RIKEN RESEARCH

JANUARY

2008 Volume 3 Number 1

Unavoidable interactions in metals

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Clockwork orange beats time for the body

Researchers find new master gene setting circadian rhythms

A RIKEN-led team of researchers from Japan and the US has used an innovative combination of genome survey techniques in live *Drosophila* fruit flies to reveal a previously unknown master gene involved in setting circadian rhythms. It is the tenth of a series of genes which generate proteins that interact in complex interlocking feedback loops to measure the 24-hour day.

This network of genes ensures that the rhythms of vertebrate animals—sleep and wakefulness, changes in body temperature and blood pressure, the secretion of hormones and regulation of fertility—are attuned to daily and seasonal cycles. The importance of the network's role is demonstrated not only by the fact that mutations in clock genes have been linked to cancer and obesity, but also that they have been highly conserved during evolution and are similar in organisms from fruit flies to mammals. The regulation of the network is intricate and complex because, in addition to the simple measurement of time, it has to respond to changing daily patterns of light and dark and seasonal patterns of temperature and the environment.

In humans, such common problems as jet lag and lack of alertness of shiftworkers arise when the body's circadian rhythms are not properly adjusted to the external environment. Permanent disruption of the body's clock can lead to much more serious disorders, such as delayed sleep phase syndrome, and has also been implicated in the depressive mental illness known as seasonal affective disorder (SAD). Work on clock genes could well have relevance to treating these conditions.

Revealing the master gene

In a recent issue of the journal *Genes & Development*[1], the research group—from RIKEN's Center for Developmental Biology in Kobe, Kyushu University, Japan's National Institute of Genetics and Texas A&M University—detailed how it found the new master gene. The gene exhibits rhythmic daily activity and codes for a protein that represses other clock genes through the regulatory DNA sequence known as E-box. Because it carries a characteristic domain known as ORANGE, the research team named the gene *clockwork orange* (*cwo*) referring to the well-known Anthony Burgess novel and Stanley Kubrick film.

The researchers uncovered *cwo* using a novel partnering of micro-array technology that shows which genes are cyclically switched on, with RNA interference techniques, whereby individual genes can be switched off at will. In previous work, using micro-arrays they had followed the daily activity pattern of all genes in the *Drosophila* genome in cells of the head region of the fruit fly, where the circadian pacemaker is located. They found about 200 genes showed a rhythmic

activity pattern over the daily cycle both under normal conditions of light and dark, and also in constant darkness.

In the recently reported study, using RNA interference techniques the researchers then switched off each of about 130 genes which showed such regular daily cycles of activity. They were looking for dramatic disturbances of overall rhythmic behavior which, they hypothesized, would only happen when they disrupted the core genes involved in setting the body's clock.

In addition to genes already known to be an integral part of the circadian mechanism in *Drosophila*, the researchers found five other candidates for such clock genes. Of these, *cwo* was the gene with the most pronounced and stable impact.

Understanding the mechanism

Using a combination of micro-array technology and antibodies, the group then set out to discover the genes with which *cwo* interacts. They found that the genes to which the protein product CWO binds tend to contain the E-box DNA sequence. These included several genes known to play a key role in the network that regulates the body's clock, as well as *cwo* itself. CWO represses the activity of all the clock genes to which it binds. Interestingly, the overall effect of lowering CWO activity is to dampen the amplitude of the circadian rhythm.

The core molecular feedback system which establishes the daily biological clock in *Drosophila* is thought to involve four proteins known as CLK (clock), CYC (cycle), PER (period) and TIM (timeless) and their linked genes (Fig 1). CLK and CYC form a complex together and stimulate the production of PER and TIM by binding to the E-box DNA sequence. As PER and TIM begin to accumulate, they feed back to inactivate the CLK–CYC complex. Several other proteins interact with this basic feedback loop, regulating and fine-tuning the mechanism.

The picture which begins to emerge from the latest work is one where CWO regulates this basic mechanism by competing with the CLK–CYC complex to bind to the E-box DNA sequence. CWO also regulates itself by binding to and repressing the transcriptional activity of the *cwo* gene.

"The work is still far from complete," says Hiroki Ueda, the research team leader. "But I feel the discovery of *cwo*, which has a counterpart in the human genome, represents an important step in deciphering biological clocks. We next want to apply our techniques to the mouse, which is very near to humans compared with the fruit fly." ■

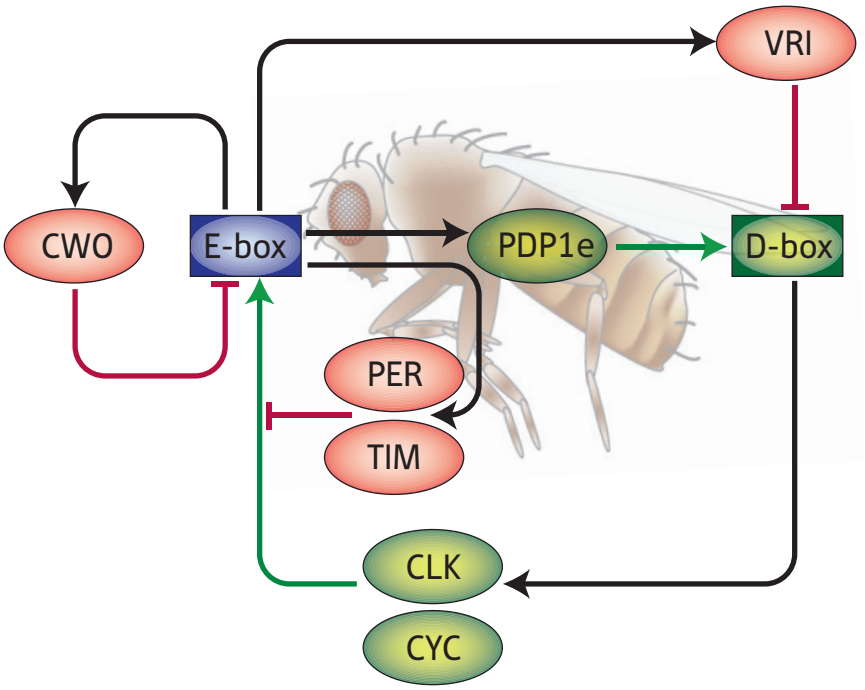


Figure 1: Schematic diagram of the relationships of the proteins now thought to be involved in the *Drosophila* circadian clock. Activators are in green, repressors in red.

1. Matsumoto, A., Ukai-Tadenuma, M., Yamada, R.G., Houl, J., Uno, K.D., Kasukawa, T., Dauwalder, B., Itoh, T.Q., Takahashi, K., Ueda, R., Hardin, P., Tanimura, T. & Ueda, H.R. A functional genomics strategy reveals *clockwork orange* as a transcriptional regulator in the *Drosophila* circadian clock. *Genes & Development* **21**, 1687–1700 (2007).

About the researcher

Hiroki R. Ueda was born in Fukuoka, Japan, in 1975. He graduated from the Faculty of Medicine, the University of Tokyo, in 2000, and obtained his PhD in 2004 from the same university. During his undergraduate studies he worked as a research assistant on a biological simulation system project at Sony Computer Science Laboratories. During his graduate studies from 2000, he went on to work as a researcher, and in 2002 became group leader at Yamanouchi Pharmaceutical, on a project studying biological-clock mechanisms in flies and mice. He was appointed laboratory head at the RIKEN Center for Developmental Biology (CDB) in April 2003 and manager of the Functional Genomics Subunit at the CDB from October 2004. He also became a visiting professor in Tohoku University between April 2005 and March 2006, and Tokushima University from April 2005, and has been an invited professor at Osaka University since April 2006. His research interests include system-level understanding of biological time, space and information, and systems-based medicine on human disease.

Against the flow

Defects in metals can actually improve the flow of electrons

Researchers at RIKEN's Discovery Research Institute in Wako, in collaboration with researchers from National Chiao Tung University, Taiwan, have made the surprise discovery that—under certain circumstances—electrons moving through a metal propagate faster as the number of defects that cause them to scatter is increased.

Intuitively, we know that if a traveling body bounces off an obstacle, its average propagation speed will reduce. As such, attempting to walk against the flow of a large crowd of people can be a futile undertaking, as it is difficult to gain any ground (Fig. 1). Similarly, electrons moving through a metal are expected to slow after scattering off inherent defects: the greater the number of impurities in the metal, the larger the electrical resistance of current flowing through the sample. This means that the time it takes for electrons to lose all prior information on their original state by scattering—the so-called 'dephasing' time—is reduced.

Writing in the journal *Physical Review Letters*[1], the researchers report that for extremely impure metallic samples at temperatures close to absolute zero, the electron dephasing time actually increases. "This observation is very surprising indeed, as one would normally expect a decreasing dephasing time with impurity content," explains Shiu-ming Huang from the RIKEN team.

In other words, the electrons are helped on their way by the 'scatterers'. This is only possible if the scattering is of a dynamic nature. In terms of walking against a crowd, this would mean that the people one hits on the way through push back and actually promote one's movement against the crowd. As Huang notes, such dynamic scattering of electrons is only possible "if not only the electron's state is changed, but also the scatterer is affected by the process."

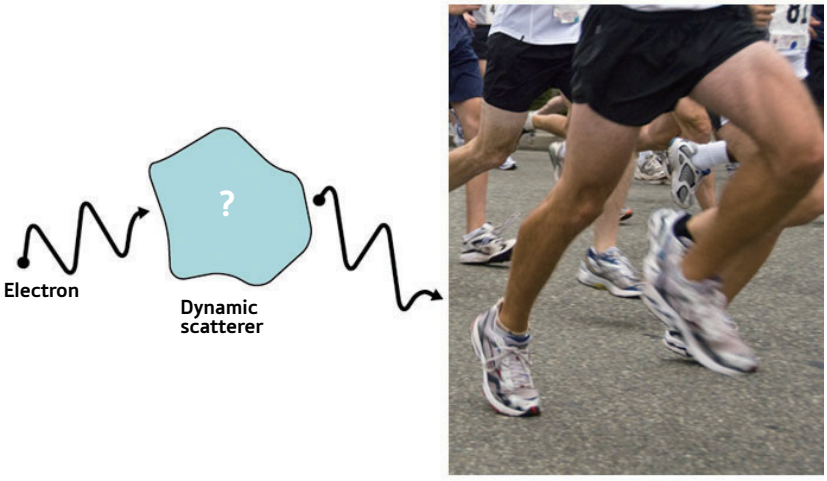


Figure 1: Scattering off impurities. The schematic diagram (left) shows how electrons scatter off dynamic impurities of an unknown nature. The process is similar to running against a tight crowd of people (right).

One explanation previously proposed by physicists is that magnetic impurities, where electrons bounce off the magnetic field, are generated by magnetic impurities. However, the researchers could rule out this conventional explanation by demonstrating that this behavior is independent of any external magnetic fields.

The origins of this effect therefore remain unknown, and our theoretical understanding of such dynamic scattering is incomplete. According to Huang, what would be needed to understand this behavior "is a series of measurements that not only investigates the temperature behavior of the dephasing time, but also the influence of the materials' properties themselves." As impurities and defects are present in many nanoscale systems, resolving this issue will be of broad and general relevance. ■

1. Huang, S. M., Lee, T. C., Akimoto, H., Kono, K. & Lin, J. J. Observation of strong electron dephasing in highly disordered $Cu_{93}Ge_4Au_3$ thin films. *Physical Review Letters* **99**, 046601 (2007).

Laser-driven harmonics hit a high note

A new technique could improve development of high-efficiency light sources

RIKEN scientists have developed a way to create incredibly brief bursts of high-frequency light that should help to take better snapshots of atoms (Fig. 1).

Short pulses of radiation are useful for studying very fast processes, such as the way that electrons dance between atoms as they form chemical bonds. This happens in mere attoseconds (10^{-18} s)—billionths of a billionth of a second—and the light acts like a camera flash, freezing the action in a subatomic snapshot.

Higher frequencies of light can capture briefer events, yet few lasers operate beyond the visible spectrum. Under certain conditions, however, laser frequencies can be multiplied many times.

This relies on the way that blasts of laser light wrench electrons away from their parent atoms. The incoming light has a varying electric field which first accelerates the electron, and then pushes it back towards the atom, where it is recaptured. The electron then releases its energy as a short, intense laser pulse, with a frequency that is a multiple of the original laser frequency. Creating 'harmonic' frequencies in this way allows scientists to turn visible laser light into higher-energy ultraviolet, or even soft x-rays.

Normally, higher harmonics are more difficult to access because as the electron becomes increasingly energized, it is more likely to give up some of its energy, rather than absorb even more.

Now, scientists at RIKEN's Discovery Research Institute, Wako, and colleagues at the University of Tokyo, have developed a technique to dramatically enhance the amount of high-frequency light generated by high-order harmonics[1].

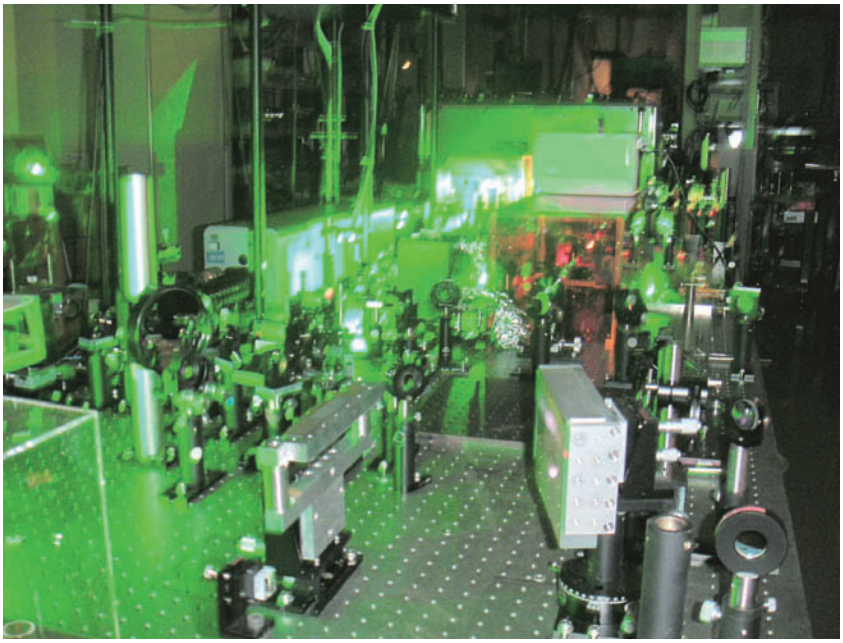


Figure 1: High-frequency lasers can help to take snapshots of atomic processes.

"A key strategy of our experiment is the use of a mixture of two kinds of rare gases as harmonic emission medium—helium and xenon," says Eiji Takahashi, part of the RIKEN team.

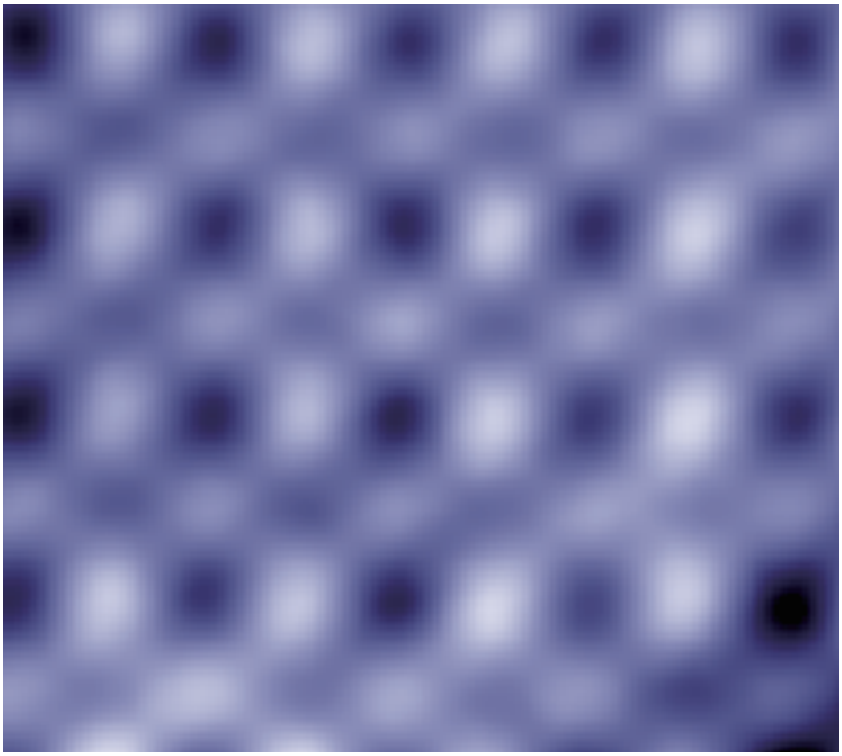
First, an infrared laser excites electrons in the xenon atoms up to the 23rd harmonic, so that they emit pulses of extreme ultraviolet light. These photons then hit the helium atoms, acting as a booster for the harmonic generation, helping it to push helium's electrons up to the 27th harmonic together with the infrared laser. These electrons finally emit soft x-ray light at an even higher frequency, producing 4,000 times more photons than a system that uses helium alone.

"Dramatic enhancement of high harmonic generation is an attractive phenomenon because it may be crucial for further development of high-efficiency soft x-ray light sources," says Takahashi. This should help to push back the frontiers of precision spectroscopy and ultrafast science, he adds. ■

1. Takahashi, E. J., Kanai, T., Ishikawa, K. L., Nabekawa, Y. & Midorikawa, K. Dramatic enhancement of high-order harmonic generation. *Physical Review Letters* **99**, 053904 (2007).

When electrons can not ignore one another

The properties of electrons on the surface of an unusual metal will supply clues—and puzzles—to theorists



Physical Review Letters

Figure 1: Electronic ordering on the surface of $Sr_3Ru_2O_7$. Larger white dots indicate greater electronic density, as measured with a scanning tunneling microscope.

A team of Japanese scientists from the RIKEN Discovery Research Institute in Wako, AIST and the University of Tokyo are gaining deeper insight into how electron–electron interactions in an unconventional metal evolve in a magnetic field. Their results are reported in *Physical Review Letters*[1].

The properties of simple metals and semiconductors can be explained by models that assume the electrons are non-interacting. However, for certain materials—notably high temperature superconductors—this approximation fails. Often, the electrons and spins in these 'strongly correlated' electronic materials form ordered phases that are highly sensitive to changes in temperature or magnetic field.

Looking for examples of this behavior is important for testing theoretical models. This is why Hidenori Takagi and Tetsuo Hanaguri and their team are studying $Sr_3Ru_2O_7$, which is a non-magnetic metal. However, experimental evidence suggests that at a high magnetic field, $Sr_3Ru_2O_7$ may become ferromagnetic—meaning the electron spins prefer to point in the same direction.

To understand the microscopic interactions that lead to this so-called 'metamagnetic' phase transition, it is useful to look at electronic excitations close to where it occurs. Hanaguri and co-workers therefore used a tunneling spectroscopy probe in which a sharp metal tip is brought close to the material surface—in this case, freshly cleaved $Sr_3Ru_2O_7$—and a voltage is applied between the tip and the surface to excite electrons in the material.

The team measured these electronic excitations as they increased an applied magnetic field, looking for changes near the metamagnetic phase transition. They found that the excitations evolve in ways that can not be explained by a model that ignores the interaction between electrons. Commenting on the impact of this result, Hanaguri notes that "If theorists want to describe the properties of this material, the many-body interaction must be taken into account."

The team also observed an unexpected feature on the $Sr_3Ru_2O_7$ surface. By scanning the tip over the surface, they can locate the positions of individual atoms. On every other atomic site they found extra electron density (Fig. 1) indicating a purely electronic ordering that has so far, only been observed on the surface of $Sr_3Ru_2O_7$.

It is unclear whether the electronic ordering that the team observed at the surface is related to their other findings, yet both results could be useful to theorists seeking to understand the unusual properties of $Sr_3Ru_2O_7$ and other strongly correlated electron materials. ■

1. Iwaya, K., Satow, S. Hanaguri, T, Shannon, N., Yoshida, Y., Ikeda, S. I., He, J. P., Kaneko, Y., Tokura, Y., Yamada, T. & Takagi, H. Local tunneling spectroscopy across a metamagnetic critical point in the bilayer ruthenate $Sr_3Ru_2O_7$. *Physical Review Letters* **99**, 057208 (2007).

Ringing the changes

A novel cyclization reaction is used to make molecules that switch between two different forms by redistributing their electrons

Chemical compounds that can be converted between two states with different physical properties are promising building blocks for molecular devices, the most obvious candidates being switches. If this process can be triggered with an external stimulus—such as heat or light—it can be controlled remotely and, therefore, integrated into a functional system.

One method of introducing bistability into a material is to exploit valence tautomerization—the phenomenon in which the bonding electrons in some molecules reorganize while the connectivity of the atoms remains the same. The two different forms—each with a different electronic structure—that result from this process are known as valence isomers, and often exhibit distinct optical and magnetic properties.

Relatively few molecules undergo valence tautomerization, and a team including Mio Kondo and Hiroshi Nishihara from the University of Tokyo and Yoshio Kobayashi from RIKEN's Nishina Center in Wako suggest that, "the development of a new class of compounds exhibiting this type of behavior is very important for the progress of materials science."

To this end, Kondo and co-workers have devised a novel chemical reaction to make cyclic structures that can switch between different valence isomers. Whereas the atomic rings in these molecules have previously been made by quite complicated procedures, their method is an efficient acid-promoted one-step process[1].

The starting point is a compound comprising an iron-containing group linked to an aromatic ring system through a carbon–carbon triple bond (Fig. 1a). When treated with a strong organic acid, an additional six-membered ring, shown in red in Fig. 1b, is formed by a cyclization reaction. As a result of this process, a larger region of alternating singe and double bonds—a so-called π-conjugated system—is created.

Expansion of the π-conjugation lowers the energy of the molecule and enables the transfer of an electron from the iron atom to the newly formed ring system in what is a valence tautomerization. This reorganization of the electronic structure can be easily detected because the iron is oxidized from Fe(II) to Fe(III) in the process, and these species can be distinguished with spectroscopic methods.

These valence isomers (Figs 1b and 1c) can be reversibly interconverted and the amount of each present in a sample depends on the temperature—with the structure shown in Fig. 1c being favored as it is heated. The team is now investigating compounds with two iron groups—they exhibit two-step protonation behavior and may have interesting valence tautomerization properties. ■

1. Kondo, M., Uchikawa, M., Zhang, W.-W., Namiki, K., Kume, S. Murata, M., Kobayashi, Y. & Nishihara, H. Protonation-induced cyclocondensation of 1-aryl ethynylanthraquinones: expanding the π conjugation. *Angewandte Chemie International Edition* **46**, 6271–6274 (2007).

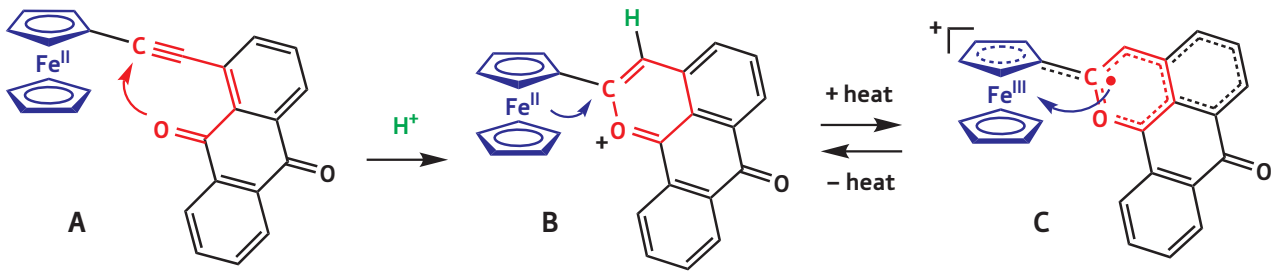


Figure 1: (a) When the molecule is treated with acid (H^+, green), a cyclization reaction occurs in which a bond forms between the carbon and oxygen atoms, shown in red, to make a six-membered ring (red) to produce a new compound (shown in Fig. 1b). (b) The Fe ion in the ferrocene group (blue) is now able to transfer one of its electrons to the red ring (blue arrow)—and is oxidized from Fe(II) to Fe(III)—to give the structure shown in Fig. 1c. (c) The donated electron is shown as a red dot. This process is reversible, and the electron can hop back to the ferrocene group (blue arrow) to reform the compound shown in Fig. 1b. The reorganization of the electronic structure depends on temperature; the structure in Fig. 1c is favored as it increases from 12 to 290 K.

A new way to tackle tumors

Japanese researchers find compound disrupts mRNA quality control

Researchers from RIKEN and several other Japanese institutions have unraveled a mechanism of action of a family of powerful anti-tumor drugs, which they have named spliceostatins. These compounds disrupt part of the quality control system by which cells ensure that messenger RNA (mRNA)—the genetic material used to transfer the plans for making proteins from the DNA to where they are built—is not defective.

The work raises the possibility of spliceostatins being used not only as the basis of drugs to fight cancer and as antiviral agents, but also as tools for analyzing the effectiveness of the quality control system itself.

The sequence for a protein printed off the nuclear DNA typically comes in sections separated by intervening segments of nonsense, known as introns. The introns must be chopped out and the remaining sections joined together to form a viable code for transfer to the ribosomes outside the nucleus where proteins are made. This splicing action is performed by a multi-component complex known as the spliceosome.

The spliceosome has to work efficiently and accurately as code containing introns (pre-mRNA) leads to aberrant proteins which can be harmful, even lethal. As a second line of defense to protect the health of the cell, intron-containing genetic material is blocked from going through the membrane which surrounds the nucleus.

In a recent paper in *Nature Chemical Biology*[1], the researchers from the RIKEN Discovery Research Institute in Wako, several Japanese universities, Astellas Pharma Inc. and the Japanese Science and Technology Corporation detail how they labeled spliceostatin A with biotin and used this combination to determine that spliceostatins bind to proteins of the SF3b subcomplex of the spliceosome.

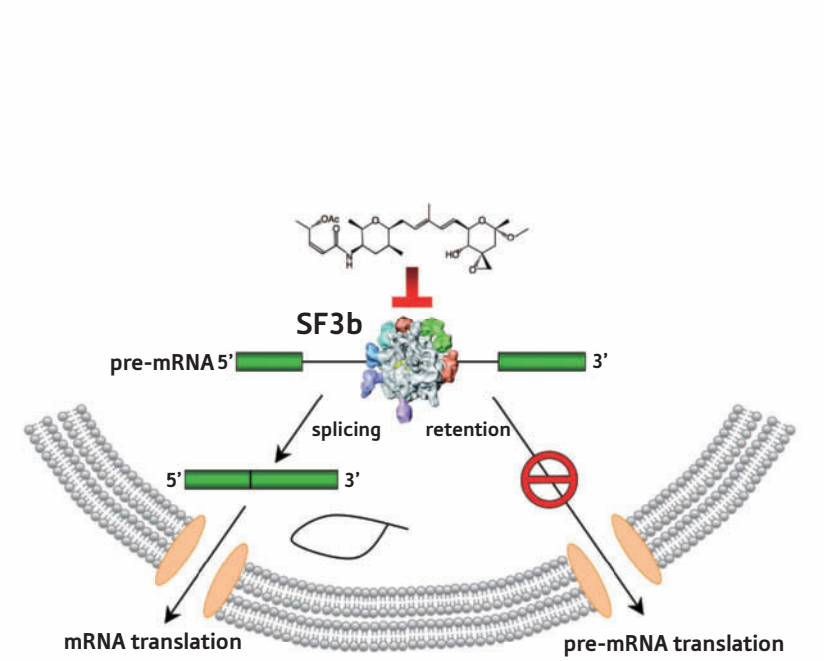


Figure 1: The spliceosome subcomplex SF3b plays an active role in splicing mRNA, and in preventing pre-mRNA from leaving the nucleus. It is inhibited by spliceostatin.

They found that not only was spliceosome activity inhibited when spliceostatin A was attached to SF3b, but intron-containing genetic material accumulated both inside and outside the nucleus, and that proteins including intron-derived sequences were generated (Fig. 1). So treatment with spliceostatin allows synthesis of potentially harmful proteins. Direct inhibition of the SF3b subcomplex using interference RNA led to the same outcomes.

Interestingly, while spliceostatin treatment appears to be lethal to tumor cells, its effects are milder in other cells. "We would now like to elucidate how the drug exerts its potent anticancer activity," says project leader, Minoru Yoshida of RIKEN, "and also how its target, SF3b is involved in the security system which prevents leakage of pre-mRNA from the nucleus." ■

1. Kaida, D., Motoyoshi , H., Tashiro, E., Nojima, T., Hagiwara, M., Ishigami, K., Watanabe, H., Kitahara, T., Yoshida, T., Nakajima, H., Tani, T., Horinouchi, S. & Yoshida, M. Spliceostatin A targets SF3b and inhibits both splicing and nuclear retention of pre-mRNA. *Nature Chemical Biology* **3**, 576–583 (2007).

Silencing allergic inflammation

Researchers reveal a new step in the regulation of allergic mediators

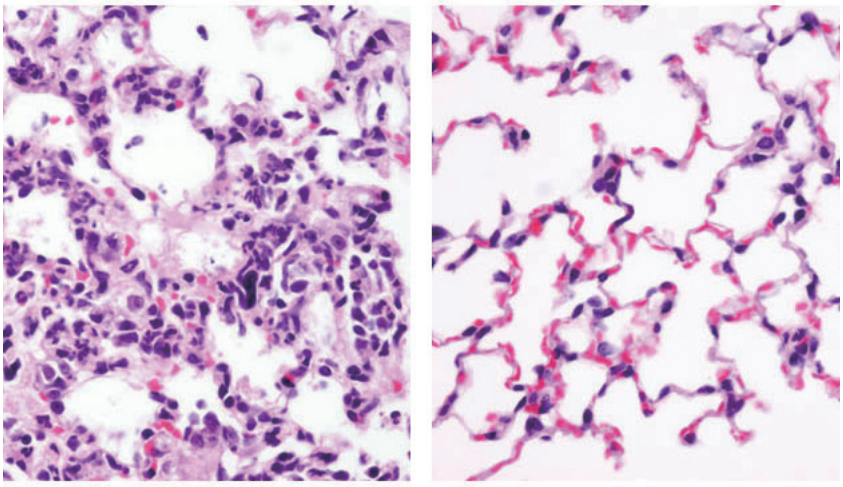
New work by Japanese scientists shows that a family of DNA-binding complexes prevents secretion of factors that trigger allergic inflammation. These complexes, which consist of so-called Runx proteins that bind to specific DNA sequences and the Cbfβ protein, exert anti-allergic effects in immune cells called helper T lymphocytes.

During immune responses, T lymphocytes acquire the capacity to produce different types of soluble factors called cytokines. Type 1 (T_H1) cytokines help eradicate intracellular bacteria and viruses, but if not controlled can exacerbate autoimmune diseases. Type 2 (T_H2) cytokines help combat extracellular bacteria and parasites, but when produced in excess can worsen allergies and asthma.

T lymphocytes produce either T_H1 or T_H2 cytokines. These mutually exclusive cellular 'fates' are shaped and maintained by distinct sets of transcription factors that bind to DNA sequences that are dedicated to enhancing or silencing expression of individual cytokine genes.

A team led by Ichiro Taniuchi, a scientist at the RIKEN Research Center for Allergy and Immunology in Yokohama, has determined that Runx complexes, which dampen expression of other genes in T lymphocytes, bind to and activate the silencer of *Il4*, a T_H2 cytokine gene. Their findings were published in a recent issue of *The Journal of Experimental Medicine*[1].

Using gene-targeting techniques, the researchers generated mice lacking either Runx3, or Cbfβ, specifically in T lymphocytes. Mice lacking CBFβ exhibited spontaneous lung infiltration (Fig. 1). Mice lacking Runx3 displayed milder versions of these asthma-like symptoms.



The Journal of Experimental Medicine

Figure 1: Spontaneous airway infiltration was observed in mice lacking the CBFß protein (left) but not in wild-type (right) mice.

Incubation with T_H1-promoting cytokines 'skews' naive T cells towards a T_H1 fate and silences T_H2 cytokine gene expression. CBFβ-mutant T cells, and, to a lesser extent their Runx3-deficient counterparts, were resistant to T_H1 polarization and failed to suppress T_H2 cytokine production.

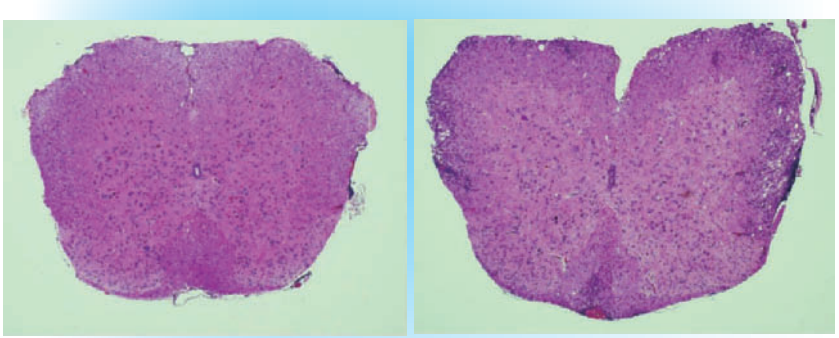
Runx complexes bind directly to the *Il4* silencer in un-polarized T cells and T_H1 cells, but not in T_H2 cells. Forced expression of GATA3, a factor known to promote the T_H2 cell fate, in T_H1 cells prevented Runx3 binding to the *Il4* silencer. Precisely how GATA3 'expels' Runx complexes from the *Il4* silencer gene remains to be investigated.

Encouragingly, as human RUNX3 lies adjacent to a cluster of genes thought to influence asthma susceptibility in humans, these data may hold clinical significance. "The *Il4* gene might not be the only immunologically relevant target of Runx complexes. Further studies focusing on the roles of Runx complexes in mice may provide further insight into the molecular pathogenesis of allergic and autoimmune human diseases," says Taniuchi. ■

1. Naoe, Y., Setoguchi, R., Akiyama, K., Muroi, S., Kuroda, M., Hatam, F., Littman, D.R. & Taniuchi, I. Repression of interleukin-4 in T helper type 1 cells by Runx/Cbf β binding to the *Il4* silencer. *The Journal of Experimental Medicine* **204**, 1749–1755 (2007).

How eating cell 'corpses' reduces inflammation

Specialized immune cells orchestrate proper elimination of dead cells to prevent inflammation



The Journal of Clinical Investigation

Figure 1: Normal (left) and inflamed spinal cord (right). The multiple sclerosis-like disease occurs when specialized macrophages that prevent inflammation are depleted.

Reporting in the August issue of *The Journal of Clinical Investigation*[1], a team of Japanese researchers has found that immune cells called 'marginal zone macrophages' prevent inflammation by promoting the elimination of cells that have just died—so-called cell 'corpses'.

It has been long known that certain types of dead cells can suppress inflammation. A cell 'programmed' to die goes through a tranquil process called apoptosis, whereas traumatically killed cells die by a process called necrosis. Only apoptotic corpses can suppress inflammation.

Led by Masato Tanaka at the RIKEN Research Center for Allergy and Immunology, Yokohama, the team observed that apoptotic corpses injected into experimental mice migrate to specific locations in the spleen and lymph nodes and then disappear—phenomena associated with suppression of experimentally-induced inflammation. Intriguingly, marginal zone macrophages are found in the same locations.

Testing whether the macrophages were important for the disappearance of the corpses and reduced inflammation, the team depleted the macrophages from mice and then injected apoptotic cells. They found that the corpses were present much longer and experimentally-induced brain inflammation could no longer be suppressed (Fig. 1).

Digging deeper to understand this, the team looked at other nearby immune cells and found differences in two types of cells called dendritic cells, one of which was known to suppress inflammation.

Studying how the two types of dendritic cells responded to apoptotic corpses when the macrophages were present or absent, Tanaka's team found that the dendritic cell type known to suppress inflammation could do so only when the macrophages were present. In the absence of the macrophages, the other dendritic cells caused inflammation.

Further observations indicated a difference in the way the dendritic cells responded to the apoptotic corpses—which are normally 'eaten' by the inflammation-suppressing dendritic cells. The team noticed that when the macrophages were absent, the second type of dendritic cells could ingest the apoptotic corpses, which caused inflammation.

"We are now currently investigating the differences between the two [types of] dendritic cells," says Tanaka. One possibility is that the specialized macrophages transport apoptotic corpses selectively to the dendritic cells that suppress inflammation, thus physically preventing the other type of dendritic cells from promoting inflammation.

Exactly how marginal zone macrophages and two types of dendritic cells effect this complex processing of apoptotic corpses remains unknown, says Tanaka. Nevertheless, the observations are clear and represent a potential interesting avenue of research in causes of inflammation. ■

1. Miyake, Y., Asano, K., Kaise, H., Uemura, M., Nakayama, M. & Tanaka, M. Critical role of macrophages in the marginal zone in the suppression of immune responses to apoptotic cell-associated antigens. *The Journal of Clinical Investigation* **117**, 2268–2278 (2007).

Cell fusion may create niche for immune cell education

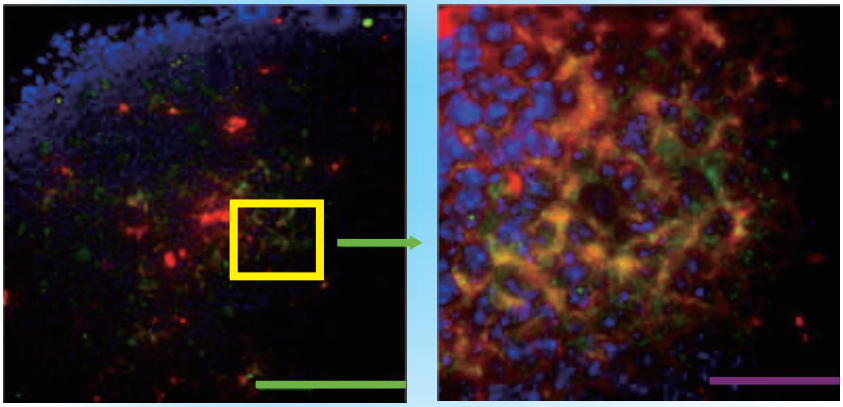
Researchers identify possible precursors of lymphoid tissue cellular network

Japanese researchers have identified a subset of cells they believe may induce the formation of a network of follicular dendritic cells (FDC) in the spleen and lymph nodes.

A recent paper published by Hiroshi Ohno and colleagues at the RIKEN Research Center for Allergy and Immunology, Yokohama, suggests that in the mouse, spleen cells expressing the cell surface marker proteins CD35, involved in processing and clearance of immune complexes, and B220, found on almost all immune system cells, can induce the formation of these networks and ultimately lymphoid follicles[1] (Fig. 1).

These so-called FDC form a reticular network of cells in the spleen and lymph nodes that trap immune complexes of antibodies, antigens and associated molecules. The network plays a critical role in the development and maturation of the antibody-producing B lymphocytes (B cells). If a B cell binds weakly to an antigen trapped on the surface of an FDC, it undergoes programmed cell death (apoptosis). On the other hand, a B cell that has a high affinity for the trapped antigen survives to become an antibody-producing plasmablast, and ultimately a memory B cell. This is the fundamental process that underpins the ability of the immune system to respond quickly to attack by pathogenic infection.

But it is not simply a matter of recognition; it appears that a complex interaction of cells and molecules and cellular architecture within the dynamic microenvironment of the lymphoid follicle is required for B cell maturation. The players include connective tissue cells called stromal cells.



Blood

Figure 1: Lymphoid follicle-like structures contain FDC (red) with B220$^+$ characteristics (green).

"The intrigue of the lymphoid follicle stems from the complexity of its microarchitecture, comprising immune cells and stromal cells, adhesion molecules, cytokines and antigen-antibody complexes, and the relationships between these components, in the formation of B cell-follicular dendritic cell aggregates and the regulation of B cell differentiation," says Takaya Murakami, the first author of the paper.

Results from a series of experiments both *in vitro* and *in vivo* suggest that the splenic cells with the CD35 and B220 proteins on their surface (CD35$^+$B220$^+$ cells) interact with stromal cells to create a niche for migrating B cells, forming cell clusters. The researchers believe that this may play a critical role in FDC network development and the subsequent formation of lymphoid follicles. There is also some evidence that the stromal cells may fuse with the CD35$^+$B220$^+$ cells during this process.

Further investigation of the role of stromal cells in the development of the lymphoid follicles and B cell maturation is planned, says Murakami. ■

1. Murakami, T., Chen, X., Hase, K., Sakamoto, A., Nishigaki, C. & Ohno, H. Splenic CD19-CD35$^+$B220$^+$ cells function as an inducer of follicular dendritic cell network formation. *Blood* **110**, 1215–1224 (2007).

Getting to the root of a developmental mystery

Researchers have revealed how two closely related proteins trigger opposing effects in developing roots

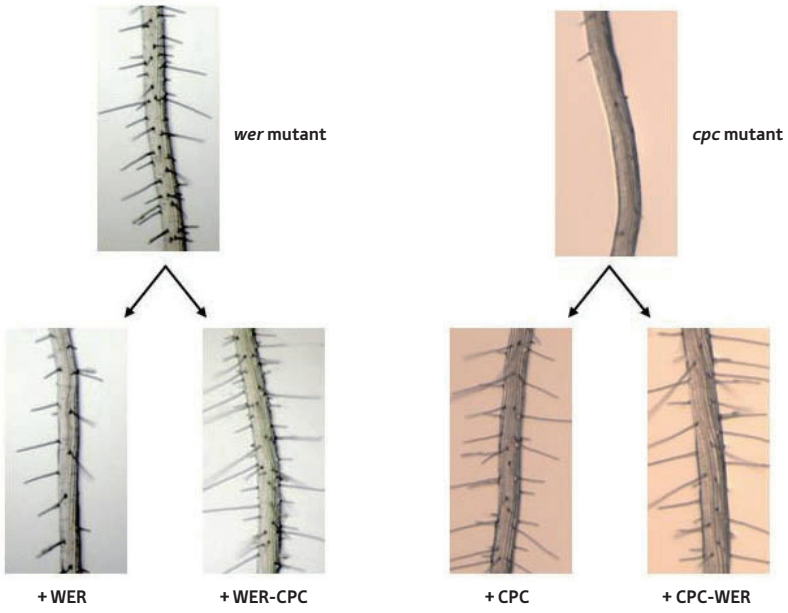


Figure 1: In *wer* mutant plants (left), only the replacement of the original WER gene (+WER) will restore a proper balance of hair and hairless epidermal cells. Roots expressing WER variants with the Myb R3 region from CPC (+WER-CPC) will only produce hair cells. In *cpc* mutants (right), on the other hand, hybrid versions of CPC (+CPC-WER) are just as effective as the native form of the CPC protein (+CPC) in regulating root epidermal development.

The formation of root epidermis in *Arabidopsis thaliana*, a popular plant research model, offers a valuable means for studying cell differentiation in developing tissues. During root development, progenitor cells yield two classes of epidermal cells, hair cells and hairless cells, which form in a fixed pattern along the root.

Previous research has identified factors that determine whether hair cells or hairless cells form. Two of the genes involved, *CAPRICE* (*CPC*) and *WEREWOLF* (*WER*), encode closely related transcription factors that exhibit notable functional differences, which piqued the interest of Takuji Wada, a researcher at the RIKEN Plant Sciences Center in Yokohama. "CPC activates root-hair cell differentiation whereas WER represses it, even though both belong to the same family of transcription factors," explains Wada, "so I wondered why these two factors have opposite effects."

CPC and WER belong to the MYB family of transcription factors, whose distinguishing characteristics include several domains with repeated amino acid sequences. Wada and his colleagues generated several CPC and WER variants, swapping different portions of one of these repeat domains (Myb R3) between the two proteins. These were expressed in plant strains that lack functional CPC or WER in order to understand the relevant regions that determine each protein's function[1].

Wada's team found that WER only inhibited hair cell formation when its entire R3 domain was intact. On the other hand, most of CPC's R3 domain could be replaced without impeding its activity (Fig. 1). Subsequent experiments showed that both proteins bind common targets—GL3 and EGL3, two proteins that induce hairless cell formation. Myb R3 substitutions had no effect on this activity, but did affect the ability of WER to bind DNA—a property absent in CPC. "The sequence of the WER MYB R3 domain is restricted—the equivalent domain of CPC cannot be substituted for it," says Wada. "Therefore, these restricted sequences are necessary for binding to DNA."

Wada's group believes that both WER and CPC compete for binding GL3 and EGL3. When WER binds, its unique DNA-binding sequences allow it to recruit these proteins in order to regulate genes responsible for hairless cell formation. However, when CPC is present as a competitor, no DNA binding takes place and hair cells develop instead. Based on the findings from this study, Wada suggests that *CPC* probably originated from a duplicate copy of the *WER* gene, a truncated younger sibling that nevertheless evolved into an effective rival. ■

1. Tominaga, R., Iwata, M., Okada, K. & Wada, T. Functional analysis of the epidermal-specific MYB genes *CAPRICE* and *WEREWOLF* in *Arabidopsis*. *Plant Cell* **19**, 2264–2277 (2007).

Thinking outside the cell

A recently developed experimental system provides new insight into how tiny RNA molecules keep a rein on gene activity

Every gene's activity is transmitted by messenger RNA (mRNA) transcripts, which subsequently serve as the template for protein-building—a process known as translation. Biologists have historically underestimated the humble mRNA, viewing it as little more than the short-lived intermediate between gene and protein, but groundbreaking work over the last decade or so has considerably changed that view.

MicroRNAs are a recently discovered class of tiny RNA transcripts that don't encode proteins at all, but instead act as regulators of the activity of other genes. These microRNAs partner with cellular proteins to form the microRNA–protein complex (miRNP). The RNA sequences of this complex enable it to directly bind to partially complementary sequences on target mRNAs. This binding can lead to greatly reduced protein production, although the mechanism of this process remains unclear.

Motoaki Wakiyama, a senior scientist in Shigeyuki Yokoyama's laboratory at the RIKEN Genomic Sciences Center in Yokohama, found it difficult to study this process in the complex environment of the living cell, and so the group attempted to instead recreate microRNA activity in a test tube. "In a cell-free system, you can specifically focus on translational control," says Yokoyama, "and it is very easy to handle various reaction conditions."

Yokoyama's group mixed extracts from mammalian cell lines expressing various miRNP component proteins in order to understand the mechanism of the microRNA *let-7*[1]. After identifying conditions that recreate *let-7* repression of target transcripts, the group focused on exactly how the microRNA blocks translation. They found that this repression relies on interactions with two core structural components of mRNA—a chemical 'cap' at one end, and a long 'tail' of adenosine nucleotides at the other. In fact, miRNP binding is followed by dramatic shortening of this tail—a process known as deadenylation—which in turn blocks mRNA translation (Fig. 1).

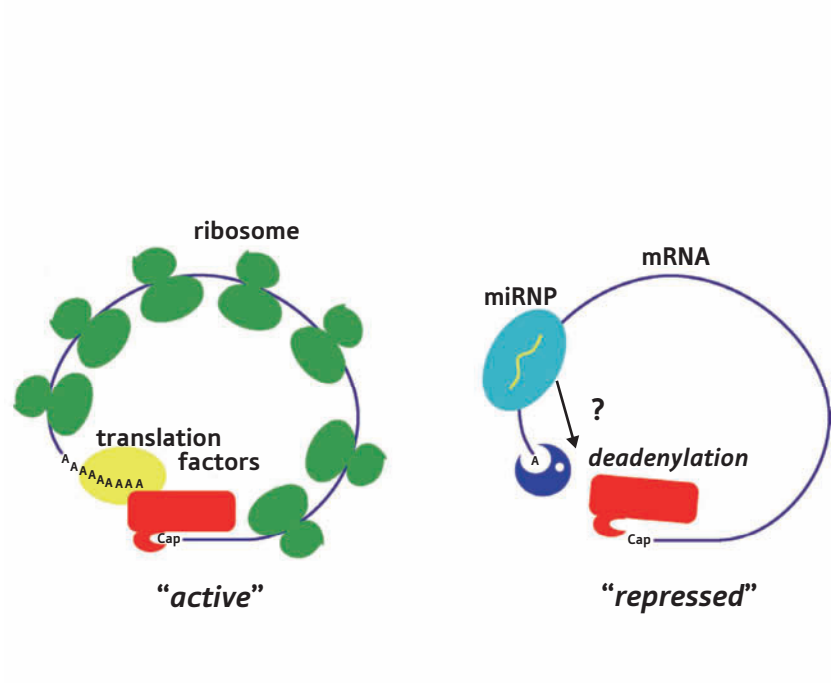


Figure 1: A model for how *let-7* represses translation. Under normal conditions (left), the cap and polyadenosine tail of an mRNA are bound by proteins (red and yellow, respectively) that make translation possible. When the miRNP is bound (right), its component proteins trigger transcript deadenylation, preventing translation.

"The most surprising finding is that microRNA induces deadenylation, causing translational repression but not rapid mRNA degradation," says Yokoyama. Based on current evidence, he believes this may represent a general mechanism by which microRNAs down-regulate target genes. "It is known that polyadenylation and deadenylation control mRNA translation," he says.

These findings lay important groundwork for future microRNA studies, and Yokoyama is now exploring the functional roles of individual miRNP components, but he also emphasizes the value of the experimental model developed here. "The recapitulation of microRNA-mediated translational repression in a test tube provides a powerful tool for studying microRNA function," says Yokoyama. ■

1. Wakiyama, M., Takimoto, K., Ohara, O. & Yokoyama, S. *Let-7* microRNA-mediated mRNA deadenylation and translational repression in a mammalian cell-free system. *Genes & Development* **21**, 1857–1862 (2007).

Using 10-femtosecond optical pulses to observe novel molecular behavior

Tahei Tahara

Chief Scientist
Director of Molecular Spectroscopy Laboratory
Discovery Research Institute

"Science, I believe, is the presentation of new possibilities," says Chief Scientist, Tahei Tahara. "Observing what we have never seen before, or what nobody has ever been able to observe, and showing what is actually happening, is sure to produce new science." The Molecular Spectroscopy Laboratory (Tahara Group) has developed a unique optical spectroscopy using extremely short optical pulses of 10 femtoseconds, and is probing molecular behavior that it was previously impossible to observe.

Optical spectroscopy that supports the very foundations of science

To begin with, Tahara took out three flasks with transparent liquids (Photograph 1). "These three flasks, almost colorless, contain molecules of the same compound called coumarin. However, they emit light of different colors when light is shone on them." Why do they emit light of different colors? Tahara explains that when placed in the path of a beam of light, a molecule only absorbs , scatters or emits (fluoresces) light of specific colors (wavelengths) because of the nature of the way it interacts with light. "Actually, these three flasks contain different solutions in which coumarin molecules are dissolved," he adds. "Thus, coumarin molecules in different solvents have different energies, interact differently with light, and hence can emit light of different colors."

Optical spectroscopy is a field that investigates the interaction between light and molecules and thus probes the properties and states of materials. "We generally use the word 'see' to suggest that we see an image of the shape of an object," says Tahara. "But in optical spectroscopy, we use the word 'observe' when we use light to probe the properties and states of molecules." He points out that optical spectroscopy uses an understanding of the interaction between light and molecules in detail and develops new methods for observing materials and objects that have never been observed before.

The knowledge derived from optical spectroscopy can be used to understand phenomena occurring in stars far away in the universe, to create new chemical

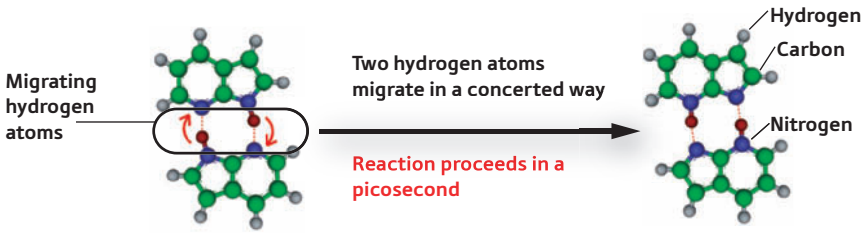


Figure 1 : **Figure 1: Double proton transfer of 7-azaindole dimer.**

agents, and to understand life phenomena. "Optical spectroscopy supports the foundations of every scientific field."

Challenging the limits of science

Tahara has developed a unique spectroscopy using extremely short pulses of 10 femtoseconds or 10^{-14} seconds, and has advanced research into observing changes in molecules during the processes of chemical reactions. In a chemical reaction, the atoms in the molecule change their positions and the overall molecular structure is rearranged. The change occurs in an extremely short time—of the order of femtoseconds. For example, it has been known for about 40 years that two hydrogen atoms can migrate when ultraviolet light is shone on 7-azaindole dimer molecules (Fig. 1). However, the process of this light-induced chemical reaction was left uninvestigated for a long period of time.

In 1995, Ahmed Zewail (1999 Nobel Laureate in Chemistry) and his co-workers claimed that the hydrogen atoms migrated one by one in sequence. However, Tahara objected to his claim in 1997. "Our experiments indicated that the two hydrogen atoms migrated in concert. We did not hesitate to present a paper about the results of our experiments because we had no idea that it would cause such a controversy." Yet, the controversy caused disturbances in the field across the world that remained unsettled for about 10 years. This was because the migration of hydrogen atoms is an event that occurs in an extremely short time, and it was very difficult to determine which argument was right.

In 2007, Tahara presented a conclusive paper that settled the long-lasting controversy. He stated that if migration occurs one by one in sequence, there should be an intermediate state in which only one of the atoms has migrated. "Thus, we tried to take 'continuous pictures' of the reaction by observing the snap-shot of the fluorescence that changes with the movement of hydrogen atoms." This finally confirmed that there was no such intermediate state; in other words, two hydrogen atoms migrated together within a picosecond. "I think we have successfully put an end to the controversy."

The structure of the 7-azaindole dimer is similar to that of the DNA base pair. This finding is expected to contribute to an understanding of the chemical mechanism of how ultraviolet light affects DNA. However, Tahara says that this is not the only reason why the controversy attracted a lot of attention.

"I think many researchers were interested in this controversy for the same reasons that they like watching a Formula 1 race," says Tahara. He says that although you cannot drive a racing car capable of running at a speed of 300 kilometers per hour on public roads, developing a Formula 1 car is significant in challenging the limits of technology to produce faster racing cars. "I think many researchers were interested in the controversy because we made efforts to clearly judge phenomena that occurred within a picosecond, thus challenging the limits of science."

Monitoring chemical reactions in real time

"The point of the controversy was whether the intermediate state really exists or not," explains Tahara. "We are now conducting research to observe in real time the process in which a molecule changes from a certain state to a different state."

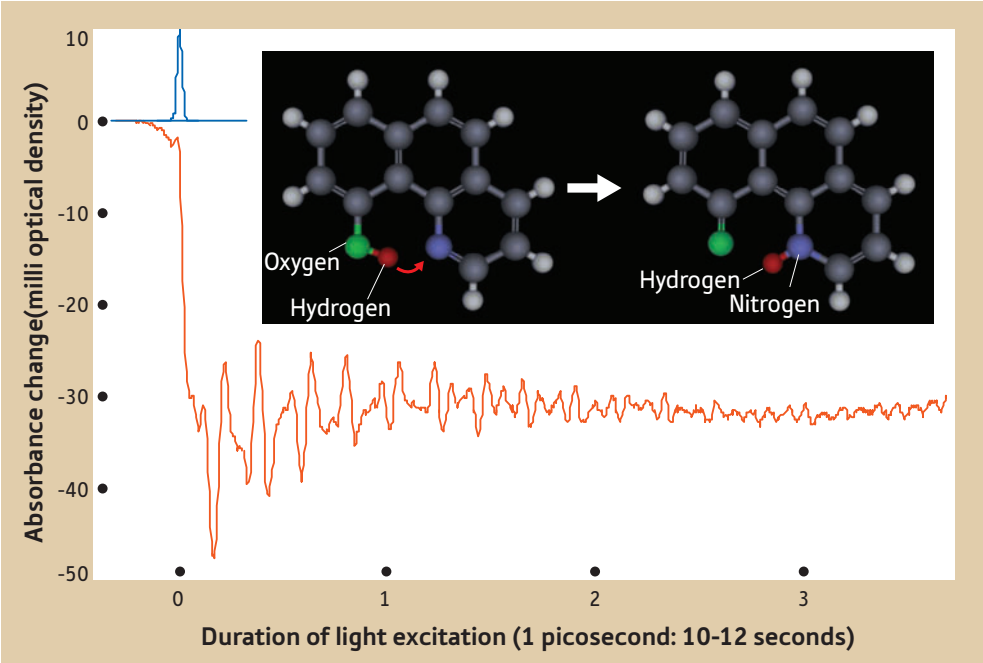


Figure 2 : Migration of a hydrogen atom in 10-hydroxybenzoquinoline

The molecule becomes unstable and starts reacting when light is shone on it. The hydrogen atom bonding to the oxygen atom, starts to migrate and combines with the nitrogen atom. The waveform in the picture shows the molecular vibration that is a 'memory' of the nuclear motion involved in the reaction.

For example, when light is shone on a 10-hydroxybenzoquinoline molecule, a hydrogen atom bonding to an oxygen atom in the molecule starts to migrate to, and combines with, a nitrogen atom (Fig. 2). A real-time observation of the process of these chemical reactions has clarified that there are various scenarios in the motion of atoms in a molecule. "When light is shone on some molecules, the atoms start moving in the direction relevant to the reaction, whereas, in other molecules, the atoms initially migrate in a direction that is not directly related to the reaction."

Speaking of his dream, Tahara says, "Observations of this kind may contribute to using light for controlling chemical reactions."

In the next step, he plans to investigate whether or not chemical reactions can be controlled by shining light in different ways so that the atoms can move in different directions.

Creating new knowledge

"Including our laboratory, there are only a few laboratories in the world in which femtosecond light pulses can be used for observing such nuclear motion of molecules during chemical reactions in real time." Tahara continues with a smile, "However, to be frank, I had a difficult time when I first joined RIKEN as chief scientist in 2001," he adds with feeling.

"Unfortunately, researchers in universities have little chance to communicate with researchers in different fields. In contrast, we have a lot of opportunities to communicate face to face with top-level scientists in many of the natural sciences at RIKEN." Tahara says that he soon understood that they have different values and different perspectives. This caused him to wonder whether his research was really significant or not, and if it was, in what way. "I had a difficult time because these different values and perspectives strongly shook my own values and perspectives," he adds. "Finally I decided to be faithful to myself. In other words, I decided to conduct research in the same manner as developing a Formula 1 racing car. I am sure that challenging research into typical leading-edge themes can contribute to deepening knowledge, leading to an understanding of the general phenomena behind them." Tahara says that although engineering uses existing knowledge to produce something useful, what is required for science is to create new knowledge.

Observing molecules at an interface

"Finally, let me introduce one of our newest research projects that is also similar to developing a Formula 1 racing car," says Tahara, taking out a flask of liquid again. "Can you guess the color of the molecules at the boundary between the liquid and the air above the liquid? We have developed a method that sees only the color in this boundary to understand the state of the molecule at the interface."

Various chemical reactions take place at interfaces. For example, understanding the chemical reactions taking place at the interface of a water droplet in the atmosphere is important to determine the mechanism of air pollution. Furthermore, analyzing the mechanisms in life processes requires an understanding of various chemical reactions that are taking place in a special interface called a biological membrane. "Unfortunately, however,

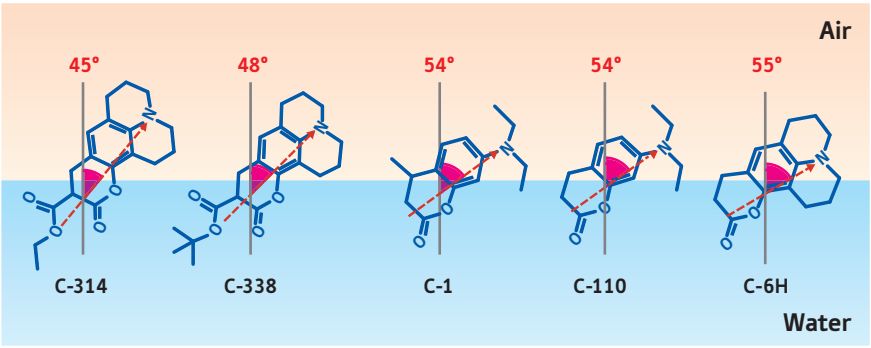


Figure 3 : A sketch of coumarin molecules at the air/water interface

Water molecules are electrically biased (polarized); the oxygen side is negatively charged whereas the hydrogen side is positively charged. Molecules with different structures have different tilting angles (refer to the red arrowheads) and floating states. Thus different molecules experience different effects of polarity, even at the same air/water interface because of their different interactions with water.

we have been very slow in developing a method to observe the molecular state at the interface."

In the 1980s, a new method called 'the second order nonlinear optical spectroscopy' was developed, in which only the molecules at the interface were observed by an intense light. In principle, the method can be used to observe the colors of molecules at the interface. "Previously, we had to spend days working on the experiment because the spectra (intensity distribution against wavelength) were measured with slowly changing colors of light (wavelengths) applied to them. Therefore, this method has not been very widely utilized."

Tahara and his group have developed a method in which the same experiment can be conducted in only about one minute. This is based on the idea of acquiring data simultaneously by shining white light femtosecond pulses that contain various colors. "So far we are the only laboratory in the world that can use this method," he adds proudly.

Use of this new method produced some amazing results. "We found that the molecules at the interface between water and the air exhibit a variety of colors as if they were in different liquids, such as oil or alcohol." Tahara explains that this is caused by the difference in their molecular structures. The difference in their molecular structures results in a difference in their tilting angles and floating states at the interface (Fig. 3). No-one had ever imagined this phenomenon before. Researchers failed to discover such a basic and simple phenomenon until the 21st century because of a lack of the relevant methods. "For this reason, we are proud of our findings," says Tahara. "I believe simplicity is the very essence of science. In the future, I would like to conduct experiments to search for simplicity in complex systems including living organisms."

How to observe new things

Tahara looks back on his college days when he used to think of strategies to become a good scientist.

"I had many smart classmates," he recalls. "They, however, were not challengers, but great critics who just criticized other people and other people's works." Tahara says that these people would succeed in one out of two trial attempts. "In contrast, I am not such a smart person, but I am confident of my guts and vitality. I may succeed in three out of ten trials, while those smart people conduct two trials. I can include an idea in those ten trials, even if it seems absurd, which may result in a truly new result emerging. I intended to take that approach." Tahara continues, "If we want to be successful in observing something new, we can be like children with a solid basic knowledge and skills, or we can be someone who has the courage to challenge an idea even if it seems absurd. I think it is important for researchers to have an inner drive or curiosity that urges them to try even absurd ideas."

He concludes, "Science, I believe, is the presentation of new possibilities." ■

Background reading/information

1. http://www.riken.jp/r-world/info/release/press/2007/070320/index.html
2. Japanese Patent, No. 2006-194770
3. Japanese Patent, No. 2006-145406

About the researcher

Tahei Tahara was born in Tokyo, Japan, in 1961. He graduated from Department of Chemistry, Faculty of Science, the University of Tokyo, in 1984, and obtained his PhD in 1989 from the same university. He became research associate of Department of Chemistry, Faculty of Science, the University of Tokyo in 1989, and then moved to the newly founded Kanagawa Academy of Science and Technology (KAST) as research associate in 1990. In 1995, he joined the Institute for Molecular Science (IMS) as associate professor and started his own research group. He was appointed chief scientist at RIKEN in 2001 and, since then, he has been director of the Molecular Spectroscopy Laboratory. His research interest is the development and application of advanced molecular spectroscopy to study the dynamics of 'complex'systems. In particular, he now focuses on femtosecond spectroscopy and nonlinear spectroscopy in solutions, at interfaces, and in microspaces.

RIKEN-Picower (MIT) Neuroscience Symposium hears about exciting "New Frontiers in Brain Science"

Gathering researchers on the cutting edge of brain science, the RIKEN-Picower (MIT) Neuroscience Symposium was held Nov. 8-9 at the Massachusetts Institute of Technology in Cambridge, Massachusetts. The symposium, the sixth such event jointly held by the RIKEN Brain Science Institute (BSI) and the Picower Institute of Learning and Memory at MIT, saw attendance around 350 people attending lectures on the theme "New Frontiers in Brain Science."

The symposium included four sessions, on "Systems Neuroscience," "Development and Cognition," "Learning and Memory," and "Molecular and Cellular Neuroscience," in which leading research results in each respective field were introduced. In particular, a new transgenic technology that Susumu Tonegawa and his team at the Picower Institute of Learning and Memory at MIT developed in order to research the mechanism of memory attracted the interest of the audience; their success in isolating synaptic pathways in vivo suggest that this technology, dubbed the DICE-K method, could find widespread application in neurological research. Mineko Kengaku of the Laboratory for Neural Cell Polarity discussed her team's work on cellular and molecular dynamics of nuclear movement in neuronal migration, and Yoshihiro Yoshihara from the Laboratory for the Neurobiology of Synapse talked about the molecular machinery of dendritic filopodia. BSI special adviser Masao Ito lectured on the 10-year history of BSI and its future outlook.

In addition, there was a poster session in which young researchers, including some from BSI, presented their research results.

The symposium was an excellent introduction to the research activities of BSI, as well as providing a clear indication of the size and extent of the research fields covered by the institute.

International symposium on advanced use of African resources in plant science

The RIKEN Plant Science Center in Yokohama hosted an international symposium on November 20 that focused on the use of African plant resources. The symposium was held under the auspices of the Japan Society for the Promotion of Science and the Japan Science and Technology Agency.

The theme of the symposium was scientific research on plants directed toward the effective utilization of African resources. The three sessions of the symposium focused on using medicinal plants in South Africa to combat infectious diseases such as malaria; effective utilization of wild-plant genetic resources from the Kalahari desert in Botswana; and in Sudan, management of water resources of the Nile river and control of parasitic striga weeds, so as to realize sustainable food production in that country.

Toshiya Muranaka of the RIKEN Plant Science Center and Marion Meyer of the University of Pretoria gave a presentation on ways of bringing technological resources to bear in strategic international technology cooperation to add value to indigenous plants in South Africa and aid combat against infectious diseases.

Akiho Yokota from the Nara Institute of Advanced Science and Technology (NAIST) and Seja Maphanyane of Botswana's Ministry of Agriculture spoke on the establishment of a high-level infrastructure to enhance the use of wild plants of the Kalahari desert, making use of post-genomic research techniques.

Kobe University's Yukihiro Sugimoto and Abdelbagi Mukhtar Ali Ghanim of Sudan's Agricultural Research Corporation presented a lecture on ways to increase food production in Sudan, and water resource management and pest control of the parasitic weed Striga, a topic of research that is currently being expanded.

The participants also discussed preparations for the Fourth Tokyo International Conference on African Development (TICAD IV) in May 2008 in Yokohama.

Honors to physicists at RIKEN

This October, Akira Tonomura and Franco Nori were elected Fellows of the American Association for the Advancement of Science (AAAS). Tonomura is presently a group director at the RIKEN Frontier Research System (FRS), and Franco Nori is a laboratory head at FRS and also a professor at the University of Michigan. Currently, they are the only AAAS Fellows based in Japan, within the Physics section.

Tonomura was selected as a member of the Japan Academy this month. He was chosen in recognition of his role in the development of electron microscopes using coherent field-emission electron beams. The Academy has three other RIKEN researchers amongst its members, including RIKEN's President, Ryoji Noyori.

Overcoming war-time difficulties: a special episode

An enduring friendship between the father of Japan's cyclotron and a young US government official saved RIKEN from demise in the postwar period

Research into particle physics using a cyclotron has been one of RIKEN's core strengths since its very early days that date back to the 1930s. Yoshio Nishina of RIKEN, Japan's top nuclear physicist at that time, avidly applied knowledge learned from the US and Europe and developed Japan's first, albeit small, cyclotron in 1937. He later witnessed preliminary experiments using the first beam of a bigger cyclotron in 1944 (Fig. 1).

By that time, Japan had forged its way into the morass of war, and its relationship with the US was rapidly deteriorating. A few days after the US dropped atomic bombs on Japan in August 1945, Japan declared its surrender. Then, Japan's science suffered a tragedy.

The US-led General Headquarters of Allied Forces (GHQ), which controlled postwar Japan, feared Japan had the capability to build nuclear bombs, and suspected that RIKEN's two cyclotrons were used to develop them. The GHQ undertook a thorough inspection of Nishina's laboratory, and destroyed the cyclotrons by plunging them into the depths of Tokyo Bay.

US scientists reading newspaper articles about their government's action became furious, and filed a complaint to then-president Harry Truman. The protest was successful as the GHQ asked the Department of Army to recruit two scientific advisors so as not to repeat the same mistake.

Young US scientists, including Harry Kelly at the Massachusetts Institute of Technology, were chosen to work for the GHQ's Scientific and Technical Division. Soon after he arrived in Japan in January 1946, Kelly came to believe that Japan would not prosper without its scientists and engineers. He then played a vital role in reconstructing war-torn Japan from a scientist's perspective.

Under the GHQ's governance for seven years until 1952, Japan faced many restrictions on its activities, including a ban on nuclear physics and other areas of scientific research. In addition, the GHQ ordered the liquidation of the powerful business conglomerates that dominated Japan's economy. That heavily affected RIKEN, as it had formed a group of flourishing venture companies in the 1930s and 1940s. Not only had the GHQ dissolved RIKEN's business group, but it began considering abolishing RIKEN itself.

In his early days in Japan, Kelly met many top-class scientists at RIKEN, and understood its importance to Japan's future. Kelly and Nishina, who was also influential to the government's scientific policies, soon started to work together and built a firm relationship of trust. They even

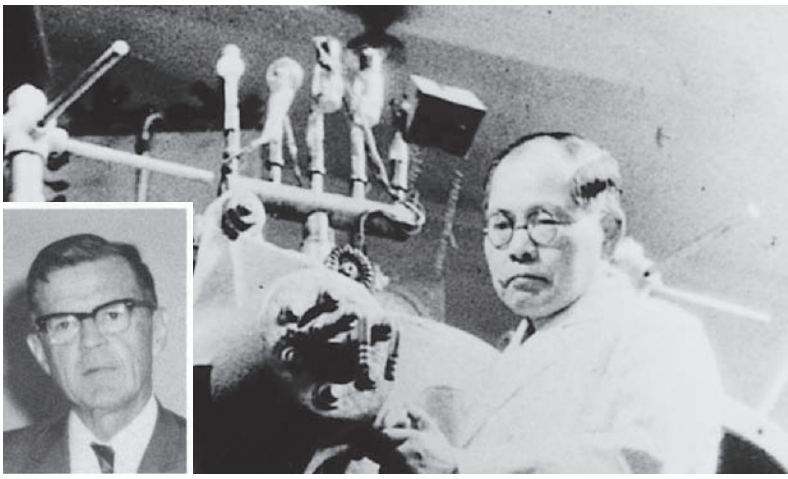


Figure 1: Harry Kelly (left) and Yoshio Nishina (right), Japan's top nuclear physicist, developed two cyclotrons but those were dumped into the Tokyo Bay after the war.

became close family friends. Backed by strong passions to save the moribund RIKEN, the two men scrambled to negotiate with tough government officials of the Allies and Japan, and spent two years persuading them to keep the research institute alive.

In 1947, RIKEN made a fresh start as Japan's first research institute to be incorporated, and Nishina was appointed as its first president. In his inauguration speech, Nishina praised Kelly by saying "today's RIKEN is indebted to efforts by the GHQ's Dr. Kelly, and this fact should be long remembered in our institute's history." Bowen C Dees, a colleague of Kelly at the GHQ, recalls in his book[1] that RIKEN would have followed the same fate as its cyclotrons without efforts by Kelly and his comrades.

In 1950, Kelly completed his mission and left Japan to work for the US National Science Foundation (and began to promote the US-Japan Scientific Cooperation as the co-chairperson of its Steering Committee). A year later, Nishina suffered from an illness and died at the age of 61. But their close bond was never severed. When Kelly died in 1976 at the age of 67, Kelly's family divided his remains and brought them from his hometown in North Carolina to Tokyo. Marked on his tombstone built at Nishina's tomb are the words, "Harry C. Kelly rests here." ■

1. *The Allied Occupation and Japan's Economic Miracle,* Bowen C. Dees, Kawade Shobo Shinsha (1997).

www.rikenresearch.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.

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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 Public Relations Office
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
TEL: +81 48 467 4094
FAX: +81 48 462 4715
E-Mail: rikenresearch@riken.jp