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Chemical reaction singled out

A reversible reaction cycle is demonstrated for a single molecule sitting on a platinum surface

Chemical reactions are traditionally performed in flasks containing vast numbers of molecules that all undergo the same transformation at more or less the same time. These processes are often studied by monitoring changes in the collective properties of the system, such as concentration, temperature or color.

Although valuable information about how a reaction works can be obtained in this way, it represents only an average of the behavior of all the molecules. To better understand what happens to any given molecule during a chemical reaction, a drastically different approach is required.

With a scanning tunneling microscope (STM), it is possible to 'see' individual atoms and molecules sitting on a surface by mapping their electron density. Moreover, the atomically sharp tip of an STM can also be used to manipulate molecules—they can be moved, their shape can be changed, and chemical bonds can be either made or broken.

Chemical reactions induced with STM tips are usually irreversible and not very selective for a particular bond. But now, a team led by Yousoo Kim and Maki Kawai from RIKEN's Discovery Research Institute in Wako have performed a highly specific and reversible reaction on an isolated molecule. "This is the first time anyone has been able to break and reform a single molecular bond," comments Kim.

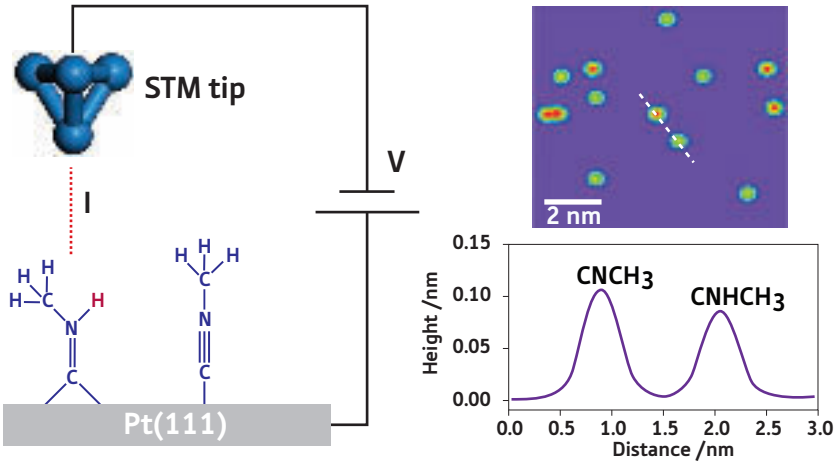


Figure 1: When a voltage (*V*) is applied between a conducting surface and an STM tip, a current (*I*) flows between the two if they are close enough to one another (left). Different signals are observed for $CNHCH_3$ and $CNCH_3$ molecules resting on a platinum surface when an STM tip is scanned across it, with the more intense signals (with red centers) corresponding to the $CNCH_3$ molecules (right).

Scratching the surface

In their study[1], reported in the journal *Science*, Kim and co-workers began by exposing a clean platinum surface to a small number of methylisocyanide (CH_3NC) molecules. The molecules adsorb to the surface by forming NC–metal bonds and an STM image revealed that they were located at so-called 'on-top' sites, where they bind to just a single platinum atom.

When the sample was treated with hydrogen gas (H_2), the platinum surface catalyzed a hydrogenation reaction in which the CH_3NC molecules were converted into methylaminocarbyne (CH_3NHC) molecules. This process resulted in significant changes to the electronic and geometric structure of the adsorbed molecules, causing them to shift to bridging—rather than 'on-top'—sites in which they bond to two surface platinum atoms.

A first glance, the STM image taken of the surface after the reaction was not very different from that obtained beforehand; in both cases, molecules simply appeared as bright protrusions. On closer examination, however, it was found that the height profile of these bright spots had decreased after the samples had been treated with H_2. This change suggests that

a transformation of the surface molecules had occurred, because theoretical models indicated that the CH_3 group in CH_3NHC should be 0.1 nm closer to the surface than the corresponding group in CH_3NC.

In an elegant control experiment (Fig. 1), it was confirmed that this difference in height profile was an intrinsic property of the molecules rather than an artifact of the experiment. Kim and co-workers added extra CH_3NC molecules to a sample that had already been treated with H_2, and an STM image of this surface—on which both CH_3NC and CH_3NHC molecules were now present—contained bright protrusions of two different heights, confirming that the two different adsorbed species could be distinguished in this manner.

Taking the pulse

The most significant finding made during this study was that individual CH_3NHC molecules could be converted back, one at a time, into CH_3NC molecules with the STM tip (Fig. 2). This reverse reaction, in which the N–H bond is broken, was done by precisely positioning the STM tip above the center of a CH_3NHC molecule, and injecting tunneling electrons into it by applying a voltage pulse.

Kim and co-workers found that this reverse reaction was sensitive to the magnitude of the voltage pulse. At a constant tunneling current of 1 nA and a pulse duration of 1 second, any voltage less than 2.7 V had no effect on the CH_3NHC molecules. However, with pulses ranging from 2.7–3.0 V, the N–H bond of a CH_3NHC molecule was selectively cleaved to reform a CH_3NC molecule. This change in chemical structure was, as expected, accompanied by a shift in adsorption site as the molecule reverts back to an 'on-top' site rather than a bridging one.

At voltages greater than 3.0 V, the CH_3NHC molecules were not cleanly converted back into CH_3NC molecules, but rather decomposed to give an unidentified product. It is thought that not only the N–H bond breaks at these values, but also C–H bonds in the CH_3 group. Breaking of the N–CH_3 bond could be ruled out, because the molecular fragments that would be formed in this process were not observed.

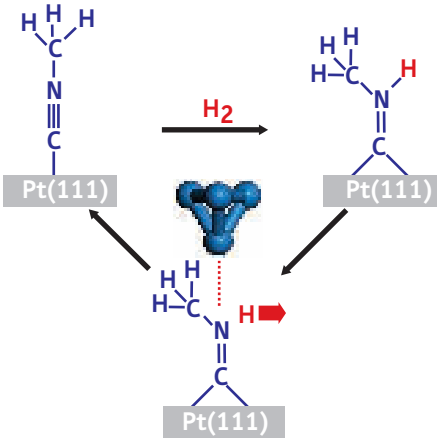


Figure 2: A reversible reaction cycle performed on a molecule adsorbed on a platinum surface. A hydrogen atom (red) can be added to each of the $CNCH_3$ molecules (blue) by exposing the sample to hydrogen gas. The hydrogen atom can be removed from individual molecules one at a time, by inject tunneling electrons into it from an STM tip position directly above it.

Looking to the future

Because the molecule–metal interface plays an important role in the conductance of molecular electronic devices, Kim suggests that being able to control interactions between single molecules and a metal surface may prove useful for such applications. Most studies to date, however, have focused on using sulfur containing compounds known as thiols to link molecules to metal electrodes.

From the standpoint of molecular devices, little experimental and theoretical research has been done on compounds containing this group. As demonstrated in this work, such molecules are appealing because the way in which they interact with a metal surface—such as bonding to one or two platinum atoms—can be reversibly modified without causing any major structural changes.

In addition to the potential of this work for applications in molecular electronics, this study could also offer a greater fundamental understanding of how chemical reactions occur on surfaces at the level of individual molecules. ■

1. Katano, S., Kim, Y., Hori, M., Trenary, M. & Kawai, M. Reversible control of hydrogenation of a single molecule. *Science* **316,** 1883–1886 (2007).

About the researcher

Yousoo Kim was born in South Korea's capital, Seoul, in 1968. In 1991, he graduated from the Department of Chemistry, Seoul National University, and obtained his masters at the same university in 1993. In 1999, he earned his doctorate in applied chemistry at the University of Tokyo. In the same year, he joined the Surface Chemistry Laboratory at the RIKEN Discovery Research Institute as a research associate, and six months later became a special postdoctoral researcher. In 2002, he was promoted to research scientist. Since 2006, he has been serving as a senior research scientist at the same laboratory. His research focuses on the fundamental studies of electron–molecule interaction at solid surfaces at the single-molecule level.

Competition boosts superconductivity

Superconductivity is found to be strengthened by a competing order of electrons

Researchers at RIKEN's Discovery Research Institute in Wako, in collaboration with colleagues at the University of Tokyo, have demonstrated that superconductivity of some crystals can be boosted by the presence of a competing electronic order, the so-called charge-density wave (CDW).

Crystals are comprised of a perfectly ordered arrangement of atoms. For many materials this regular arrangement, or atomic lattice, represents the most stable state over a broad range of temperatures and influences the behavior of electrons in the crystal. As such, electronic states such as superconductivity strongly depend on the interaction between the electrons and the atomic lattice.

However, there are electron–lattice interactions that compete with superconductivity. One example is CDW, where the density of the electrons varies periodically throughout the crystal. As superconductivity and CDW both compete for the same electrons, scientists assumed that these two electronic states exclude each other.

The researchers, led by Takayuki Kiss and Shik Shin, report in the journal *Nature Physics*[1] that they have found that these two states not only co-exist, but can strengthen each other. This discovery was enabled by recent advances in the spectroscopy technique known as 'ARPES', which is used to measure the electronic states of electrons moving in different directions of the crystal. "In the past, it was impossible to map the electronic structure with the necessary resolution … for example, in the 1990s, the energy resolution of ARPES was one to two orders of magnitude worse than at present," comments Hidenori Takagi from the RIKEN team.

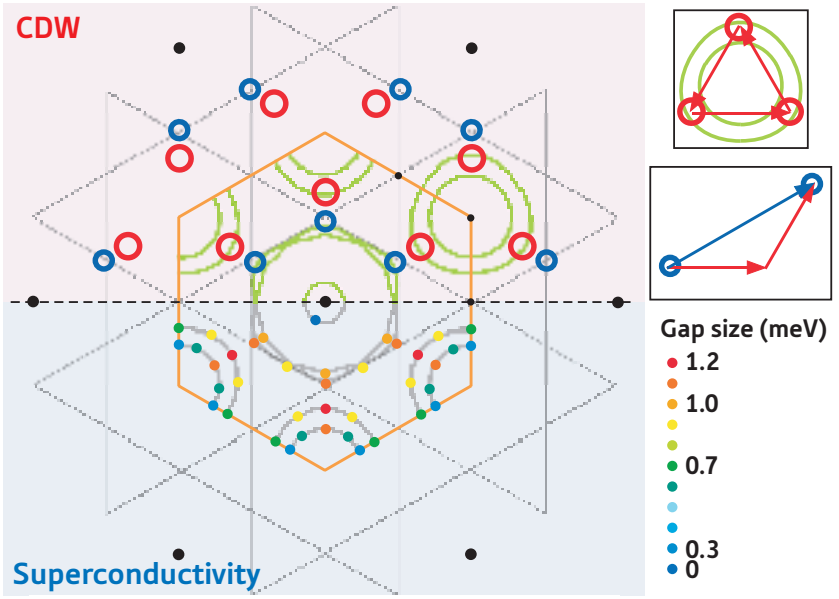


Figure 1: A boost for superconductivity. The upper part of the figure shows the points in the electronic structure of 2H-$NbSe_2$ where CDWs are found to exist (red and blue open circles). At the same points in the mirror image, superconductivity is enhanced (red and orange dots) compared with other areas (blue and green dots).

In the teams' experiments, ARPES was used to map CDW in the energy diagram of the superconductor 2H-$NbSe_2$. Simultaneously, the strength of the superconducting state was measured. Surprisingly, the researchers discovered that for certain electronic states, CDW actually enhances the superconducting state (Fig. 1). This finding suggests that the strong coupling between electrons and the atomic lattice is facilitated by the CDW and provides a positive feedback to superconductivity—as long as the CDW state is imperfect and provides room for superconductivity to develop as it does in 2H-$NbSe_2$.

In the long term, the researchers are confident that, based on these findings, it might be a good idea to look for new superconductors with increased transition temperatures in systems related to the occurrence of CDW. Certainly, these results show that many aspects of CDW reach far deeper than originally thought.■

1. Kiss, T., Yokoya, T., Chainani, A., Shin, S., Hanaguri, T., Nohara, M. & Takagi, H. Charge-order-maximized momentum-dependent superconductivity. *Nature Physics* **3**, 720–725 (2007).

Nuclei unplug a spin-valve

A team of scientists shows how to electrically control the polarization of nuclear spins

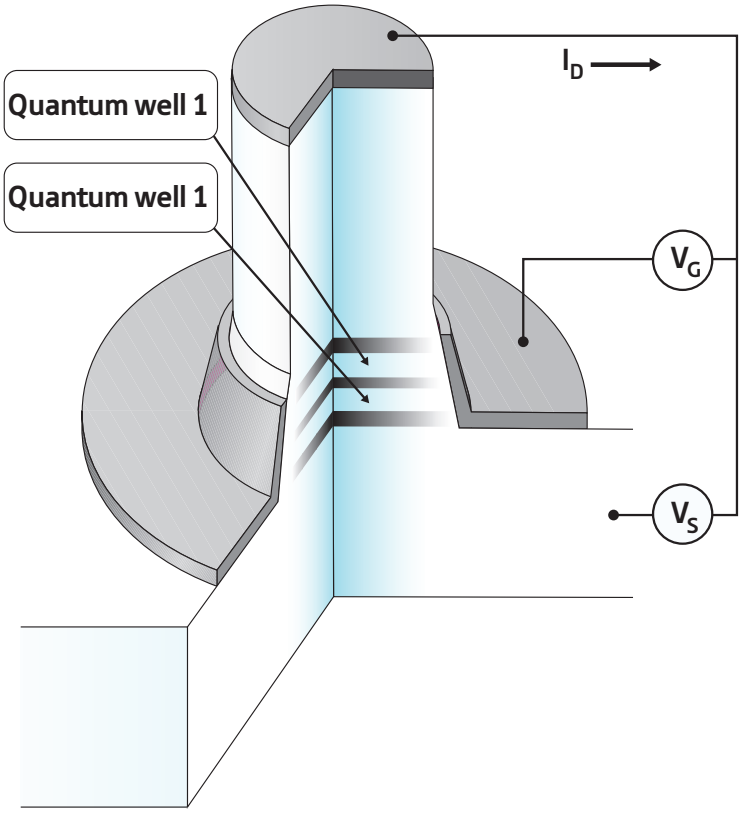


Figure 1: Schematic of the vertical double quantum dot, identifying the two thin layers of GaAs that act as quantum wells. Electrons tunnel from the base of the device, through the $Al_{0.3}Ga_{0.7}As$ tunnel barriers (dark layers), and into the quantum wells. At certain applied voltages VG and VS, interactions between the tunneling electrons and the nuclear spins in the GaAs quantum wells enhance the current and lead to a net polarization of the nuclear spins.

In any spin-based memory device—or qubit—a major challenge is preserving the spin state of an electron over reasonable times. The reason is that the electron interacts with nearby spins that cause it to 'flip' and lose information.

The greatest contribution to this electron 'dephasing' in semiconductor spin qubits is from random fluctuations of the surrounding nuclear spins. This is why a group of scientists, including Keiji Ono from the RIKEN Discovery Research Institute, Wako, and colleagues at the University of Waterloo in Canada and the University of Tokyo, are exploring a way to electrically suppress nuclear spin fluctuations. Their results are reported in the journal *Physical Review Letters*[1].

The team built an electronic device called a vertical double quantum dot (Fig. 1) that consists of two 10 nm-thick layers of the semiconductor GaAs, separated from one another and from metallic contacts by thin layers of the semiconductor $Al_{0.3}Ga_{0.7}As$. The $Al_{0.3}Ga_{0.7}As$ layers act as 'tunnel barriers' that confine electrons to one of the thin GaAs layers, which are therefore called 'quantum wells'.

The team has shown previously that it can control the transport of electrons, one at a time, through the quantum wells and that this transport depends on the spin state ('up' or 'down') of the electron. In fact, under certain conditions, an electron with one particular spin state (say, 'up') cannot tunnel across the double-dot structure without first flipping its spin.

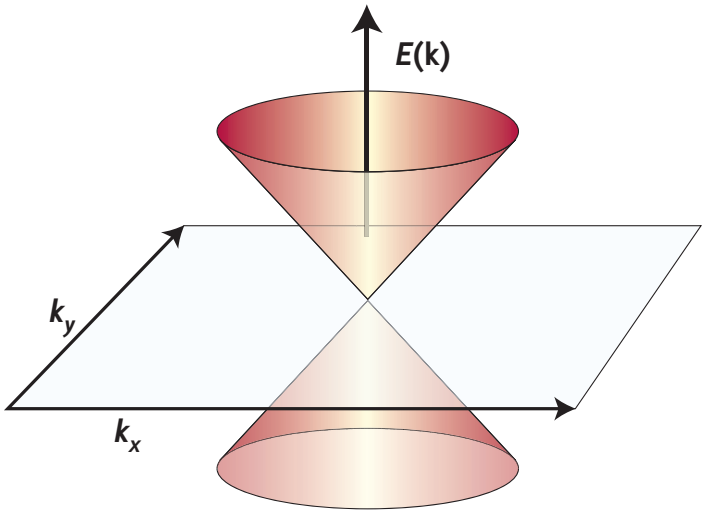
In their new work, the team uses this 'spin blockade' effect to polarize the nuclear spins in the GaAs. This superconductor contains three isotopes—^{71}Ga, ^{69}Ga and ^{75}As—each of which has a large nuclear spin that interacts with an electron moving through the double dot. When the device is set to the spin-blockade mode that prevents spin 'up' electrons from tunneling across, the nuclear spins open the door: the interaction between the electron and nuclear spins allows the electron spin to flip from 'up' to 'down' and tunnel through the device, while the nuclear spin flips from 'down' to 'up'.

The process polarizes the surrounding nuclear spins by as much as 40%. Ono notes that these measurements are the first to show that nuclear spin fluctuations can be controlled electrically and could be useful in designing spin-memory devices with longer electron spin lifetimes or based entirely on storing information in the nuclear spins themselves. ■

1. Baugh, J., Kitamura, Y., Ono, K. & Tarucha, S. Large nuclear Overhauser fields detected in vertically coupled quantum dots. *Physical Review Letters* **99**, 096804 (2007).

The indecisive insulator

Researchers are applying relativistic quantum theory to explain how graphene could switch from a metal to an insulator



Akira Furusaki

Figure 1: In two dimensions, the electronic energy band in graphene follows a cone-shaped distribution, similar to the behavior of relativistic massless Dirac fermions.

Graphene, which consists of single sheets of carbon atoms peeled off graphite, has recently been fabricated for the first time. Graphene has unusual electrical properties that originate from the unconventional manner in which its electrons behave. A team from the University of California, the Paul Scherrer Institute in Switzerland and the RIKEN Discovery Research Institute in Wako are gaining insight into graphene by expanding the quantum theory for relativistic particles[1].

Electron transport in solids is usually non-relativistic and governed by the Schrödinger equation. However the electrons in graphene effectively behave like massless relativistic particles, which are described by a Dirac equation. This means that in two dimensions the electronic energy band is cone-shaped (Fig. 1), and gives graphene the potential to switch from a conducting metal to an insulator.

"Electrons are scattered randomly by impurities and defects in a solid," explains project-member Akira Furusaki from RIKEN. "When such scattering happens sufficiently frequently, electrons become localized in a finite region and cannot propagate over a distance. This phenomenon is called Anderson localization."

During Anderson localization, the wavefunction—or probability distribution of different states—of an electron is very narrow in space. If all the electrons in a solid are Anderson localized, the solid is an insulator. In contrast, electrons in a conducting metal are free to move, having wavefunctions extended over the entire system.

Furusaki and co-workers extended an aspect of quantum field theory called the nonlinear sigma model to examine Anderson localizations in graphene. The model is defined whenever electrons move by diffusion, and has been a standard tool to describe transport properties of electrons in disordered solids.

The researchers discovered that when the nonlinear sigma model is used to describe the transport of two-dimensional Dirac electrons in a random electrostatic potential, a topological term is required in the mathematical formulation (at the same time, a German and Russian team reached a similar conclusion independently[2]).

The topological term arises from Majorana fermions—theoretical particles that are their own antiparticles—originating in the theory of the Anderson localization in graphene. "The presence of a topological term can change low-energy (long-distance) properties of the model drastically and is responsible for metallic transport in graphene," says Furusaki.

In future the researchers hope to generalize their theory to three dimensions. "We also plan to examine other systems such as disordered superconductors," says Furusaki, "in which the transport of low-energy quasiparticles may be highly complex." ■

1. Ryu, S., Mudry, C., Obuse, H. & Furusaki, A. Z_2 topological term, the global anomaly, and the two-dimensional symplectic symmetry class of Anderson localization. *Physical Review Letters* **99,** 116601 (2007).
2. Ostrovsky, P.M., Gornyi, I.V. & Mirlin, A.D. Quantum criticality and minimal conductivity in graphene with long-range disorder. *Physical Review Letters* **98,** 256801 (2007).

Hidden surface chemistry revealed

A new technique that works at normal pressures shows molecular interactions at liquid interfaces

RIKEN scientists have developed a technique that opens a window into a previously shadowy realm—the point where liquids and solids meet.

"Liquid interfaces play crucial roles in many phenomena, but only little is understood about what really happens at the interface," explains Tahei Tahara of RIKEN's Discovery Research Institute in Wako. Whether studying how a solid catalyst speeds up an industrially useful chemical reaction, or watching the biochemistry inside a human cell, understanding liquid–liquid and solid–liquid interfaces is crucial.

But studying the chemistry of submerged surfaces at a molecular scale is not trivial. "Most of the surface analysis techniques need a high vacuum," says Tahara. "They cannot be applied to liquid interfaces, because liquids cannot be kept in the vacuum."

Tahara and his colleague, Shoichi Yamaguchi, have now developed an alternative technique that works at normal pressures, based on a form of spectroscopy called $\chi^{(4)}$ Raman[1]. This uses visible and near-infrared light to vibrate molecules at interfaces, and then detects the light they emit as they return to their normal state. The emitted light carries information about the strength of the chemical bonds that hold the molecule together, and also how these molecules interact with their neighbors at the interfaces.

In Tahara and Yamaguchi's method, ultrashort laser pulses of light interact with a sample material four times in quick succession. This allows them to selectively observe only those molecules which lie at interfaces, says Tahara.

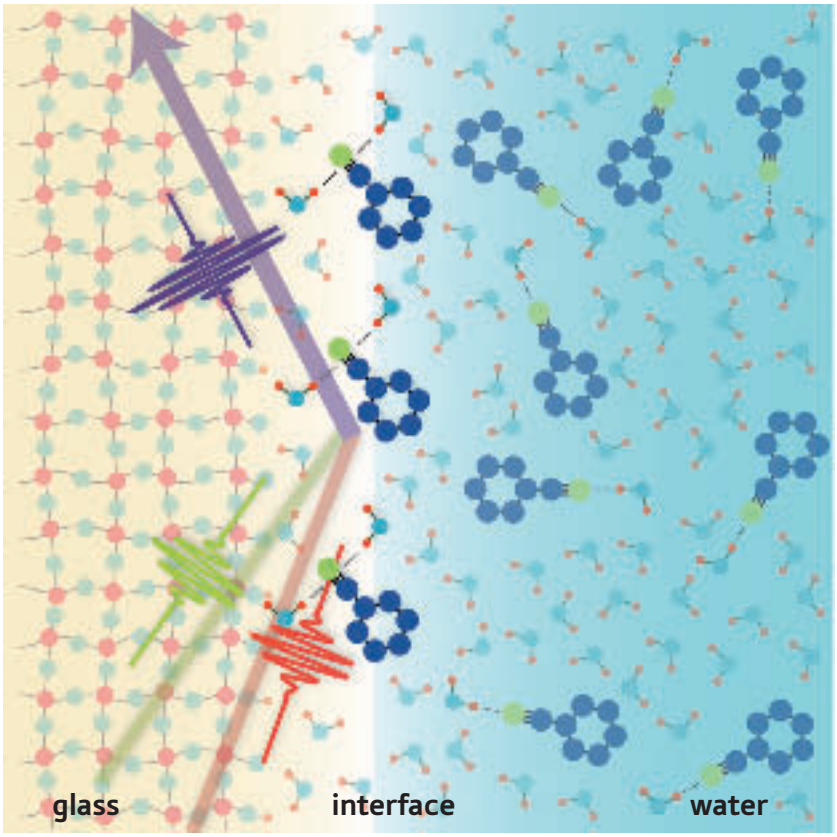


Figure 1: Molecules with a CN group at a fused silica glass/water interface. pi-type H-bonds that are not found in bulk liquid phases, where sigma-type H-bonds prevail, were detected at the glass/ water interface using $\chi^{(4)}$ Raman spectroscopy.

To test their method, the scientists dissolved a dye molecule called rhodamine 800 in water and mixed in a pure form of sand called silica glass.

They used $\chi^{(4)}$ Raman to measure the stretchiness of the chemical bond that connects a particular carbon atom to a nitrogen atom (forming a CN group) within rhodamine. This in turn revealed the pattern of water molecules that were assembled around it (Fig. 1).

In water, rhodamine normally has many water molecules forming a network around the nitrogen atom of the CN group. But by comparing their experimental results with theoretical calculations, they found that this pattern changed as rhodamine approached a solid fragment of silica, until just one or two water molecules were connected to the bond between nitrogen and carbon.

"Our finding is the first step that clearly shows that the fashion of molecular interaction is significantly different at the interface," says Tahara. Being able to study this difference should help scientists interested in areas as diverse as catalysis and biology. ■

1. Yamaguchi, S. & T. Tahara, T. $\chi^{(4)}$ Raman spectroscopy for buried water interfaces. *Angewandte Chemie International Edition* **46,** 7609–7612 (2007).

Genes, disease and ethnicity

Statistical analyses demonstrate variability in association between genes and osteoarthritis links to ethnicity

Genes can affect disease differently depending on one's ethnicity, concludes a team of international researchers reporting in the July 2007 issue of *Human Molecular Genetics*[1].

It has been long known that some diseases have genetic risk factors that determine whether a person is susceptible. Because some diseases have many genetic factors associated with them, they are called 'polygenic' diseases. The greater the number of genes associated with a disease, the more difficult it can be to show a causal link between one specific gene and disease.

Led by Shiro Ikegawa at the SNP Research Center of RIKEN in Yokohama, the team analyzed published studies that showed inconsistent results on the importance of one particular gene in the susceptibility to osteoarthritis (OA) (Fig. 1). The gene in question codes for a protein called asporin, which accumulates in arthritic joints.

A previous study positively linked OA of the knee and a specific change in asporin in a population of Japanese people; the association was replicated in a separate study of OA of the knee and in another study of OA of the hip. However, other studies of people from the United Kingdom, Greece, China and Spain found either positive or insignificant associations of genetics changes in asporin and OA in the knee and/or hip.

With the hope of shedding light on these inconsistencies, Ikegawa's team performed a type of statistical analysis called 'meta-analysis', which takes the information from separate studies and analyzes it with special types of statistical formulae that can factor out confounding factors present in each individual study.

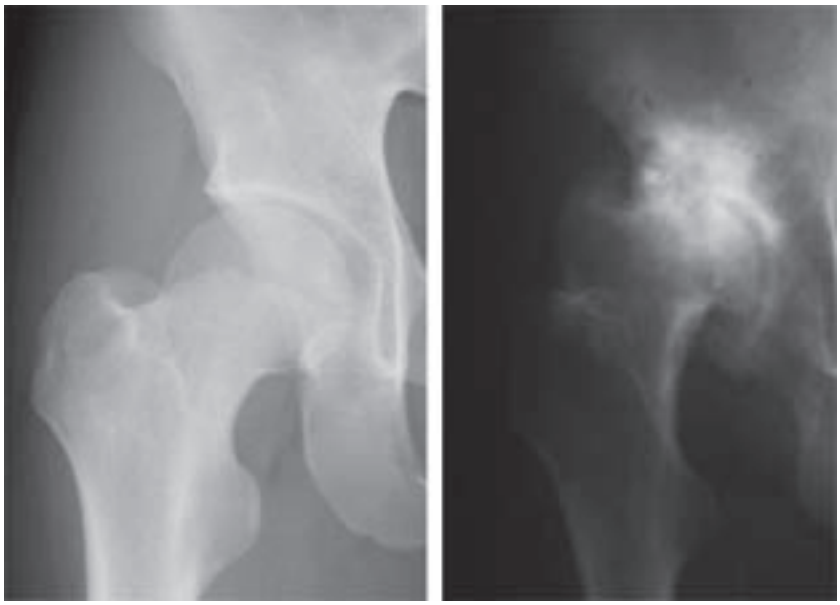


Figure 1: X-rays of a normal hip joint (left) and one affected by osteoarthritis (right).

"Meta-analyses can solve the problem of inconsistent studies by considering and compensating for the differences of the observers [the researcher]," says Ikegawa. Meta-analyses remove types of bias inherent in the complex and unpredictable nature of studying human diseases.

From their analyses, Ikegawa and team concluded that the genetic link between asporin and knee OA has global relevance and that while asporin is clearly the susceptibility gene with a modest effect in Asians, it is less so for Europeans.

Commenting on their success in achieving these results and developing a center of international collaboration in this field, Ikegawa says: "The road to collaboration was long and winding but the world is one, and so it should be for science and patients in every aspect." Such collaboration will no doubt be required to help solve other puzzling mysteries that link genes to human disease. ■

1. Nakamura, T., Shi, D., Tzetis, M., Rodriguez-Lopez, J., Miyamoto, Y., Tsezou, A., Gonzalez, A., Jiang, Q., Kamatani, N., Loughlin, J. & Ikegawa, S. Meta-analysis of association between the ASPN D-repeat and osteoarthritis. *Human Molecular Genetics* **14,** 1676–1681 (2007).

Solid facts to understanding shock

Discovering the structure of a key protein in human cells may lead to treatment for asthma and shock

The structure of a complex, human protein that has been uncovered by collaborators from Japan and the US could lead to new treatments for chronic inflammation illnesses such as asthma.

Good anti-inflammatory drugs are essential for the treatment of chronic conditions such as asthma and anaphylaxis, in which the lungs are severely restricted—sometimes fatally. According to the World Health Organization, it is estimated that as many as 300 million people worldwide suffer from asthma, so effective treatments are imperative.

The causes of chronic inflammation in humans are complex. The main compound known to trigger asthmatic symptoms is leukotriene C_4, which is synthesized in the body by an enzyme known as leukotriene C_4 synthase (LTC_4S). This enzyme is of great interest to scientists, because if drugs can be designed to regulate the activity of LTC_4S in the body and control the amounts of inflammation inducing leukotriene C_4, then a cure for asthma could be possible.

Now, a research team led by Hideo Ago at the RIKEN SPring-8 Center in Harima, in collaboration with K. Frank Austen at the Harvard Medical School and Division of Rheumatology, Immunology, and Allergy in Massachusetts, has solved the crystal structure of LTC_4S which shows the enzyme as a trimer (Fig. 1). Their work provides a breakthrough to scientists and opens the door to structure-based design of possible drug compounds.

From the crystal structure, published in the journal *Nature*[1], Ago and colleagues can now also look more closely at the biological function of the enzyme and its mechanism in cells. This significant achievement was not without challenges. The team also had to develop a way of producing the active human enzyme in sufficient quantities to form crystals for study. This was done using a recombinant technique—a procedure that allowed large quantities of LTC_4S to be produced using fission yeast instead of human cells.

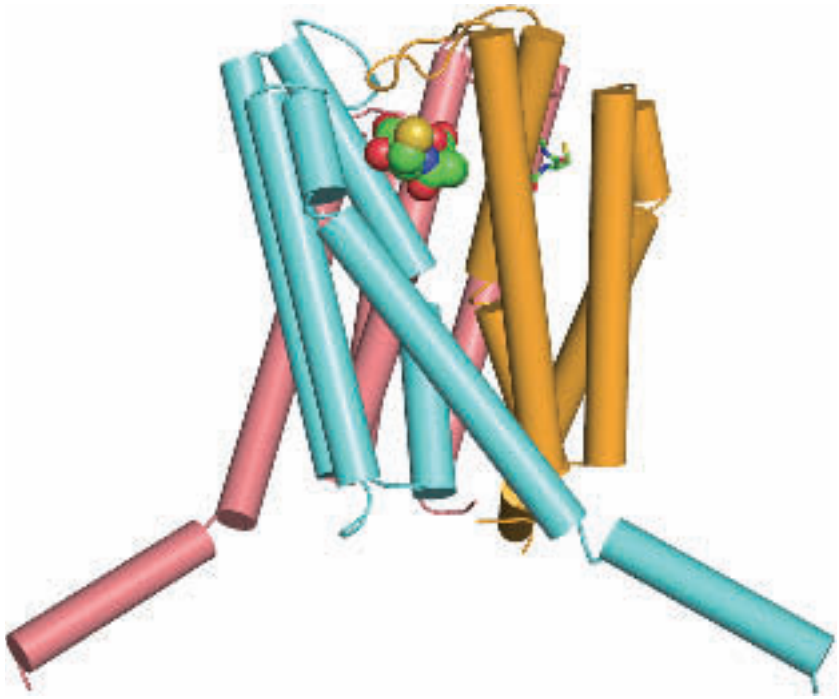


Figure 1: The crystal structure of the trimer of the enzyme, leukotriene C_4 synthase, binding a small, natural compound, points to how drug molecules could be designed to bind in a similar fashion.

The research program to date has involved the work of eight scientists over four years from both institutes. Ago explains that the next step in this research will be to use this new crystal structure to screen, using computers, potential drug candidates for effective inhibitors of the enzyme. This approach may lead to better therapeutic drugs. The group will also study similar biological systems that produce active compounds.

Ago is very optimistic about the future. "In the new project, the technical know-how established through the study on LTC_4S will be a great help," he says. ■

1. Ago, H., Kanaoka, Y., Irikura, D., Lam, B.K., Shimamura, T., Austen, K.F. & Miyano, M. Crystal structure of a human membrane protein involved in cysteinyl leukotriene biosynthesis. *Nature* **448,** 609–612 (2007).

Finding the path to a source of stem cells

The first wave of cells giving rise to an early stem cell population are derived from cells of the neural tube

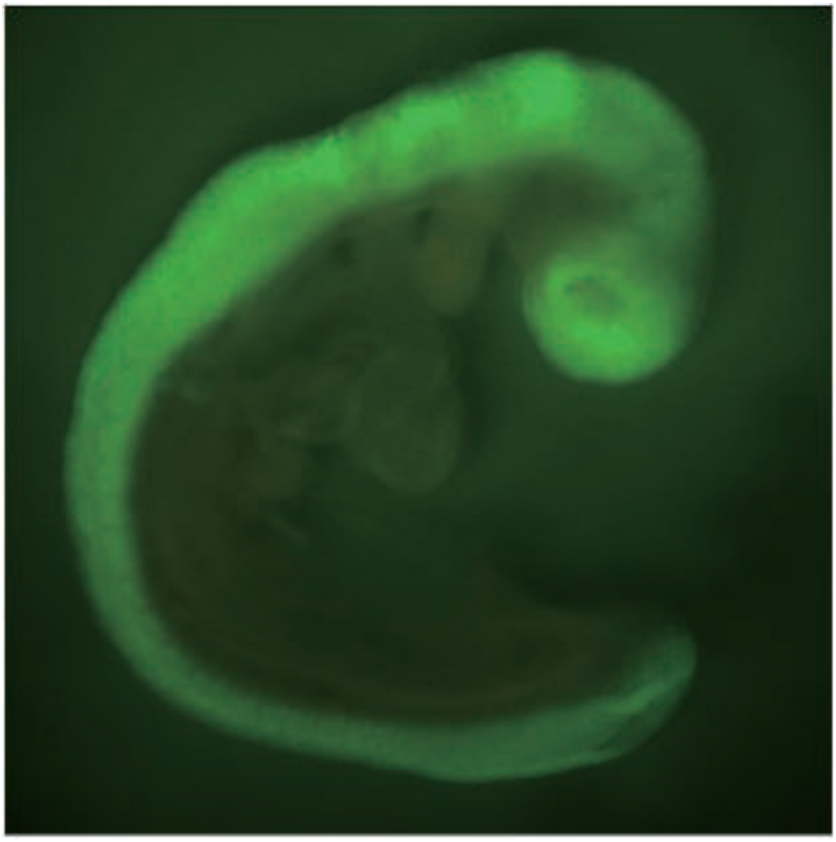


Figure 1: A mouse embryo used to show that Sox1$^+$ cells of the trunk can give rise to MSCs in culture.

Researchers from Japan and the UK have identified a source of cells that give rise to mesenchymal stem cells (MSCs)—a population of stem cells that can develop into various mature cell types, including bone, cartilage and fat cells.

MSCs have received much attention recently due to their pluripotency, or ability to generate numerous cell types, their ready availability from adult animals, including humans, and their successful use for stem cell therapy in the clinic. Although thought to originate from either the mesoderm or neural crest of the embryo, the exact origins and endogenous function of these cells in the body have eluded scientists.

Now, Takumi Era, Shin-Ichi Nishikawa at the RIKEN Center for Developmental Biology, Kobe, and colleagues have identified the initial source of these cells as the neuroepithelium—the sheet of cells derived from neural crest cells that contain sensory neurons—along the body's trunk[1].

Initially working *in vitro,* the team used a mouse embryonic stem cell line to show that cells that start out expressing Sox1, a genetic marker of neuroepithelial cells, end up expressing PDGFRα, a marker of MSCs, before the cells eventually differentiate into fat cells. The researchers then genetically marked the Sox1$^+$ cells of the mouse trunk (Fig. 1), mechanically isolated all the cells from this location of the body and showed that only the Sox1$^+$ cells could behave like valid MSCs in culture, indicating that MSCs start out as neuroepithelial cells and not other cell types.

To then show that this differentiation pathway also occurs *in vivo,* the team performed lineage analyses by using a Sox1$^+$-marked mouse strain and following the fate of these cells as the embryo developed. The team found that the marked cells in the body also switched to expressing PDGFRα after a few days, indicating their conversion from neuroepithelial cells to MSCs. However by the neonatal stage, the number of marked MSCs was reduced significantly by the time they had migrated to the bone marrow, indicating that these MSCs are derived from a transient wave of differentiation.

Given that the researchers detected many more unmarked MSCs in the bone marrow, they intend to explore whether other sources of MSCs may occur later in embryonic development, independent of the neuroepithelium.

Era and Nishikawa feel that, in addition to identifying the initial source of MSCs *in utero,* they have developed methods to enrich MSC progenitors and to identify the cell lineage of additional cell types that could give rise to other types of adult stem cells. ■

1. Takashima, Y., Era, T., Nakao, K., Kondo, S., Kasuga, M., Smith, A.G. & Nishikawa, S. Neuroepithelial cells supply an initial transient wave of MSC differentiation. *Cell* **129,** 1377–1388 (2007).

Guided nerves in the embryonic brain

Japanese biologists identify a protein critical to the normal development of the embryonic brain

Early in embryonic development, nerves grow and spread through the brain. If the nerves grow in the wrong direction or are stunted, it is fatal to the embryo. Growing nerve fibers appear to be guided by an invisible cue to travel along specific pathways making the decision to change direction or branch out at particular points.

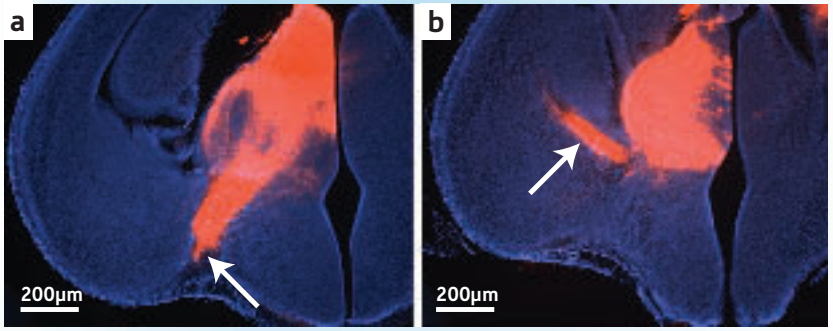
This specific directional growth of embryonic nerve fibers has been the focus of a study recently published in *Nature Neuroscience*[1]. Japanese biologists have demonstrated that a protein called OL-protocadherin (OL-pc) is crucial to the correct growth of particular nerves in the developing brain.

The team, led by Shinji Hirano and Masatoshi Takeichi of the RIKEN Center for Developmental Biology, Kobe, developed a population of mice that lack the gene for OL-pc and therefore don't produce the protein. The team was able to show that, in these mutant mice, particular nerve fibers grew in a disorganized manner or were stunted and the embryos died within weeks. In normal mice, comparable nerve fibers grew in an orderly fashion (Fig. 1). Stained sections of brain tissue showed that the presence of OL-pc matched the regions of nerve growth. The protein was found both along the nerve fibers and at their growing tips.

Hirano and colleagues found OL-pc most abundantly in the small striatal region of the forebrain. This is the major input station of nerves associated with bodily movement. The group showed that striatal fragments transplanted outside their normal area extended nerve fibers in the normal orientation, suggesting the existence of a guidance mechanism. Also, if these striatal nerve fibers did not grow properly, the team found that non-striatal nerves travelling to other parts of the brain became tangled or misrouted, suggesting that other nerves require normal striatal nerve extension for their progression.

OL-pc molecules tend to stick to each other and so interaction between them along nerve fibers may give rise to a signal that guides growth. Alternatively, OL-pc may act as a receptor for an, as yet, unknown cue.

Although the results suggest that OL-pc is important for the growth of striatal nerve fibers, other mechanisms seem to coexist for ensuring the correct migration of these nerves. The cooperative mechanisms between these mechanisms need to be determined in the future. Further study of importance of striatal nerve fibers in guiding nerves to other brain areas and the unveiling of the signaling mechanism of OL-pc are next, says Hirano. ■



Nature Neuroscience

Figure 1: (a) Nerve fibers are misrouted in various ways in the brain of a mutant mouse deficient in the protein OL-protocadherin. (b) In a normal mouse brain, nerve fibers grow towards the cortex. (The slices of brain tissue were labeled with DiI).

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Hopping mad for the nervous system

Mutant mice that hop like rabbits are helping scientists to identify proteins that mediate the nervous system

The development of the nervous system depends on proteins that guide the growth of axons—the long, slender parts of nerve cells that conduct electrical impulses. A research team, led by scientists at the RIKEN Brain Science Institute in Wako, is uncovering these proteins by studying spontaneous nervous system mutations in mice.

The researchers discovered mice with a mutation that caused them to move their left and right legs simultaneously when they walked. The resulting gait resembled a rabbit's hop (Fig. 1), so they named the mutation 'Miffy' (*mfy*) after the popular cartoon rabbit.

"The mutant animals cannot control the left and right sides of their bodies independently," says RIKEN scientist Takuji Iwasato. "It is especially inconvenient for them when they are babies."

The mutation causes an error in part of the nervous system called the corticospinal tract (CST)—a massive collection of axons that travel from the cerebral cortex of the brain to the spinal cord. Usually, axons grow from one side of the CST to the other (Fig. 1, left inset), but in the *mfy* mice several axons cross back over the midline (Fig. 1, right inset). The *mfy* mutation also disturbs the 'central pattern generators' in the nervous system, which usually generate the repetitive left–right sequence of stepping limbs during normal walking.

The researchers managed to isolate a 30-gene part of the mouse chromosome that is responsible for *mfy* mutations. Among these 30 genes, one was found to be disrupted in *mfy* mice, which encodes a protein called α-chimerin. Furthermore, when α-chimerin was reactivated in *mfy* mice, their gait was improved.

Hye-Soo Kim

Figure 1: Rear views of walking mice. Wild-type mice (left) have normal alternating left–right leg motions, while mice with the *miffy* mutation (right) move legs simultaneously, resembling a rabbit's hop. Insets show schematic cross-sections of the corticospinal tract—axons (red) project over the midline in the *miffy* mice.

α-chimerin appears to be an important downstream component of the 'ephrin-Eph' protein-signaling system, which stops axons from growing when they reach the spinal cord midline. Usually, Eph proteins on the growth cones of the axons react with ephrin on the midline—this sends signals to stop axon growth. The new findings suggest that α-chimerin is required to pass the signal forward, by inhibiting polymerization of the structural protein actin.

"Ephrin and Eph are the main players in nervous system development," explains Iwasato. "We provided the first *in vivo* evidence for a downstream component of ephrin-Eph forward signaling."

The *mfy* mice are therefore a very promising experimental model. In future work, the team may use these mice to investigate the roles of α-chimerin and ephrin-Eph signaling in various aspects of brain development, learning and memory. ■

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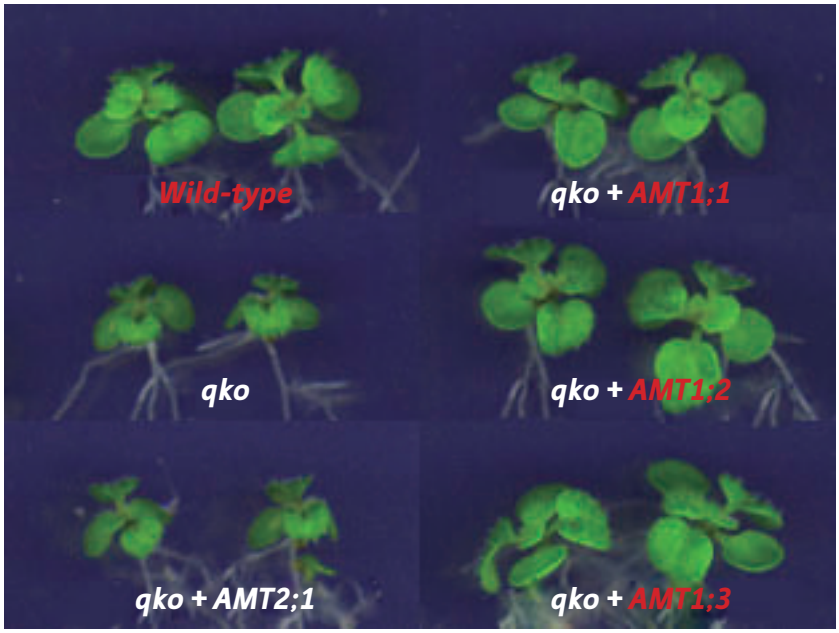
Soaking up ammonium

The uptake and transport of ammonium in plants depends on a small set of highly specialized genes



Takahashi and von Wirén

Figure 1: A comparison of wild-type plants and quadruple mutants (*qko*) in which four ammonium transporter genes were inhibited. The *qko* mutant plants had a tenth of the ammonium uptake capacity and half the shoot biomass of the wild-type plants when grown with ammonium. The growth of *qko* was recovered by restoring the genes *AMT1;1*, *AMT1;2* or *AMT1;3*.

Nutrients, water and other essentials are delivered into plant cells by special genetic proteins known as membrane transporters. For example, several membrane transporter genes have been identified in thale cress, *Arabidopsis thaliana,* which affect the transport of ammonium—an important source of nitrogen that assists plant growth and crop-yield quality.

Now, according to work undertaken at the RIKEN Plant Science Center in Yokohama, in collaboration with a team led by Nicolaus von Wirén from the University of Hohenheim in Germany[1], it seems that the ammonium transporter genes in *Arabidopsis* have highly specialized roles in different parts of the plant.

The researchers disrupted four out of the six ammonium transporters in *Arabidopsis* to create the first quadruple mutant plant—then they restored the transporters one at a time to determine their individual roles.

The quadruple mutant plants lost 90 to 95% of their ammonium uptake capacity. When they were exposed to ammonium, their shoots only grew to half the size of wild-type plants (Fig. 1). In the presence of nitrate (the other form of the nitrogen source) there were no differences in shoot size—implying the importance of the so-called 'high-affinity ammonium uptake system' in intake of ammonium. Restoring the genes *AMT1;1, AMT1;2 or AMT1;3,* but not *AMT2;1,* recovered the growth of the quadruple mutant (Fig. 1).

"The high-affinity system can facilitate the uptake of low concentrations of ammonium," says RIKEN scientist Hideki Takahashi. "Therefore, the system is particularly important when supply of ammonium is limited—the usual situation in soil."

The researchers found that a fifth transporter gene called *AMT1;5* was activated in the quadruple mutant. *AMT1;5* appears to act alongside two of the other ammonium transporter genes, *AMT1;1* and *AMT1;3,* in the outermost cells of the root tips and in the root hairs—where ammonium first enters the plant directly from the soil. On the other hand, *AMT1;2* works in inner cells called the 'endodermis'.

The research is not only relevant to *Arabidopsis.* "Rice and poplar have similar ammonium transporters," says Takahashi, "and the transporters are also likely to be similar in other crops, grasses and trees."

Takahashi believes that, given this new genetic knowledge, we could eventually produce plants that use nitrogen more efficiently, thereby reducing the need for artificial ammonium fertilizer. He explains: "We may need to manipulate both the expression levels and transport capacities of ammonium transporters to acquire such useful traits." ■

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Elucidating the mechanism behind immunity using dendritic cells

Tsuneyasu Kaisho

Team Leader
Laboratory for Host Defense
Research Center for Allergy and Immunology
RIKEN Yokohama Institute

When a pathogen enters the body, the immune systems in organisms are activated to eliminate the invader. At the Laboratory for Host Defense in the RIKEN Research Center for Allergy and Immunology, headed by team leader Tsuneyasu Kaisho, research activities are ongoing to elucidate the mechanism behind immunity, focusing on dendritic cells. They have succeeded in identifying a substance that plays an essential role in the production of interferon, a key bioactive substance in the immune mechanism. This achievement is expected to open the way to treatment of autoimmune disease, in which the body is attacked by its own immune system, and allergic disease, the prevalence of which is increasing dramatically. Described below is the mechanism for the protection of the body against pathogens.

Bridging innate and adaptive immunity

We are surrounded by a wide variety of viruses, bacteria, and other microorganisms, including pathogens that can enter the body. To cope with this, organisms have a system for eliminating pathogens to protect themselves. This is immunity.

Tsuneyasu Kaisho explains the essential features of the immune system. "When a pathogen enters the body, mammals initially attempt to eliminate it by innate (natural) immunity. If the pathogen has previously infected the animal, adaptive (acquired) immunity then operates to specifically exterminate the returning invader (Fig. 1)."

From the 1970s to the 1990s, adaptive immunity was highlighted as a prime research theme in immunology. "A great many researchers were engaged in active research to elucidate the mechanisms behind the responses of B cells and T cells to reportedly more than ten billion different kinds of pathogens," says Kaisho. Pathogen-recognizing receptors on the surfaces of B cells and T cells consist of several parts, and they increase their repertoire by recombining these different

parts. "The figure most responsible for demonstrating this fact was Dr Susumu Tonegawa," says Kaisho. This mechanism is known as gene recombination. Tonegawa became the 1987 Nobel laureate in medicine and is now serving as the group director of the RIKEN-MIT Neuroscience Research Center.

As for innate immunity, research progress was tardy, with the mechanism for pathogen recognition by macrophages and dendritic cells remaining unclear even after the advent of the 1990s. The situation changed dramatically in the second half of the decade. "Toll-like receptors (TLR) were discovered and shown to recognize pathogens at the starting point of immune reactions," explains Kaisho. "At last, this brought innate immunity into the limelight." To date, 12 types of TLR have been found in mice and 10 in humans."

However, a question arises. It is most unlikely that 10 billion kinds of pathogens in nature are specifically recognized by between 10 and 20 TLR types. The B cells and T cells involved in adaptive immunity are capable of adding as many as a quadrillion (1015) pathogens to their repertoire by gene reconstitution, whereas the immune cells responsible for innate immunity cannot. Then, how does innate immunity cope with the diversity of pathogens?

"Between 10 and 20 receptors would seem to be insufficient," says Kaisho. "Toll-like receptors respond to the invasion of diverse pathogens, despite their limited repertoire, by recognizing something not found in our body, but occurring somewhat ubiquitously in all pathogens as an essential component for their survival." Innate immunity is not specific to each pathogen, but capable of responding to a group of pathogens. Then adaptive immunity targets the pathogens that have escaped the foregoing attacks. Elimination of pathogens cannot be secured unless the two types of immunity work cooperatively.

"The key players in bridging innate and adaptive immunity are dendritic cells, so called because they have projections extending in all directions, like branches of a tree," explains Kaisho, "And there are different types of dendritic cells." As such, dendritic cells recognize pathogens by means of Toll-like receptors and produce a wide variety of bioactive substances known as cytokines. Cytokines serve to eliminate pathogens on one hand, and activate adaptive immunity on the other. Even when the same type of Toll-like receptor is involved, different signals are transmitted to cause different immune reactions depending on the type of dendritic cell in which the receptor is expressed. This variation in dendritic cells is now attracting great attention in immunology. "We want to elucidate how dendritic cells transmit signals for adaptive immunity, and what the mechanisms are for the production of the cytokines that take part in the process," says Kaisho.

A contributor to interferon production

The most unique of the various types of dendritic cells is the plasmacytoid dendritic cell. "Although plasma–cell-like dendritic cells had long been known morphologically, their function remained unclear," says Kaisho. Several years ago, however, plasma-cell-like dendritic cells were found to produce

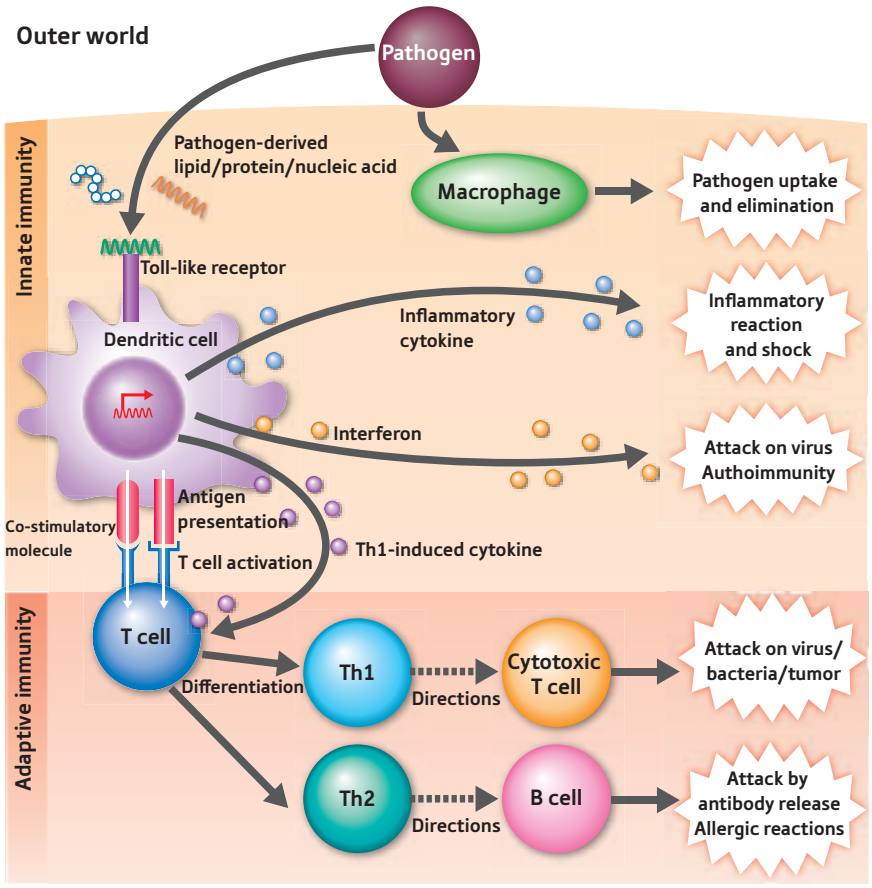

Figure 1: **Visiome Platform**

large amounts of interferon—a type of cytokine having high anti-viral activity—when infected with a virus. Interferon production is a characteristic function of plasma-cell-like dendritic cells. "Hence," adds Kaisho, "We began investigations to elucidate the mechanism behind interferon production in this type of dendritic cell (now called plasmacytoid dendritic cells)."

Plasmacytoid dendritic cells have two types of Toll-like receptors: TLR7 and TLR9 (Fig. 2). Both are localized on the surface of an organelle known as an endosome, rather than on cell surfaces, and both bind to virus-derived nucleic acid components, that is, single-stranded RNA for TLR7 and the DNA fragment CpG DNA for TLR9.

When the nucleic acid components bind to TLR7 and TLR9, information is transmitted via several substances, resulting in interferon production. It had been known that IRF7 is essential for interferon production. IRF7 regulates genetic expression by binding to a particular DNA sequence, however, it cannot function unless it is phosphorylated by a mediator and enters the nucleus in which DNA is present. The substance with the central role in this process had remained unidentified.

Kaisho took note of a substance known as I-kappa-B kinase alpha (IKKα). The IKK family consists of four members, three of which had been known to function in innate immunity. Unlike these, IKKα alone had been functionally unidentified in innate immunity. "An idea hit me," says Kaisho in retrospect. And his prediction hit the mark. IKKα was proven to phosphorylate IRF7 and play a critical role in interferon production.

"Since this finding was announced, I have received an increased number of requests to give lectures, which have included inquiries from pharmaceutical companies," says Kaisho. This discovery was important to fundamental science because it explained the mechanism of interferon production, but it also holds great potential for practical applications.

A potential treatment for autoimmune disease

As described above, Toll-like receptors recognize components that are normally absent from the body, but there are some exceptions. For example, single-stranded RNA and CpG DNA are also found in the bodies of healthy people. However, their abundance is by far smaller than that of pathogen nucleic acid and they are usually soon decomposed, posing no problem. Once bound to an antibody against one's own nucleic acid, however, they become unlikely to decompose and stay in the blood for a long time. In this situation, stimulation of Toll-like receptors via nucleic acid can cause health problems such as autoimmune disease, characterized by the body being attacked by its own immune system .

"Our achievement is expected to open the way to treatment of autoimmune disease," Kaisho claims. "It is known that patients with autoimmune disease have extremely elevated interferon levels. Interferon production may be suppressed by inhibiting the function of IKKα."

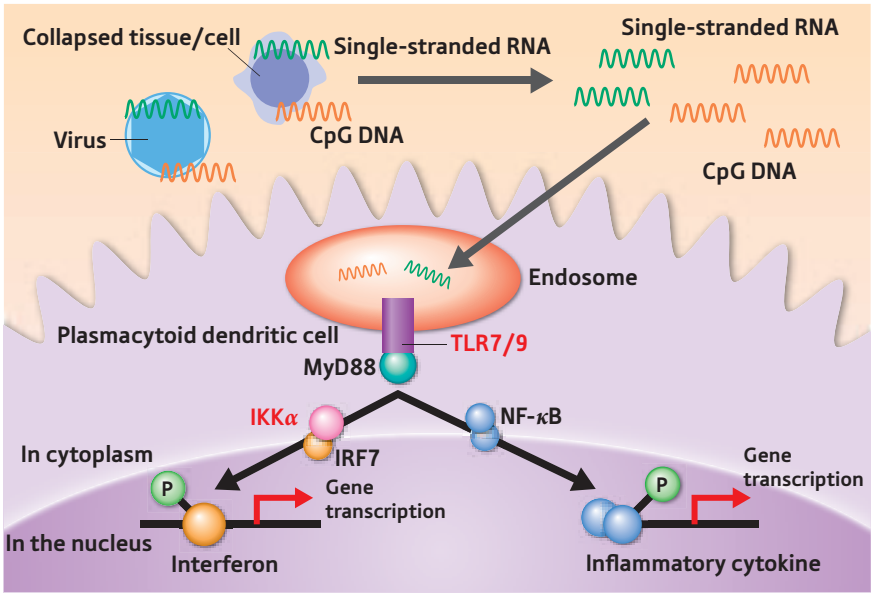

Figure 2: **INCF Japan-Node Scheme**

Signaling mediated by TLR7 and TLR9 is involved not only in interferon production, but also in the production of inflammatory cytokines that eliminate pathogens. If possible, interferon production would be suppressed while maintaining inflammatory cytokine production. "Because IKKα is predominantly involved in interferon production, it is the ideal target for this approach," says Kaisho. "Although relevant studies use mice, we believe the mechanism is shared by humans. We are conducting joint research on human cells in cooperation with universities and others."

Kaisho continues, "IKKα also has the potential for clinical application in the treatment of allergies." The interferon produced by dendritic cells is also involved in T cell differentiation. T cells differentiate into two types: type 1 helper T cells (Th1), which attack bacteria and viruses; and type 2 helper T cells (Th2), which trigger allergies (Fig. 1). The interferon produced by plasmacytoid dendritic cells, in particular, stimulates T cells to differentiate into Th1. "If the functionality of IKKα is enhanced to increase interferon production, and hence to increase Th1, allergies could be treated," Kaisho suggests. "To this end, however, further investigation will be necessary because excess interferon production may pose a problem with autoimmune disease."

When asked about his motivation to begin his studies in immunology, Kaisho replied, "When I was a medical student, I wanted to conduct research that would lead to the development of cures for disease." In those days, immunology was being actively studied using newly introduced techniques of molecular biology, but little was known about immune disease. "It all began owing to my misunderstanding that I might be able to produce a significant achievement with little effort," he laughs.

Then, what is the ultimate goal of his work? "It's a pleasure for me to discover interesting biological phenomena for myself," he explains. "If possible, I would like to apply my findings to the treatment of autoimmune disease and allergic disease, since I am a physician. Although it will be a long way to that goal, I am somewhat confident about it."

Kaisho is now working in search of substances that play a major role in interferon production, as IKKα does. It is hoped that a new therapy for autoimmune disease, the cause of which remains unknown, and allergic disease, which reportedly affects one-third of the Japanese population, will be developed by the Laboratory for Host Defense.

Kaisho concludes, "I make the last verse by Shinsaku Takasugi, who contributed a lot to the modernization of Japan at the end of the Edo Period, my motto: Doing something meaningful in this meaningless world depends on how we feel and react."

About the researcher

Tsuneyasu Kaisho was born in Osaka, Japan, in 1959. He graduated from the School of Medicine, Osaka University, in 1984, and obtained his PhD in 1990 from the same university. He worked as a research associate at Osaka University and as a postdoctoral fellow at the Genetic Institute in Cologne University in Germany. He then returned to Japan as a research associate at Hyogo Medical College and moved back to Osaka University. He has been a member of RIKEN RCAI as a team leader since 2002. His research focuses on the clarification of the molecular and cellular mechanisms by which immune adjuvants activate the function of various types of dendritic cells, which are critical for linking innate and adaptive immunity.

RIKEN Brain Science Institute and Toyota tie up for smarter machines

On November 1, 2007, the RIKEN Brain Science Institute, Toyota Motor Corp., Toyota Central R&D Labs Inc., and Genesis Research Institute Inc. established the RIKEN BSI–Toyota Collaboration Center (BTCC). The Center will promote collaborative research into the integration of neuroscience and industrial technology.

The idea behind the BTCC is that BSI and Toyota can better contribute to society by working together to bring new technologies into reality through studying the mechanisms of the brain and applying their findings. Both should be able to enjoy a multiplier effect from cooperating in the integration of brain science and technology in 'mind, intelligence, and machine', according to a statement by the joint venture.

In particular, the tie-up will investigate the causes of accidents, improve affinity between machines and humans, and clarify the relation between the brain and both physical and mental health.

Studies will focus on three broad fields—'neuro driving', which studies brain function as drivers perceive and react to traffic conditions; 'neuro robotics', which studies how the brain processes information; and 'the brain and health', which examines the physiology of the brain and the nervous system, in particular focusing on the relationship between the brain and physical health.

RIKEN BSI, as it conducts world-leading basic research into neuroscience, tackles its subject strategically, focusing on the mechanisms of brain function. It sees applying its research results to benefit society as one of its core missions. For its part, Toyota, as a world leader in advanced manufacturing, is actively promoting greater cooperation of the individual and society via the car. The BTCC tie-up will help the two organizations construct a base for innovation by applying their respective strengths.

The center's labs and other facilities will be housed at the RIKEN Wako Institute in Saitama Prefecture and Bio-Mimetic Control Research Center in Nagoya, which is near Toyota's headquarters in the city of Toyota, Aichi Prefecture.

BNL and RIKEN co-host life sciences workshop

In the 10 years that RIKEN and Brookhaven National Laboratory (BNL) in the USA have operated the RIKEN BNL Research Center (RBRC), the center has concentrated its efforts on high-energy physics. But both RIKEN and BNL are active in the life sciences as well, and a workshop held on September 20–21 gave the two institutions an idea of the range of their respective activities.

Japan is at the forefront of biological research, and RIKEN is one of the major health and biological institutes in Japan, involved in all aspects of the life sciences. Brookhaven National Laboratory, for its part, is active in structural and plant biology, DNA damage restoration, and cutting-edge research in biology, including neuro- and molecular imaging.

During the two-day workshop, visitors from RIKEN, led by Executive Director Yoshiharu Doi, toured BNL's facilities, including the lab's Relativistic Heavy Ion Collider, the Center for Functional Nanomaterials, the National Synchrotron Light Source, and the Center for Translational Neuroimaging. They also attended talks, in which BNL and RIKEN scientists presented their findings in a variety of fields.

Both RIKEN and BNL expect that the fusion of physics and the biosciences will be important in the future.

The RBRC focuses on three main aspects of high-energy physics—spin physics; lattice-quantum-chromodynamics computational physics; and the physics of quark–gluon plasma. The center has achieved a host of groundbreaking results in these fields during the decade since it was established.

Many in attendance felt that the workshop was a valuable experience, and that such events increase mutual understanding between researchers at RIKEN and BNL. A second symposium is planned for next year at the RIKEN Wako campus near Tokyo, when the agenda will be expanded beyond physics and life sciences to include nanotechnology and computer science.

Exhibition goes 'Beyond DNA' at National Science Museum

An exhibition created by RIKEN researchers at the National Science Museum in Tokyo is educating the public about the sequencing of the human genome and new directions in the post-genomic world. Yoshihide Hayashizaki, project director of the Genome Exploration Research Group at the RIKEN Genomic Sciences Center, was the driving force behind the show.

"We are putting this exhibition on now because research in this field is at a turning point," Hayashizaki said. "This is very important work, and people should know about it."

With informative panel displays and monitors showing exciting three-dimensional computer animations about various stages of the transcription of RNA into proteins as it occurs in the cell, the exhibition traces the history of the sequencing of the genome and the methods used, including the RIKEN Integrated Sequence Analysis system (RISA) for automated masssequencing, which has greatly sped up the process.

RISA, old (left) and new (right).

The exhibition also describes some new directions of genetic research. Since the sequencing of the human genome was completed, researchers have found that information can go in more than one direction—from genes and nucleotides to proteins, but also the other way around. In fact, analysis of the genome has shown that there are networks of information pathways and feedback loops that re-circulate genetic information back and forth in the process of expressing the gene and helping the organism adapt to the environment.

This information network is the focus of Hayashizaki's research on elucidating the genome and the mechanism for gene expression. This is expected to lead to breakthroughs in medicine, agriculture, and a host of other fields.

"I hope this exhibition will help the general public to understand this important scientific research, and also encourage young people to enter this exciting field," Hayashizaki said.

Figure 2: The main hall of Universiti Sains Malaysia in Penang

Figure 1: Polymer Chemistry Laboratory more than 10 years ago and some of its members. Standing from left to right: H. Abe, T. Fukui, H. Matsusaki, M. Isa (visiting scientist from USM) and T. Hisano. Sitting: K. Sudesh.

Dr. Yoshiharu Doi
Executive Director
Polymer Chemistry Laboratory,
RIKEN Discovery Research Institute,
Wako-city, Saitama, Japan.

Dear Dr. Doi,

It's amazing how fast time passes by. I still remember vividly the day when I first joined your laboratory in 1995. Back then, the Polymer Chemistry Laboratory was located on the fifth floor of the main research building at RIKEN's Wako campus. The lab was small and congested (Fig. 1), and the furniture was old and mostly made of wood—truly 'biobased.' Nevertheless, the research output from your lab was outstanding. You are now recognized globally as one of the pioneers who has contributed much to the field of biodegradable and biobased polymers. The knowledge that I have gained from you is being transferred faithfully to my students here at Universiti Sains Malaysia (USM) (Fig. 2).

Besides scientific knowledge, I have also gained much cultural knowledge during my affiliation with RIKEN. Meeting and interacting with leading scientists and distinguished personalities from all over the world are additional opportunities provided by RIKEN. In order to create a more peaceful world, knowing and understanding various cultures are, in my opinion, equally as important as acquiring scientific knowledge. So RIKEN, through the pursuit of scientific excellence, has also been functioning as a unique melting pot for foreign scientists and their family members. Over the past 10 years, I have noticed that RIKEN has been increasingly devoting much effort to make life more comfortable for visiting scientists and students from other countries.

My research activities are still focused on biodegradable and biobased polymers. The research collaborations between RIKEN and USM have produced important results to show that palm oil is an excellent substrate for the fermentative production of microbial polyesters. Therefore, there is much interest here to develop the technology for the large-scale production of microbial polyesters from palm oil. Although this is a good development, I am a little pessimistic. This is because increasing amounts of human food are being converted to fuel and material. Therefore, I am currently also looking at other possibilities of producing microbial polyesters.

Recently, we managed to extract small but significant amount of microbial polyesters from the gut of a class of termite that feeds on decaying plant matter (Fig. 3). The termite gut contains various microbes that help in the decomposition of plant biomass. This exploratory research was started because termites are abundant in USM. Their nests can be found easily all around USM!

Lastly, I hope that RIKEN and USM through programs such as the Asian Program Associate (APA) can continue to nurture future leaders in science and technology as well as help bridge the gap between developed and developing countries.

With best regards,

Kumar Sudesh
School of Biological Sciences
Universiti Sains Malaysia, Penang, Malaysia

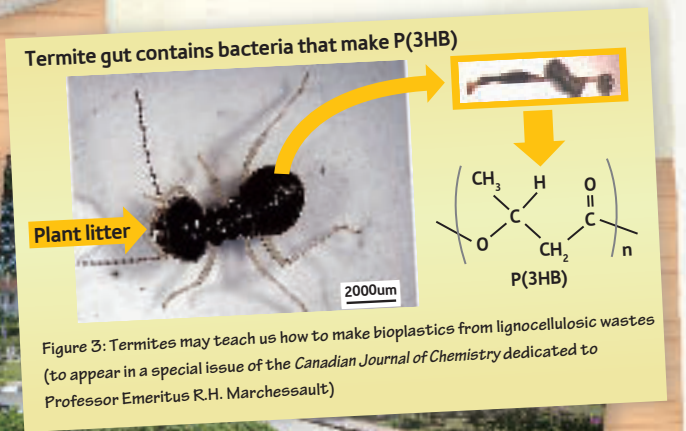

Figure 3: Termites may teach us how to make bioplastics from lignocellulosic wastes (to appear in a special issue of the *Canadian Journal of Chemistry* dedicated to Professor Emeritus R.H. Marchessault)

Dear Dr. Sudesh,

I remember that my close relationship with the Universiti Sains Malaysia (USM) started in 1993 when Professor Dato' Mohamed Isa stayed for seven months as a visiting scientist at the Polymer Chemistry Laboratory. You joined us in 1995 and received your PhD in 1999. Then, you continued your excellent research on the biosynthesis of polyesters as a postdoctoral researcher at RIKEN, until you became a lecturer at USM in 2001.

In the same year that you returned to Malaysia, RIKEN started its Cooperation Program for Asian Graduate Schools. Through this Program, RIKEN accepts brilliant young researchers who are enrolled in doctoral programs at universities across Asia. USM joined the Cooperation Program in November 2001, and Dr. Normi became the first USM graduate student to work in our lab through this program. She received her PhD from USM in 2006, before becoming a lecturer at USM. Currently, Miss Tang of USM is pursuing research on biopolymers at RIKEN as a participant in the Cooperation Program. We hope we will continue to strengthen our relationship.

With my best regards,

Yoshiharu Doi
Executive Director
RIKEN

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