Research

Luminescent Molecules that Inhibit Cancer Metastasis (Ru-complex)

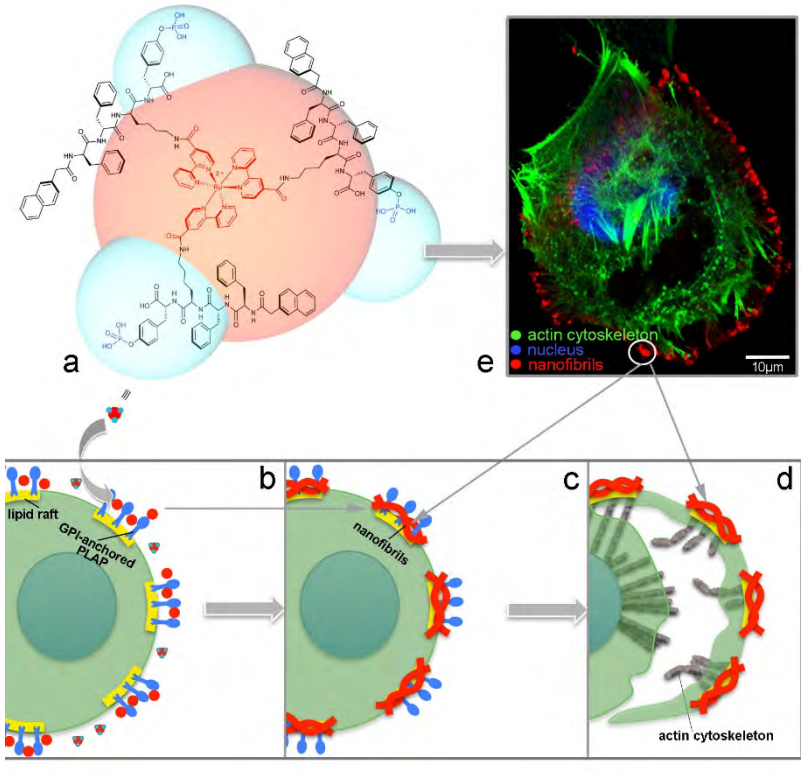
Expectations for the new therapy development that prevents cancer metastasis

Research background

Cancer metastasis, that is another tumor formation by cancer cell migration from the original site to a distant site, is a major health threat. In order to inhibit the cancer cell migration (locomotive movement of a cancer cell), scientists have tried to approach the problem of cancer migration by targeting molecules that are specifically or highly expressed in cancer cells, but finding an appropriate target has proved challenging.

Research

For cell morphogenesis and cell migration, a cytoskeleton, that is a complex network of interlinking filaments inside the cell, is necessary. The cytoskeleton is combined with the lipid raft on the cell surface. The research team in OIST succeeded in producing the luminescent molecule (Ru-complex) which inhibits cell migration by interacting with this lipid raft. The luminescent molecules are selectively combined with the enzyme “glycosyl phosphatidylinositol anchor placentas alkaline phosphatase (GPI-anchored PLAP)“ highly expressed on lipid rafts of cervical cancer cells and they self-assemble into nano-scale fibers (nanofibers). Lipid rafts are further tied off by formation of nanofibers on lipid rafts. Consequently, the associated cytoskeleton components get tied up, pinning the cancer cell on the substrate and preventing it from moving at that site. In response, the cancer cell tries to migrate away from the immobilized site and expands the cytoskeleton, but the mechanical force by the cytoskeleton ultimately ruptures the cell. It is also possible to target different types of cancer cells by modifying the structure of the luminescent molecule. A new window can be opened in cancer therapy if it works on real tumors in animals. (Published in "Chem" magazine of Cell Press)



Luminescent molecules that inhibit cell migration:
a) A luminescent molecule is combined of three peptide molecules which attach the phosphate group (light blue) centering on the Ru- complex (red). b) The luminescent molecules react with PLAP on lipid rafts of cancer cells to lose phosphate groups, c) self-assemble to form nanofibers and fix the cells at the periphery of the cancer cells. d) Cancer cells rupture and die as a result of excessive expansion of the cytoskeleton to escape. e) Visualization of cell rupture by immunostaining of cervical cancer cells.

Keywords

Polymer chemistry, Soft matter, Tumor biology, Molecular biology, Cell biology

Applications/Future development

- Operative verification of the luminescent molecule by animal experiment
- Development of luminescent molecules targeting different types of cancer cells

Opportunity for joint research and technology transfer

- Contract research companies in biopharmaceutical R&D : provide luminescent molecules.

Introduction of the research unit

Bioinspired Soft Matter Unit

Unit leader : Ye Zhang Assistant Professor

Nature designs materials as hierarchical architectures with complex composite structures spanning the nano to near-macro length scales to create unique combinations of properties that are often difficult to achieve with synthetic materials. The task of the Bioinspired Soft Matter Unit is to understand such amazing mechanisms and develop new man-made materials to mimic the structure, properties or performance of natural materials or living matter.

<Related research theme>

Development of the photosensitizer for more effective photodynamic therapy

In the photodynamic therapy used for the treatment of a brain tumor, when a drug called a photosensitizer is injected into the bloodstream and then the drug-filled cell is exposed to light, the photosensitizer in the drug will emit active oxygen and it will annihilate a cell. Photodynamic therapy is a precise targeted therapy that acts locally on the area containing cancer cells and does not damage normal surrounding cells. On the other hand, for further improvement of photodynamic therapy, research of the more effective photosensitizer is continued. In Bioinspired Soft Matter Unit, hypothesis on a new way of constructing a photosensitizer by adding the natural amino acid taurine into the Ru-complex's chemical makeup. After observing the effects of this new photosensitizer on cancer cells, it was found that the taurine-modified Ru-complexes were able to enter cells effectively while maintaining the conventional function, and that a large amount of active oxygen was generated when exposed to light. Furthermore, it became clear that the new substance developed this time is effective especially for brain tumors among cancer cells. (Published in "Chemical communications" published by the Royal Institute of Chemistry)

Research unit website : https://groups.oist.jp/bsmu

Targeted Drug Delivery System

Development of the drug delivery system opening new therapies

Research background

Currently, drugs are administered in a systemic way and tissues or organs that do not need the drug receive it, leading to unwanted side effects. Recent advances in nanotechnology and biology are opening up the possibilities in targeted drug delivery system (DDS), where drugs or compounds can act specifically on target tissues or pathogens, and it is expected to be put to practical use at an early stage.

Research

In Parkinson's disease, a neurodegenerating disease, impairment appears in a motion of the body with shortage of neurotransmitter dopamine. In OIST, the research team discovered a new method to repetitively release dopamine freely using a laser, through interdisciplinary study beyond the field of neurobiology and physics.

As for the method, at first, dopamine is confined in a lipid or fat capsule called liposome tethered to a gold nanoparticle. When the capsule is irradiated with femtosecond laser, the energy of laser is absorbed by the gold nanoparticles and then transferred to the liposome, the capsule is opened and the inner dopamine is released.

The length of time and therefore amount of dopamine released can be precisely controlled by the intensity and length of time the laser is on. Moreover, since liposome is not destroyed by laser, the release of dopamine contained within the liposome can be repeated and controlled.

From now on, the actual proof using living body tissues or animal organisms progresses, and if patterns that dopamine is secreted in a normal brain can be copied and reproduced, great progress will be brought to the treatment of Parkinson's disease. The technology of releasing a wide variety of drugs, compounds and naturally derived compounds to the necessary places in the required amount and timing as desired expands new possibilities to the medical field, not limited to Parkinson's disease. (Published in the electronic journal "Scientific Reports")

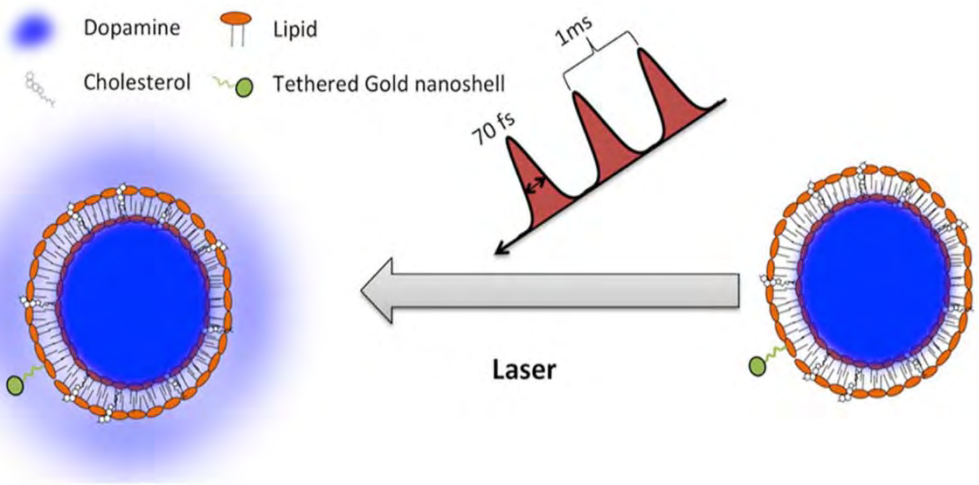


Diagram of liposome encapsulating dopamine that is tethered to a gold nanoparticle. The liposome is then activated with the laser, which releases the dopamine. Diagram courtesy *Scientific Reports*

Keywords

Neuron・Synapse・Neural circuit, Neurodegenerative disease, Femtosecond laser, Drug delivery system

Applications/Future development

- Verification of the effectiveness of laser-activated liposomes in living tissues and animals.
- Identification of the DDS targets in other diseases.

Opportunity for joint research and technology transfer

- Currently accepting contacts from companies interested in joint research and licensing of this technology

Patent protection
PCT/JP2014/083496「METHOD FOR CONTROLLED RELEASE WITH FEMTOSECOND LASER PULSES」（US : 15/103,423 EU : 14870369.7）

Introduction of the research unit

Neurobiology Research Unit

Unit leader : Jeff Wickens Professor/Dean of Graduate School

The goal of the Neurobiology Research Unit is to understand neural mechanisms of learning in the brain. The Unit studies physical changes that take place in synapses due to learning experiences, and how these changes depend on dopamine, a chemical that plays a key role in motivation. This research has the forward goal of developing better treatments for disorders such as Parkinson's disease and attention-deficit hyperactivity disorder.

Research unit website : https://groups.oist.jp/nru

Femtosecond Spectroscopy Unit

Unit leader : Keshav Dani Assistant Professor

Using intense, ultrafast laser pulses, the Femtosecond Spectroscopy Unit explores the optical properties of matter. Its members study graphene and other two-dimensional materials for their potential in transparent, flexible electronics; research semiconductors for photocatalytic and solar energy applications; and investigate applications of ultrafast laser pulses to biology and medicine.

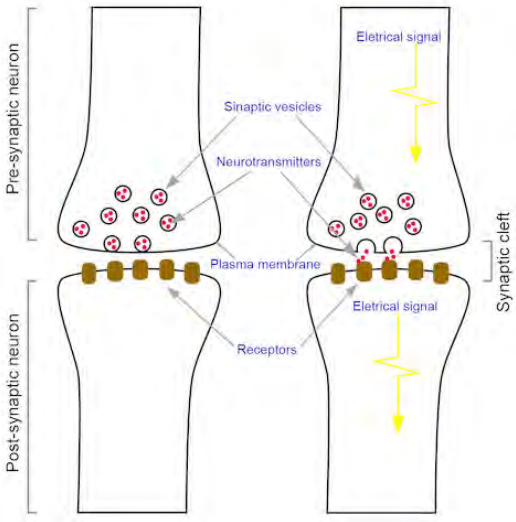
Research unit website : https://groups.oist.jp/fsu

Media Supplement for Giant Synapse Culture

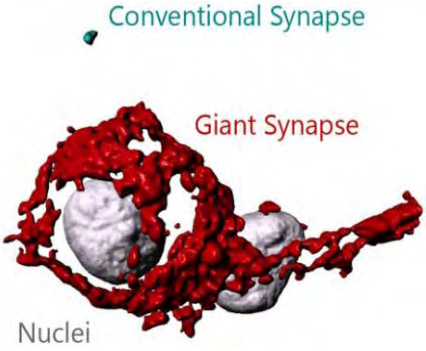
Technology for giant synapse culture may pave the way for progress in synaptic research

Research background

Transmission of information between neurons is carried out via synapses, the point of contact between two neurons. Recent research suggests that synaptic malfunction occurs in the early stages of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, requiring scientists to elucidate the synaptic mechanism which may subsequently lead to the development of remedies for treating such diseases. In their inherent state, synapses are far too small, leaving it difficult for scientists to observe its internal dynamics, even with the assistance of powerful microscopes. Brain stem sections of mice can provide researchers with big synapses called calyx of Held, which are serviceable for scientific analysis, though such brain stem sections are perishable and can only be used for experiments of up to 24 hours. In addition, the neuron cell density of such sections is high, a restriction that renders it nearly impossible for scientists to isolate a single synapse for experimentation.



When an electrical signal arrives at a terminal of one neuron, chemical messengers called neurotransmitters contained within synaptic vesicles are released in the synaptic cleft. The released neurotransmitters bind to receptors on the cell membrane of the next neuron(post-synaptic neuron), which in turn trigger an electrical signal that is transmitted along the next neuron.

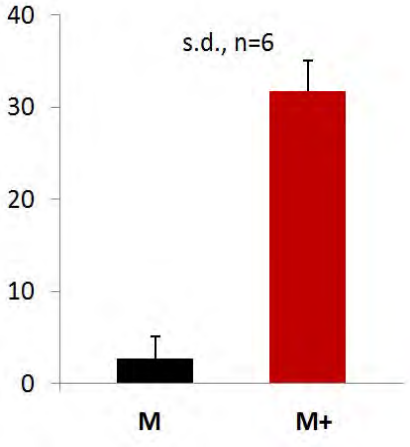


3D reconstruction of different types of synapses.

Research

Following the discovery of some specific factors vital to promoting the formation of giant synapses, a type of media supplement was successfully developed to cultivate large synapses with morphologically and physiologically similar properties to those of calyx of Held. The cultured synapse has a volume ratio 2000 times the size of a normal synapse, making it possible for scientists to conduct studies using high-resolution imaging as well as oversee long-term experiments of up to about 30 days which allow them to manipulate and record the effects of gene expression in neurons. What's more, drug screening through in-vitro testing can be efficiently managed. These potential undertakings provide new possibilities for specific research which aims to elucidate the function of synapses. With the technology to cultivate giant synapses, mechanisms of synaptic malfunction can be investigated and the development of new therapeutic agents for some neurological diseases can be expected to accelerate.

(Published in "Journal of Neuroscience")



Assessment of synaptogenic effect of standard culture medium without (M) and with (M+) the medium supplement of this technology. Vertical scale is number of giant synapses per 35 mm dish.

Keywords

Neuron･Synapse･Neural circuit, Neural information processing, Neurodegenerative disease, Electrophysiological screening

Applications/Future development

- Construction of a synapse model for identifying neural signaling pathways
- Identification of novel neural drug targets for neurological conditions, including Alzheimer's and Parkinson's diseases

Opportunity for joint research and technology transfer

- Reagent manufactures (cell culture technology) : create in vivo-like environment on a plate to culture giant synapses, including those from the central nervous system, the auditory and visual system, and the neuromuscular junction.
- Contract research companies in biopharmaceutical R&D : provide accessible synapses in-vitro for the development of new treatments for neurological diseases including Parkinson's, Alzheimer's, and ADHD diseases

Patent protection

PCT/JP2012/002129 "Neuronal culture medium and method for producing in vivo-like and enhanced synaptogenesis neuron model" (JP : Patent 2014-547209 US : 14/388,340 EP : 12872506.6)

Introduction of the research unit

Cellular and Molecular Synaptic Function Unit

Unit leader : Tomoyuki Takahashi Distinguished Professor (Fellow)

The Cellular and Molecular Synaptic Function Unit strives to understand the mechanisms that regulate neurotransmitter release at synapses by studying the calyx of Held, a synapse large enough to enable simultaneous measurements od presynaptic and postsynaptic electrical signals. Insights into synaptic transmission should lead to a better understanding of neuronal communication.

<Related research unit>

Elucidation of the mechanism for synaptic vesicle transportation within the presynaptic terminal

Impairment in the release of neurotransmitters is known to cause certain neurological diseases. Neurotransmitters carried within synaptic vesicles may fail to reach their intended targets along the passage. By tracking the trajectory of vesicle movement using giant synapses, scientists have noted that the movement of a vesicle within the presynaptic terminal is not randomized by simple diffusion as thought before, but rather active towards its intended target and has been found to have mobility in its movement. Further comparison experiments with smaller synapses have revealed that the movement of vesicles varies with size and type of synapses as well as with the molecules that form the vesicles. (Published in "eLife")

Elucidation of the mechanism responsible for the onset of Parkinson's disease

Research has found that excessive expression of the protein "alpha-synuclein" in neurons is associated with the development of Parkinson's disease, a neurodegenerative disease. Experiments using giant synapses have revealed a mechanism which results in toxicity due to excessive expression of alpha synuclein, causing impairment of the sustained maintenance of neurotransmission. (Published in the online version of "The Journal of Neuroscience" published by the North American Neuroscience Society)

Research unit website : https://groups.oist.jp/cmsfu

Mechanism of Differentiation of Rogue Th17 Cells Causing Autoimmune Disease

Discovery of new molecular mechanisms leading to the development of breakthrough therapies for autoimmune diseases

Research background

The self-defense mechanism to protect the body from invasion of pathogens such as bacteria and viruses is called “immunity”. When the immune system stops functioning normally, its biogenic substances and cells will be recognized as "foreign bodies" and will be attacked, and the symptoms of autoimmune diseases, such as rheumatoid arthritis, ulcerative colitis and multiple sclerosis, will appear. These diseases are increasing especially in advanced countries, and it is supposed that there are 700,000-800,000 patients of rheumatoid arthritis also in Japan. Many autoimmune diseases are designated intractable diseases selected by Japanese government, and development of the therapeutic methods have been an important issue.

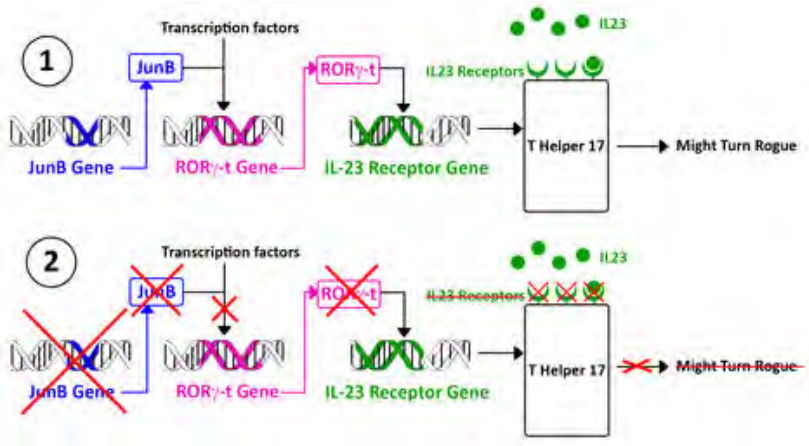
Until now, it is already clear that “Th17 cell” a type of T Helper cell (lymphocyte) which is an immune cell, is closely involved in the onset of autoimmune diseases. However, there are healthy and rogue ones in Th17 cells, and Th17 cells help maintain the normal function of the intestine, while they differentiate into rogue and have a very high ability to induce inflammation. Therefore, the therapy development for the autoimmune disease targeting only Th17 rogue cells, rather than healthy Th17 cells, is underway around the world.

Research

The differentiation to Th17 cells from T Helper 17 cells (naive T cells) produced in the thymus is induced by two or more cytokines (TGF-beta, IL-23, etc.). In particular, it is known that IL-23 is involved in the differentiation of naive T cells to rogue Th17 cells and induces autoimmune diseases by differentiating healthy Th17 cells into rogue cells. However, it was not clear what kind of molecular mechanism promotes the differentiation of rogue Th17 cells by IL-23.

In OIST, 283 transcription factor proteins expressed in Th17 cells was investigated, and it was shown clearly that the transcription factor "JunB" is necessary for differentiation inducing of rogue Th17 cells by IL-23. On the other hand, in mice experiments, it was also found that JunB is not required for differentiation of healthy Th17 cells.

This suggests that JunB may be a therapeutic target for new autoimmune diseases with minimal side effects that aim only at toxic Th17 cells and do not affect healthy Th17 cells. Regarding autoimmune diseases, the current central therapy is to suppress the whole immune system, but with this therapy there is a problem of reducing the ability of the patient's body to fight the disease. This research result will bring a new way to the present situation. (Published in a English science journal "Nature Communications")



1) The normal process in which JunB can activate the Interleukin 23 (IL23) receptor gene to make the T Helper 17 cell sensitive to Interleukin 23. This potentially lead to the T Helper 17 cell to turn toxic. 2) Knocking down JunB prevents the production of Interleukin-23 receptors, and the T-Helper 17 cell cannot turn rogue any longer, but is still able to fight infections.

Keywords

Autoimmune diseases, Immunology, Molecular biology, Cell biology

Applications/Future development

- Elucidation of the transcription control mechanism by JunB in Th17 cell
- Elucidation of JunB's involvement with diverse functions of Th17 cells

Opportunity for joint research and technology transfer

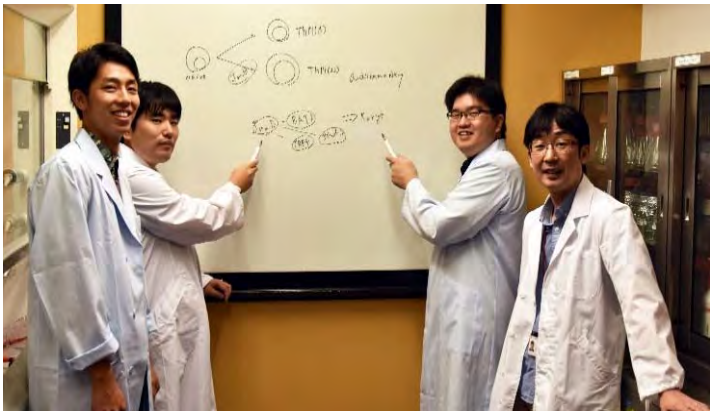
- Joint research with pharmaceutical companies: identify the drugs that control the activity of JunB

Introduction of the research unit

Immune Signal Unit

Unit leader : Hiroki Ishikawa Assistant Professor

All animals and plants have an innate, or non-specific, immune system to fight infection and disease. Unlike innate immune system remember pathogens they have encountered. The immune Signal Unit studies how cells in the adaptive immune system and form memories of pathogens, with the aim to design more and better vaccines.



<Related research theme>

Elucidation of molecular mechanism of innate immune system

All animals and plants have some form of non-specific innate immune system, that is an organism's first and immediate weapon against infection or disease. This system is considered evolutionarily older than the adaptive immune system, a more specialized defense that researchers believe evolved in the first jawed vertebrates over 450 million years ago. The innate system always responds to pathogens first and this subsequently activates the adaptive system. Only working as a pair can they defend the body successfully.

"STING (stimulator of interferon genes)" is an important gene that controls the response of immune cells, and in knockout mice lacking STING, the entire innate immune system cannot defend the mice themselves against these pathogens, leaving them lethally susceptible to even the weakest infections.

Research unit website : https://groups.oist.jp/isu

Mechanism of Post-transcriptional Regulation of Fat-burning Gene (Ucp1)

Elucidation of a fat-burning promotion mechanism by latest gene research

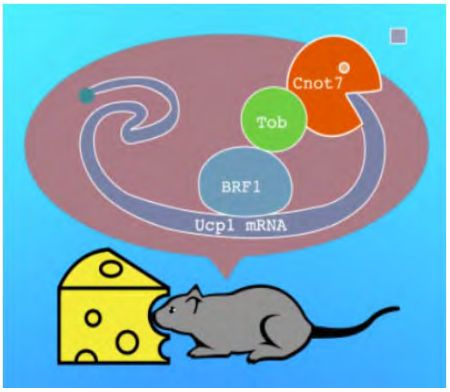
Research background

Obesity is a risk factor for lifestyle-related diseases such as diabetes, hypertension, heart disease, cancer, and has become a global problem. However, no safe and effective medical treatment is available so far, and countermeasures are limited to individual efforts such as healthy lifestyle, exercise and dietary restrictions.

Up to 100 kinds of genes related to body shape or metabolism have been identified so far, and uncoupling protein 1 (UCP 1) is synthesized by one such gene. UCP 1 has the function of generating heat from stored fat as a raw material in mitochondria of brown fat cells. It is already known that UCP1 decreases with obesity, its decrease causes less heat generation that proceeds fat accumulation, and obesity progresses further. However, the detailed mechanism at the genetic level of the increase and decrease of UCP1 was not known.

Research

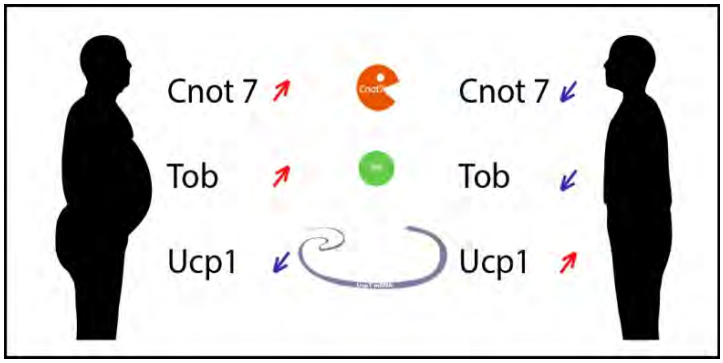
Since the genetic information of DNA is copied to a messenger RNA (mRNA) (transcription) and protein is synthesized (translation) based on mRNA information, mRNA is an important substance which controls the gene expression amount. In OIST, the experiments using mouse fat tissues revealed that the proteins called Cnot7 and Tob bind to Ucp1 mRNA and degrade it, then expression of Ucp1 gene is suppressed, and fat burning is inhibited as a result.



Decomposition of Ucp1 mRNA by Cnot7 and Tob :
The degradation of UCP1 mRNA in fat cells is mediated by Cnot7 and Tob.

While the expression amount of genes synthesizing Cnot7 and Tob increases in fat tissues of obese mice, the expression amount of Ucp1 gene in fat tissues of mice deficient of these genes increases remarkably, and even when eating the same amount of high calorie diet compared with normal mice, obesity tended to be less likely to occur.

If identification of compounds that inhibit the function of Cnot7 and Tob and suppress Ucp1 mRNA degradation proceed, it may lead to discovery of anti-obesity drugs. Moreover, it can be expected to be applied to livestock industry etc. by promoting Ucp1 mRNA degradation and increasing the weight of livestock. (Posted on Cell Press's open access electronic journal "Cell Report")



The mechanism of obesity at the gene level:

Obesity correlates with the increase of Cnot7 and Tob, which reduce Ucp1. This suggests that lean individuals have less Tob, Cnot7, and higher concentrations of Ucp1.

Keywords

DNA, mRNA degradation, Gene, Obesity, Deadenylase enzyme

Applications/Future development

- Identification of the compound promoting fat burning

Opportunity for joint research and technology transfer

- Contract research companies in biopharmaceutical R&D : required material transference agreement (MTA) on candidate inhibitory compounds
- Pharmaceutical company: conduct joint development of anti-obesity drugs

Introduction of the research unit

Cell Signal Unit

Unit leader : Tadashi Yamamoto Professor

Using a mouse model, the Cell Signal Unit explores the cause of various diseases that include cancer, neuronal disorders, immunological diseases, and diabetes/obesity at the molecular level. Practically, the Unit studies biochemical reactions that cells use to respond to environmental cues with special emphasis on mechanisms by which unneeded RNA copies are destroyed to silence gene expression.

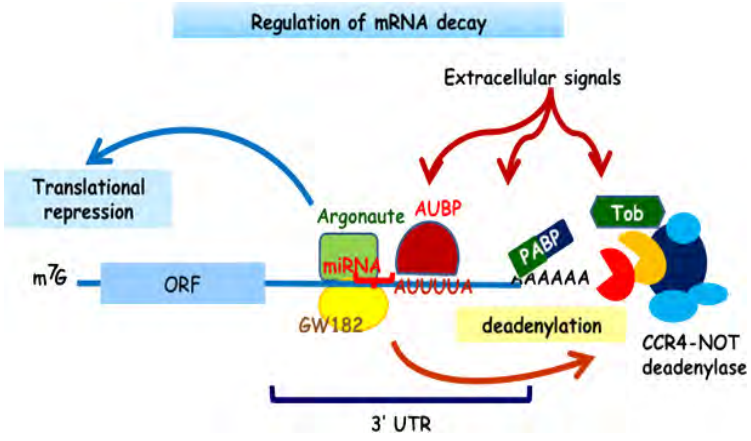
<Related research theme>

Revealing the physiological role of CCR4-NOT complex

The CCR4-NOT complex composed of at least 11 subunits including Cnot7 plays an important role in deadenylation (mRNA degradation) of mRNA as a transcriptional regulatory factor. By creating and analyzing knockout mice lacking the genes of each subunit of the CCR4 - NOT complex, it has been elucidated that the CCR4 - NOT complex is involved in a wide range of biological phenomena such as energy metabolism and spermatogenesis.

Elucidation of the molecule mechanism of programmed cell death

Planned suicide of cells is called "programmed cell death (PCD)", which is an important mechanism in maintaining organismal development and tissue homeostasis, such as eliminating old cells that are incapable of maintenance or dividing, or potentially harmful cells. On the other hand, neurodegeneration results from too many cells being culled by PCD and leads to incurable diseases such as Huntington's, Alzheimer's, and Parkinson's. It became clear that deficiency of Cnot3 which is a subunit of a CCR4-NOT complex leads to necroptosis, which is a kind of PCD, and some human inflammatory diseases such as rheumatoid arthritis and psoriasis have been shown to be due to dysregulation of the CCR4-NOT complex.



Research unit website : https://groups.oist.jp/csu