selectively attach methyl chemical groups onto the catalytic subunit of protein phosphatase 2A (PP2A), a multi-protein complex that deactivates a variety of receptors and other signaling proteins. Accordingly, Wu, Kamiya and colleagues found evidence that *SBI1* methylates PP2A within *Arabidopsis* cells. This chemical modification activates the complex and alters its localization within the cell, bringing it into close proximity to *BRI1* and thereby enabling it to switch off the receptor. SBI1 production is directly stimulated by BR signaling, further reinforcing this negative feedback loop.

These newly inactivated receptor molecules appear to be subsequently targeted for destruction. "We found that activated receptors that have bound BR transfer their signal to the nucleus and then get degraded, while unbound BR receptor is recycled rather than being degraded," explains Kamiya. "By this mechanism, receptor levels are controlled in plants."

Although similar regulatory systems are known to operate in animal cells, PP2A function is poorly understood in plants, and further investigation will be needed to determine whether this represents a general mechanism for constraining receptor signaling in *Arabidopsis* and other species. ■

1. Wu, G., Wang, X., Li, X., Kamiya, Y., Otegui, M.S. & Chory, J. Methylation of a phosphatase specifies dephosphorylation and degradation of activated brassinosteroid receptors. *Science Signaling* **4**, ra29 (2011).

A break for bone disease research

A variant of a newly identified gene is linked to increased risk of developing osteoporosis in Japanese individuals

Osteoporosis is the reduction in bone strength that occurs during aging, which increases the chance of elderly people experiencing breaks (Fig. 1). A genome-wide association study in the Japanese population has revealed that a genomic variant within a newly identified gene, which the discoverers have named *FONG*, enhances susceptibility to osteoporosis[1].

Led by Shiro Ikegawa of the RIKEN Center for Genomic Medicine, the researchers began by examining the entire genomes of 190 Japanese individuals with osteoporosis and 1,557 controls. Based on the results of this initial study, they focused on 3,000 single nucleotide changes in the genomes of an additional 526 individuals with osteoporosis and 1,537 controls. Additional analyses in two further population samples led to the identification of the genomic variant, found on chromosome 2; however, there was no known gene around the variant. Instead, the researchers found only representations of portions of expressed genes in the form of several expressed sequence tags.

By analyzing messenger RNAs (mRNAs) expressed from the genomic region around the variant, Ikegawa and colleagues discovered that the genomic variant is within *FONG*, which stands 'formiminotransferase N-terminal sub-domain containing gene'. This previously unknown gene is expressed in various human tissues, including bone. Because the genomic variant resides outside of the FONG protein-coding region, Ikegawa and colleagues hypothesized that the variant may somehow affect the expression levels of the *FONG* gene.

Figure 1: In the Japanese population a specific gene is linked to osteoporosis that can lead to broken bones in the elderly.

One domain of the *FONG* gene, the formiminotransferase N-terminal sub-domain, is common in many different species, which indicates that it could have a very important function for maintaining life. "This domain appears to be an enzyme that is responsible for converting the amino acid histidine to the amino acid glutamic acid," says Ikuyo Inaba (nee Kou), a researcher in Ikegawa's laboratory and the first author of the study.

Glutamic acid and its breakdown products are known to play an important role in maintaining the bones, so any problems with the creation of these compounds may lead to osteoporosis. "The glutamic acid signaling pathway may also affect osteoporosis risk in non-Japanese individuals," she explains. "So, the association of this variant of the *FONG* gene with disease in other populations is worth investigating in the future."

According to Inaba, further work is needed to determine how the osteoporosis-linked variant of the *FONG* gene can affect its expression. The identification of this variant in *FONG*—and its link to osteoporosis—can aid in the development of new therapies for this disease. ■

1. Kou, I., Takahashi, A., Urano, T., Fukui, N., Ito, H., Ozaki, K., Tanaka, T., Hosoi, T., Shiraki, M., Inoue, S., *et al*. Common variants in a novel gene, *FONG* on chromosome 2q33.1 confer risk of osteoporosis in Japanese. *PLoS ONE* **6**, e19641 (2011).

Immunity restrained by ion influx

A calcium-driven signaling pathway helps prevent immune cells from contributing to autoimmune disease

B cells maintain stockpiles of calcium ions (Ca^{2+}), which are released during the course of the immune response. When the presence of a foreign antigen stimulates the B cell receptor (BCR) complex, these internal reserves of Ca^{2+} get released into the cell, subsequently triggering the opening of channels in the cell membrane that allow the entry of even more Ca^{2+}.

Immunologists generally considered these ions as essential currency for many key cellular processes. "Ca^{2+} signaling in B cells is widely assumed to be responsible for functions including B cell development, immune response and antibody production," says Yoshihiro Baba of the Immunology Frontier Research in Osaka University and formerly with the RIKEN Research Center for Allergy and Immunology in Yokohama. However, the direct effects of this bulk Ca^{2+} entry, also known as store-operated Ca^{2+} (SOC) influx, are poorly understood.

To examine the importance of this mechanism, Baba and colleagues genetically engineered mice whose B cells lack the genes encoding STIM1 or STIM2, two proteins involved with SOC influx[1]. Their results suggest that this pathway plays a far more narrowly defined role than was previously expected.

The researchers determined that these two proteins cooperatively contribute to the management of Ca^{2+} influx, and facilitate B cell proliferation following BCR-mediated signaling. However, they appear to have no role in the actual immune response, as mice with STIM1- and STIM2-deficient B cells were still capable of mounting an antibody response against foreign antigens.

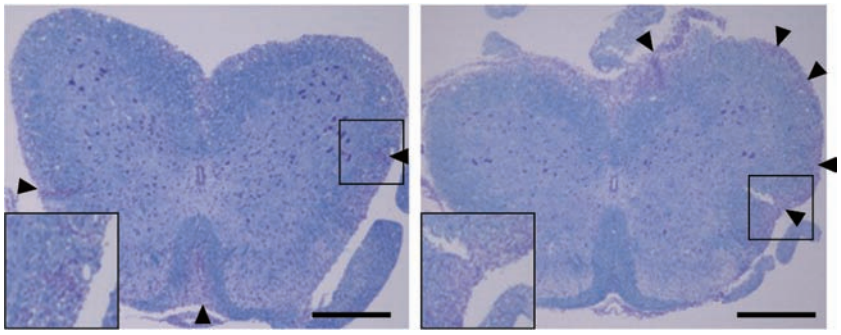


Figure 1: Spinal cord sections from a mouse model of multiple sclerosis (left) display increased autoimmune damage when B cells in these mice lack the genes encoding STIM1 and STIM2 (right). Arrowheads indicate regions of inflammatory damage, with inset images offering a magnified view of boxed regions. Scale bars, 100μm.

On the other hand, both factors proved important for the function of regulatory B cells, which produce anti-inflammatory factors such as interleukin-10 (IL-10) and help prevent the immune system from over-reacting or attacking host tissues. Without these STIM proteins, mouse B cells produced only minimal amounts of IL-10. Baba and colleagues determined that the absence of STIM1 and STIM2 greatly exacerbates the incidence and severity of inflammatory pathology in a mouse model of multiple sclerosis (Fig. 1). Since the action of IL-10 suppresses a variety of autoimmune conditions, these findings may indicate a general mechanism that could be targeted for the treatment of such disorders. "Our study suggests that a failure to balance Ca^{2+} levels may lead to autoimmune disease. This is a very exciting finding," says Baba.

He and his colleagues are now keen to better understand the Ca^{2+}-dependent anti-inflammatory B cells. "We are trying to show when and where regulatory B cells function, and what cells are targeted by them," he says, "and to understand what type of inflammation—chronic or acute—is sensitive to IL-10-producing B cells." ■

1. Matsumoto, M., Fujii, Y., Baba, A., Hikida, M., Kurosaki, T. & Baba, Y. The calcium sensors STIM1 and STIM2 control B cell regulatory function through interleukin-10 production. *Immunity* **34**, 703–714 (2011).

Tracking a moving target

A family tree of the 2009 pandemic influenza viruses in Japan reveals a high rate of viral evolution

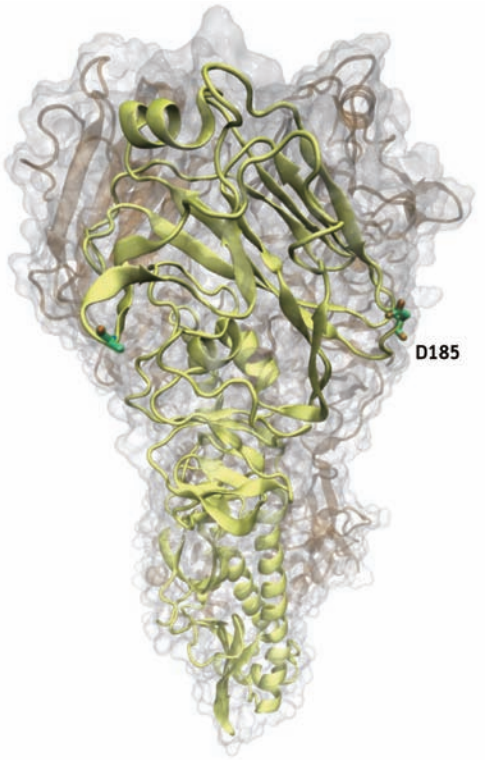


Figure 1: The molecular structure of hemagglutinin (HA), where D185 shows the part of the protein that was mutated in severe cases of flu infection.

The influenza pandemic that began in Mexico in April 2009 rapidly spread throughout the world and arrived in Japan one month later. Now, a research team led by Toshihisa Ishikawa at the RIKEN Omics Science Center in Yokohama has revealed what a portion of the pandemic influenza virus looked like when it emerged in Japan (Fig. 1), and how it has changed over time[1]. The findings will help to guide influenza vaccine development and will aid in preparations for future influenza pandemic outbreaks.

The researchers collected swab samples from the respiratory system of 253 individual flu sufferers in Osaka, Tokyo and Chiba, and sequenced the influenza genes encoding the proteins hemagglutinin (HA) and neuraminidase (NA). Although these genes represent only 10% of the influenza viral genome, they demonstrate more variability than other influenza genes, Ishikawa explains, so are likely to mediate any emerging changes in flu severity or antiviral drug resistance.

The sequencing showed that the pandemic influenza samples from the individuals in Japan fell into two groups: those that were collected at the time of the initial outbreak in May 2009, and those that were collected a few months later, during the most rapid spread of the virus throughout the country from October 2009 to January 2010.

Importantly, when the researchers compared the sequences between these two groups of viruses, they found that they fell into two totally separate clusters. This indicated that there were many differences between the two groups of pandemic influenza viruses, including the emergence of a mutation in an important site—the so-called 'Ca antigen site' of HA—that is known to be subject to pressure by the immune system. This mutation, as well as some others that the researchers identified, may account for the more rapid spread of the pandemic influenza virus later in the year.

Ishikawa and colleagues also found other mutations in the Ca antigen site of HA that conferred a more severe disease course, as well as mutations in NA that led to resistance to currently available antiviral drugs.

The rapid emergence of these mutations suggests that "the 2009 pandemic influenza viruses have a genome with an extremely high evolutionary rate," says Ishikawa. Moreover, "the mutated viruses seemed to rapidly circulate around Japan via modern traffic networks," he explains. These characteristics of the virus and its spread are important factors to consider when designing future vaccines or when deciding how best to slow any future influenza pandemic outbreaks. ■

1. Morlighem, J.-É., Aoki, S., Kishima, M., Hanami, M., Ogawa, C., Jalloh, A., Takahashi, Y., Kawai, Y., Saga, S., Hayashi, E., *et al*. Mutation analysis of 2009 pandemic influenza A(H1N1) viruses collected in Japan during the peak phase of the pandemic. *PLoS ONE* **6**, e18956 (2011).

The long and short of sperm tails

Experiments using fruit flies as a model system reveal a molecular mechanism underlying sperm morphogenesis in insects

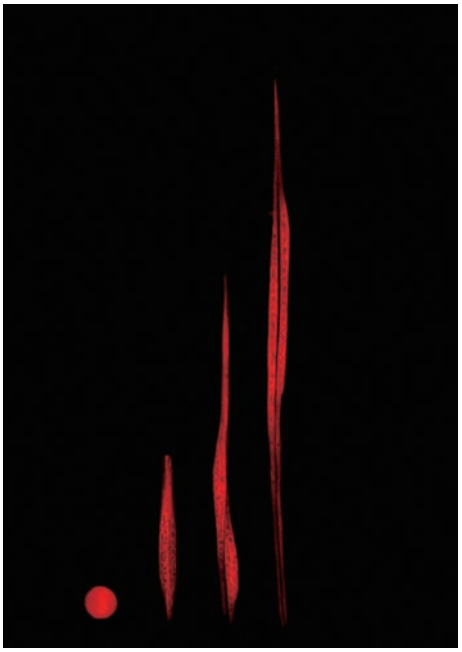


Figure 1: Giant mitochondria in the tail of fruit fly sperm elongate and show an increase in length, while the volume remains constant.

A team of biologists in Japan has uncovered an unexpected role for mitochondria[1], the power houses of cells, in the development of sperm in the fruit fly *Drosophila melanogaster*.

Drosophila melanogaster belongs to a family of two-winged flies called the drosophilids. Some drosophilid species have sperm with short tails, but others have exceptionally long tails. Males of *D. bifurca*, for example, produce sperm with tails that are over twenty times as long as the insect itself. "The diversity of sperm morphology among drosophilid flies has long fascinated reproductive and evolutionary biologists alike," says Shigeo Hayashi of the RIKEN Center for Developmental Biology, Kobe, who led the team.

Biologists believe that the long sperm found in some drosophilid species evolved in response to strong post-mating selection driven by 'sperm competition', the race between sperm from different males to fertilize an egg. Longer sperm would have the advantage of positioning their head closer to the egg.

Sperm movement is driven by waves that propagate along a hair-like motile structure called the flagellum within the sperm tail. The flagellum core, called the axoneme, is composed of microtubules formed of tubulin molecules arranged in chains. "We were aware from previous studies using mutant flies that the axoneme is dispensable for sperm cell elongation, so we set out to understand the underlying mechanism," explains Hayashi.

In addition to the axoneme, the membrane-bound sperm tails of insects typically contain giant mitochondria that extend along their entire length, as well as free microtubules. Working with *D. melanogaster*, Hayashi and his colleagues showed that sperm tail growth is driven by the mutually dependent extension of the giant mitochondria and microtubules that form around them (Fig. 1).

Experiments with cultured spermatids, the precursors of sperm, revealed that sperm elongation crucially depends upon the integrity of mitochondria and the reorganization of microtubules at the growing tip. In addition, the researchers found that the essential sliding movement of microtubules at the tip requires accumulation of Milton, a mitochondria–microtubule linker protein.

Hayashi and colleagues showed that experimentally disrupting Milton and its associated protein dMiro, as well as the potential microtubule cross-linking proteins Nebbish and Fascetto, caused defective tail elongation, resulting in abnormal sperm. They also showed that spermatid tail elongation requires both the association between mitochondria and microtubules, and microtubule cross-linking. "We have demonstrated that mitochondria form a structural platform for microtubule reorganization, which supports robust elongation at the growing tip of the long sperm tail," Hayashi concludes. ■

1. Noguchi, T., Koizumi, M. & Hayashi, S. Sustained elongation of sperm tail promoted by local remodeling of giant mitochondria in Drosophila. *Current Biology* **21**, 805–814 (2011).

Lending a helping hand

Zinc-transporting protein complexes are found unexpectedly to steer the maturation of an essential enzyme

Many proteins, the primary building blocks of life, depend on elements such as copper, zinc and other trace elements to function properly. "Some metal molecules are required as a structural component for proteins, while others are used as catalytic cofactors," explains Ayako Fukunaka, a researcher working with Makoto Hiromura and Shuichi Enomoto at the RIKEN Center for Molecular Imaging Science in Kobe.

Specialized zinc transporter (ZnT) proteins help maintain a steady supply of zinc for various proteins that incorporate this element. Now, new work from this RIKEN team, in collaboration with Taiho Kambe's group at Kyoto University, has revealed an additional mechanism by which ZnTs contribute to the production of certain zinc-binding proteins[1].

The enzyme called tissue nonspecific alkaline phosphatase (TNAP) incorporates zinc while undergoing processing in the secretory pathway, a system that subsequently delivers the mature enzyme to the cell membrane. In a series of prior studies, the researchers determined that cells fail to produce stable, functional TNAP in the absence of two particular ZnT complexes. "However, we still did not know whether TNAP degradation results from a decrease in zinc content, lack of ZnT proteins, or both," says Fukunaka.

To resolve this, she and her colleagues tinkered with cellular expression of ZnT5, ZnT6 and ZnT7, the three proteins that compose these essential zinc-transporting complexes. In the absence of these factors, levels of TNAP dropped dramatically. However, this decrease was only slightly mitigated by treatment with a compound that promotes zinc uptake, suggesting that these proteins also contribute to TNAP production via a second, parallel mechanism.

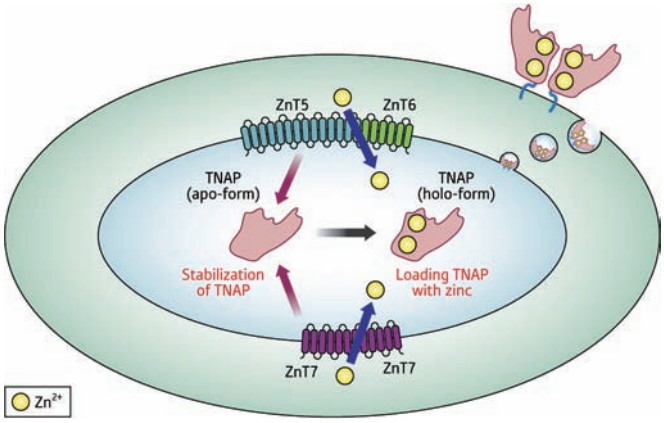
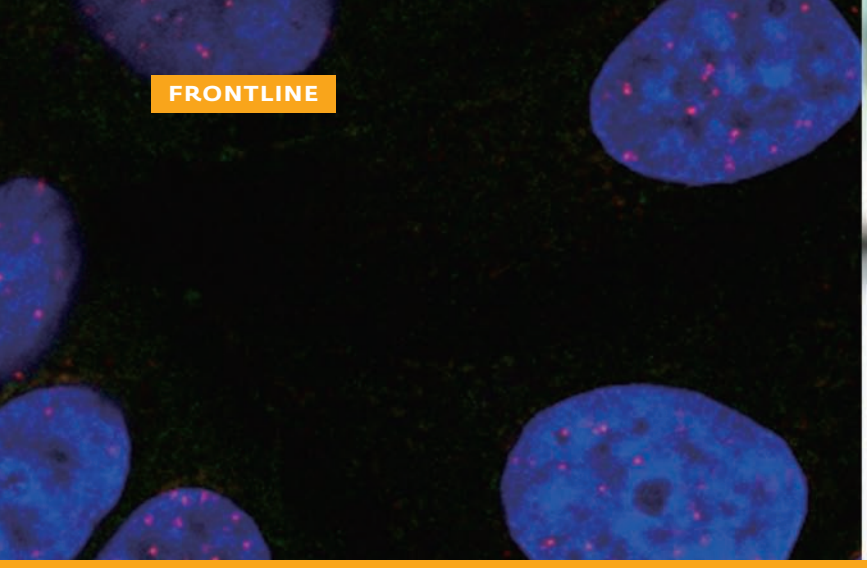


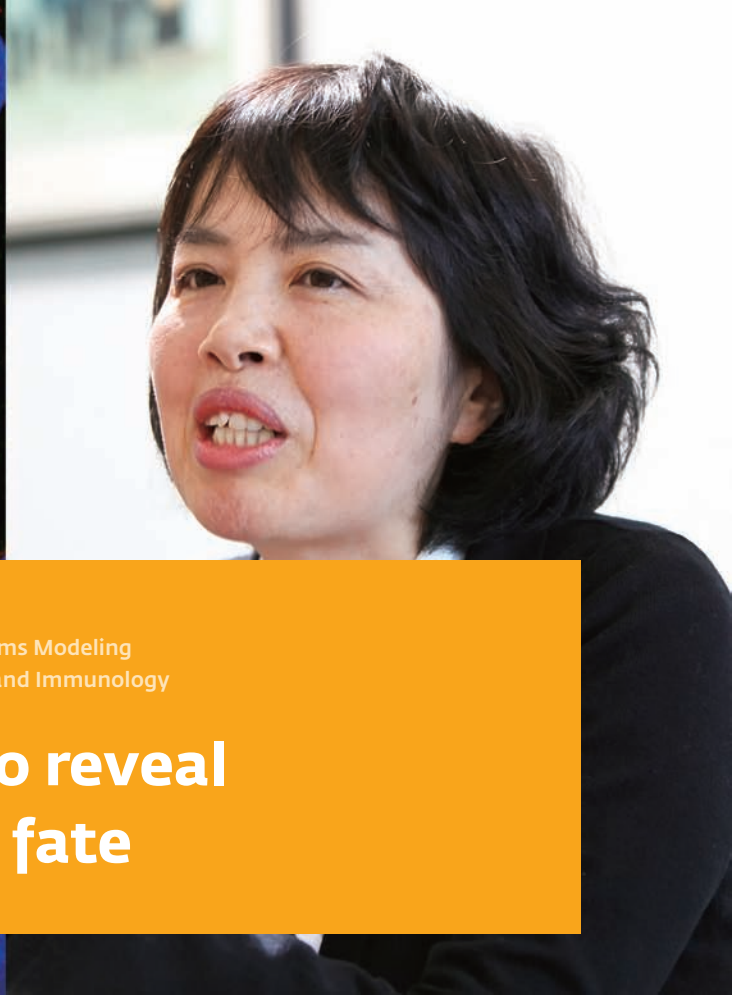
Figure 1: Within the secretory pathway, ZnT complexes (ZnT5/ZnT6 and ZnT7/ZnT7) facilitate the processing of the TNAP protein from the immature 'apo-form' to the mature 'holo-form' in two steps. First, ZnTs help stabilize it against degradation and then, the ZnTs load TNAP with zinc, yielding the fully functional membrane-bound holo-enzyme.

At an early stage in the secretory pathway, TNAP undergoes chemical modifications that render it resistant to degradation. Fukunaka and her colleagues determined that ZnT complexes appear to facilitate this stabilization. Experiments with mutated versions of these proteins indicated that this stabilization is independent of ZnT-mediated zinc transport, which only becomes important once the immature enzyme has been sufficiently protected against degradation (Fig. 1). "We named this phenomenon the elaborate 'two-step mechanism', in which TNAP protein stabilization by ZnT complexes is followed by conversion of the enzyme to its mature form through the loading of zinc by ZnT complexes," says Fukunaka.

This dual role for the ZnT proteins is as mysterious as it is surprising, and the researchers are now working to clarify the details of this process and determine whether similar mechanisms are also involved in shepherding other zinc-containing proteins to maturity. ■

1. Fukunaka, A., Kurokawa, Y., Teranishi, F., Sekler, I., Oda, K., Ackland, M.L., Faundez, V., Hiromura, M., Masuda, S., Nagao, M., *et al*. Tissue nonspecific alkaline phosphatase is activated via a two-step mechanism by zinc transport complexes in the early secretory pathway. *The Journal of Biological Chemistry* **286**, 16363–16373 (2011).





MARIKO OKADA

Team Leader
Laboratory for Cellular Systems Modeling
Research Center for Allergy and Immunology

Using systems biology to reveal the determinants of cell fate

Proliferation, differentiation or death? How is the fate of a cell determined? This system is a fundamental phenomenon in living organisms, but it has not yet been analyzed. Mariko Okada, team leader of the Laboratory for Cellular Systems Modeling at the RIKEN Research Center for Allergy and Immunology (RCAI), is working to analyze the fate-determining mechanisms in cells using systems biology, a new field of science in which experiments and theory are combined. She recently succeeded in revealing a molecular network that appears in cell differentiation processes and identified incoming information that triggers cell differentiation, thus establishing a model for mathematical prediction of input to output. The results can be used in various applications, such as computer-aided searches for drug candidates and measurement of their effects.

The determination of cell fate

"The cellular world resembles human society," says Okada. "A cell contains various molecules such as proteins, including enzymes and growth-promoting substances as well as nucleic acids—DNA and RNA. Molecules have likes and dislikes; they combine or react with specific molecules. However, their preferences vary depending on the surrounding circumstances, such as the molecular shapes of their counterparts. I believe we all experience something similar."

"I want to know how the fate of a cell is determined," says Okada. Each cell that constitutes an individual living organism has DNA with exactly the same base sequence as every other cell; that is, the same set of DNA. However, cells differentiate, proliferate, or die depending on their sites, the point in time, and the surrounding circumstances. "What determines the fate of a cell is basically the preferences of its molecules."

Many types of receptor are embedded in the cell membrane that covers a cell. When molecule A binds to a certain receptor, the information that "molecule A has bound to the receptor" is sent into the cell. Intercellular molecule B then reacts with molecule C, which in turn reacts with molecule D and so on, causing a chain reaction. The information is finally sent into the nucleus, leading to gene expression. The fate of a cell is thus determined by the amount and types of genes expressed in the cell.

"Many molecules involved in the information transmission process up to the determination of the fate of the cell have been discovered. However, when, where, and how these molecules work is not well understood. In addition, almost the same molecules involved can lead to different fates. I believe that not all the molecules involved in the transmission of information play major roles, but that there is a core group of molecules that play an important role in cell fate determination. I really want to provide a convincing explanation of the fate-determining system of the cell."

Encountering systems biology

Before joining RIKEN, Okada conducted research on cell biology at the University

of California, Davis in the US. "I originally majored in biochemistry and conducted research on enzymes both at graduate school and at the company I worked for. Enzymes have definite likes and dislikes and combine only with specific molecules, changing their chemical properties. Some enzymes, when combined with another molecule such as a co-enzyme or subunit, can accelerate chemical reactions. To understand cell phenomena, it is essential to know the behavior of these individual molecules. I was not completely satisfied with the research on cell biology and I was not provided with the necessary research tools," says Okada, reflecting on days past.

After returning home in 2000, Okada joined the RIKEN Genomic Sciences Center and became a research scientist on the Computational Genomics Team in the Bioinformatics Group. "Before joining the team, the only experience I had was doing experiments on living organisms. However, I found that most of my fellow scientists were information science researchers. It was while I was thinking about what to do here in this team that I found a paper written by Boris Kholodenko."

Now, Kholodenko is the deputy director of Systems Biology at University College Dublin in Ireland. He published a paper in 1999 on the 'quantification of short-term signaling by the epidermal growth factor receptor'. "A cell begins to proliferate when epidermal growth factor binds to a receptor. Doctor Kholodenko described the intermolecular reactions during the information transmission process that occurs in a cell as a combination of differential equations and established a mathematical model. Aiming to establish a prediction system, he considered the information on a molecule binding to a receptor as an input and the information on gene expression as an output. He viewed the process from input to output as a prediction system. This paper proposed a novel idea at that time because it dealt not only with theory, but also with experiment."

Researchers in life sciences have recently been paying increasing attention to systems biology. They are striving to find effective means for viewing individual life phenomena as a system to clarify their working principles. The general research process in systems biology proceeds as follows (Figure 1):

(1) Extraction of genes involved in target life phenomena or interactions between proteins from papers and experimental data to establish a molecular network.

(2) Comprehensive chronological and quantitative measurements of individual expression levels of genes, and concentrations and distributions of proteins by experiment.

(3) Mathematical analysis of huge amounts of data to establish a molecular network.

(4) Computer simulation under various conditions and comparison with experimental results to study the working principles and control system of life phenomena.

(5) Clarification of the relationship between input and output information to predict how a cell responds to the input and to identify input conditions that lead to a desirable output, so that the results can be applied to drug discovery.

The paper by Kholodenko is regarded as a precedent for systems biology. "On reading his paper, I thought, 'This is it!' Soon I started research activities modeled on his example. I felt that I could, but this was more than I could have dreamed of," says Okada with a smile on her face.

Cell differentiation-inducing systems

Aiming to advance her own research into the fate-determining systems of the cell using systems biology, in which experiment and theory are combined, Okada started the Laboratory for Cellular Systems Modeling at the RCAI in 2008. In May 2010, one of her research results was published in the journal *Cell*. "This

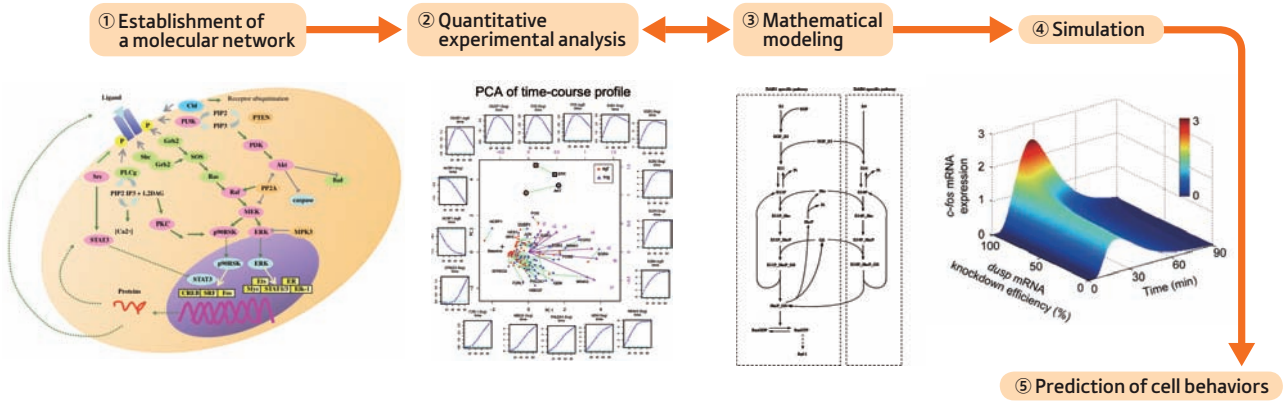


Figure 1: The research process in systems biology

research was conducted in collaboration with Dr Kholodenko. In this paper, we used a breast cancer cell line called MCF-7 and successfully established a mathematical model that can simulate the differentiation-inducing network of the cell."

To be more precise, epidermal growth factor that promotes cell proliferation and heregulin, a molecule that promotes cell differentiation, were administered to breast cancer cells. Measurements of the concentration or distribution of proteins related to proliferation and differentiation, the speed of association with or dissociation from other proteins, and gene expression were taken from every few minutes to every few tens of minutes. The measured data were analyzed to create a mathematical model, which was then used for computer simulation under various conditions, comparisons between the calculated and experimental results, and verification of the mathematical model. As a result, she successfully clarified a molecular network that worked only when the breast cancer cell differentiated, as well as the control system for the molecular network.

Figure 2 shows the differentiation-inducing molecular network that she clarified this time. When heregulin binds to a receptor on the cell membrane, the information is sent to an ERK molecule through many molecules. The ERK molecule then moves into the nucleus to activate RSK. Both ERKs and RSK activate a transcription factor (protein that binds to a specific DNA sequence and controls gene expression), which in turn promotes expression of the gene called *fos*. The *fos* RNA is then carried to the cytoplasm, where the FOS protein is produced. This FOS protein is also a transcription factor; when activated, it moves to the nucleus to express differentiation-inducing genes.

This is the ingenious way in which the differentiation-inducing system is controlled. The *fos* gene expresses itself only when information is received from both ERK and RSK at the same time through a transcription factor. Here, the control logic that is turned on and produces an output only when two information inputs are provided is known as an 'AND' gate. There are various sources of noise in a cell, which may cause improper operating signals when a switch is turned on by a single input. Introduction of an AND gate thus avoids the occurrence of malfunction and helps ensure a stable output.

"FOS protein activation is also controlled by an AND gate, because FOS protein is activated only when both the *fos* gene and ERK activity exist in the cytoplasm at the same time. We also found that the input from ERK in the cytoplasm was controlled by a 'feed-forward' loop."

With most transmission of information, the information from a molecule is sent only to the molecule located next to that molecule. With feed-forward-based information transmission (Figure 2), on the other hand, information from the molecule is sent not only to the molecule located next to that molecule, but also to the molecule located several steps ahead. Feed-forward and the AND gate are general strategies used in

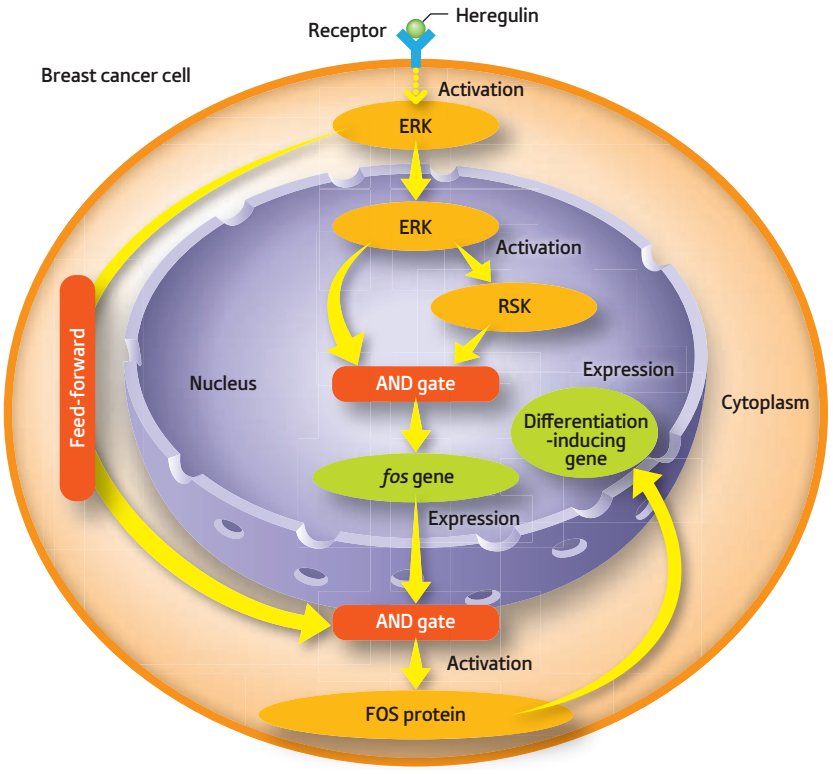


Figure 2: Molecular network inducing differentiation in breast cancer cells.

(1) First, heregulin binds to a receptor on the cell membrane of the cell, which leads to the activation of ERKs through multiple molecules.
(2) An activated ERK moves into the nucleus of the cell, and in turn activates RSK.
(3) Both the ERK and RSK activate a transcription factor and express the *fos* gene.
(4) The *fos* RNA is carried to the cytoplasm to form FOS protein.
(5) The FOS protein is activated and then moves into the nucleus to express the gene and induce differentiation. The AND gate controls *fos* gene expression. In addition, the AND gate and the feed-forwarding exercise double control over the activation of FOS protein.

control engineering, especially to prevent malfunction due to noise. They can also respond to the constantly changing cellular environment.

"Activation of ERKs that have moved to the nucleus from the cytoplasm has been known to last only several minutes, whereas activation of ERKs in the cytoplasm continues, although the roles of the ERKs have remained unclear. This time, however, we have clarified that ERKs play a role in feed-forward control."

The production of FOS protein requires about 30 minutes after the initial entry of information from ERK into the nucleus. If the activation of ERK continues in the cytoplasm, double control by feed-forward and the AND gate results in activation of the FOS protein, leading to cell differentiation. However, the situation around the cell is changing from moment to moment. If activation of ERKs in the cytoplasm is stopped for some reason, the AND gate cannot be turned on because there is no incoming feed-forward information. As a result, the FOS protein is not activated and decomposes, resulting in the inhibition of cell differentiation.

"We have shown that the cell differentiation-inducing system consists of various control processes nested in several steps. It is the rigorous control of these control processes that converts analog information such as changes in the concentration of molecules into digital information to determine whether to differentiate or not. Viewing this molecular network model, I felt that it was great and beautiful."

After publishing the paper, Okada received many praising emails from overseas researchers. There are several reasons for such a positive response. "The cell differentiation system we have clarified this time seems to be the common basic system, not only for the breast cancer cells we actually experimented on, but also for other types of cells. In other words, our model provides a useful means for computer simulation of differentiation in various cells types. The process can also be applied to selecting drug candidates and predicting their effects," says Okada.

Overseas drug companies and venture companies are also interested in this paper. "The output from the AND gate changes if one of the inputs is inhibited. This fact means that the cell may proliferate rather than differentiate. If we can develop techniques to control cell differentiation and proliferation, to differentiate cells into the desired types of cells, and furthermore, if we can get them to proliferate as we want, the techniques will also contribute to regenerative medicine."

Okada is offering the published molecular network model for any researcher to use freely. "If other researchers actually use the model and improve on the defects, the molecular network model will improve and will in turn be used by other researchers, thus producing numerous results. Knowledge-sharing is crucial to the development of science."

The next target is immunity

"The term 'systems biology' sounds attractive, but it requires enormous and persistent efforts," says Okada. "There are virtually no researchers who are talented in both biology and information science at the same level. For example, I have trouble with mathematics. When I listen to conversations between researchers in biology and researchers in information science, I have trouble even understanding what the problem is. However, I know that we need to be patient when talking to one another." Okada insists that what is required in systems biology is patience. "We need to conduct discussions and experiments using a lot of patience. Fortunately, I am a patient person."

Okada's next research subject will be immunity. "Doctor Masaru Taniguchi, director of the RCAI, has asked me to use systems biology to explain immunological diseases. This subject is our long-term target. It is a challenging theme, but we believe that the approach we used for breast cancer cells can also be applied to immune cells. Since cultured cells are frequently used in experiments on systems biology, we often hear the criticism that whether you can apply results from experiments on cultured cells to actual biological systems to explain biological phenomena is questionable. I therefore want to use experimental data at the individual level to bridge the gap between the model and the real world. First of all, I want to produce some significant results within five years.

"I want to logically understand the fate-determining system of the cell, but humans tend to believe in their intuitive understanding. They want to follow their intuition while using highly complicated experiments and mathematical analysis. This fact contains a contradiction, but I am interested in it precisely because of the contradiction."

ABOUT THE RESEARCHER

Mariko Okada was born in Chiba, Japan, in 1962. After obtaining a MS degree at the Tokyo University of Agriculture and Technology, she joined Novo Nordisk, a Danish pharmaceutical company and studied enzymes in metabolic and catabolic processes and secondary metabolites produced by micro-organisms. Afterwards, based on studies of membrane receptor activation and breast cancer at the University of California, Davis, USA, she obtained a PhD from the Tokyo University of Agriculture and Technology. From 2000, she started at RIKEN with a systems biology project on the ErbB signaling network to clarify the kinetic and mechanical features of this pathway. She now leads the Laboratory for Cellular Systems Modeling in the RCAI. Her experiences in different fields of science have inspired her to study the common regulatory machinery of living organisms at the systems level.

CHONG LI
Research Scientist
RIKEN Center for Developmental Biology

Breeding rewards in mouse cloning research

What do you do at RIKEN?

I am a postdoctoral researcher working on genomic reprogramming at the RIKEN Center for Developmental Biology (CDB). My main task is to develop novel methods in germ cell preservation and somatic cell nuclear transfer.

How and when did you join RIKEN?

I joined RIKEN in 2007 while studying for my PhD at Kwansei Gakuin University in Hyogo, Japan. It had always been my dream to work at RIKEN because of its strong research prowess in many scientific fields. When I contacted my current team leader, Teruhiko Wakayama, who was an affiliate professor at my university, he fortunately agreed to allow me to become a member of his group.

What attracted you to RIKEN?

The two times that I visited RIKEN during my master's course, it left a very strong impression on me of being a great research institute. There are so many top-notch research groups covering a variety of fields, and researchers are able to share cutting-edge equipment to conduct their experiments—something that would not be possible at a university. RIKEN provides researchers with a strong support network for research, such as good support for the laboratories. This allows me to confidently carry out creative research here.

How was the transition to life at RIKEN?

My transition to RIKEN was smooth because I had lived in Japan for three years prior to joining. The Chinese and Japanese cultures are also similar. I love being at RIKEN. At my laboratory we usually have lunch together and talk about Japanese and international current affairs. My colleagues are like a big, welcoming family—I often forget that I am a foreigner.

Please tell us about your research or other work at RIKEN.

My research is divided into two parts. One of these parts is focused on improving the cloning efficiency of mice. The first mouse was cloned by our team leader Dr Wakayama in 1998, but the low offspring rate is still a big limitation for the technology. We are trying to address this using such agents as histone deacetylase inhibitor or DNA methyltransferase inhibitor to increase the full-term development of cloned mice. The other part of my research involves investigating ways to preserve germ cells, or spermatozoa, over long time periods without freezing them. Most germ cell preservation methods require liquid nitrogen, which poses safety problems during the transportation stage. I preserve germ cells in a single medium with an additional protectant to ascertain the storage limitation at a refrigerator temperature.

What have been the highlights of your time at RIKEN so far?

There have been countless memorable moments so far. For example, I will never forget the birth of my first cloned mouse or the first time one of my papers was accepted for publication. The time I won an award at an international conference for the first time was also very memorable.

What has been the best thing about working at RIKEN?

RIKEN is not only a great research institute, it also provides opportunities to study while conducting research. The CDB holds symposia and lunch forums every week at which members from other groups as well as overseas scientists give presentations in their respective fields. Finding out about different fields is a great learning experience that allows me to broaden my horizons for future research.

What would you say to other people considering joining RIKEN?

RIKEN is an international institute for everyone who wants to do great research. Working at RIKEN is an invaluable experience in a researcher's career.

CONTACT INFORMATION

For details about working at RIKEN, please contact the RIKEN Global Relations Office:
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New agreements strengthen RIKEN's ties with China

On 24 June 2011, around 250 people from throughout China attended an event to commemorate the opening of the RIKEN Beijing Representative Office, which was formally established in December 2010. At the opening ceremony, RIKEN's executive director Akihiro Fujita introduced Kangbin Lei, director of the RIKEN Beijing Representative Office. "RIKEN would like to further strengthen its research collaboration with China," said Fujita. Yasutaka Moriguchi, Vice Minister of the Japanese Ministry of Education, Culture, Sports, Science and Technology, made a point of thanking China for the help it provided in the recent Tohoku–Kanto earthquake. "The Beijing Representative Office will be a center for 'brain circulation'—encouraging international mobility and attracting scientists back to their home country later in their careers—and a hub for research exchange between Japan and China," said Moriguchi.

At the event, RIKEN president Ryoji Noyori presented a lecture on 'Science and Technology for Future Generations', where he emphasized "the need for Japan and China to work together to solve the global issues of energy, food, health and the environment that confront humanity today." As examples of RIKEN's contribution to science, Noyori mentioned the K computer, recently ranked as the most powerful supercomputer in the world in the TOP500 list of the world's most powerful supercomputers, and the launch of the SPring-8 Angstrom Compact Free Electron Laser (SACLA) at the RIKEN Harima Institute.

RIKEN president Ryoji Noyori speaks at the event commemorating the opening of the RIKEN Beijing Representative Office

Another highlight of the ceremony was the signing of a memorandum of understanding between RIKEN and the Department of International Cooperation of the Chinese Ministry of Science and Technology, demonstrating the strong resolve of both parties to promote research cooperation between RIKEN and its partners in China. ■

The K computer takes first place

Japan's new supercomputer known as the K computer—its name derived from the Japanese *kei* for the number '10 peta'—has taken first place on the 37th TOP500 list announced at the 26th International Supercomputing Conference in June 2011. The TOP500-ranked K computer system, currently in the configuration stage, has 672 computer racks equipped with a current total of 68,544 processors. The system achieved the world's best LINPACK benchmark performance of 8.162 petaflops, placing it at the head of the TOP500 list. This is the first time that a Japanese supercomputer has achieved world number-one status since June 2004, when the Earth Simulator took first place on the TOP500 list.

Among its many achievements, the K computer boasts an extraordinarily high computing efficiency ratio of 93.0%. This achievement is made possible thanks to the K computer's integration of technologies: its massive number of processors, the interconnectivity that links them together and the software that maximizes hardware performance.

Jointly developed by RIKEN and Fujitsu, the K computer is part of the High-Performance Computing Infrastructure (HPCI) initiative of Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT). All elements of the supercomputer, from the research and development of its processors to system design and manufacturing, are Japan-made. The supercomputer is designed to achieve a LINPACK performance of 10 petaflops when completed in 2012, and will be applied for research in a range of areas of computational science, where it promises to open many new doors in fields from global climate research to meteorology, disaster prevention and medicine.

"As we move forward to complete this project by June 2012, we will maintain our firm commitment to the maintenance and operation of the system, and I hope to see wonderful results when we begin to make the world's top-performing supercomputer available to users around the world," says RIKEN's president Ryoji Noyori. "I very much believe that the strength and perseverance that was demonstrated in this project will also make possible the recovery of the devastated Tohoku region." ■

The K computer under construction in Kobe

www.riken.jp

RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology fields including physics, chemistry, medical science, biology and engineering. Initially established as a private research foundation in Tokyo in 1917, RIKEN became an independent administrative institution in 2003.

RIKEN RESEARCH is a website (www.rikenresearch.riken.jp) and print publication intended to highlight the best research being published by RIKEN (www.riken.jp). It is written for a broad scientific audience and policy makers interested in science and aims to raise global awareness of RIKEN and its research.

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