



# RIKEN RESEARCH

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## Earthly elements, stellar origins

### HIGHLIGHT OF THE MONTH

#### Pushing the boundaries of the isotope frontier

### RESEARCH HIGHLIGHTS

Molecular blockade  
A cosmic show-down  
Carving up water  
Unraveling how bacteria motor along  
Decoding monkey movements  
Critical viewing  
Mapping brain development  
Inviting arthritic trouble  
The aging stem cell  
A matter of give and take

### FRONTLINE

Omics analysis nurtures the creation of functional plants

### ROUNDUP

RIKEN's young scientists meet the giants of science at the Lindau Meeting

### POSTCARDS

Dr Marsha Quallo (University College London Institute of Neurology, London, United Kingdom)

# Pushing the boundaries of the isotope frontier

## Discovery of 45 rare neutron-rich isotopes provides clues to the stellar formation of heavy elements

Many of Earth's resources, from copper to more precious metals, are often taken for granted, but the only place to make more of these elements lies at the interior of stars. Despite this cosmological reality, however, scientists are yet to fully understand the stellar process that produces many of the heavier elements in the periodic table. Now, with the discovery of 45 new, rare isotopes by a team of scientists lead by Toshiyuki Kubo at RIKEN's Nishina Center in Wako, hopes are high to establish an understanding of the nuclear process that produces roughly half the elements heavier than iron. The discoveries, published in the *Journal of the Physical Society of Japan*<sup>1</sup>, are some of the first results from the Radioactive Isotope Beam Factory (RIBF) (Fig. 1), a next-generation heavy-ion accelerator designed to explore the structure of exotic, neutron-rich isotopes.

### Stellar insights

All of the known elements and their isotopes are collected in the 'Table of Nuclides', a continuously updated chart that is organized according to how many protons and neutrons each isotope contains (Fig. 2).

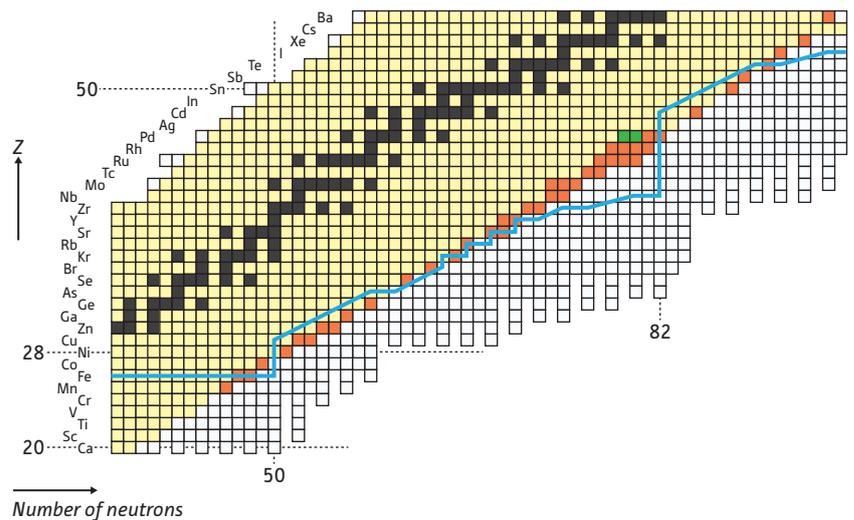


Figure 2: A portion of the chart of known isotopes. Each row, starting with calcium (Ca) on the bottom, represents a different element in the periodic table. The 45 new isotopes discovered at the RIKEN RIBF are shown in pink, many of which lie on the path (blue line) of an important nuclear process for creating heavy elements. The edge where the white squares end is called the 'drip-line'.

The RIBF was designed to explore the outer limits of this chart, near the so-called neutron 'drip-line', where nuclei can be produced only by collisions in particle accelerators. These nuclei contain so many neutrons they survive for only fractions of a second before decaying to more stable forms.

Neutron-rich isotope research is important for understanding how stars produce elements of the periodic table. Fusion, where two high-energy nuclei merge, occurs in stars and can form elements up to iron. However, scientists believe that roughly half of the elements heavier than iron are produced by the so-called 'r-process', where r stands for rapid. During the r-process, a nucleus is bombarded and bloated with neutrons so rapidly that it has no time to stabilize by beta decay; instead, it decays through a series of unstable intermediate nuclei. According

to theoretical models, many of the rare isotopes discovered using the RIBF act as the intermediate nuclei in the r-process.

"If we understand the structure of the nuclei of these new neutron-rich isotopes, we can better understand the path and pace of the r-process and how the process is constrained by temperature and density," says Mike Famiano, a member of Kubo's team.

The rapid-fire flux of neutrons required for the r-process likely only occurs at the interior of exploding stars called supernova (Fig. 3). As such, the RIBF research is providing a unique glimpse into a rare and distant stellar process.

### Break and measure

The RIBF produces rare isotopes by accelerating ionized uranium-238—an element heavy enough to break into other large nuclei—to close to the speed of light

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Figure 1: The 'BigRIPS' separator at the RIKEN RIBF allows researchers to identify the rare isotopes produced after heavy ion collisions.

ESO/NASA



Figure 3: An image of a supernova in Spiral Galaxy M100. The high neutron flux in supernova is needed for the process that underlies the synthesis of roughly half the elements heavier than iron.

and then smashing these ions into a target of beryllium or lead. The collision causes the uranium nucleus to undergo fission and split into smaller nuclear ‘fragments’ that are collected and analyzed in the fractions of a second before they decay.

It was in such fragments that Kubo and colleagues discovered the 45 new isotopes, which span the periodic table from manganese to barium. To produce fragments over this wide range, Kubo’s team designed a means of identifying the nuclear fragments quickly and accurately, and the RIBF accelerator group designed a cyclotron capable of accelerating uranium.

The RIBF cyclotron uses powerful superconducting magnets to cycle the uranium ions through an accelerating voltage multiple times, until the ions reach speeds 70% of the speed of light.

The ‘brains’ of the RIBF is the in-flight separator, dubbed ‘BigRIPS’, which analyzes the fragments of the fissile uranium. Superconducting magnets in the separator force the fast-moving nuclei to fan out with different curvatures, allowing the team to determine the atomic number and the ratio of charge to mass of each nucleus—some of which were produced only once in the collision.

Kubo and his team’s results not only provide insights into the stellar production of heavy elements, but also enable them to test the limits of theoretical models for more stable nuclei. Kubo says they will next focus on the new isotopes palladium-128 and nickel-79 because they are similar to the nuclei with a so-called ‘magic’ number of neutrons or protons—2, 8, 20, 28, 50 and 82—which are extraordinarily stable. Palladium-128 has 82 neutrons, while nickel-79 has one more than the magic number of 50 neutrons. Near the neutron drip-line, however, nuclei may have different magic numbers, a possibility that the new isotopes will allow nuclear physicists to test.

### A pioneer

As the first next-generation accelerator for studying rare isotopes, the RIBF is in prime position to keep opening new doors in nuclear physics research. Similar facilities are under construction in Germany and in the US and Kubo points out that the teams working at three new-generation facilities are already collaborating with each other. Given the funding necessary to plan, design and construct such large facilities—on the

order of 500 million US dollars (50 billion yen)—the results from RIKEN’s RIBF will continue to provide motivational fuel for these efforts.

“The discovery of new, rare isotopes is the first validation of the extended capability of these new-generation facilities,” explains Kubo. The aim now is to increase the intensity of the uranium beam at RIBF by 1,000 times higher than present. “We expect to discover many new isotopes and expand the frontier of nuclear physics to a large extent.” ■

1. Ohnishi, T., Kubo, T., Kusaka, K., Yoshida, A., Yoshida, K., Ohtake, M., Fukuda, N., Takeda, H., Kameda, D., Tanaka, K., *et al.* Identification of 45 new neutron-rich isotopes produced by in-flight fission of a  $^{238}\text{U}$  beam at 345 MeV/nucleon. *Journal of the Physical Society of Japan* **79**, 073201 (2010).

### About the researchers

Toshiyuki Kubo was born in Tochigi, Japan, in 1956. He received his BS degree in physics from The University of Tokyo in 1978, and his PhD degree from the Tokyo Institute of Technology in 1985. He joined RIKEN as an assistant research scientist in 1980, and was promoted to research scientist in 1985 and to senior research scientist in 1992. He spent time at the National Superconducting Cyclotron Laboratory of Michigan State University in the USA as a visiting physicist from 1992 to 1994. In 2001, he became leader of the BigRIPS team, and was promoted to group director of the research instruments group at the RIKEN Nishina Center in 2007. He is in charge of the design, construction, development and operation of major research instruments, as well as related infrastructure and equipment, at the RIKEN Nishina Center. His current research focuses on the production of rare isotope beams, in-flight separator issues, and the structure and reactions of exotic nuclei.



# Molecular blockade

Artificial ‘molecules’ with an asymmetric structure can control the flow of electrons in semiconductor materials

Nanoscale devices confine electrons and enable manipulation of electron spin—an inherent property akin to the direction in which the particle is rotating. An unexpected mechanism for this control in asymmetric structures has now been reported by Keiji Ono at the RIKEN Advanced Science Institute, Wako, in collaboration with a team of researchers from Japan and Taiwan<sup>1</sup>.

Artificial systems that trap electrons in a tiny volume can display many of the properties of atoms because they create an analogous series of discrete electron energy levels. “One example is the Zeeman Effect in which an applied magnetic field splits a single electron energy level into two, depending on its spin,” explains Ono.

Taking this analogy further, two closely spaced ‘artificial atoms’ can behave like an artificial molecule. In principle, it is possible to transfer an electron between these atoms by tuning the energy level of an electron in one atom to that of the second by, for example, applying an electric field. Indeed, this phenomenon, known as resonant tunneling, occurs in artificial molecules consisting of two identical atoms. Ono and his team showed, however, that the situation is not so simple in artificial molecules comprising two different atoms.

They investigated a structure that was a stack of alternating layers of semiconductor (Fig. 1). Electrons become trapped in the semiconductor with the smaller bandgap by the surrounding layers of wide-bandgap material. The top ‘atom’ was 7.5 nanometers thick and made of indium gallium arsenide.

A 6.5-nanometer barrier separated this from the second atom: 10 nanometers of gallium arsenide. Etched pillars with a diameter of less than one micrometer confined the electrons in the transverse direction.

The difference in size and composition meant that the Zeeman Effect was stronger in the top atom than the bottom one. This made it impossible to align both of the Zeeman-split levels in the two atoms at the same time. Ono and colleagues demonstrated that because of this, when an energy state from one atom is aligned with one in the second, the electron flow through the molecule

reduces, an effect they call spin blockade. The flow increased when they tuned the two Zeeman levels in one atom to the midpoint of those in the other atom.

“This finding can be used as a basic tool for selecting, filtering, or initializing an individual electron spin,” comments Ono. “I hope this can be applied to quantum information technology.” ■

- Huang, S.M., Tokura, Y., Akimoto, H., Kono, K., Lin, J.J., Tarucha, S. & Ono, K. Spin bottleneck in resonant tunneling through double quantum dots with different Zeeman splitting. *Physical Review Letters* **104**, 136801 (2010).

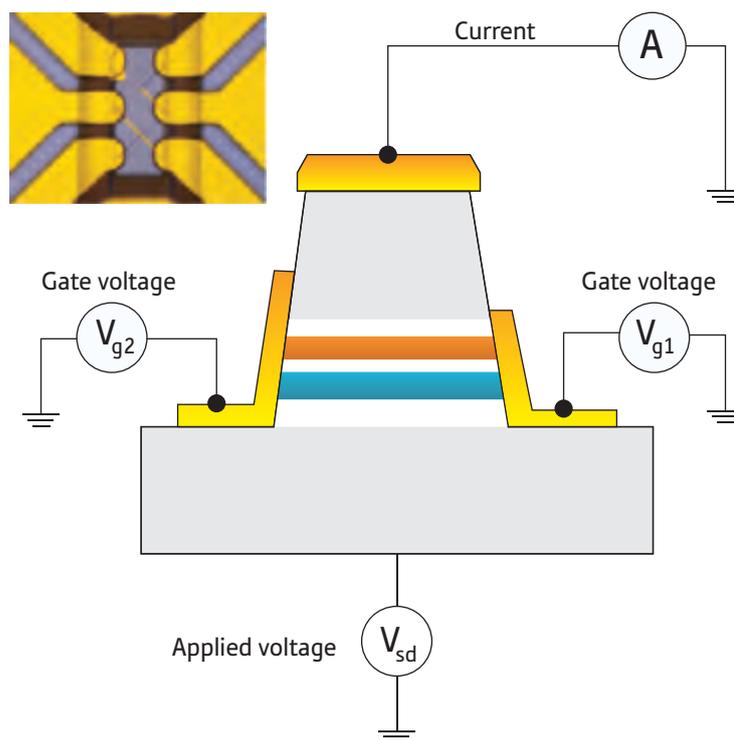


Figure 1: Electrons are confined in semiconductor layers with a small bandgap (shown in orange and blue) creating so-called ‘artificial atoms’. Gate voltages tune the electron states in these artificial atoms. The effect of this tuning is monitored by measuring the current flowing through the device. A top view of the device is shown in the inset (top, left).

# A cosmic show-down

The interaction between dense galaxy clusters and large-scale cosmic structures leads to intense shock waves that illustrate the evolution of the universe

Galaxy clusters, which are assemblies of hundreds or even thousands of galaxies, are some of the densest structures in the universe. By studying the growth and dynamics of galaxy clusters, researchers from the RIKEN Advanced Science Institute, Wako, and the Academia Sinica Institute of Astronomy and Astrophysics, Taiwan, have provided valuable clues on the evolution of the universe<sup>1</sup>.

Huge numbers of stars are not the only distinctive feature of galaxy clusters. Another important component is the intracluster medium (ICM), a hot plasma consisting of electrons and protons, that has a greater mass than the galaxies and extends throughout the vast intergalactical space of the cluster.

The researchers focused their study on the ICM of the galaxy cluster known as A1689. They analyzed x-ray observations made by the Japanese satellite Suzaku; its high sensitivity for x-ray radiation enabled the observation of A1689's ICM to very large distances away from the center. The researchers also analyzed gravitational lensing effects, where—following Einstein's theory of relativity—they estimated the total mass of the cluster by the way light from distant galaxies bent around different regions of A1689.

"From the gravitational lensing analysis, the mass distribution of A1689 is precisely known," notes Madoka Kawaharada from the research team. "Therefore, by adding x-ray information ... to the cluster outskirts, we [could] compare the gas dynamics directly with the mass distribution."

Kawaharada and colleagues found

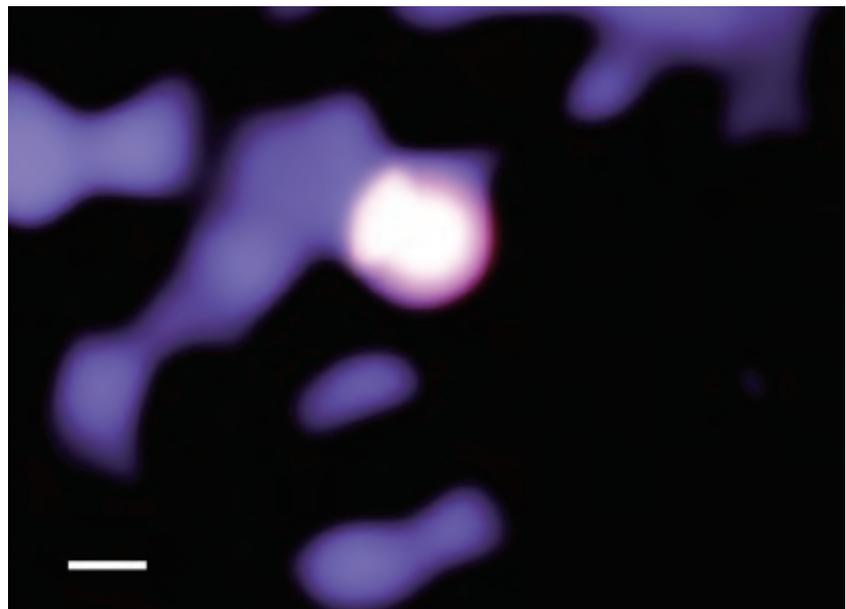


Figure 1: The reconstructed image of the hot galaxy cluster A1689. The pink area depicts the temperature variation of the ICM within A1689. Where the galaxy cluster meets large-scale galaxy structures (purple), a shock wave leads to a detectable rise in temperature of the ICM (scale bar, 10 million light years).

significant interactions between the ICM and the large-scale structure of galaxies, sometimes called the 'cosmic web' that extends throughout the universe (Fig. 1). At the region where the A1689 cluster meets the large-scale structure, its ICM gets even hotter than its usual 20 megakelvin, with temperatures reaching 60 megakelvin. This suggests a heating effect by the shock wave that develops where the hot ICM plasma meets 'colder' gas from the large-scale structure. In addition, the gravitational lensing data suggest that the ICM in the shock wave region is static, whereas it is moving elsewhere, which supports it against the strong gravitational force of the cluster.

These results provide a valuable insight into the dynamics of these huge cosmic

structures, particularly if they can be confirmed for other galaxy clusters, says Kawaharada. "If they behave similarly, it will be evidence that galaxy clusters do interact with the large-scale structure, confirming that they are a continuously evolving product of the structure formation in the universe." ■

1. Kawaharada, M., Okabe, N., Umetsu, K., Takizawa, M., Matsushita, K., Fukazawa, Y., Hamana, T., Miyazaki, S., Nakazawa, K. & Ohashi, T. Suzaku observation of A1689: Anisotropic temperature and entropy distributions Associated with the large-scale structure. *The Astrophysical Journal* **714**, 423–441 (2010).

# Carving up water

Single water molecules can now be sliced into different atomic components, thanks to the electronic properties of ultrathin oxide films

In its bulk state, magnesium oxide (MgO) is a chalky white, rather unreactive mineral that is best known as an ingredient in antacid medication. But when this compound is formed into nanoscale films, only a few atoms deep, things begin to change. While bulk MgO is an insulator, ultrathin MgO can transfer small amounts of charge to substances, such as metal catalysts, adsorbed on its surface—giving these films the ability to tune chemical reactivity and unlock new reaction routes.

Now, researchers led by Yousoo Kim and Maki Kawai at the RIKEN Advanced Science Institute in Wako have used MgO films to establish unprecedented control over bond-breaking pathways at the single molecule level. The team reports that water molecules adsorbed onto ultrathin MgO can be selectively split apart using the sharp tip of a scanning tunneling microscope (STM)<sup>1</sup>.

According to lead author Hyung-Joon Shin, understanding the activity of MgO films required a detailed study with a well-known compound. “The atomic-scale picture of a single water molecule on the MgO surface has been [in] demand for a long time,” says Shin. “And, we expected to see interesting dynamics from the water molecules.”

In their STM experiment, the researchers worked at temperatures close to absolute zero to produce stable images of water molecules adsorbed on ultrathin MgO (Fig. 1). By injecting small amounts of tunneling current with the STM tip, they could make the water molecules ‘hop’ laterally around the surface—but only at applied voltages corresponding to

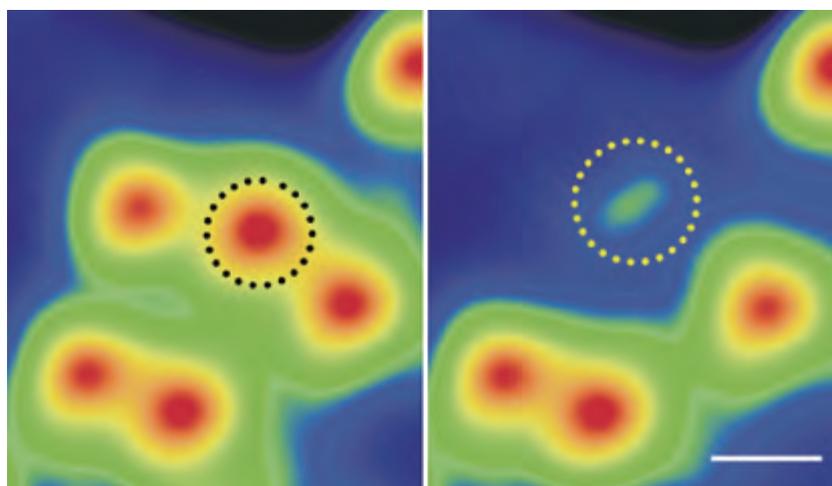


Figure 1: STM images record the transformation of an individual water molecule on ultrathin MgO (center of left panel) into a hydroxyl group (center of right panel) through vibration-enhanced resonance (scale bar, 1 nanometer).

the vibrational frequencies of hydrogen–oxygen bonds. Excitations beyond these vibrational thresholds caused a chemical reaction: the water molecules dissociated into a new species, which STM images and theoretical analysis revealed was a hydroxyl group.

Because the energy required to split water on the MgO film was much lower than the hydrogen–oxygen bond energy, the researchers theorized that ultrathin MgO traps tunneling electrons in the molecule—generating a resonance-enhanced vibration that shakes the molecule apart. “The vibrationally induced dissociation of single water molecules has never been observed before,” says Shin.

The team’s experiment yielded a third

discovery about the MgO surface. By injecting tunneling electrons at voltages close to the hydrogen–oxygen bond energy, STM images showed that another chemical transformation occurred: this time, water molecules split into atomic oxygen. Having two selectable water dissociation pathways—one vibrational, one electronic—has potent implications for ‘green’ energy research, because water splitting is one of the simplest way to produce clean hydrogen fuel. ■

1. Shin, H.-J., Jung, J., Motobayashi, K., Yanagisawa, S., Morikawa, Y., Kim, Y. & Kawai, M. State-selective dissociation of a single water molecule on an ultrathin MgO film. *Nature Materials* 9, 442–447 (2010).

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# Unraveling how bacteria motor along

Motile bacteria switch between swimming patterns through conformational changes of a constituent protein of the propeller-like flagellum

Analysis of the protein structure of the ‘motor’ of motile bacteria at high resolution by Saori Maki-Yonekura and Koji Yonekura of the RIKEN SPring-8 Center, Harima, and Keiichi Namba of Osaka University has revealed the mechanism for transitioning between different movements.

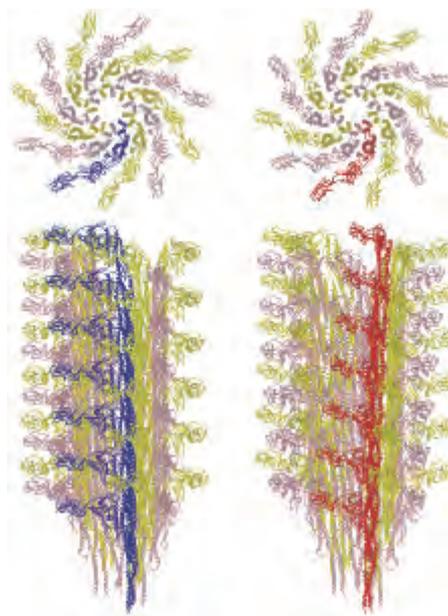
The flagellum has a rotary motor embedded in the cell membrane and a propeller-like filament connected to the motor by a universal joint. “It’s a tiny machine, but amazingly well designed for its function,” says Yonekura.

When moving along chemical or temperature gradients, bacteria alternate between ‘running’ and ‘tumbling’. Switching between these swimming patterns involves a reversal in motor rotation every few seconds.

Although the complete flagellum has many proteins, the flagellar filament is composed solely of the protein flagellin. The amino-acid sequence of flagellin is conserved among bacterial species, as is its structure.

In most species of bacteria the flagellar filament is formed of 11 ‘protofilaments’, the flagellin subunits of which are arranged to form nearly longitudinal helical arrays. Motor reversal switches the structure between left-handed and right-handed helical shapes, involving different combinations ‘L-type’ and ‘R-type’ protofilaments.

Biologists usually study protein structure using X-ray crystallography. But flagellin forms filaments that prevent crystallization. Cryo-electron microscopy (cryo-EM) can be used, but the resolution is usually not high enough to see atomic



**Figure 1:** Transition between the L-type (left) and R-type flagellar filaments (right). The upper panels show the distal end view. The lower panels show the side view. One of the 11 protofilaments is colored blue for the L-type and red for the R-type.

details, because electron irradiation severely damages biological samples. “We developed techniques to analyze the structure at high resolution using cryo-EM,” explains Yonekura.

The researchers previously derived the structure of the R-type flagellar filament of *Salmonella enterica*, the bacterium responsible for many cases of human food poisoning<sup>1</sup>. Their latest analysis has revealed the structure of the L-type filament using cryo-EM<sup>2</sup>.

In the running mode of swimming, the flagellar motor rotates counter clockwise as viewed from outside the cell, and several flagellar filaments in the left-handed helical shape form a bundle that propels the bacterium forwards from behind. On motor reversal, twisting causes these filaments to transform into a right-handed shape and to disengage from the bundle, causing the cells to tumble and change direction.

By comparing the structures of the

L- and R-type filaments (Fig. 1), the researchers found flexible changes in the conformation of flagellin within the filament. “The flagellar filament must be flexible enough for morphological transitions needed to change swimming direction, but strong enough to withstand high-speed rotation of the motor,” explains Yonekura. The researchers hope that their research will help in the development of new drugs against pathogenic bacteria, and eventually lead to an artificial nano-screw. ■

1. Yonekura, K., Maki-Yonekura, S. & Namba, K. Complete atomic model of the bacterial flagellar filament by electron cryomicroscopy. *Nature* **424**, 643–650 (2003).
2. Maki-Yonekura, S., Yonekura, K. & Namba, K. Conformational change of flagellin for polymorphic supercoiling of the flagellar filament. *Nature Structural & Molecular Biology* **17**, 417–422 (2010).

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# Decoding monkey movements

High-performance neuroprosthetic devices may result from a new technique for recording neuronal activity

Producing accurate and stable, long-term readings of neuronal activity using a brain-machine interface (BMI) is now possible thanks to work by Naotaka Fujii and his colleagues at the RIKEN Brain Science Institute, Wako<sup>1</sup>. Their results could help researchers to develop durable and versatile neural prostheses for rehabilitation patients.

BMIs read neural activity associated with planning and executing movements and decode it into commands that are relayed to an external device such as a computer cursor or robotic arm. This normally involves recording simultaneously from multiple, single neurons, so the recordings are unstable and the decoding model needs re-calibration on a daily basis.

Fujii and colleagues used an alternative technique called electrocorticography, in which an array of electrodes is used to record the population activity of cortical neurons.

Electrocorticography is often used to evaluate epileptic patients before neurosurgery but is not normally used for longer than two weeks. It was thought to provide a low fidelity signal for BMIs, because the electrodes record neural activity from the cortical surface, rather than within the cortex.

To overcome this, the researchers designed an electrode array for long-term recording (Fig. 1), and developed a novel decoding algorithm that samples neural activity from multiple brain regions.

After implanting the electrodes into the brains of monkeys, so that they spanned multiple brain regions, Fujii and colleagues trained the animals to

spontaneously reach out and grasp food presented to them. The monkeys wore custom-made jackets fitted with reflective markers at the shoulders, elbows and wrists. The researchers then recorded the monkeys' arm movements using a motion capture system, and correlated them with the neuronal activity recorded by the electrodes.

By decoding the signals, they could predict the trajectory and orientation of the monkeys' arms in three dimensions. The accuracy of the decoding was comparable to that of existing BMIs which record activity from single cells. Furthermore, the recordings were highly stable, and could be decoded for several months without recalibration.

The new recording technique should prove to be useful for researchers

investigating movement control and higher cognitive functions. It could also lead to versatile devices that can be implanted for long periods of time, to aid patients with brain damage, spinal cord injury, and neurodegenerative conditions such as amyotrophic lateral sclerosis, notes Fujii.

“Our electrode array is still not ready for long-term use in patients, because of the risk of infection,” says Fujii, “but we are now developing a fully implantable wireless device to prevent this.” ■

1. Chao, Z.C., Nagasaka, Y. & Fujii, N. Long-term asynchronous decoding of arm motion using electrocorticographic signals in monkeys. *Frontiers in Neuroengineering* 3, 3–13 (2010).

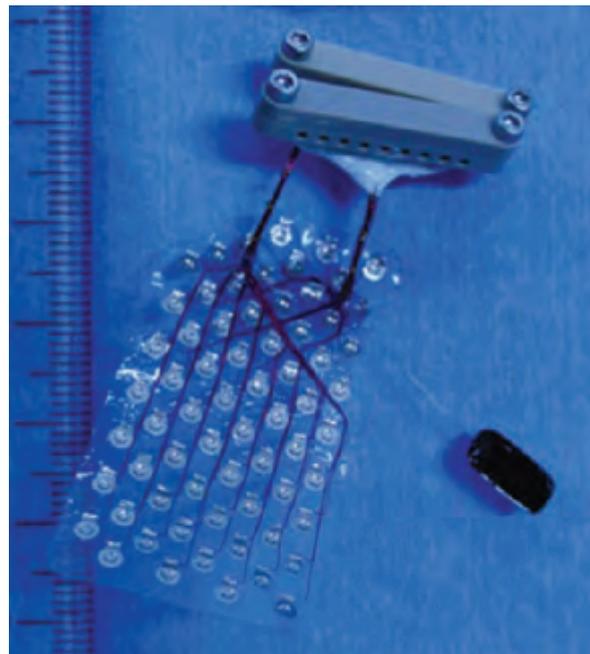


Figure 1: A photograph of a 64-channel electrode array used for electrocorticographic recordings from the monkey brain.

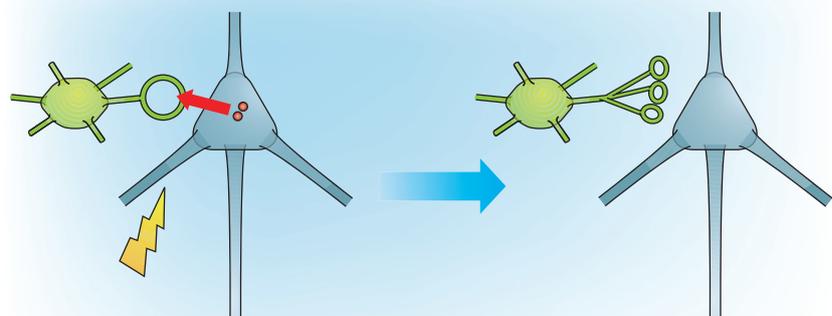
# Critical viewing

## The maturation of inhibitory synapses in the visual cortex is modulated by visual experience

Sensory experience changes the way humans see the world during early postnatal development. Now, an international team of researchers, including Tadaharu Tsumoto from the RIKEN Brain Science Institute in Wako, may have an explanation. They report in the journal *Neuron* that visual experience drives the maturation of inhibitory synapses in the visual cortex during a critical period of early postnatal development by activating endocannabinoid receptors<sup>1</sup>. “This maturation makes synaptic transmission more reliable,” explains Tsumoto. These findings may be crucial to understanding the changes in the way the brain processes visual information from early postnatal life to puberty.

The researchers electrically stimulated the visual cortex and measured the resulting inhibitory currents in the superficial layer of visual cortex slices from 3-week-old rats, a time during development soon after the initial opening of the eyes. High-frequency stimulation of the slices—similar to input that visual cortex neurons may receive during visual experience—led to a long-lasting drop in the amount of inhibitory current that the stimulation could elicit. This is called long-term depression of inhibitory currents (iLTD). Tsumoto and colleagues could not induce iLTD in the visual cortex of 5-week-old rats, a stage in development akin to puberty. The researchers therefore realized that there was a ‘critical period’ for the induction of visual cortex iLTD that occurred after eye opening.

Interestingly, Tsumoto and colleagues were able to delay the onset of the critical



**Figure 1:** Schematic diagram of an excitatory neuron (blue) just after eye opening in young rats (left). Stimulation (yellow bolt) of this neuron produces endocannabinoids (red dots) and results in iLTD at inhibitory synapses (green, open circle). Through this process, inhibitory synapses develop to the mature state (right).

period by raising the rats in darkness, and even brief exposure of dark-reared rats to light induced the loss of iLTD in the visual cortex. The research team realized that visual experience therefore plays an important role in regulating the timing of the critical period.

Endocannabinoids are signaling molecules that regulate neuronal activity throughout the nervous system. The researchers showed that a drug that activates endocannabinoid receptors can induce the loss of iLTD in the visual cortex in dark-reared animals that would normally still exhibit iLTD, while a drug that blocks endocannabinoid signaling could inhibit the loss of iLTD that is normally induced by light. This suggested to Tsumoto and colleagues that visual experience drives endocannabinoid

signaling to induce iLTD during visual cortex development (Fig. 1).

The researchers argue that endocannabinoid-mediated iLTD seems to be important for the maturation of inhibitory synapses that occurs during development of the visual cortex. Tsumoto suggests that this maturation could help to “make responses of neurons in the visual cortex selective to a particular feature of visual stimuli,” such as orientation of contours or direction of movement. ■

1. Jiang, B., Huang, S., de Pasquale, R., Millman, D., Lee, H.-K., Tsumoto, T. & Kirkwood, A. The maturation of GABAergic transmission in visual cortex requires endocannabinoid-mediated LTD of inhibitory inputs during a critical period. *Neuron* **66**, 248–259 (2010).

# Mapping brain development

A large-scale genetic analysis provides a molecular atlas of a complex brain structure, the hypothalamus

The hypothalamus is a small part of the brain that regulates many behaviors that are critical for survival, including circadian rhythms, food intake, temperature regulation and the release of hormones from the pituitary gland. Abnormal development of this structure causes hormonal imbalances thought to underlie multiple diseases, including autism, mood disorders and obesity.

Anatomically, the hypothalamus is highly complex, with many distinct nuclei each containing a cluster of unique cells. Since little is known about the molecular mechanisms mediating the development of this well-characterized structure, Tomomi Shimogori of the RIKEN Brain Science Institute, Wako, and her multinational colleagues performed a genome-wide DNA microarray analysis to investigate gene expression at 12 different intervals during development of the mouse hypothalamus<sup>1</sup>.

They found that, between embryonic days 10 and 16 when immature neurons are being generated by cell division, the expression of 1,045 genes is enhanced. The researchers also noted that expression of some of these genes, which are known to be expressed in all immature neurons, peaked early then declined steadily. Those expressed uniquely in the hypothalamus peaked between embryonic days 12 and 14, when the production of hypothalamic cells also peaks.

After examining the expression patterns of all 1,045 genes, the researchers used the data to produce a molecular atlas, showing when and where each is expressed in the hypothalamus. This not only revealed several molecular ‘markers’

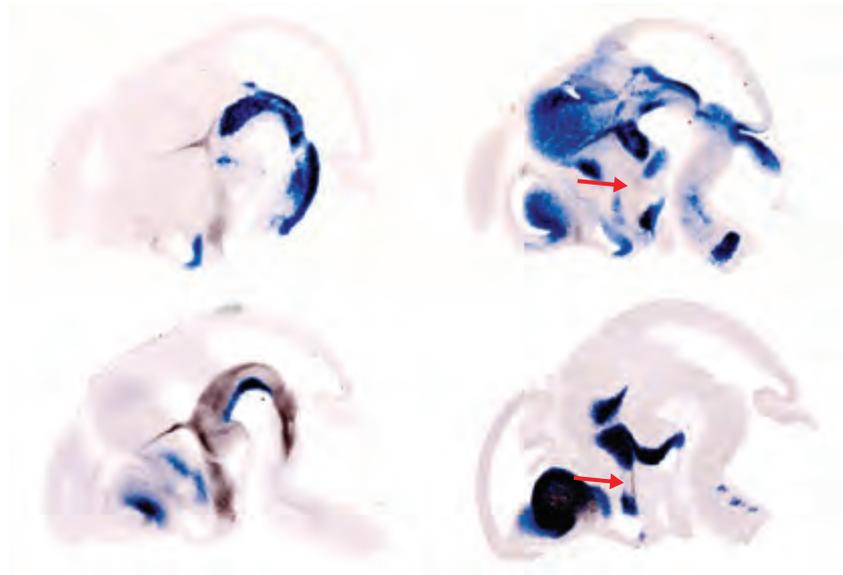


Figure 1: Light microscope images of four different embryos, showing longitudinal whole brain sections viewed from the side, at the same developmental stage. Molecular markers delineate the borders of distinct nuclei, or groups of neurons, in the hypothalamus (bottom center of each brain section). *Sonic Hedgehog* (dark brown) in the left column is required for differentiation of cells in the nuclei at the front of the hypothalamus. The function of another marker, *Lhx6* (dark brown, red arrows) in the right column is now under investigation.

that label each of the hypothalamic nuclei throughout the entire course of development, but also delineated their borders (Fig. 1).

One gene, *Sonic Hedgehog* (*Shh*), is well known to be expressed along the bottom of the developing neural tube and to induce a specific pattern of motor neurons in that region. Shimogori and her colleagues found another *Shh* expression domain, at the base of the developing hypothalamus, and speculated that it might also be involved in cell patterning.

To investigate, they created genetically engineered mice in which *Shh* is selectively deleted from the hypothalamus. The hypothalamus was notably thinner in these animals, and expression of several genes, normally

found later on in nuclei at the front of the hypothalamus, was missing. This suggests that cells at the front of the hypothalamus fail to differentiate in the absence of *Shh*.

“The next step is identifying the genes responsible for shaping the hypothalamus,” says Shimogori. “To do this, we are currently overexpressing patterning molecules, analyzing the effects and using our gene atlas to predict their role.” ■

1. Shimogori, T., Lee, D. A., Miranda-Angulo, A., Yang, Y., Wang, H., Jiang, L., Yoshida, A. C., Kataoka, A., Mashiko, H., Avetisyan, M., Qi, L., Qian, J. & Blackshaw, S. A genomic atlas of mouse hypothalamic development. *Nature Neuroscience* **13**, 767–775 (2010).

# Inviting arthritic trouble

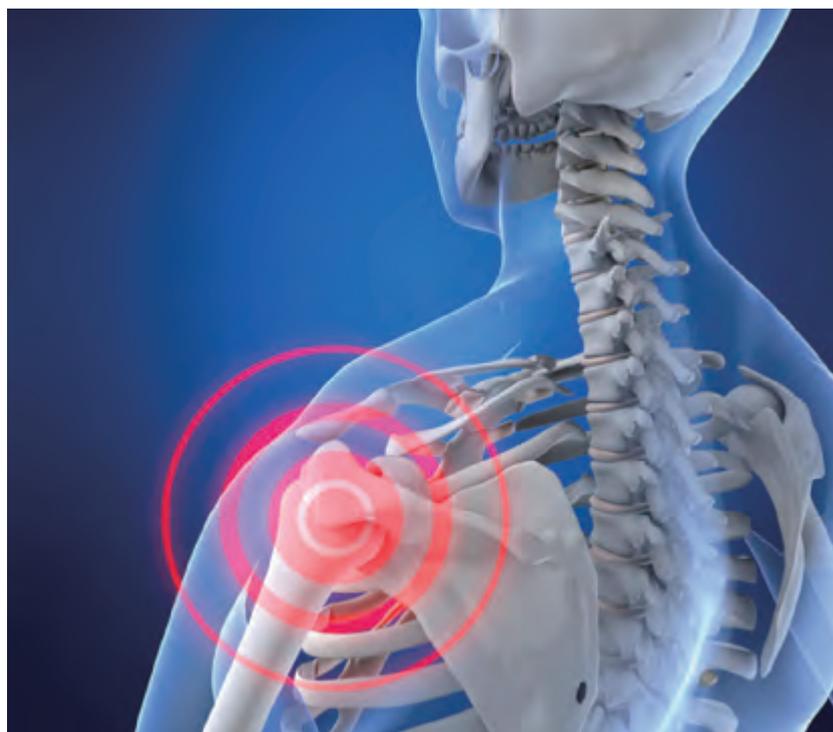
A large-scale genetic screen reveals a factor that makes rheumatoid arthritis patients' joints vulnerable to immune attack

Under normal conditions, the body is protected against immune system-mediated self-destruction by marker proteins that indicate that host cells are 'off limits' and should be ignored. In patients with rheumatoid arthritis (RA), however, such safeguards fail to prevent immune cells from damaging joint tissues (Fig. 1).

Although an estimated 1% of the world's population is affected by RA, the roots of this disorder are poorly understood. Now, a multi-institutional team of Japanese researchers led by Yuta Kochi and Kazuhiko Yamamoto of the RIKEN Center for Genomic Medicine in Yokohama has characterized potential genetic risk factors<sup>1</sup>.

The researchers performed a large-scale 'genome-wide association study', screening thousands of Japanese individuals to identify small genomic sequence variations—so-called 'single-nucleotide polymorphisms' (SNPs)—that are linked with RA susceptibility to a statistically meaningful degree. The strongest association they identified was for a SNP in the vicinity of the gene encoding chemokine (C-C motif) receptor 6 (CCR6). Subsequent analysis of two large, independent cohorts of Japanese subjects provided further confirmation of the connection between this CCR6 SNP and RA.

The CCR6 receptor recognizes signals that stimulate immune cell development, and triggers immune system effects that could be directly relevant to RA. "This receptor has been shown to be important for the migration and recruitment of immune cells such as dendritic cells, T



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Figure 1: Inflammatory responses triggered by an unrestrained immune system contribute to the painful joint disease known as rheumatoid arthritis.

cells, and B-cells during inflammatory and immunological responses" says Kochi, "and it may also regulate the differentiation and maturation of these cells." Closer examination by the researchers subsequently revealed a second potentially important genetic variation affecting CCR6 expression. They also determined that the elevated CCR6 activity resulting from this variation was strongly associated with RA.

CCR6 appears to exert its pathological effects by promoting the inflammatory response triggered by a recently identified class of helper T cells known as Th17 cells. "We believe the primary role of CCR6 in RA pathogenesis is facilitating the entry of Th17 cells into the joints," says Kochi. "And as CCR6 is also involved in the migration and differentiation of

B-cells, it could also influence the activity of auto-reactive B-cells." Strikingly, these CCR6 variants also appear to contribute to two other inflammatory conditions, Graves' disease and Crohn's disease.

Following on from this discovery, Kochi and Yamamoto are hopeful that their data will yield additional candidate genes that enable further insights into how RA patients' immune systems end up going off-course. "Many other genetic factors other than CCR6 remain to be discovered," says Kochi. ■

1. Kochi, Y., Okada, Y., Suzuki, A., Ikari, K., Terao, C., Takahashi, A., Yamazaki, K., Hosono, N., Myouzen, K., Tsunoda, T. *et al.* A regulatory variant in CCR6 is associated with rheumatoid arthritis susceptibility. *Nature Genetics* **42**, 515–519 (2010).

# The aging stem cell

The discovery that secreted protein *Ecrq4* slows neural precursor cell division during aging could point the way to treatments for age-related diseases

Stem cells and precursor cells can proliferate to repopulate damaged tissues. During aging, however, these cells lose their ability to divide—a process that is called senescence. Now, a team of researchers led by Toru Kondo at the RIKEN Center for Developmental Biology, Kobe, has identified esophageal cancer-related gene 4 (*Ecrq4*) as being responsible for senescence of precursor cells in the central nervous system during aging<sup>1</sup>. This finding could explain why neurodegenerative diseases, such as Alzheimer's disease, are prevalent in elderly individuals.

Addition of serum to oligodendrocyte precursor cells (OPCs) in culture drives them toward a senescent phenotype, making them an ideal model system to study genes that induce senescence. Kondo and colleagues looked at changes in gene expression during induction of senescence in mouse OPCs and found that the expression of *Ecrq4* increased the most in senescent OPCs.

When the researchers overexpressed *Ecrq4* in rat OPCs, this arrested the cell cycle, and increased the proportion of cells that were labeled by a marker of cell senescence. The protein *Ecrq4* seemed to act by inducing the degradation of proteins called cyclins, which drive cell cycle progression. When they reduced *Ecrq4* expression, it blocked the induction of OPC senescence that is normally induced by serum.

In the culture medium of OPCs that were already senescent, Kondo and colleagues found that *Ecrq4* protein was present. Administering recombinant *Ecrq4* protein onto OPCs in culture also

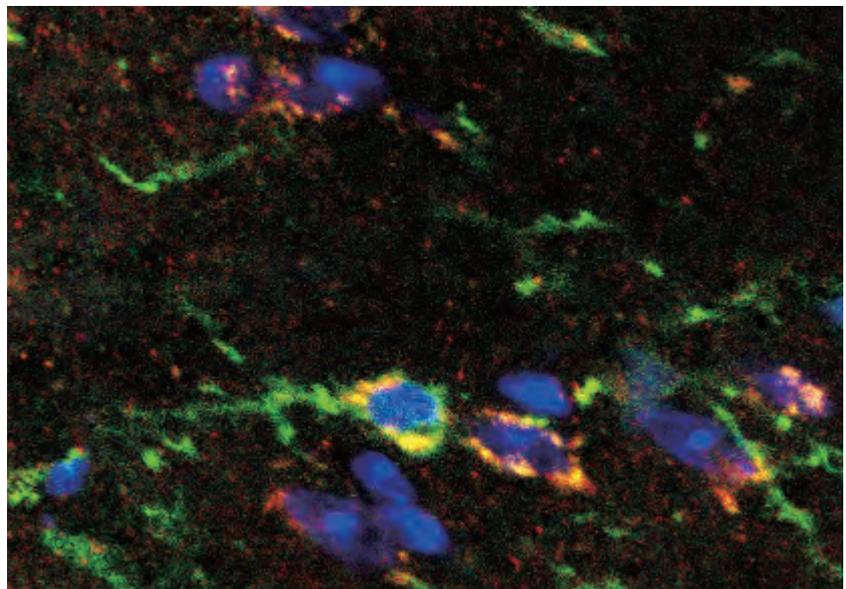


Figure 1: The protein *Ecrq4* (red) is expressed in oligodendrocyte progenitor cells (green) in the brain of aged, but not young, mice indicating that it is involved in inducing the senescence of these cells during aging.

induced senescence, suggesting that *Ecrq4* is a secreted protein that drives OPC senescence.

They also observed that *Ecrq4* was highly expressed in the brains of old—but not young—mice, in brain regions rich with neural precursor cells and OPCs (Fig. 1). Further, they found that the cells expressing *Ecrq4* in the aging brain were not proliferating. In fact, *Ecrq4*-expressing cells in the aging brain seemed to be senescent, since they were co-labeled with a senescence marker. “An important next step in this research,” says Kondo, “is to make *Ecrq4* knockout mice to examine the functions of *Ecrq4* *in vivo*.”

Identifying factors that drive neural precursor cell senescence may one day

lead to therapies that can kick-start their proliferation that has stalled during aging, which could help restore neuronal loss in diseases such as stroke or Parkinson's disease. “Our findings provide a new clue to investigate the mechanism of brain aging,” explains Kondo, “and may lead to the development of new methods to prevent aging and age-related diseases.”

1. Kujuro, Y., Suzuki, N. & Kondo, T. Esophageal cancer-related gene 4 is a secreted inducer of cell senescence expressed by aged CNS precursor cells. *Proceedings of the National Academy of Science USA* **107**, 8259–8264 (2010).

# A matter of give and take

Sheets of cells stick together by monitoring and responding to the pull of their neighbors

Many surfaces within the body are lined with tightly interconnected sheets of epithelial cells, with individual cells tethered to one another via complexes known as adherens junctions (AJs).

These sheets undergo considerable reorganization during embryonic development and wound healing; accordingly, AJs are not merely ‘cellular staples’, but appear to provide an important mechanism for monitoring adjacent cells. “I imagine that cells confirm whether their neighbors are alive and have the same adhesion molecules by ‘pulling’ adjacent cells through AJs,” explains Shigenobu Yonemura, of the RIKEN Center for Developmental Biology in Kobe. “Dead cells cannot pull back, and thus would not be recognized as members of the epithelial cell sheet.”

Yonemura’s team has uncovered evidence that AJs counter tensions generated through intercellular interactions via their associations with cytoskeletal actin filaments, spotlighting a potentially important association between AJ component  $\alpha$ -catenin and the actin-binding protein vinculin<sup>1</sup>. By further exploring the relationship between these two proteins, his team has now achieved a breakthrough in understanding AJ-mediated force detection<sup>2</sup>.

The researchers identified a vinculin-binding region in the middle of  $\alpha$ -catenin, but also identified a second segment of the protein that actively inhibits this interaction. At one end,  $\alpha$ -catenin also contains an actin-binding region, and Yonemura and colleagues found that this association appears to be essential for relieving this self-inhibition, suggesting



**Figure 1:** When AJs experience tension from the pull of neighboring cells,  $\alpha$ -catenin is stretched out to expose the vinculin binding site, enabling reinforcing interactions with other actin filaments.

that the  $\alpha$ -catenin–vinculin interaction is force-dependent.

Subsequent experiments enabled the team to construct a model in which  $\alpha$ -catenin is normally collapsed like an accordion, with the inhibitory domain masking the vinculin binding site. However, increased tension extends the protein and exposes this site, enabling further interactions with the cytoskeleton that effectively counter the force pulling against a given AJ (Fig. 1). The result is essentially a ‘tug of war’ between cells, with the integrity of the epithelium hanging in the balance.

If accurate, this model offers a simple explanation for how epithelial cells can react rapidly to rearrangements in their local environment. “The central part of the mechanism involves the protein structure of  $\alpha$ -catenin—no enzymatic reaction is required,” says Yonemura. “Because of this, sensing and response

take place at the same time and place.”

His team is now designing experiments to confirm this  $\alpha$ -catenin rearrangement in response to applied force, but Yonemura believes they may have potentially uncovered a broadly relevant model for cellular communication. “Because the mechanism is so simple, I think that it could be fundamental and used among a wide variety of cells,” he says. ■

1. Miyake, Y., Inoue, N., Nishimura, K., Kinoshita, N., Hosoya, H. & Yonemura, S. Actomyosin tension is required for correct recruitment of adherens junction components and zonula occludens formation. *Experimental Cell Research* **312**, 1637–1650 (2006).
2. Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A. & Shibata, M.  $\alpha$ -Catenin as a tension transducer that induces adherens junction development. *Nature Cell Biology* **12**, 533–542 (2010).

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# Omics analysis nurtures the creation of functional plants

## Masami Yokota Hirai

Team Leader  
Metabolic Systems Research Team  
Metabolomics Research Division  
RIKEN Plant Science Center

Plants produce a wide variety of metabolites from inorganic compounds, some with useful functions including health-promoting effects. The ability to harness these metabolites by creating 'functional plants' that produce these compounds in large quantities could therefore be of considerable benefit to society. It is also an intriguing research topic for plant scientists. Progress in this field relies on our understanding of how the hundreds of thousands of unique metabolite compounds are produced in plants. Masami Yokota Hirai at the RIKEN Plant Science Center (PSC) is investigating the mechanism of metabolism in plants by linking metabolites to genes through omics analysis—a combination of metabolome and transcriptome analyses. The knowledge obtained from this approach is leading steadily to the successful development of functional plants.



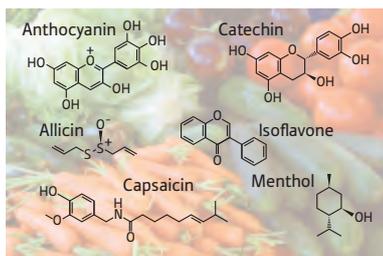
### Compound synthesis by metabolism in plants

“The word ‘metabolism’ may remind many people of a reaction in which the proteins or lipids we consume as food are degraded and converted into energy. Metabolism in plants, however, is different from this reaction,” says Masami Yokota Hirai, team leader of the Metabolic Systems Research Team at the RIKEN Plant Science Center (PSC). “Metabolism in plants is a reaction in which inorganic compounds such as nitrogen, phosphorus, and sulfur are absorbed through the roots and light energy is used to produce various organic compounds including amino acids and sugars such as starch. These organic compounds are called metabolites.”

The production of compounds such as amino acids, sugars and vitamins, which make up the body of a plant, from inorganic compounds is called ‘primary metabolism’, whereas the production of more complex compounds from primary metabolites is called ‘secondary metabolism’. “A plant is rooted in

place and cannot move. To cope with environmental hazards, such as insects, dry weather or salt damage, plants produce secondary metabolites as they are exposed to these stresses. A plant maintains a constant amount of primary metabolites, but produces secondary metabolites on an as-needed basis.”

Hirai’s focus on metabolism in plants is motivated by the potential uses of the vast array of metabolites that plants produce. “Plants produce metabolites that specific to the plant species. There are more than 200,000 known unique metabolites, some of which contain nutrient, health-promoting and medical ingredients.” Examples of secondary metabolites include isoflavone, anthocyanin, menthol, catechin and capsaicin (Figure 1). These compounds are drawing attention for their health-promoting functions. “Efficient production of useful secondary metabolites will greatly help improve our health. For this reason, we are working hard to elucidate the metabolic mechanism in plants.”



**Figure 1: Examples of secondary metabolites with health-promoting effects**

Plants use inorganic compounds to produce primary metabolites such as amino acids or sugars, which are then used to produce more complex secondary metabolites. Different plant species produce different kinds of secondary metabolites, some with health-promoting effects.

### Metabolome studies

“A metabolic map illustrates how metabolites are produced from inorganic substances through specific reactions, and can be as complicated as a subway route map. A partial metabolic map does not provide enough information to understand the whole picture of metabolism. We need to understand the metabolic system as a whole. To help with this, we have started to take advantage of omics analysis.”

Omics is a science that comprehensively embraces the four disciplines of genomics, transcriptomics, proteomics and metabolomics (Figure 2), and has developed rapidly in the past decade triggered by improvements in genome decoding techniques and processing speed. These improvements have led to some remarkable milestones in genomic research, including sequencing of the complete genomes of the flowering plant *Arabidopsis thaliana*, rice and soy-bean.

Similarly, the DNA microarray technique used in transcriptome analysis, the analysis of RNA transcribed from DNA, has also improved dramatically over the past decade. In this technique, hundreds of thousands of single-stranded DNA fragments are fixed in holes or ‘spots’ on a glass substrate, and fluorescently labeled RNA are dropped onto the substrate surface. RNA complementary to a DNA fragment will become bound

to the DNA, which causes the combined compound to emit fluorescent light. From the fluorescence intensity of each spot, researchers can determine which genes are being expressed and to what extent. The expression of *Arabidopsis* genes has been analyzed using this method and the data has been made publicly available via the AtGenExpress database (<http://igr0.t.psc.riken.jp/>).

Progress in metabolome analysis, however, lags considerably behind that of genomic and transcriptome analyses. “Metabolome analysis is the least developed part of omics,” says Hirai. “In metabolome analysis, a mass spectrometer is used to determine the mass of molecules and electrical charges contained in a specimen. From this data we can determine the types and quantities of metabolites in a specimen. The work, however, is extremely difficult. Genomics focuses only on DNA and transcriptomics on RNA, and the same method can be used for all types of organism. In metabolomics, on the other hand, we deal with metabolites with a wide range of characteristics, such as volatility and water solubility, which makes it impossible to conduct investigations under fixed conditions. The metabolites are also produced in highly variable amounts, tiny to large quantities, and with a wide range of concentrations. So we need to share a single specimen among a number of measuring instruments so that enough data can be collected.”

The DNA microarray technique is almost entirely automated, which allows almost anybody to use it, whereas mass spectroscopy requires a highly skilled operator. This has obstructed rapid developments in metabolome analysis. Another factor lies with the collected data itself. “The data obtained by mass spectrometry are plotted on a graph with mass along the horizontal axis and intensity along the vertical axis. A peak in the graph corresponds to a single metabolite. Of the thousand or so peaks that are produced, only about 10% have been assigned to specific metabolites.

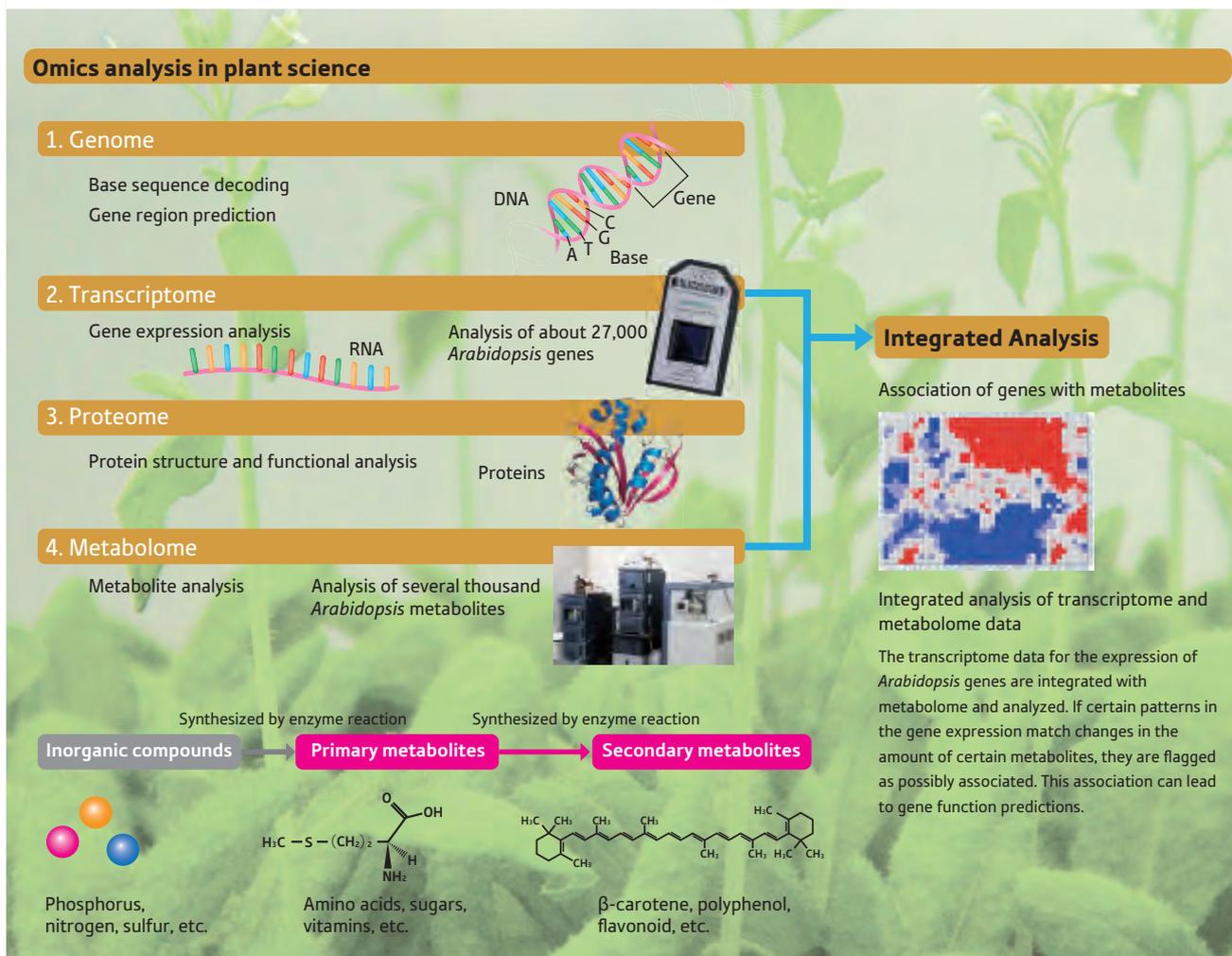
Most of the metabolites remain unknown. We are at a loss regarding where to begin,” says Hirai.

Research into metabolomics started in 2000. In Japan, Kazuki Saito, group director of the Metabolomic Function Research Group at the PSC, took the initiative in research on metabolomics. In those days, Saito was a professor at the Graduate School of Pharmaceutical Sciences at Chiba University, and Hirai attended his laboratory. “I was confident that the research was not only interesting but also very important. However, I had a hard time for about three years because I could not find a way to understand the data itself,” says Hirai, looking back on those days.

### The world’s first omics analysis

In 2004, Hirai published a paper on metabolome analysis in the *Proceedings of the National Academy of Sciences, USA*. The article would become the most-cited paper in the field of plant biotechnology in 2005. “This paper is a collection of results obtained from an integrated analysis of the transcriptome and metabolome of *Arabidopsis thaliana*. The paper does not provide new information on gene functions or metabolite synthesis, so I am not completely satisfied with the paper because it is a simple description of my research results. But in those days, few papers could be found on metabolome analysis. I think that the paper was highly evaluated under such circumstances because I tried to derive something new by combining transcriptome analysis with metabolome analysis for *Arabidopsis*. It was a pioneering attempt at omics analysis.”

Investigation of all 27,000 *Arabidopsis* genes shows that there are multiple genes that express with the same timing. These genes are likely to be involved in the same function. If the population of a metabolite increases while a certain gene cluster is expressing and decreases when the gene cluster is not expressing, the metabolite could be associated with



**Figure 2: Omics analysis**

Omics analysis combines (1) genome (complete genetic information), (2) transcriptome (all RNA transcribed from DNA), (3) proteome (all proteins) and (4) metabolome (all metabolites) analyses.

the gene cluster. In this way, omics analysis allows genes to be linked with metabolites, making it possible to understand metabolite function.

### Creating vegetables with cancer-preventing effects

One successful application of omics analysis is the 2007 discovery of a new gene that makes cruciferous vegetables produce cancer-preventing components. Cruciferous vegetables such as broccoli, radish, horse radish and mustard have a ‘spicy’ flavor that has been attributed to pungent components that originate as metabolites called glucosinolates, among which sulforaphane is known to enhance the functions of enzymes that detoxify carcinogens. Using *Arabidopsis*,

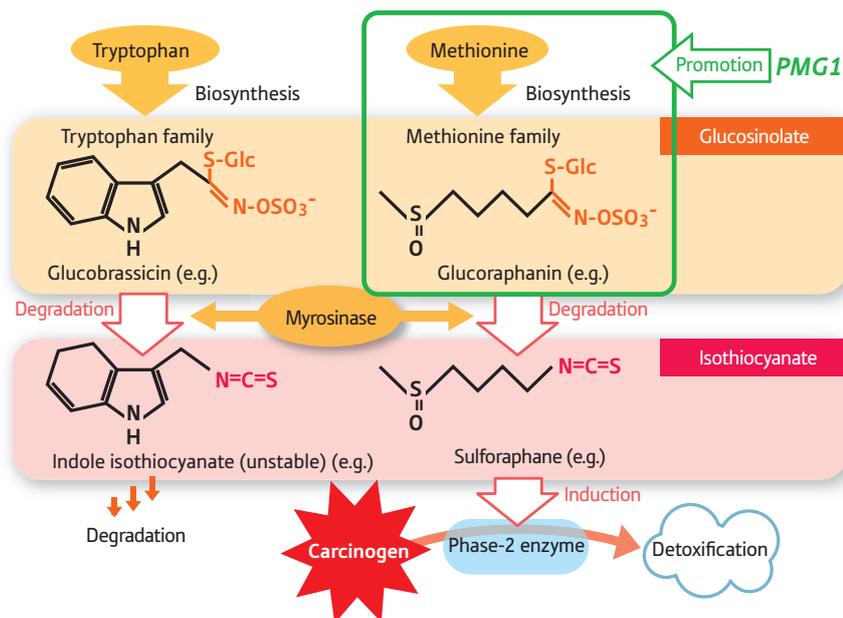
a member of the cruciferous family, Hirai successfully showed that the gene *PMG1* controls the synthesis of glucosinolates (Figure 3).

“Through an integrated analysis of the transcriptome and metabolome of *Arabidopsis*, we found a gene cluster that changed with the same pattern. The gene cluster was found to contain the genes that are known to be involved in the synthesis of glucosinolates. In this way, we looked into the genes, and finally reached *PMG1*.”

It was also confirmed that the functional enhancement of *PMG1* in *Arabidopsis* promotes glucosinolate synthesis. “As the amount of glucosinolate increases, the amount of sulforaphane increases. This could allow

us to grow vegetables with enhanced cancer-preventing effects.”

A study focusing on gene clusters associated with the synthesis of glucosinolates is now under way. Hirai is interested in the gene *BASS5*. The base sequence of *BASS5* is similar to that of the genes for bile acid transporter, an animal protein. Bile acid transporter is present in the cell membrane and is responsible for the intercellular movement of bile acids. When the base sequences are similar, their functions are also often similar. But since there are no bile acids in plants, the role of the proteins created by *BASS5* is particularly interesting. “The proteins were thought at first to be present in the cell membrane where



**Figure 3: Synthesis, degradation and physiological effects of glucosinolates**

*Arabidopsis* synthesizes about 30 kinds of glucosinolates from methionine and tryptophan, which can be degraded by myrosinase (an enzyme) into isothiocyanate (a 'spicy' flavor component). Sulforaphane is a kind of methionine-derived isothiocyanate and induces the production of phase-2 enzymes that detoxify carcinogens. The gene *PMG1* has a stimulating effect only on the synthesis of glucosinolates from methionine.

they mediate the intercellular movement of glucosinolates. However, we have come to understand that the proteins are likely to be present not in the cell membrane but on the surface of the cell's chloroplast. This demonstrates that secondary metabolites are synthesized not only in the cellular cytoplasm, but also in the chloroplasts. We think *BASS5* might be associated with glucosinolate intermediates moving in and out of the chloroplasts." By omics analysis it was confirmed that glucosinolates are not created when *BASS5* function is inhibited. Omics analysis has been demonstrated in this way time and time again to be a very effective tool for elucidating metabolic pathways.

Hirai is also researching the synthesis of amino acids, particularly methionine, the primary metabolite from which glucosinolates are produced. "An increase in a metabolite requires an increase in the supply of its source material, namely amino acids. We should know how to synthesize amino acids if we are to attempt to create plants that produce large amounts of useful secondary metabolites."

### Metabolome analysis in full swing

"Metabolome analysis will proceed rapidly in the years to come," says Hirai with confidence. This is thanks to an analytical technique called widely targeted metabolome analysis developed by Yuji Sawada, a special research scientist in the Metabolic Systems Research Team. Associating the thousands of peaks produced by mass spectrometry with metabolites has been one of the obstacles to metabolome research. "In conventional targeted metabolomics, observations are made with the aim of identifying a single known kind of metabolite," says Hirai. "Widely targeted metabolomics is based on the idea that if the number of target metabolites can be increased, eventually all metabolites could be targeted, which could lead to full metabolome analysis. In widely targeted metabolomics, all of the peaks in the data correspond to known metabolites. This allows us to proceed to the next stage of the research program immediately. Usually, analytical methods are developed by analytical chemists and information scientists, but Dr Sawada

and myself are biologists. Widely targeted metabolomics is a very convenient analytical method for biologists." Widely targeted metabolomics currently handles about 700 target metabolites, a number that will be increased in the near future.

Hirai also hopes to develop a new analytical method for omics analysis. "It is essential to develop additional tools if we are to remain pioneers in this field because integrated analysis of transcriptome and metabolome data is now available to everyone. We are now working on developing, by trial and error, a new analytical method that can suggest unforeseen results."

### The eureka moment, the best part of being a researcher

"The analytical transcriptome and metabolome data are a description of the state of a plant. Using the data to understand the biological implications depends on our ability as scientists, so I feel the data is testing us," says Hirai. "Sometimes, an idea flashes through my mind when I look at the same data for hours or even days, which could lead to a discovery. I find it interesting to look back over my laboratory notebook to find exclamation marks written next to certain notes. I believe I had little eureka moments when I wrote those exclamation marks. Those moments are the best part of being a researcher." ■

#### Masami Yokota Hirai

Masami Yokota Hirai was born in Chiba, Japan, in 1965. She graduated from the Department of Agricultural Chemistry in the Faculty of Agriculture at The University of Tokyo in 1989, and received her PhD from the Graduate School of Agriculture at the same institution in 1994. She moved to RIKEN in 2005 after working as a research associate in the Graduate School of Pharmaceutical Sciences at Chiba University. She has been in her current position since 2008 as team leader of the Metabolic Systems Research Team at the RIKEN Plant Science Center.

# RIKEN's young scientists meet the giants of science at the Lindau Meeting

Between 27 June and 2 July 2010, 61 Nobel laureates gathered with more than 650 young researchers from around the globe for the 2010 Lindau Meeting of Nobel Laureates in the small town of Lindau, Germany. In addition to RIKEN President Ryoji Noyori, who was invited to Lindau as one of the Nobel laureates at the event, five young researchers from RIKEN centers and institutes also attended this year's meeting.

Malaysian researcher Li Foong Yoong of the RIKEN Brain Science Institute, whose research explores developmental mechanisms that control complex neuron morphology, was one of these five attendees. In the article below, Yoong recounts how the inspiring words of Nobel laureates at the meeting, and encounters with leading young researchers from many different nationalities, brought a renewed sense of excitement to her research work and reignited her passion for science. ■



## Inspired by Lindau

This year, nominated and sponsored by the Human Frontier Science Program, I had the great fortune to attend the 2010 Lindau Meeting of Nobel Laureates. This is the third year in which the meeting has focused on interdisciplinary dialogue, bringing together Nobel laureates and young scientists from across the fields of physics, chemistry and medicine/physiology.

As someone working in the field of neurobiology, the Nobel lectures on medicine and physiology were naturally of particular interest to me. To hear the history of the work that led to great discoveries in these fields, the twists and turns involved, was intensely inspiring. The lectures on physics and chemistry were also fascinating in their own way. I have only ever attended meetings and conferences in my own field of research,



RIKEN delegates to the Lindau Meeting with Nobel Laureate Osamu Shimomura (second from right), discoverer of green fluorescent protein.

and thus learning about the topics presented in these lectures was an eye-opening experience for me.

Beside the lectures, there were also many other social events on the program that allowed close interaction between the laureates and young researchers. Dinner was one of these, offering us the chance to speak to the laureates and talk about science while enjoying local food and culture. One of my fondest memories from the Lindau Meeting was of interacting with highly talented young researchers from countless countries and research backgrounds. I will always remember the breaks and meal times spent sitting by the beautiful and peaceful Lake Constance, deeply engaged in discussions and debates with these new friends.

Two other memories from the Lindau Meeting stand out in my mind. The first was a lecture by Dr Osamu Shimomura, who discussed green fluorescent proteins (GFPs). While I use GFPs routinely in my own research, this was the first time for me to attend a lecture by Dr Shimomura and actually meet him in person. He is a very humble scientist, but he amazed all of us at the end of his lecture when he vividly demonstrated the bright green fluorescent light of GFP by shining an ultraviolet light on a glass tube containing purified GFP.

The second memory I have is of the World Cup football games, which were taking place during the Lindau Meeting.



Lindau attendees from the Human Frontier Science Program.

The World Cup and the Lindau Meeting were huge international events that filled the small town of Lindau with passion. With a group of young Japanese researchers, I cheered for the Japanese team in the Japan versus Paraguay game, which we watched together with other international attendees. In this way, both inside and outside of the lecture room, I established strong friendships with other young researchers at Lindau.

The Lindau Meeting has offered me more than I could have imagined. One week in Lindau, away from the bench, was like a rejuvenating vacation for my mind, which is so constantly occupied with work. I came back with a fresh perspective on my research and a reignited passion for science. The wisdom of Nobel laureates and the enthusiasm of fellow young researchers have reminded me once again of the simple joys of science. ■



Atsushi Iriki  
Team Leader  
Laboratory for Symbolic Cognitive Development  
RIKEN Brain Science Institute  
Wako, Saitama, Japan

Dear Prof. Iriki

It was a great pleasure working in collaboration with your laboratory over the past four years as a doctoral student at University College London (UCL) in the UK. I recently submitted my PhD thesis, and as I was writing the acknowledgments section, I was reminded of all the wonderful people I met at RIKEN. There were so many people from RIKEN to thank for their help and friendship. My last visit to RIKEN was in the summer of 2008, which sounds like a while ago but as the collaboration between our labs has continued I don't feel like I have really left.

From my very first visit to the RIKEN Brain Science Institute (BSI) in March 2007, I was impressed by the facilities and the exciting research taking place. On my second visit we started our collaborative project. From the moment I arrived I was made to feel so welcome by the lab members. The project was very intense but whenever we encountered a problem there was always an innovative solution. I took the data back to the UK to begin my analysis. My next visit was the following summer, and I couldn't wait to return! On that trip I finished collecting the data and we started writing our first paper.

The collaboration between your lab at the BSI and my PhD supervisors, Profs. Roger Lemon from the UCL Institute of Neurology and Cathy Price from the UCL Wellcome Trust Centre for Neuroimaging, has been very successful. Our first paper, on how the areas of gray and white matter change when monkeys learn to use a tool, was recently published in the *Proceeding of the National Academy of Sciences*. Our second paper presenting a magnetic resonance imaging template of the Japanese Macaque Brain was published in *NeuroImage*, and we also have a third paper under review based on our continued collaboration.

I would like to extend a special thanks to you, Prof. Iriki. I loved working at RIKEN and I made so many wonderful friends in Tokyo, it was a truly wonderful experience.

Best wishes

Marsha Quallo  
Sobell Department of Motor Neuroscience and Movement Disorders  
University College London Institute of Neurology,  
London WC1N 3BG, United Kingdom

P.S.

I have to admit that I think about the RIKEN staff canteen every lunch time, I miss eating *shoyu* ramen every day!



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For further information on the research presented in this publication or to arrange an interview with a researcher, please contact

RIKEN Global Relations Office  
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan  
TEL: +81 48 462 1225  
FAX: +81 48 463 3687  
E-Mail: [rikenresearch@riken.jp](mailto:rikenresearch@riken.jp)

[www.rikenresearch.riken.jp](http://www.rikenresearch.riken.jp)

