TMDU Research Activities 2021-2022

TMDU - Committed to Pioneering Medical Research

TOKYO MEDICAL AND DENTAL UNIVERSITY

Research Activities 2021-2022

TMDU - Committed to Pioneering Medical Research

Contents

TOKYO - The past and present

1800s

This landscape shows a view of Ochanomizu, where TMDU is located today. The buildings on the right-hand side, Yushima Seido and Shoheizaka School, were the center of scholarship since the 17th century during the Edo Period in Japan. Mt. Fuji can be seen in the far distance.
View of the Eastern Capital, Edo-Ochanomizu (woodblock by Shotei Hokuju)

1930s

This photo depicts the Tokyo National School of Dentistry No. 1 Hospital, in Yushima, circa 1930.

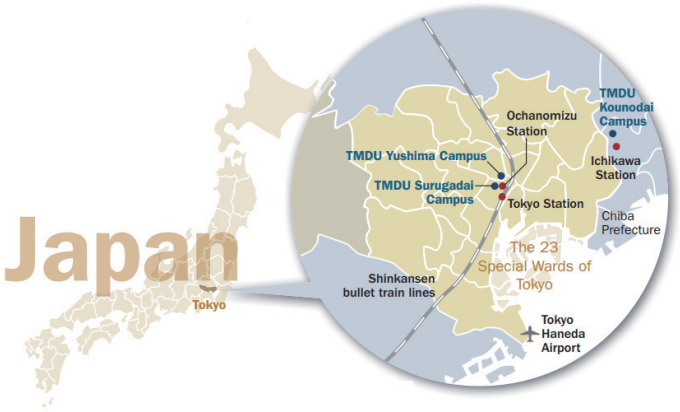
History and Location of TMDU

Standing at the sacred birthplace of scholarship in Japan

Tokyo Medical and Dental University (TMDU) was established as a national medical and dental educational institution on October 12, 1928. Currently, TMDU is located in the Yushima / Shoheizaka area of Tokyo, which is considered sacred ground for scholarship and learning in Japan. As Japan's only comprehensive medical university and graduate school, TMDU has provided advanced medical treatment through a fusion of the medical and dental fields. It has worked to cultivate professionals with knowledge and humanity, thereby contributing to human health and the well-being of society.

The "knowledge" referred to here includes learning, technology, and self-identity, while "humanity" means culture, sensitivity, and the ability to communicate openly and accept diversity.

We believe that the fusion of these elements paves the way to becoming a true "professional."



2022

Today, TMDU is still located in Ochanomizu/ Yushima district where its predecessor, the Tokyo National School of Dentistry, had moved in 1930, two years after its founding.

TMDU has become known as one of the most excellent research universities in Japan.

TThis monument at TMDU's Ochanomizu Gate commemorates the Birthplace of Modern Education. It honors Japan's modern education system, which was developed in this neighborhood after the Meiji Restoration, and marks TMDU's emergence at this site in 1930 as the world's first comprehensive medical-dental graduate school.

Yasunari Miyazaki

Paper Information

Alternative gene expression by TOLLIP variant is associated with lung function in chronic hypersensitivity pneumonitis

Shinji Katayanagi, Yasuhiro Setoguchi, Sayoko Kitagawa, Tsukasa Okamoto and Yasunari Miyazaki

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/miyazaki/

Genetic variant linked to prognosis of chronic hypersensitivity pneumonitis

by Yasunari Miyazaki

Chronic hypersensitivity pneumonitis (CHP) is a long-term lung condition where the interstitial tissue surrounding the alveoli (air sacs) of the lungs becomes inflamed and develops “fibrosis”, or scar tissue. It occurs when susceptible individuals inhale allergens. The full process and circumstances underlying the development of the condition are currently unknown, but it is thought to have a strong genetic component.

Now, in a study published in the journal Chest, a team at Tokyo Medical and Dental University (TMDU) have discovered a link between the condition and a variant in a gene known as TOLLIP. This gene encodes TOLLIP (Toll-interacting protein), which acts as a negative regulator of innate immunity. The innate immune pathway is the body’s first defense against pathogens and is also involved in the response to allergens. The researchers took a cohort of patients with CHP and looked at the genetic variation in single-nucleotide polymorphisms (SNPs), places in the genome where variation occurs at a single position in the DNA sequence.

“We found that one genotype of an SNP known as rs5743899 was associated with a higher degree of immune activation and an increase in the cellular signaling responses leading to fibrosis. This causes a progressive reduction in lung function in patients with CHP”, says lead author Shinji Katayanagi. The patients with the “GG” genotype of this SNP showed more severe disease progression and a steeper decline in the forced vital capacity (FVC), a test of lung function that measures the maximum amount of air able to be expelled from the lungs after a maximum inhalation.

The team observed that patients with the GG genotype had lower levels of TOLLIP in the lungs compared with patients with the other genotypes. They also showed increased fibrotic activity in the lungs in these patients, as they detected both a higher level of the phosphorylated form of a protein called Smad2, a major component of the fibrotic pathway, and increased levels of periostin, a marker of fibrosis. “It seems that the functional changes caused by the TOLLIP variant are associated with rapid FVC decline in CHP due to the dysregulation of fibrosis-related signaling pathways such as Smad/TGF-β and NF-κB signaling”, says senior author Yasunari Miyazaki.

The identification of the association between this genotype of the rs5743899 SNP and a poorer prognosis of CHP could prove invaluable for assessing patients at their initial diagnosis, and for guiding their treatment.

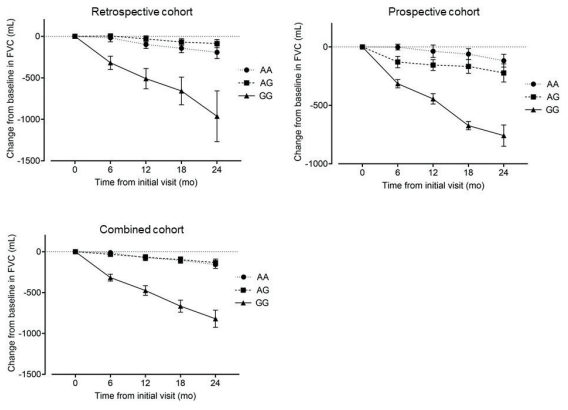


Figure 1. Mean observed changes from baseline in forced vital capacity (FVC) over time in chronic hypersensitivity pneumonitis subgroups stratified by genotype at rs5743899.

Super-Enhancers: The Villain Fueling Certain Cancers

by Johji Inazawa and Yasuyuki Gen

In a study published in CANCER RESEARCH , a team led by researchers at Tokyo Medical and Dental University (TMDU) identified a specific small RNA molecule, called a microRNA (miRNA or miR), that has the potential to be used as an anti-cancer therapeutic. The new research indicates that the molecule, called *miR-766-5p*, can significantly reduce levels of the oncogene *MYC*—a specific gene that is expressed at high levels in tumor cells and helps fuel cancer growth and progression.

At its most basic level, cancer is driven by abnormal and uncontrolled gene expression. Numerous different molecular mechanisms contribute to the activation and overexpression of oncogenes in cancer. MiRNAs work as negative regulators of gene expression. This means that they can directly bind and interact with certain gene messages and block them from being translated into a protein. Therefore, any molecular pathway controlled by that specific protein is also affected by this miRNA-mediated regulation. In a previous study, the TMDU group used cell culture experiments to demonstrate that treating cancer cells with *miR-766-5p* resulted in lower MYC expression and inhibited cancer cell growth rates. Following these intriguing findings, the group aimed to determine the specific mechanism behind these results.

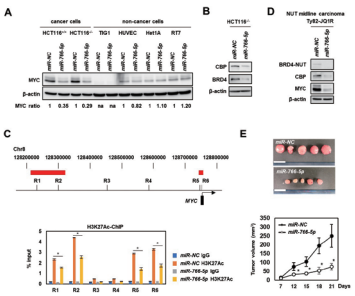


Figure 1. Tumor suppressive functions of *miR-766-5p*

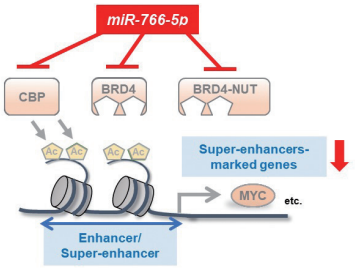
"*MYC* is a critical oncogene in many tumor types," says lead author of the study Yasuyuki Gen. "It can promote cancer cell proliferation, can suppress the body' s immune response to fighting the cancer, and can generally be the main driver of tumor progression in many patients."

The researchers found that *miR-766-5p* could directly target and reduce expression of two proteins called CBP and BRD4. CBP can induce a molecular change called acetylation that causes DNA to become more "open", which allows genes present in that area to be more easily expressed. BRD4 can then be recruited to these sites and help promote transcription of these gene messages.

"Areas of DNA with high activity of proteins like CBP and BRD4 are known as super-enhancers," explains Johji Inazawa, senior author. "Many cancer cells develop super-enhancers near oncogenes, like *MYC*, that drive increased oncogene expression and therefore promote cancer."

The team then experimentally treated cells with a synthetic version of *miR-766-5p*, finding that the resulting suppression of CBP and BRD4 caused decreased MYC levels in cancer cells, but not in normal cells. Additionally, tumors that were engrafted in lab mice showed significantly suppressed growth when treated with *miR-766-5p* compared with a control miRNA.

"Our findings suggest that *miR-766-5p*-mediated control of CBP and BRD4 blocks formation of the super-enhancers that contribute to MYC overexpression in cancer cells," explains Gen.

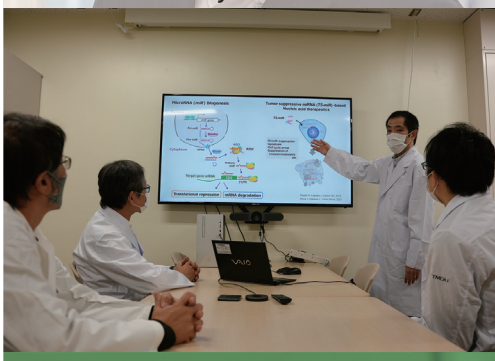


In recent years, efforts have been made to develop specific miRNAs into targeted therapies for various cancers. This study provides considerable evidence that *miR-766-5p* could be used to fight MYC-driven cancers by targeting super-enhancers.

Figure 2. Diagram summarizing the mechanism by which *miR-766-5p* reduces the activity of super-enhancers in cancer cells.

Johji Inazawa

Yasuyuki Gen



Paper Information

miR-766-5p targets super-enhancers by downregulating CBP and BRD4

Yasuyuki Gen, Tomoki Muramatsu, Jun Inoue and Johji Inazawa

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/inazawa/

Nobuhiko Yui

Bringing cells closer to form new tissues

by Nobuhiko Yui

The field of tissue engineering is constantly exploring the possibility of using different properties of various biomaterials to achieve tissue regeneration. However, a key factor in creating effective tissues that can ameliorate and act as physical barriers is the strength of cell-cell adhesion.

In a study published as an editor's-choice HOT article in Biomaterials Science, researchers from Tokyo Medical and Dental University (TMDU) have shown that culturing epithelial cells on a biomaterial surface using polyrotaxane can ameliorate cell-cell adhesion to repair the damaged tissues for regeneration.

Polyrotaxanes are supramolecular polymers that, at a molecular scale, resemble a beaded chain. Polyrotaxanes can exhibit molecular mobility, which is the movement of certain molecules in relation to others, such as sliding or rotation of ring-shaped molecules along an axle molecule. When cells are cultured on this biomaterial the molecular mobility of polyrotaxanes can affect cell–cell adhesion through one of its main players, a protein called yes-associated protein (YAP). "We knew that cell–cell adhesion is closely related to the subcellular localization of YAP," says Ryo Mikami, one of the lead authors of the study. "For instance, increasing cytoplasmic YAP localization promotes the organization of tight junctions, which are specialized connections between two adjacent cells. Therefore, we hypothesized that cell–cell adhesion of epithelial cells could be enhanced by YAP being affected through the molecular mobility of polyrotaxane surfaces."

The researchers used cells derived from mouse lung as a model of epithelial cells. They cultured them on the polyrotaxane surfaces with different mobility and investigated their proliferation and morphology. Using fluorescent staining, they visualized the subcellular localization of YAP to assess whether it was in the cytoplasm or in the nucleus. Polyrotaxane surfaces with high mobility led to cytoplasmic localization of YAP, while those with low mobility induced nuclear YAP localization. These results suggest that polyrotaxane surfaces with higher mobility induce cytoplasmic YAP localization, leading to stronger cell–cell adhesion due to an increased number of tight junctions. "In the future, polyrotaxane-based biomaterials with tuned molecular mobility represent promising implantable biomaterials for reinforcing the physical barrier function of epithelial tissues and inhibiting the progression of inflammation", says Nobuhiko Yui, senior author on the study. For example, a potential application could be in clinical dentistry, where damage to tight junctionsdue to bacterial infections is known to cause periodontal disease, including gingivitis and periodontitis. In this context, biomaterials that ameliorte cell–cell adhesion are expected to not only support the reconstruction of biological tissues but also to heal and repair the damaged tissues by reducing inflammation restoring the physical barrier to microorganisms.

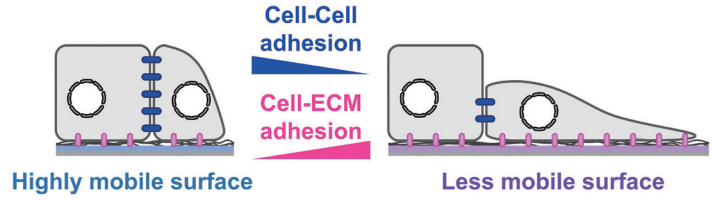

Figure: Relationship between cell-cell adhesion and cell-extracellular matrix (ECM) adhesion in epithelial cells on polyrotaxane surfaces with different molecular mobility.

Paper Information

Improved Epithelial Cell-Cell Adhesion Using Molecular Mobility of Supramolecular Surfaces

Ryo Mikami, Yoshinori Arisaka, Masahiro Hakariya, Takanori Iwata and Nobuhiko Yui

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https://www.tmd.ac.jp/english/research_activities/Vol-7/yui/

Lighting the LAMP to Reveal Mystery of Lysosomes

by Miki Hara-Yokoyama

A cell is composed of numerous organelles, each with a unique role that helps contribute to its overall functionality. The lysosome is an organelle that contains digestive enzymes and functions as a molecular garbage disposal and recycling center. Since the role of lysosome is crucial to maintain the cellular homeostasis, the lysosomal dysfunction causes neurodegenerative and metabolic diseases, cancer, as well as lysosomal storage disorders.

In an article published in Autophagy, researchers at Tokyo Medical and Dental University (TMDU) performed a novel type of structural analysis to demonstrate how a certain molecular interaction is crucial for one lysosomal membrane protein to perform effectively.

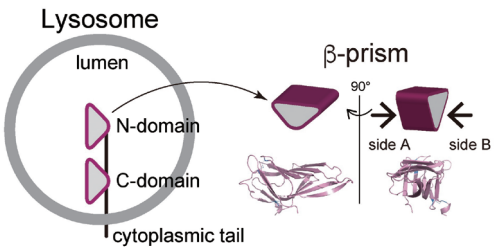

Figure.1 The two-domain architecture of LAMP1 and LAMP2

Domain architecture and orientation of LAMP1 and LAMP2 in the lysosome lumenal membrane(left). Schematic β-prism shapes and the structures of the C-domain of LAMP1(5GV0) are shown in two perpendicular views(right).We defined the surface of the N-terminal(N) side as SideA, and that on the C-terminal(C)side as Side B.

LAMP1 (lysosomal-associated membrane protein 1) and LAMP2 the most abundant protein components of lysosome membranes. Both LAMP1 and LAMP2 are composed of a large lumenal domain, a transmembrane domain, and a short C-terminal cytoplasmic tail (Fig. 1). The lumenal domains of LAMPs are composed of two domains (N-domain and C-domain, which are membrane-distal and -proximal, respectively). Each domain has the unique β-prims fold structure (a triangular prism). On the other hand, genetic experiments have shown that mice embryos without both LAMP-1 and 2 die a little more than two weeks after fertilization. Mice without LAMP-1 are born and can thrive, while those without LAMP-2 often die a few weeks after birth, suggesting that LAMP-2 is more important for lysosome activity. The research of the TMDU group further investigates this protein's biological role.

"Mice lacking LAMP-2 also display issues with autophagy progression," says one of the lead authors of the study Kazue Terasawa. "Expanding our knowledge of how LAMP-2 interacts and operates at the molecular level will ultimately help us understand autophagy better."

The researchers demonstrated LAMP2 molecules assemble by facing each other with one side the β-prism (defined as side A, as shown in Fig. 1) of the C-domain (Fig. 2). The N-domain truncation permitted the nonspecific involvement of both sides of the β-prims (side A and side B). In combination with some biochemical studies, "we believe that the homophilic interaction we demonstrated is crucial for function of LAMP-2, via ensuring a proper arrangement of the cytoplasmic tails, which is crucial for the function of LAMP2, on the lysosome membrane," says Miki Hara-Yokoyama, senior author.

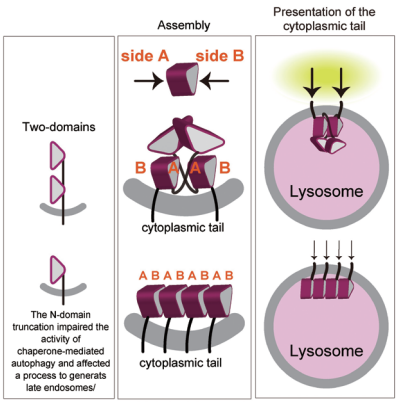

Figure.2 Effect of the truncation of one β-prism domain

Schematic representation of the interaction of the full-length LAMP2A molecules and the N-domain truncated LAMP2A molecules on the lumenal membrane

Paper Information

Direct homophilic interaction of LAMP2A with the two-domain architecture revealed by site-directed photo-crosslinks and steric hindrances in mammalian cells

Kazue Terasawa, Yuji Kato, Yuta Ikami, Kensaku Sakamoto, Kazumasa Ohtake, Seisuke Kusano, Yuri Tomabechi, Mutsuko Kukimoto-Niino, Mikako Shirouzu, Jun-Lin Guan, Toshihide Kobayashi, Takanori Iwata, Tetsuro Watabe, Shigeyuki Yokoyama and Miki Hara-Yokoyama

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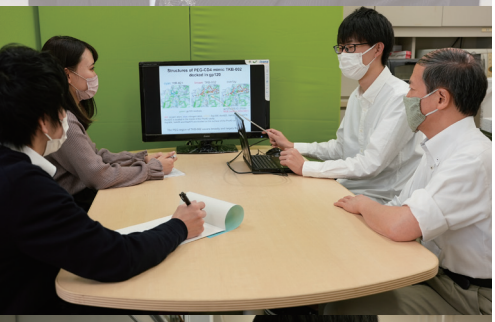
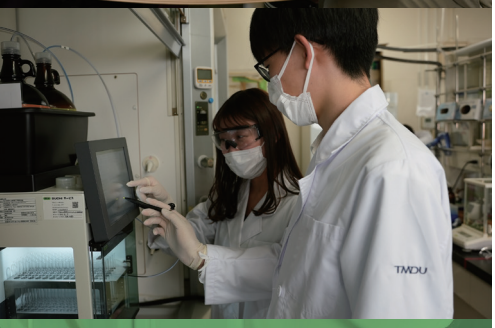
Hirokazu Tamamura





HIV has been Had

by Hirokazu Tamamura

A team of scientists led by the Institute of Biomaterials and Bioengineering at Tokyo Medical and Dental University (TMDU) have created novel molecules that prevent human immunodeficiency virus (HIV) particles from attacking immune cells. This is accomplished by injecting compounds mimicking the protein the virus usually uses to enter the cells. This work may lead to new treatments for HIV that may be more effective at stopping the proliferation of the virus with fewer side effects.

HIV is a very dangerous pathogen because it attacks the very immune cells, including T helper cells, that are needed for the body to fight back. An HIV particle first gains entrance to a T helper cell by attaching to a CD4 protein on its surface. Once inside, the reproduction machinery of the T helper cell is hijacked to make copies of HIV, ultimately killing the host cell. Many treatments, such as antiretroviral drugs, attempt to block this reproduction process, but finding a way to prevent the HIV from attaching in the first place would be a better approach.

Now, a team of researchers led by TMDU created a new family of molecules that act as decoy CD4 proteins. The HIV particles preferentially attach with the fake molecules, instead of those at the surface of a cell. The scientists found that adding a polyethylene glycol (PEG) improved the pharmacokinetics. “Hybrid molecules that mimic CD4 and also have a PEG unit attached with an uncleavable linker showed better anti-HIV activity with lower cytotoxicity,” first author Takuya Kobayakawa says.

Computer simulations run by the team supported the hypothesis that the hybrid molecule works better because it can interact electrostatically with a carboxylate group on the virus. In tests with a rhesus macaque, the hybrid molecule remained in the system longer compared with the parent compound. “These CD4 mimics have strong synergistic interactions with neutralizing antibodies for fighting HIV,” senior author Hirokazu Tamamura says. New combined treatment protocols may be developed to help take advantage of the new molecules.

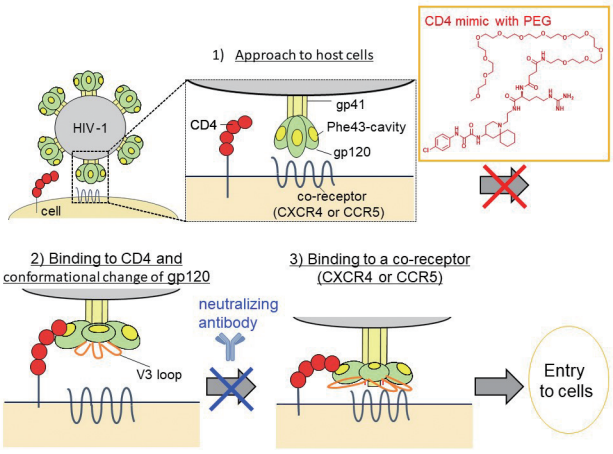


Figure: Mechanism of the HIV entry to cells and its block by a CD4 mimic bearing PEG and a neutralizing antibody.

The V3 loop of an HIV envelope protein gp120 is exposed by the conformational change of 2). A CD4 mimic with PEG blocks the progress from 1) to 2) (the first arrow), and a neutralizing antibody blocks the progress from 2) to 3) (the second arrow). Without these drugs, HIV enters cells.

Paper Information

Hybrids of Small-Molecule CD4 Mimics with Polyethylene Glycol Units as HIV Entry Inhibitors

Takuya Kobayakawa, Kohei Tsuji, Kiju Konno, Ai Himeno, Ami Masuda, Tingting Yang, Kohei Takahashi, Yusuke Ishida, Nami Ohashi, Takeo Kuwata, Kaho Matsumoto, Kazuhisa Yoshimura, Hiromi Sakawaki, Tomoyuki Miura, Shigeyoshi Harada, Shuzo Matsushita and Hirokazu Tamamura

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Using Mice to Open the Way to Prevent Blocked Arteries

by Masayuki Yoshida

It's long been known that a high-fat diet can lead to clogged arteries, but we have only recently begun to learn in detail how the process works. A new study in experimental mice could go a long way to finding treatments to keep arteries open and flowing.

In a study published in JACC Basic To Translational Science, researchers from Tokyo Medical and Dental University (TMDU) have continued their research into how a high-fat diet causes atherosclerosis, the fatty buildup of plaques on the walls of blood vessels that can lead to heart attacks and other vascular disease. Atherosclerosis is not as simple as fats getting stuck in your arteries—it's actually an inflammatory disease driven by the body's own immune response, particularly neutrophils, the white blood cells that attack infections and respond to injuries.

Normally, neutrophils act to regulate the immune response, so that inflammation can resolve the problem allowing the body to return to its normal state. But when a stimulus is persistent, the immune response can shift strategies, becoming a long-term chronic condition.

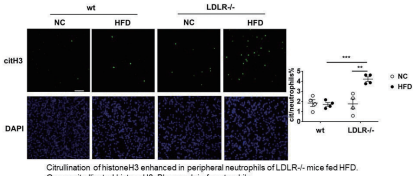
"We applied this theory to what happens in atherosclerosis—in this case, the persistent stimulus is dyslipidemia (unhealthy levels of fats and cholesterol in the blood)," says lead author of the study Mizuko Osaka. "So detailing the role of neutrophils in acute inflammation can help us understand how it becomes chronic inflammation."

The group compared a group of regular wild-type mice against mice specially bred to genetically lack low-density lipoprotein (LDL) receptors on their cell membranes. This is because mice carry most plasma cholesterol in high-density lipoprotein and overall have far lower cholesterol levels; lacking these receptors means these lab mice metabolize LDL (the "bad" cholesterol) more like humans do. When fed a "humanized" high-fat diet, these mice developed high triglycerides and cholesterol, showed significantly increased levels of neutrophil adhesion to their blood vessel walls, and experienced much more inflammation.

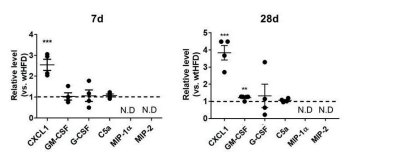
"On the basis of certain biomarkers in the LDLR-null mice, we suspected that neutrophil extracellular traps (NETs, which help trap and eliminate pathogens from the body) could be involved in activating neutrophils," explains Masayuki Yoshida, senior author of the study. "And indeed, we found enhanced citrullination of histone H3, a known marker of NETs, in these mice. Going further, we specifically identified plasma levels of CXCL1 (a peptide that acts to attract immune cells to the site of an injury or infection) to be significantly increased in the LDLR-null mice after 7 days and 28 days of the high-fat diet."

This suggests that CXCL1 is the link between the high-fat diet and citrullination, part of the process of making NETs—and which leads to neutrophils forming plaques on the blood vessel walls when overstimulated in the long term. In fact, blocking the citrullination process led to a reversal of the increased neutrophil adhesion from the high-fat diet.

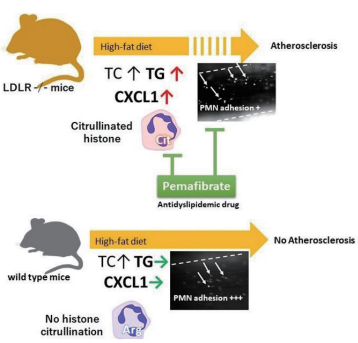
Once we fully understand how a disease happens, it's easier to develop strategies to prevent it. In fact, although mice are metabolically different from people, it's possible that certain medications already being used to control cholesterol could be used to decrease neutrophil adhesion by affecting the pathways identified in this study.



Citrullination of histoneH3 enhanced in peripheral neutrophils of LDLR-/- mice fed HFD.
Green: citrullinated histoneH3, Blue: nuclei of neutrophils.
**P<0.001, **P<0.01.



Cytokines and chemokines in blood of LDLR-/- mice fed HFD relative to wild-type mice fed HFD.
***P<0.001, **P<0.01



Proposed mechanisms of vascular inflammation in LDLR-/- mice fed HFD.

Masayuki Yoshida

Paper Information

Targeting necroptosis in muscle fibers ameliorates inflammatory myopathies

Mizuko Osaka, Michiyo Deushi, SaJiro Aoyama, Dac Tomoko Funakoshi, Akihito Ishigami and Masayuki Yoshida

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Hiroshi Asahara

Yoshiaki Ito

Getting You Moving Again: A Possible New Treatment for Joint Issues

by Hiroshi Asahara and Yoshiaki Ito

Osteoarthritis (OA) is a debilitating joint disease that affects millions of individuals worldwide. Common in the older adult population, OA is associated with loss of cartilage over time. Because joint replacement and treatment of symptoms are the only current options, efforts have been made to identify mechanisms governing OA to find new therapeutic methods. In a recent study published in Nature Communications, a team led by researchers at Tokyo Medical and Dental University (TMDU) identified a small regulatory RNA molecule known as a microRNA (miRNA or miR) that participates in the balance between cartilage production and degeneration. They examined the miR-455 parent molecule that is an unusual one in that it creates two different strands of functional miRNA, 5p and 3p.

Individual miRNAs target a repertoire of genes that contain their specific binding sequence in the gene message. Because of this, they can regulate numerous genes simultaneously. When binding to a gene message, the miRNA can block it from being converted into protein or cause the message to be degraded entirely. A previous study has shown that deleting the miR-455-3p strand in mice causes degeneration of the mouse knee cartilage but the details, and the effect of the 5p strand, remained unclear.

“miR-455 clearly plays a significant role in cartilage regulation, but we do not fully understand the mechanism controlling it,” says lead author of the study Yoshiaki Ito. “Our interest in the topic was aroused by this lack of information and reinforced by the exceptionality of miR-455 in generating two distinct strands of miRNA that both have biological effects.”

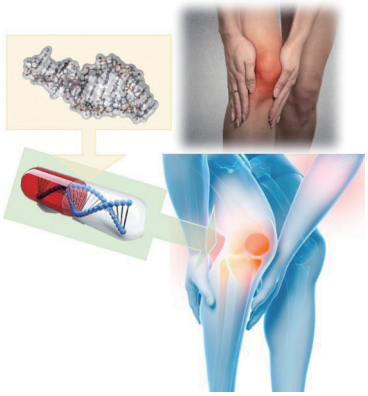
The researchers examined miR-455 levels in human cartilage samples and found that individuals with OA had significantly lower amounts of this miRNA. They then generated miR-455 knockout mice and confirmed OA-like cartilage degeneration in the knee joints once the mice were six months old.

“We became interested in which specific genes were overexpressed in these mice because of the absence of miR-455-mediated regulation,” states Hiroshi Asahara, senior author. “We performed a detailed genetic screening and found that the gene message for a protein called hypoxia-inducible factor-2α (HIF-2α) was amongst the targets of miR-455.”

HIF-2α is a protein that is involved in the breakdown of cartilage. Therefore, the team injected synthetic versions of miR-455-3p and 5p into OA-model mice knee joints and identified inhibited degeneration of the cartilage. HIF-2α expression also significantly decreased following miR-455 treatment.

“Our findings not only help us better understand the biology of cartilage regulation and OA pathogenesis, but also show that miR-455 has the potential to be developed into a novel therapeutic method for treating OA,” explains Ito.

Considerable research is ongoing to utilize miRNAs as targeted therapies for a wide variety of diseases. This study provides strong support for using both strands of miR-455 in such a manner for OA.



Treatment of osteoarthritis by miRNA introduction

Paper Information

Both microRNA-455-5p and -3p repress hypoxia-inducible factor-2α expression and coordinately regulate cartilage homeostasis

Yoshiaki Ito, Tokio Matsuzaki, Fumiaki Ayabe, Sho Mokuda, Ryota Kurimoto, Takahide Matsushima, Yusuke Tabata, Maiko Inotsume, Hiroki Tsutsumi, Lin Liu, Masahiro Shinohara, Yoko Tanaka, Ryo Nakamichi, Keiichiro Nishida, Martin K. Lotz and Hiroshi Asahara

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/asahara/

One protein to rule them all: a central target for treating dementia

by Hitoshi Okazawa, Hikari Tanaka and Hidenori Homma

Dementia has many faces, and because of the wide range of ways in which it can develop and affect patients, it can be very challenging to treat. Now, however, using supercomputer analysis of big data, researchers from Japan were able to predict that a single protein is a key factor in the damage caused by two very common forms of dementia.

In a study published in Communications Biology, researchers from Tokyo Medical and Dental University (TMDU) have revealed that the protein HMGB1 is a key player in both frontotemporal lobar degeneration and Alzheimer disease, two of the most common causes of dementia.

Frontotemporal lobar degeneration can be caused by mutation of a variety of genes, which means that no one treatment will be right for all patients. However, there are some similarities between frontotemporal lobar degeneration and Alzheimer disease, which led the researchers at TMDU to explore whether these two conditions cause damage to the brain in the same way.

“Alzheimer disease pathology and frontotemporal lobar degeneration often coexist in the postmortem brain,” explains lead author of the study Meihua Jin. “Because of this overlap, we wanted to investigate whether the molecular mechanisms of disease were also similar.”

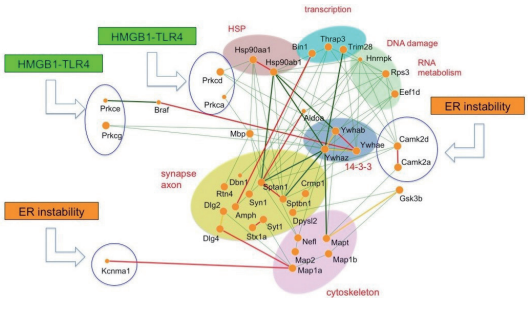
To do this, the researchers used a sophisticated technique called molecular network analysis to take a snapshot of which proteins are expressed, and to what degree, in mice that had been genetically engineered to mimic Alzheimer disease and frontotemporal lobar degeneration. Supercomputer analysis of these protein networks was performed in mice of different ages to capture a dynamic picture of how they changed over time.

“The results were surprisingly clear,” says senior author Hitoshi Okazawa. “We found that the core protein–protein interaction networks in Alzheimer disease and in frontotemporal lobar degeneration were highly similar, sharing almost 50% of core nodes.”

Further analysis of these core protein nodes predicted that signaling through HMGB1, which is a critical factor in Alzheimer disease, also plays a key role in frontotemporal lobar degeneration. Importantly, this result was confirmed by the researchers, who found that treating mice with frontotemporal lobar degeneration with an antibody to HMGB1 improved their long-term memory, short-term memory, and spatial memory.

“Our new method successfully predicted and identified HMGB1 as a key target for treating patients who have dementia due to frontotemporal lobar degeneration, regardless of the genetic basis of the disease,” says Jin.

Given the fact that the mice recovered their memory after several months of treatment with the anti-HMGB1 antibody, it is possible that treatments targeting this protein could actually reverse damage in patients with frontotemporal lobar degeneration. Because similar molecular changes are seen in many different types of dementia, a treatment based on this antibody could be effective in a wide range of patients.



The core molecular network shared by Alzheimer’s disease and frontotemporal lobar degeneration.

Supercomputer-based dynamic molecular network analysis predicted HMGB1-TLR4 induced signal as the most important target of two major neurodegenerative dementias. The prediction was verified by significant phenotypic and pathological improvements of four types of mouse model of frontotemporal lobar degeneration treated by anti-HMGB1 antibody.

Hitoshi Okazawa

Hikari Tanaka

Hidenori Homma

Paper Information

Prediction and verification of the AD-FTLD common pathomechanism based on dynamic molecular network analysis

Meihua Jin, Xiaocen Jin, Hidenori Homma, Kyota Fujita, Hikari Tanaka, Shigeo Murayama, Hiroyasu Akatsu, Kazuhiko Tagawa & Hitoshi Okazawa

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/okazawa/

Itsuki Ajioka

Paper Information

Efficient protein incorporation and release by a jigsaw-shaped self-assembling peptide hydrogel for injured brain regeneration

Atsuya Yaguchi, Mio Oshikawa, Go Watanabe, Hirotsugu Hiramatsu, Noriyuki Uchida, Chikako Hara, Naoko Kaneko, Kazunobu Sawamoto, Takahiro Muraoka and Itsuki Ajioka

Publication: Nature Communications, 2021 Nov 19;12(1):6623.
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Jigsaw-Shaped Peptide Solves Tissue Regeneration Puzzle

by Itsuki Ajioka

Recreating native physiological processes in manmade materials imitating the biological structures involved in wound healing has proved to be a lasting challenge. The main problems are modeling the appropriate functions that prompt cell growth, and oversimplified frameworks that do not reflect the complex network of interactions. Researchers from Japan may have found a solution to this puzzle.

In a study published in Nature Communications, a research team from Tokyo Medical and Dental University (TMDU) has developed a jigsaw-shaped peptide that performs the basic functions of the extracellular matrix (ECM), serving as an artificial ECM for injured tissue regeneration.

The ECM is a network of biomolecules that facilitates the control and coordination of various cellular events, such as adhesion, migration of signaling molecules, and tissue repair. It achieves this through the binding and release of secreted proteins, including growth factors that stimulate cell growth. Although many artificial ECMs have been reported for tissue regeneration, few studies have explored the development of peptide-based ECM mimics that can both incorporate and release secreted proteins, something the research team at TMDU aimed to address.

“Because of their cell-adhesive properties and ability to degrade into chemically defined molecules, self-assembling hydrogels have great potential for use in clinical applications,” says senior author of the study Itsuki Ajioka. “However, it is difficult to combine the ability to both incorporate and release secreted proteins. This is a challenge that we have worked to overcome in the design of our artificial ECM.”

To do this, the researchers designed a jigsaw-shaped self-assembling peptide (JigSAP) that mimics the hydrophobic surface of the dovetail-packing motif of the intracellular protein glycophorin A. JigSAP formed a hydrogel with evenly distributed nanofibers under physiological conditions. The arrangement of these fibers enabled the incorporation and release of vascular endothelial growth factor (VEGF), facilitating regenerative therapeutic effects in a mouse stroke model.

“We rationally designed JigSAP based on structural motifs known to undergo conformational transitions leading to nanofiber formation, and which are found in homodimeric proteins such as glycophorin A,” explains Takahiro Muraoka, senior collaborator from Tokyo University of Agriculture and Technology. “Our characterization of JigSAP in an aqueous environment showed the proper nanofiber distribution in the hydrogel, providing advantageous properties that enabled it to mimic the native ECM functions required for tissue repair.”

Injection of JigSAP with VEGF—which stimulates the growth of new blood vessels—in a mouse stroke model suggested enhanced blood vessel formation. The mice also demonstrated some functional recovery one week after treatment in a test assessing their post-treatment motor skills.

“Because our technology only requires the simple design of various proteins that will be incorporated and released by JigSAP, this method can be broadly applied to targeted drug delivery, tissue reconstruction frameworks, and sustained protein release,” says Ajioka.

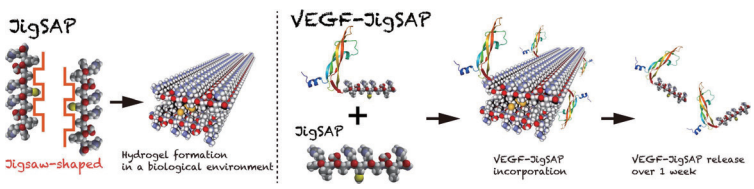


Figure 1: VEGF-JigSAP incorporation into and release from JigSAP hydrogels.

(Left) Jigsaw-shaped hydrophobic surface is the key structure forming nanofiber through β-sheet assembly. (Right) JigSAP-tagged VEGF (VEGF-JigSAP) is efficiently incorporated into and released from JigSAP hydrogels.

The Xa Factor : Pushing Back on Atherosclerosis

by Yasuhiro Maejima

New research by a team led by researchers from Tokyo Medical and Dental University (TMDU) and Tokyo Kyosai Hospital has opened up interesting pathway towards the attenuation of atherosclerosis, potentially giving a brighter future to many millions of sufferers of this often fatal disease.

Atherosclerosis is a chronic disease and is one of the major causes of death worldwide. The current situation as regards treatment for this disease is mainly based on drug therapy, however, the maximum efficacy of these therapies for inhibiting the progression of the disease remains at only 30%–40%.

For some time now there has been increasing evidence that a direct oral factor Xa inhibitor plays a large role in the attenuation of atherosclerosis by the suppression of protease-activated receptor 2, which we shall call PAR2. The problem to this point however, has been in coming to an understanding of the precise mechanism by which the promotion of this atherogenesis occurs.

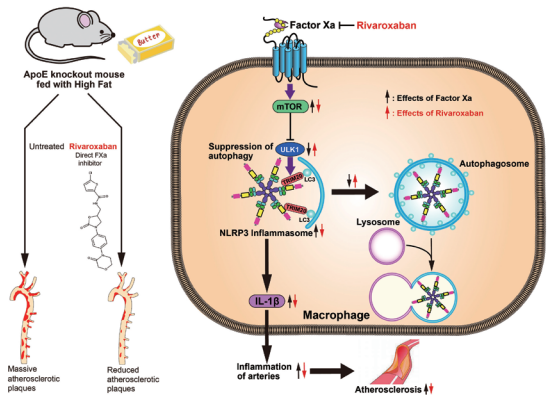
New research by the team now shows that the administration of Rivaroxaban (RIV) in a sufficient dosage can enable the suppression of activity by the factor Xa, and effectively attenuates the atherosclerotic areas in mice. RIV is widely used as a potent anticoagulant agent for preventing cerebral embolism in patients with atrial fibrillation and pulmonary thromboembolism. Studies have demonstrated that it can be greatly effective in reducing the risk of death from coronary artery diseases and that it can also play a significant role in suppressing the progression of atherosclerosis.

In the present study, the focus was on exploring the detailed mechanism whereby RIV attenuates atherosclerosis progression and thus aids in the stability of advanced atherosclerotic lesions in mice.

Several previous preclinical studies had clearly demonstrated that RIV alleviated the progression of atherosclerotic lesions and promoted plaque stability in mice, however, details with regard to the mechanism by which RIV negatively regulates the progression of atherosclerotic lesions and plaque instability still remain unknown.

Observations made in these previous studies led the team to hypothesize that factor Xa-mediated PAR2 activation and thus played a critical role in the progression of atherosclerosis, partially through the downregulation of the autophagy machinery. The new research shows clearly that RIV actually attenuates atherogenesis by inhibiting the factor Xa–PAR2-mediated suppression of macrophage autophagy, and thus abrogates inflammasome activity.

Though previous studies supported the anti-atherosclerotic effects of RIV, there were a lot of divergence in results. It was therefore postulated that the possibly small dosage of RIV administered was not sufficient. To solve this problem, the optimal dosage of RIV to effectively suppress Factor Xa activities in mice was determined.



Visual abstract

Factor Xa–PAR2 signaling promotes atherogenesis by accelerating inflammasome activities through the suppression of macrophage autophagy.

Yasuhiro Maejima

Paper Information

Rivaroxaban, a Direct Oral Factor Xa Inhibitor, Attenuates Atherosclerosis by Alleviating Factor Xa–PAR2-Mediated Autophagy Suppression

Yusuke Ito, Yasuhiro Maejima, Shun Nakagama, Yuka Shiheido-Watanabe, Natsuko Tamura and Tetsuo Sasano

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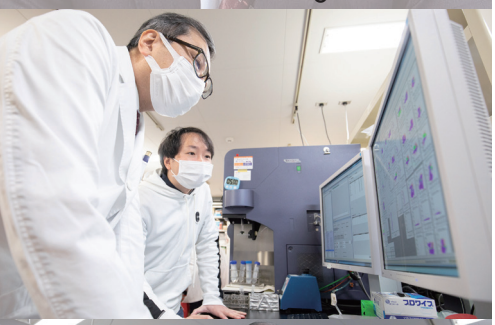
Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/maejima/

Hirokazu Kanegane



Restoring healthy gut bacteria through blood stem cell transplantation

by Hirokazu Kanegane

What does hematopoietic cell transplantation (HCT)—where stem cells that can differentiate into different types of blood cells are taken from a donor individual and transplanted into a recipient individual—have to do with bacteria in the digestive tract, commonly known as the gut microbiota? Although they might seem unrelated, researchers in Japan have recently uncovered a link between the two.

X-linked inhibitor of apoptosis protein (XIAP) deficiency is a rare immunodeficiency disorder that presents in infancy or early childhood. It is often accompanied by severe inflammatory bowel disease (IBD) that doesn't respond well to drugs, but patients can be cured by HCT. In a study published last month in The Journal of Allergy and Clinical Immunology: In Practice, researchers from Tokyo Medical and Dental University (TMDU) have revealed that, as well as improving symptoms, HCT normalizes the gut microbiota of patients with IBD associated with XIAP deficiency.

"We know that the gut microbiota is altered in patients with IBD," says lead author of the study Shintaro Ono. "Because HCT can cure IBD in patients with XIAP deficiency, we wanted to investigate whether the gut microbiota also changed in these patients."

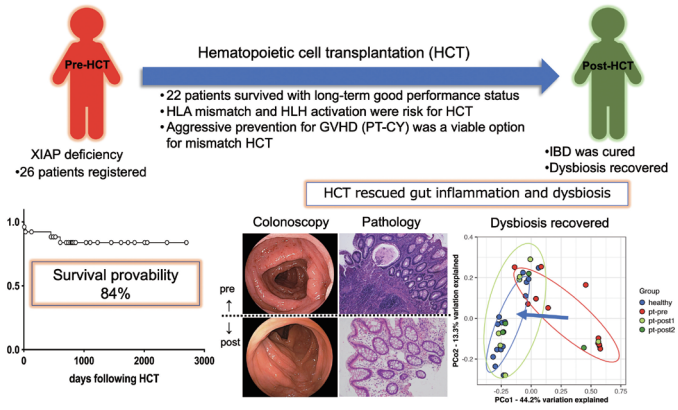
To do this, the researchers examined the gut microbiota of patients before they underwent HCT, and then looked at the microbiota again after HCT. They then compared the makeup and diversity of each patient's microbiota with those of close relatives of the patients, who were used as healthy controls.

"As expected, almost all patients achieved remission from IBD," explains Hirokazu Kanegane, senior author. "We also found that the gut microbiota of patients went from being very different to that of their family members before HCT, to very similar after HCT."

In particular, the gut microbiota of each patient pre- HCT was less diverse and contained fewer bacteria from the Bacteroidetes group, which have been linked to diabetes, obesity, and irritable bowel syndrome. After HCT, both microbiota diversity and makeup were very similar to those of close relatives.

"Our findings indicate that HCT decreases gut inflammation and restores the gut microbiota in patients with XIAP deficiency," says Kanegane.

Thus, although the survival rate for HCT remains at around 85%, it is a very promising treatment for patients with IBD associated with XIAP deficiency. Research aimed at improving the survival rate will provide even greater hope for patients and their families.



Hematopoietic cell transplantation rescues gut inflammation and dysbiosisi in patients with XIAP deficiency

Twenty-six patients with XIAP deficiency underwent HCT by the end of March 2020, and 22 (84.6%) survived. IBD improved remarkably after HCT. Gut microbiota indicated dysbiosis before HCT; however, it was improved to resemble that of the healthy family members after HCT. This study revealed that HCT has a favorable outcome for XIAP deficiency. HCT rescues gut inflammation and dysbiosis in patients with XIAP deficiency.

Paper Information

Hematopoietic cell transplantation rescues inflammatory bowel disease and dysbiosis of gut microbiota in XIAP deficiency

Shintaro Ono, Kozue Takeshita, Yuko Kiridoshi, Motohiro Kato, Takahiro Kamiya, Akihiro Hoshino, Masakatsu Yanagimachi, Katsuhiro Arai, Ichiro Takeuchi, Nariaki Toita, Toshihiko Imamura, Yoji Sasahara, Junichi Sugita, Kazuko Hamamoto, Masanobu Takeuchi, Shoji Saito, Masaei Onuma, Hiroshi Tsujimoto and Hirokazu Kanegane

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/kanegane/

A new polarized fluorescent probe for revealing architectural dynamics of living cells

by Sumio Terada, Keisuke Sato and Ayana Sugizaki

Monitoring alignments of the building blocks of cells is important to understand how the cells are built. By collaborating with imaging scientists at the Marine Biological Laboratory (MBL), researchers from Tokyo Medical and Dental University (TMDU) have developed a new probe which they call POLArIS, allowing real-time imaging of molecular orientations in live cells.

A fluorophore emits polarized light as it glows. The orientation of polarized fluorescence is closely related to the orientation of the fluorophore. If a molecule of interest is rigidly connected with a fluorescent tag such as Green Fluorescent Protein (GFP), the polarized fluorescence from the fluorophore reports the orientation of the molecule.

"In previous approaches for monitoring the orientation of the protein of interest, researchers needed to develop effective constrained GFP tagging methods which might be different for each protein of interest," says one of the lead authors of the study, Ayana Sugizaki. "POLArIS uses an antibody-like binder that is rigidly connected with GFP, allowing both specific and versatile constrained labeling," adds another lead author Keisuke Sato. The team used a commercially available Adhiron molecule (now rebranded as "Affimer") as the binder molecule to link GFP to a target protein, and developed POLArIS by connecting Adhiron and GFP in a rotationally constrained manner (Figure 1). Because an Adhiron molecule that specifically binds to a molecule of interest can be easily selected from a library of molecules through phage display screening, POLArIS can be designed for any biological molecules of interest. POLArIS can be expressed in specific cell types and organelles, and will be useful for studying architectural dynamics of molecular assemblies in a broad range of cell cultures, tissues and whole organisms. "From the point of view of fluorescence polarization imaging, POLArIS has significant advantages because of its genetically encoded nature," says Tomomi Tani, a Senior Researcher at the National Institute of Advanced Industrial Science and Technology (AIST) in Japan, who has joined this project since he was an Associate Scientist at the MBL.

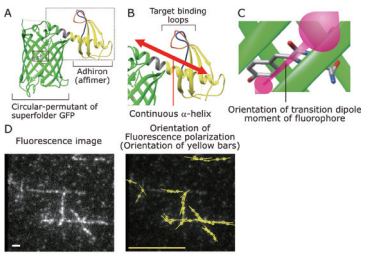


Figure 1

A. Overview of POLArIS structure. Green, Circular-permutant of superfolder GFP (cpGFP); Yellow, Adhiron (Affimer); Gray, α-helical linker connecting cpGFP and Adhiron; Blue and orange, Target binding loops.
B. Enlarged picture of the region of dashed-line box in A. cpGFP and Adhiron are rigidly connected by an α-helical linker.
C. Enlarged picture of the region of solid-line box in A. The orientation of fluorescence polarization of POLArIS reflects the orientation of transition dipole moment of fluorophore indicated by the magenta double-headed arrow.
D. Purified POLArIS protein that specifically binds to F-actin was added to actin filaments reconstituted in vitro, and was observed with fluorescence polarization microscopy. Left: Fluorescence image. White scale bar, 1 μm. Right: Polarization state of fluorescence spots in the left picture was analyzed. Orientation and length of yellow bars indicate the orientation and the strength of fluorescence polarization, respectively. Yellow scale bar, polarization factor=0.5.

By using the probe for actin, the team uncovered transient emergence and dissolution of highly ordered F-actin architecture that they named FLARE structure, in dividing cells of starfish embryo (Figure 2). "We found that the structure extends up to the cell cortex in association with the astral microtubules," says the corresponding author, Sumio Terada, who had frequently visited the MBL from Tokyo, together with his colleagues in TMDU. "The astral microtubules are responsible for connecting the spindle to the cell cortex and orientating it correctly, controlling the plane of cell divisions." The mechanism that determines the cell division plane is a key for controlling many aspects of development, and yet remains a mystery. The discovery of radially aligned actin architectures will shed light on the most fundamental unanswered questions of cell biology.

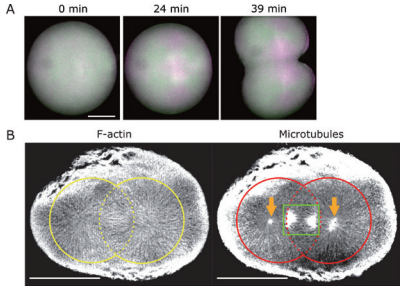
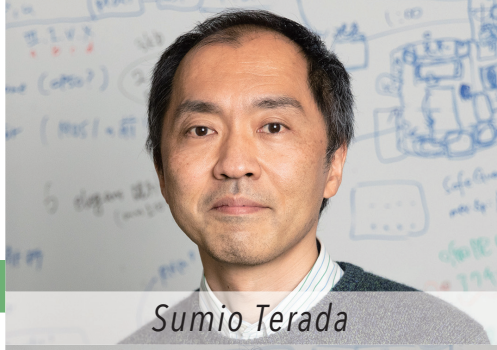
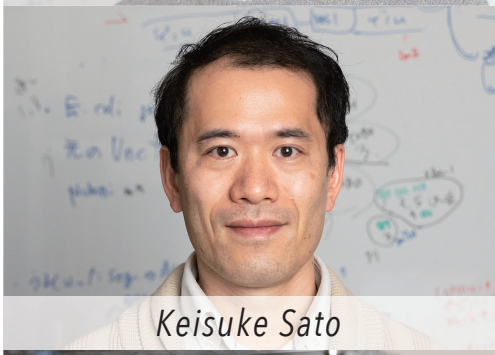


Figure 2

A. Live-cell fluorescence polarization imaging of the first cleavage of a starfish embryo expressing POLArIS that specifically binds to F-actin. Vertical and horizontal actin filaments are shown in magenta and green, respectively. FLARE structures made of radially extending actin filaments were observed as cross-patterns of magenta and green. Scale bar, 50μm.
B. A starfish embryo in the first cleavage was fixed, stained with fluorescent-dye-conjugated phalloidin (stains F-actin) and anti-tubulin antibody (stains microtubules), and observed with confocal laser scanning microscope. Yellow circles, regions of FLARE structure; Red circles, regions of astral microtubules; green box, mitotic spindle; orange arrows, centrosomes. Scale bar, 100 μm.


Sumio Terada


Keisuke Sato


Ayana Sugizaki

Paper Information

POLArIS, a versatile probe for molecular orientation, revealed actin filaments associated with microtubule asters in early embryos

Ayana Sugizaki, Keisuke Sato, Kazuyoshi Chiba, Kenta Saito, Masahiko Kawagishi, Yuri Tomabechi, Shalin B. Mehta, Hirokazu Ishii, Naoki Sakai, Mikako Shirouzu, Tomomi Tani and Sumio Terada

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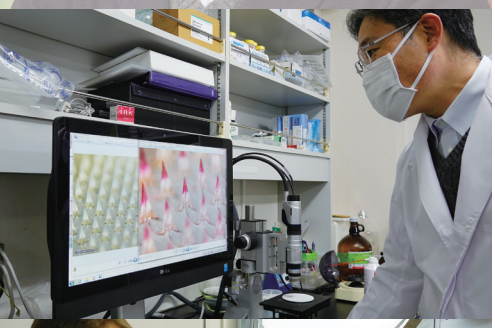
Akira Matsumoto



"On-skin-pancreas" technology for precision medicine in diabetes

by Akira Matsumoto

Insulin therapy remains the most common and effective therapy for diabetes. However, self-administration of insulin often fails to achieve tight glycemic control. The use of an electronics-based artificial pancreas is an increasingly prevalent option in clinical practice.

However, this technology also poses a number of limitations, including high cost, the burdens of frequent sensor calibration and the risk of electronic failures. With these in mind, we have developed an "electronics-free", chemically-controlled system, using a synthetic smart gel technology. A key component here is phenylboronic acid or PBA.

PBA undergoes a glucose-dependent shift in the equilibria between uncharged and anionically charged boronate. The resultant change in counterions' osmotic pressure translates into a change in the hydration state of the gel on its surface.

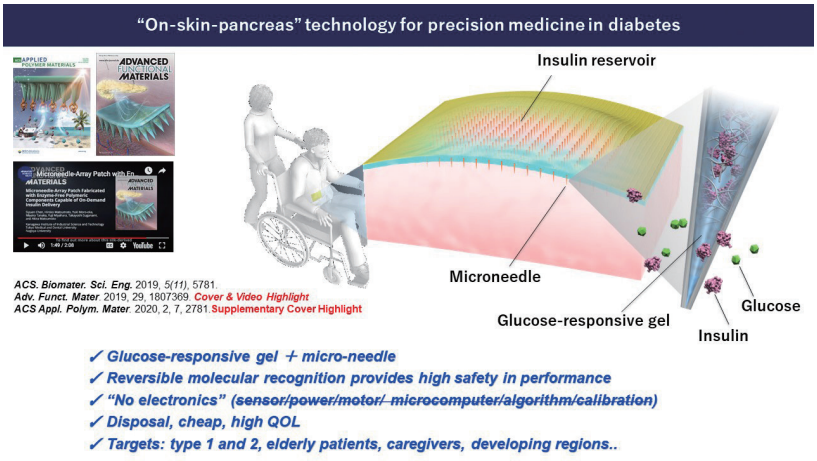
This surface-localized, microscopically dehydrated layer, so-called "skin layer," plays a role for diffusion-control of the gel-loaded insulin, providing a function of artificial pancreas. Using this smart gel technology, we demonstrated a catheter-combined device, scaled suitable for mouse experiments. This device could control the glucose metabolism under both insulin-deficient and insulin-resistant conditions with at least 3-week durability.

Further, a hemodialysis fiber-combined device not only normalized average glucose level of rats, but also markedly ameliorated the glucose fluctuations over timescale of a day without inducing hypoglycemia. This is, indeed, the first successful experiment demonstrating the efficacy for daily glucose fluctuation by an "electronics-free" technology.

Our recent projects focuses on the development of a painless, low-cost and noninvasive microneedle-combined device. We already have developed a prototype device achieving both at once weekly sustained release and acute response on a timescale of tens of seconds in combination. We are currently working on the preclinical study.

Our "electronics-free," smart gel based "on-skin-pancreas" platform should offer a promising candidate to solve a number of unmet medical needs in the treatment of diabetes.

It should also facilitate availability of effective insulin treatment not only to diabetic patients in developing countries but also to those patients who otherwise may not be strongly motivated, such as the elderly, infants, and patients in need of nursing care.



Paper Information

Synthetic "smart gel" provides glucose-responsive insulin delivery in diabetic mice

Akira Matsumoto, Miyako Tanaka, Hiroko Matsumoto, Kozue Ochi, Yuki Moro-Oka, Hirohito Kuwata, Hironori Yamada, Ibuki Shirakawa, Taiki Miyazawa, Hitoshi Ishii, Kazunori Kataoka, Yoshihiro Ogawa, Yuji Miyahara and Takayoshi Suganami

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Link to the Paper

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/matsumoto/

Ventilating the rectum to support respiration

by Takanori Takebe

Oxygen is crucial to many forms of life. Its delivery to the organs and tissues of the body through the process of respiration is vital for most biological processes. Now, researchers at Tokyo Medical and Dental University (TMDU) have shown that oxygen can be delivered through the wall of the intestine to compensate for the reduced availability of oxygen within the body that occurs in lung diseases that cause respiratory failure.

To breathe is to live; for higher animals, respiration involves absorbing oxygen and excreting carbon dioxide at gills or in the lungs. However, some animals have evolved alternative ventilatory mechanisms: loaches, catfish, sea cucumbers and orb-weaving spiders can absorb oxygen through their hindgut to survive in situations where the availability of oxygen is limited. Inspired by these unique adaptations, the team at TMDU devised strategies to allow gas exchange through the lining of the intestine, a process termed as enteral ventilation or EVA.

“The rectum has a mesh of fine blood vessels just beneath the surface of its lining, which means that drugs administered through the anus are readily absorbed into the bloodstream,” first author Ryo Okabe explains. “This made us wonder whether oxygen could also be delivered into the bloodstream in the same way. We used experimental models of respiratory failure in mice, pigs and rats to try out two methods: delivering oxygen into the rectum in gas form, and infusing an oxygen-rich liquid via the same route.”

The researchers prepared the lining of the rectum by rubbing it to cause inflammation and increase blood flow; these changes were confirmed by increased genetic markers and improved the effectiveness of the oxygen delivery. However, because such a preparation requirement would be unacceptable for human patients, the researchers also tried using oxygenated perfluorodecalin (PFD), a liquid that can be safely used in the human body and is already in selective clinical use, and that can carry large amounts of oxygen and carbon dioxide.

The team demonstrated that delivery of oxygen both as a gas and in liquid form was beneficial: oxygenation levels increased and behavior normalized, while survival was prolonged. The team also confirmed the improvement in oxygenation at the cellular level by immunochemical staining. Furthermore, they found that the minimal amount of PFD that was absorbed along with the oxygen caused no harm, and gut bacteria were not disrupted, indicating the safety of these methods in the animal models.

“Patients in respiratory distress can have their oxygen supply supported by this method to reduce the negative effects of oxygen deprivation while the underlying condition is being treated,” foresees Takanori Takebe, corresponding author. “Enteral ventilation showed great promise in our asphyxia-like experimental model. The next steps will be to test safety of the EVA approach with more profound mechanistic understanding by which it works; and to establish effectiveness in humans in a clinical setting.”

Conventional therapeutic respiratory support comprises complex technological protocols such as ventilators and artificial lungs. The current SARS-CoV-2 pandemic has highlighted the high need for development of less invasive alternatives such as EVA for short-term support of respiratory function. These new findings from the researchers at TMDU may pave the way for new ventilation strategies in the future.

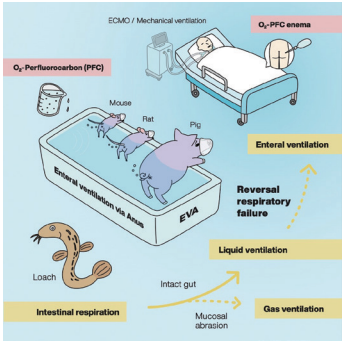

Fig 1. Schematic diagram of EVA method

Based on the fact that loaches have intestinal respiration under hypoxic conditions, the efficacy of the EVA method was examined in mammals such as mice and pigs. The EVA method may be effective for patients with respiratory failure.

Takanori Takebe

Paper Information

Mammalian Enteral Ventilation Ameliorates Respiratory Failure

Ryo Okabe, Toyofumi F.Chen-Yoshikawa, Yosuke Yoneyama, Yuhei Yokoyama, Satona Tanaka, Akihiko Yoshizawa, Wendy L.Thompson, Gokul Kannan, Eiji Kobayashi, Hiroshi Date and Takanori Takebe

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Publication Date: 11 June 2021
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https://www.tmd.ac.jp/english/research_activities/Vol-7/takebe/

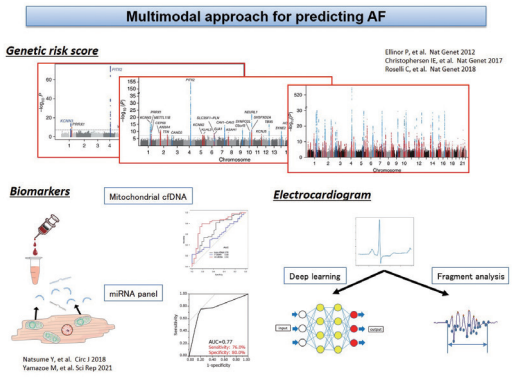
Tetsuo Sasano

Prediction and detection of atrial fibrillation for reducing cardiogenic stroke

by Tetsuo Sasano

Stroke, it suddenly happens and destroys your healthy life. Stroke is classified into several subtypes of hemorrhages and infarctions. One of the most severe types of stroke is cardiogenic embolism. Cardiogenic embolism occurs on the basis of an arrhythmia, called atrial fibrillation, AF. When the heart has AF, thrombus, a blood clot, is generated in the left atrium, and if the thrombus jumps into the blood flow, it may cause a huge cerebral infarction. It is a cardiogenic embolism.

The question is how many people suffer from AF. Currently, the estimated number of patients with AF is approximately 1 million in Japan. Since it is well known that the prevalence of AF increases in the elderly population, the number of patients with AF will increase in the future. AF is diagnosed by electrocardiogram, ECG. However, AF occurs in a paroxysmal form in its early phase, and we cannot diagnose or predict AF from an ECG recorded during sinus rhythm in current technology. Thus, we need to record the ECG during AF attack. It is sometimes difficult, and in that case the patient may have strokes before the diagnosis of AF.

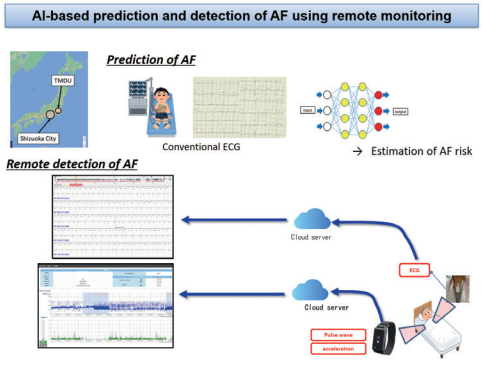


Multimodal approach for predicting AF

We have been developing a prediction of AF with various modalities. The first is genetic information. Several studies, including from our group, published the risk of SNPs (Single Nucleotide Polymorphism) in relation to AF. The genetic risk score derived from these SNPs can predict the risk of AF from the genetic aspect. The second is the biomarker. We reported that atrial myocytes released nucleotides such as DNA and RNA into the extracellular space. We can measure these extracellular nucleotides in peripheral blood samples. Recently we found that mitochondrial cell-free DNA and microRNA diagnostic panel could predict AF only from blood test. The third is the ECG. As mentioned above, it was hard to say whether the subject has AF or not, only from the ECG recorded during the normal sinus rhythm. However, we developed deep learning and newly invented fragment analysis to predict the substrate of AF. Using these methods, we can estimate the risk of AF from the ECG even during sinus rhythm.

Combining these approaches, we generated multimodal risk assessment of AF only by blood test and conventional ECG. This assessment will be applicable to regular medical check. Based on these findings, we are now moving onto the social application of this AF prediction system in a large cohort. We perform a large-scale experiment in Shizuoka city, 200 km distant from our university. When the participant has a regular medical check with conventional ECG, we estimate the risk of AF using deep learning and fragment analysis.

If the ECG analysis determines that the participant has a risk of AF, we perform remote monitoring to detect paroxysmal AF. We use 2 equipments: small telemetry ECG, or pulse wave sensor as in smart watch. The ECG or pulse wave data are transferred to the cloud server, and we performed AI-based automatic diagnosis using these data.



AI-based prediction and detection of AF using remote monitoring

Using this AF prediction and detection system, we try to reduce cardiogenic stroke. The system is applicable even in local area with limited medical resources. Participants only have to have regular medical checkup with conventional ECG. Our goal is to contribute to the maintenance of a healthy life in the whole country.

Paper Information

Sparsely methylated mitochondrial cell free DNA released from cardiomyocytes contributes to systemic inflammatory response accompanied by atrial fibrillation

Masahiro Yamazoe, Tetsuo Sasano, Kensuke Ihara, Kentaro Takahashi, Wakana Nakamura, Naomi Takahashi, Hiroaki Komuro, Satomi Hamada and Tetsushi Furukawa

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Publication Date: 18 March 2021
DOI: 10.1038/s41598-021-85204-7

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Social pathways between oral and general health

by Jun Aida

Speaking and eating are fundamental oral functions that sustain our social life. Poor oral health possibly affects general health through a reduction in social interactions. However, according to laboratory research, it is difficult to determine these kinds of social pathways. Therefore, we conducted epidemiological research focusing on people in real society to improve our social life by maintaining oral health.

This figure illustrates the concept of the relation between oral and general health. Oral diseases deteriorate oral health and oral functions. There can be physical and social pathways. As to the physical pathways, deterioration in oral health causes changes in food and nutrition intake and oral bacteria. Also, malnutrition, aspiration pneumonia, and chronic periodontal inflammation can possibly be increased, and they can affect general health.

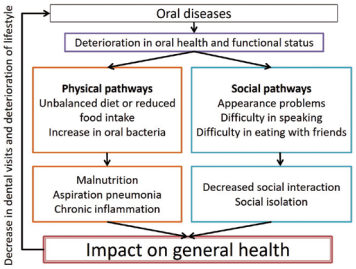


Figure
The concept of the relation between oral and general health

As to the social pathways, deterioration in oral health increases appearance problems in the mouth, difficulty in speaking, and eating with friends. These problems can reduce social interaction and increase social isolation, which possibly affect general health. However, few studies have examined these pathways.

Our cohort study analyzed 35,700 participants aged 65 years or older in Japan. Among the participants with 20 or more teeth in 2010, 3.2% experienced incidence of dementia between 2013-16. This percentage was higher, 6.0 %, among those with 0-19 teeth. After adjusting for confounders such as age, health status, and socioeconomic status at the baseline, having 0-19 teeth showed a 1.14 times higher hazard ratio for incidence of dementia. To examine the physical and social pathways, we conducted mediation analysis, and these mediators partially explained the association between teeth and dementia.

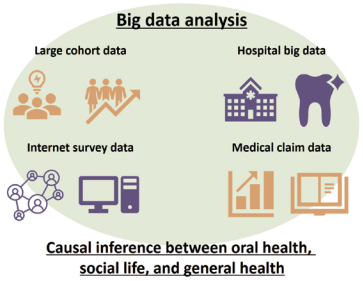
Social networks explained 7.65% of the association, which was comparable to vegetable and fruit intake and weight loss. So, we can conclude that there are both social and physical pathways between oral health and dementia.

Our study focuses on people in societies. Therefore, an experimental study is often not feasible or unethical. So, sophisticated contemporary technics are required for the causal inference between exposure and outcome from the observational dataset.

We also need big data that enable causal inference. Our department uses large cohort data, flexible internet survey data, hospital big data, and medical claim data.

We are also conducting international collaborative researches with many overseas researchers.

Through these efforts, we hope to determine the interaction between oral health, social life, and general health.




Jun Aida

Paper Information

Oral Status and Dementia Onset: Mediation of Nutritional and Social Factors

S. Kiuchi, U. Cooray, T. Kusama, T. Yamamoto, H. Abbas, N. Nakazawa, K. Kondo, K. Osaka and J. Aida

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https://www.tmd.ac.jp/english/research_activities/Vol-7/aida/

Takahiro Adachi

No IgA leads to intestinal inflammation in mice

by Takahiro Adachi

While researchers have known for years that immunoglobulin A (IgA) is important for gut health, it has remained unclear exactly what role it plays in preventing infection and disease. But now, researchers from Japan have found that eliminating IgA disrupts the balance of the intestinal ecosystem, making it susceptible to disease.

In a study published online in May 2021 in Gut, researchers from Tokyo Medical and Dental University (TMDU) have revealed that IgA deficiency results in substantial inflammation of the ileum, a specific part of the small intestine.

IgA is present in large quantities in the small intestine, where it helps protect the body against microorganisms that could potentially cross the lining of the gut to cause disease. People who do not produce IgA are more likely to develop inflammatory bowel disease, allergies, or autoimmune disease, or to get repeated infections. However, attempts to explore the connection between IgA and disease in the laboratory have been hampered by contradictory results, with some studies suggesting that IgA is not important for gut health, and others concluding it is crucial.

“We sought to resolve this apparent discrepancy by generating a definitive mouse model of IgA deficiency,” says senior author of the study Takahiro Adachi. “To do this, we used a cutting-edge gene engineering technology called CRISPR/Cas9 to delete the gene encoding IgA.”

The researchers then analyzed the IgA-deficient mice in detail to determine the effect on gut health, inflammation, and the gut microbiota (the microorganisms that live in our digestive tract).

“The results were striking,” explains Adachi. “We found that the IgA-deficient mice had spontaneous inflammation in the ileal portion of the small intestine, with enhanced immune cell activation and the production of pro-inflammatory cytokines”(Figure.1).In addition, the gut microbiota in these mice was unbalanced, especially in the ileum.

“Our findings suggest that IgA plays a protective role in the intestine by maintaining a healthy balance of microorganisms in the gut and preventing pathologic inflammation,” says Adachi.

Given that IgA deficiency is a known risk factor for inflammatory bowel disease such as Crohn’ s disease and ulcerative colitis, this new mouse model could be helpful for investigating these inflammatory conditions in the future. According to Takashi Nagaishi, lead author of the paper, the specific inflammation observed in the ileum of these mice, instead of the colon, makes this especially promising as a model of Crohn’ s disease in humans.

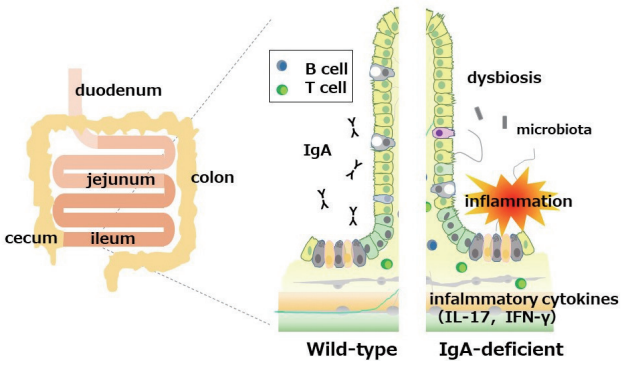

Figure 1. IgA deficiency induces ileitis

The small intestine is composed of duodenum, jejunum and ileum (left). IgA deficiency causes distortion of the gut microbiota, especially in the ileum, and inflammatory cytokines are secreted from T cells, resulting in in inflammation of the ileum (right).

Paper Information

Immunoglobulin A–specific deficiency induces spontaneous inflammation specifically in the ileum

Takashi Nagaishi, Taro Watabe, Kunihiko Kotake, Toshihiko Kumazawa, Tomomi Aida, Kohichi Tanaka, Ryuichi Ono, Fumitoshi Ishino, Takako Usami, Takamasa Miura, Satomi Hirakata, Hiroko Kawasaki, Naoya Tsugawa, Daiki Yamada, Kazuhiro Hirayama, Soichiro Yoshikawa, Hajime Karasuyama, Ryuichi Okamoto, Mamoru Watanabe, Richard S Blumberg and Takahiro Adachi

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A new agent for the brain diseases: mRNA

by Keiji Itaka and Yuta Fukushima

A lack of oxygen to brain tissue—known as ischemia—leads to the death of neurons, which results in stroke. Despite considerable research, there are currently no treatments that successfully prevent neuronal death. Now, Tokyo Medical and Dental University (TMDU) researchers have reported a way of delivering mRNA to produce a therapeutic protein that protects neurons. Their findings, demonstrated in rats, are published in Biomaterials.

Brain-derived neurotrophic factor (BDNF) is a protein that enhances the survival and function of neurons. However, it is difficult to deliver BDNF molecule into the brain by crossing the protective barrier, and BDNF is rapidly removed from the central nervous system, making it difficult for BDNF to make its mark as a treatment.

The researchers therefore devised a way of producing BDNF where it is needed most. They used mRNA as a new therapeutic agent by encoding BDNF. To deliver the mRNA into the brain, they applied their original delivery system, which is constructed by synthetic biocompatible polymers. When the mRNA gets inside a cell, it can be used as a blueprint to make the protein.

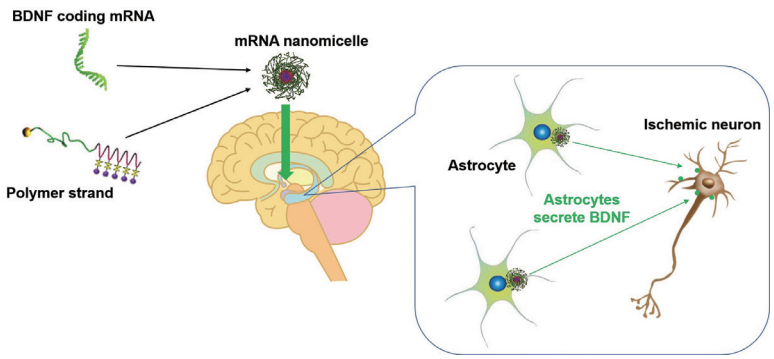
Their system—known as an mRNA-loaded polyplex nanomicelle—is a tiny ball-like parcel of mRNA surrounded by polymer strands. The polymer protects the mRNA from molecules that might break it down and helps to disguise it from the immune system.

“As well as protecting the mRNA by providing containment, the polymer allows the release of the cargo to be controlled,” study first author Yuta Fukushima explains. “By selecting polymers with particular properties, we can ensure the mRNA is released when and where it is needed.”

The effectiveness of the mRNA therapy was tested on rats that had experienced brain ischemia. The nanomicelles were found to increase the survival of hippocampal neurons. In particular, the nanomicelles showed better effects when administered 2 days after the ischemia than when given immediately. This indicates that the nanomicelles extend the opportunity for providing effective treatment.

In addition, long-term therapeutic benefits were observed 20 days after ischemia when the nanomicelle was administered on both days 2 and 5. Treated rats showed better spatial memory than untreated rats in a maze experiment.

“We are very encouraged by the performance of our system,” says study corresponding author Keiji Itaka. “Our experiments not only demonstrated that the nanomicelle could prevent neuron death, but also that the potential treatment window could be extended. We expect these findings to have a significant impact on the development of practical clinical treatments.”



Brain-derived neurotrophic factor mRNA therapeutics for ischemic neuronal death using polyplex nanomicelle.
Brain-derived neurotrophic factor (BDNF) serves as a potential candidate neuroprotective agent, but there are almost no successful clinical trials due to high hurdle in brain access and short half-life. Fukushima et al. show intraventriclarly administered BDNF mRNA using polyplex nanomicelle exerted a prominent effect to prevent neuronal death with the unique mechanism of action. BDNF mRNA was extensively introduced into the astrocytes to generate a higher level BDNF protein in ischemic lesion.


Keiji Itaka


Yuta Fukushima

Paper Information

Treatment of ischemic neuronal death by introducing brain-derived neurotrophic factor mRNA using polyplex nanomicelle

Yuta Fukushima, Satoshi Uchida, Hideaki Imai, Hirofumi Nakatomi, Kazunori Kataoka, Nobuhito Saito and Keiji Itaka

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Publication Date: Published online 21 January 2021
DOI: 10.1016/j.biomaterials.2021.120681

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Tomohiro Morio

Motoi Yamashita

When mad AIOLOS drags IKAROS down: a novel pathogenic mechanism

by Tomohiro Morio and Motoi Yamashita

Primary immunodeficiencies, such as severe combined immunodeficiency disease (SCID), occur when the immune system does not work properly, leading to increased susceptibility to various infections, autoimmunity, and cancers. Most of these are inherited and have an underlying genetic causes. A team at Tokyo Medical and Dental University (TMDU) has identified a novel disorder resulting from a mutation in a protein called AIOLOS, which functions through a previously unknown pathogenic mechanism called heterodimeric interference.

The gene family known as IKAROS zinc finger proteins (IKZFs) is associated with the development of lymphocyte, a type of white blood cell involved in the immune response—meaning that mutations in this family can be involved in immune system deficiencies. Most research so far has focused mainly on IKAROS protein, encoded by the *IKZF1* gene, although the underlying mechanism by which IKAROS mutations cause the immune deficiencies is not yet fully understood. A mutation in AIOLOS—another member of the IKZF family that is encoded by the *IKZF3* gene—has now also been revealed to cause a hereditary immune deficiency. In addition to not functioning properly itself, the resultant mutant protein interferes with the functioning of IKAROS protein.

TMDU researchers uncovered this new mechanism while investigating the cause of a previously undescribed inherited B cell deficiency observed in a family of patients. After sequencing all of the protein-coding genes, the team focused their research on AIOLOS as IKAROS is known to be the cause of B cell deficiency. They showed that the mutant form of AIOLOS that was present in this family did not just fail to function, but actively bound to a different DNA sequence than the normal version of the protein.

They went on to use a mouse model that harbors equivalent AIOLOS mutation identified in the patients to outline the underlying pathogenic mechanism. AIOLOS and IKAROS bind together to form a "heterodimer". The mutant form of AIOLOS retained the ability to bind IKAROS but then interfered with the normal function of IKAROS, and led to the heterodimer being recruited to the incorrect regions of the genome.

"This is a novel pathogenic mechanism that we termed heterodimeric interference," says lead author Motoi Yamashita, "where a mutant protein in a heterodimer hijacks the function of the normal partner protein."

The team were then able to rescue some of the immune function in the mouse model by deleting the dimerization domain of the mutant AIOLOS.

"The fact we could rescue the phenotype in our mouse model indicates a potential therapeutic approach," says Tomohiro Morio, senior author. "The deletion of the domain responsible for binding IKAROS in the mutant AIOLOS protein could ameliorate the immunodeficiency observed in the patients."

The discovery of this new pathogenic mechanism, heterodimeric interference, may well help to shed light on many other disease processes such as autoimmunity and cancer development where mutant proteins act in the same way.

Figure 1.
Fallen IKAROS blown by AIOLOS.

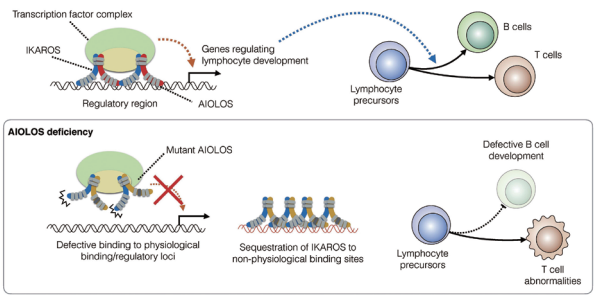

Figure 2. Mutant AIOLOS interfere with IKAROS via heterodimers — Heteromeric interference.

AIOLOS forms heterodimer with its partner IKAROS. They comprise transcription factor complex which regulates genes involved in lymphocyte development. In the patients and the patient-mimic mouse model, mutant AIOLOS forms heterodimer with IKAROS and interferes with its function by blocking AIOLOS-IKAROS bindings to their physiological binding sites and sequestrating IKAROS to non-physiological binding regions in the form of heterodimers.

Paper Information

A Variant in Human AIOLOS Impairs Adaptive Immunity by Interfering with IKAROS

Motoi Yamashita, Hye Sun Kuehn, Kazuki Okuyama, Satoshi Okada, Yuzaburo Inoue, Noriko Mitsuiki, Kohsuke Imai, Masatoshi Takagi, Hirokazu Kanegane, Masahiro Takeuchi, Naoki Shimojo, Miyuki Tsumura, Aditya K. Padhi, Kam Y. J. Zhang, Bertrand Boisson, Jean-Laurent Casanova, Osamu Ohara, Sergio D. Rosenzweig, Ichiro Taniuchi and Tomohiro Morio

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DOI: 10.1038/s41590-021-00951-z

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https://www.tmd.ac.jp/english/research_activities/Vol-7/morio/

Osteoarthritis of the knee is evaluated with 3DMRI and regenerated with stem cells

by Ichiro Sekiya

Osteoarthritis of the knee is a serious, painful disease that gets worse with age. At present, there is no approved conservative treatment to regenerate lost cartilage. The difficulty in its development comes from the lack of a highly accurate way to measure cartilage quantity.

X-rays are the most common examination for osteoarthritis. The joint space in an X-ray image consists of three layers, femoral cartilage, meniscus, and tibial cartilage. An X-ray image does not demonstrate each layer.

We are developing a 3D analysis software for a knee MRI. After importing the MRI DICOM data, this software automatically extracts bone, cartilage, and meniscus and shows 3D images in a few minutes, even on a notebook computer.

The following x-ray shows a slight narrowing of the medial joint space but provides no information about the cartilage and meniscus. The 3D MRIs demonstrates cartilage thickness. In this case, we can find cartilage loss at the femoral side. In addition, the 3D MRI indicates that the medial meniscus is displaced medially. The 3D MRIs reveals the pathology in the knee joint.

We are developing an osteoarthritis treatment using mesenchymal stem cells derived from synovium. Synovium is a membrane that lines the inside of joints. Synovium itself has a high regenerative potential.

We collected bone marrow, synovium, periosteum, adipose tissue, and skeletal muscle. We then prepared mesenchymal stem cells and differentiated them into cartilage pellets in vitro. The cartilage pellet derived from synovium was the largest due to its high production of cartilage matrix as shown below. This indicates that synovial MSCs have a high chondrogenic potential.

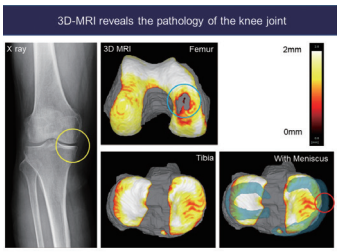
After enzyme digestion, synovial cells are plated, and 10% of the cells adhere to the dish and proliferate, forming colonies. Approximately 50 million synovial MSCs can be harvested in two weeks, and these are used for cell therapy.

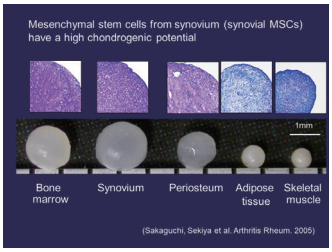
In a rat study, we transected the anterior cruciate ligament to induce osteoarthritis. In the control, the femoral cartilage was degenerated. Intraarticular injection of synovial MSCs inhibited progression of osteoarthritis in rats.

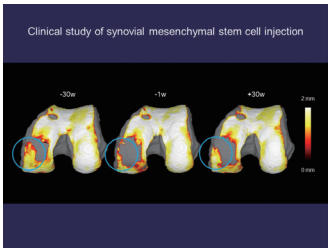
As for a possible mode of action in synovial MSC injection therapy for osteoarthritis, synovial MSCs injected into the knee joint mostly migrate to the synovium, and act as anti-inflammatory, lubrication, and cartilage matrix synthesis. Consequently, exogenous MSCs can inhibit the progression of osteoarthritis.

We performed a clinical study of a synovial mesenchymal stem cell injection for osteoarthritis. The following 3D MRI images show a representative case. The cartilage decreased in the 30 weeks before injection but increased in the 30 weeks after injection.

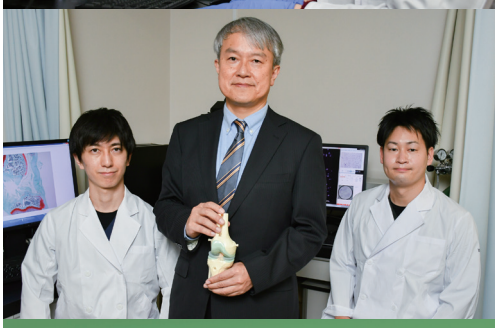
We have just begun to develop the treatments to improve the progression of osteoarthritis. We expect further advances in both evaluation methods and cell therapies. I would be very honored if you would take an interest in this field.








Ichiro Sekiya



Paper Information

Comparison of human stem cells derived from various mesenchymal tissues: Superiority of synovium as a cell source

Yusuke Sakaguchi, Ichiro Sekiya, Kazuyoshi Yagishita and Takeshi Muneta

Publication: Arthritis & Rheumatism, 2005 Aug;52(8):2521-9.
Publication Date: 28 July 2005
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Link to the Paper

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/sekiya/

Kyoko Ohno-Matsui

Paper Information

Myopia

Ian G Morgan, Kyoko Ohno-Matsui and Seang-Mei Saw

Publication: Lancet, 2012 May 5;379 (9827):1739-48.
Publication Date: 2012 May DOI: 10.1016/S0140-6736(12)60272-4

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Link to the Video

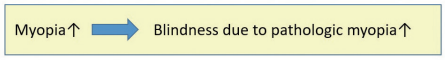
https://www.tmd.ac.jp/english/research_activities/Vol-7/ohnomatsui/

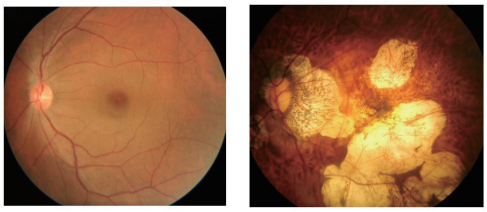
Pathologic myopia - The major cause of visual impairment

by Kyoko Ohno-Matsui

Myopia is known as short—sightedness. Pathologic myopia is the most serious form of myopia which causes the visual impairment and blindness. Recently, the rate of myopia has been increasing worldwide especially in East Asian countries known as myopia boom.

If the current trend of myopia increase continues, it is estimated that by year 2050, a half of the world population becomes myopia and about 10% of the world population becomes high myopia. The increase of myopia is considered to cause the increase of blindness due to pathologic myopia. This is fundus photo of normal eye. And in eyes with pathologic myopia, various lesions develop and they impair the vision.



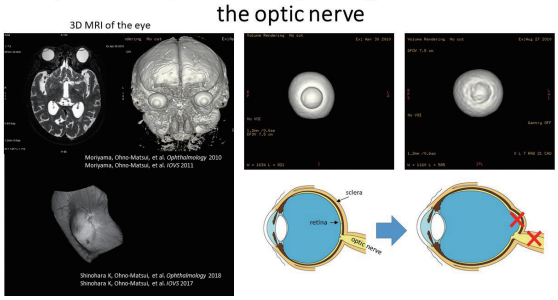


Normal Pathologic myopia

Eyes with myopia becomes longer than normal eyes. We have established the technique called 3D MRI of the eye for the first time in the world and successfully visualized the entire shape of the eye. With 3D MRI, we have found that the eyes with pathologic myopia were not simply elongated but they were severely deformed especially in its posterior part.

Recently we have used widefield OCT and now routine examination of the eye shape is possible. This is a scheme of normal eye. The outermost shell of the eye is sclera which is composed of collagen fibers like cornea. The major role of sclera is to protect the central nervous tissue inside the eye, which are retina and the optic nerve.

Eye deformity mechanically damages the retina and the optic nerve



In eyes with pathologic myopia, following the deformity of sclera, the retina and the optic nerve are mechanically damaged.
So, to prevent blindness, it is ideal to treat and prevent the eye deformity before blinding complications occur.

For this purpose, we are currently working for clinical trials of scleral collagen crosslinking to stiffen the sclera. Collagen crosslinking is currently used for keratoconus in which cornea becomes thin and deformed. After topical application of photosensitizer, the ultraviolet light is applied to cause crosslinking. We have conducted animal studies and confirmed its efficacy and safety. And now we are collaborating with Santen toward clinical trials with the governmental support.

With this therapy, it will be possible to stop and prevent the deformity of the eye and to eliminate the development of blinding complications, and finally to maintain the good vision in the entire life.

Infusion of 3D cellular structures might repair damaged intestine

by Shiro Yui and Satoshi Watanabe

Ulcerative colitis is an inflammatory bowel disease (IBD) that causes inflammation and ulcers (sores) in the digestive tract. Ulcerative colitis affects the innermost lining of the colon and rectum. It can be a debilitating condition and can sometimes lead to life-threatening complications. Most importantly, it does not have a cure at the moment.

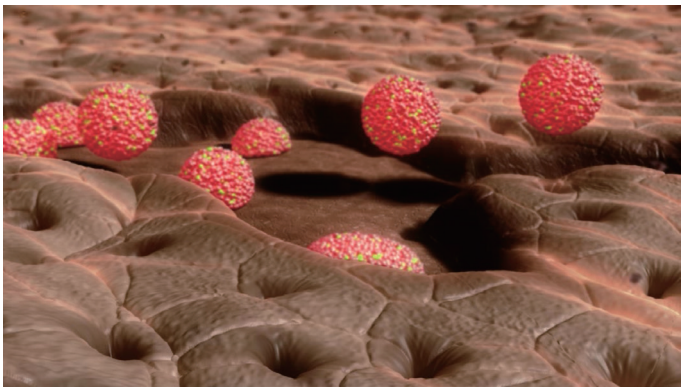
In a recently published article, researchers from Tokyo Medical and Dental University (TMDU) have presented a detailed protocol for transplanting 3D cellular structures that can regenerate the intestinal tissue that gets damaged in colitis. To develop this approach, they used a mouse model of colitis, obtained by the administration of dextran sulfate sodium, which destroys the intestinal epithelium in a way similar to colitis.

The 3D cellular structures that the team transplanted are called organoids and represent one of the biggest revolutions in the field of biomedicine in the last decade. Organoids are a miniaturized and simplified version of an organ produced in the laboratory, made of agglomerates of cells; they are three-dimensional and show realistic micro-anatomy. Organoids are used for several applications, including as an in vitro tool to study diseases, for regenerative medicine, and to develop precision medicine approaches.

In the present study, the investigators used intestinal organoids to replace damaged intestinal tissue, a regenerative medicine application. “We infused around 1000 organoids via a flexible catheter into the colon where most epithelial damage occurred. The cultured epithelial cells of the organoids attached to the injured surfaces and integrated into the host epithelium, the cell layer lining the inside of the colon,” explains Satoshi Watanabe, lead author of the paper. “This resulted in an intact epithelium where part of the recipients’ epithelial lining has been replaced by donor cells.”

The total time taken for the rectal infusion of the organoids was 10 minutes, and, importantly, the researchers found that the method was reproducible across different culture conditions of the organoids. These features make it very attractive for a clinical application as it is a quick, reproducible, and minimally invasive method. Moreover, organoids can potentially be derived from the cells of the recipient patient, minimizing the risk of rejection after transplantation.

“This is a versatile protocol, which has been previously used to investigate cellular function, and formed the basis for the first-in-human clinical trial using colonic organoid transplantation therapy for hard-to-treat cases of ulcerative colitis”, explains Shiro Yui, senior author on the study. Thus, the protocol developed in this study has already been translated into clinical practice, and both the scientific and clinical communities are excited about the future clinical applications.



Schematic presentation of future organoids therapy

Stem cells and functional differentiated cells in organoids support a faster repair of ulceration

Shiro Yui

Satoshi Watanabe

Paper Information

Transplantation of Intestinal Organoids into a Mouse Model of Colitis

Satoshi Watanabe, Sakurako Kobayashi, Nobuhiko Ogasawara, Ryuichi Okamoto, Tetsuya Nakamura, Mamoru Watanabe, Kim B. Jensen and Shiro Yui

Publication: Nature Protocols, 2022 Feb 2. Online ahead of print.
Publication Date: 2 February 2022
DOI: 10.1038/s41596-021-00658-3

Link to the Paper

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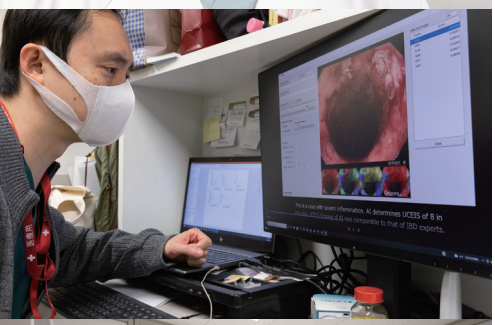
Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/yuishiro/

Kento Takenaka



Machine learning to synthesize endoscopy findings in ulcerative colitis

by Kento Takenaka

When visiting a doctor, many patients prefer non-invasive procedures over invasive and potentially painful ones. Fortunately, researchers at Tokyo Medical and Dental University (TMDU) have developed a tool that can reduce the need for invasive diagnostic procedures in ulcerative colitis.

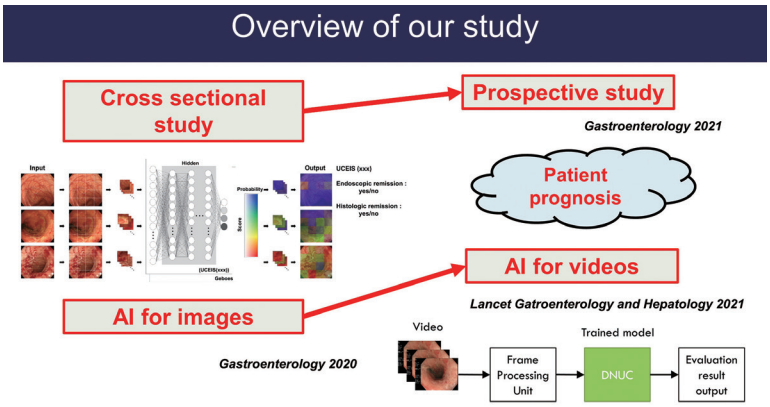
Both endoscopic and histologic assessments are important in diagnosing various diseases. In an endoscopic assessment, a long flexible tube with a light and a camera is directly inserted into a patient' s body to assess a particular organ or tissue. For a histological assessment, a biopsy, i.e., a sample of tissue from the patient' s body, is extracted and tested outside the body. With an aim to prevent unnecessary biopsies and improve medical diagnoses, researchers at TMDU previously developed a deep neural network system called DNUC to assess ulcerative colitis, a chronic disease occurring in the large intestine characterized by chronic inflammation in the lining of the colon. Without requiring biopsies, this artificial intelligence tool can evaluate images of tissues to identify and quantify areas of inflammation and disease.

In their latest study, the team extended the application of DNUC from still images to live colonoscopy videos of patients with ulcerative colitis. A total of 770 patients were included in the prospective, multicenter study. The researchers demonstrated that DNUC can determine the presence or absence of inflammation in real time, with a high rate of agreement between the DNUC results and expert diagnoses. DNUC was also able to predict cases of remission with a high level of accuracy.

"We confirmed that DNUC can automatically identify areas of inflammation and provide an endoscopic score for those areas," says study lead author Kento Takenaka. The scores obtained by DNUC were compared with scores assigned by an expert and showed a high level of agreement, confirming the accuracy of the DNUC algorithm.

This artificial intelligence tool can provide many benefits to the medical field. "The use of DNUC can reduce the need for biopsies, thus saving time and costs for both patients and doctors," says Mamoru Watanabe, senior author of the study. The DNUC system also has the potential to evaluate images and video footage more quickly than a physician. Moreover, endoscopy requires training and interpretations of endoscopic results can be subjective, varying for each endoscopist. DNUC can allow for more quantitative standards in evaluations, addressing these current issues regarding variability and bias in medical diagnoses.

This system can be applied to commercially available colonoscopy platforms, thus facilitating its adoption in clinical practice. DNUC could also facilitate the training of junior gastroenterologists. Overall, this work highlights the potential for artificial intelligence to improve current medical care.



Overview of the present study

First, we conducted cross-sectional study to create AI system for endoscopic images in ulcerative colitis. Then, we conducted prospective study to evaluate whether AI system could predict patient prognosis. Finally, we applied our AI system to video-colonoscopy.

Paper Information

Deep neural network for video colonoscopy of ulcerative colitis: a cross-sectional study

Kento Takenaka, Toshimitsu Fujii, Ami Kawamoto, Kohei Suzuki, Hiromichi Shimizu, Chiaki Maeyashiki, Osamu Yamaji, Maiko Motobayashi, Akira Igarashi, Ryoichi Hanazawa, Shuji Hibiya, Masakazu Nagahori, Eiko Saito, Ryuichi Okamoto, Kazuo Ohtsuka and Mamoru Watanabe

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Link to the Video

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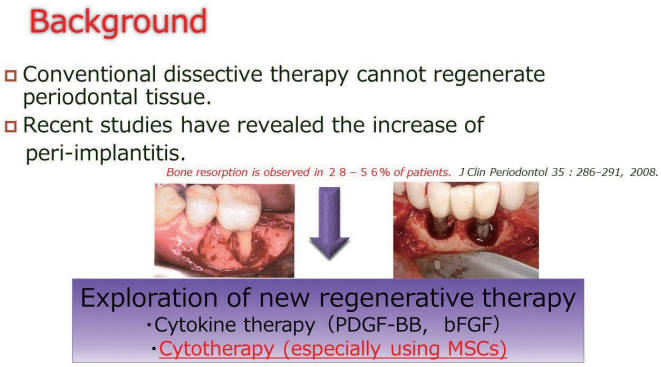
Periodontal Regeneration with Cell Sheet Technology

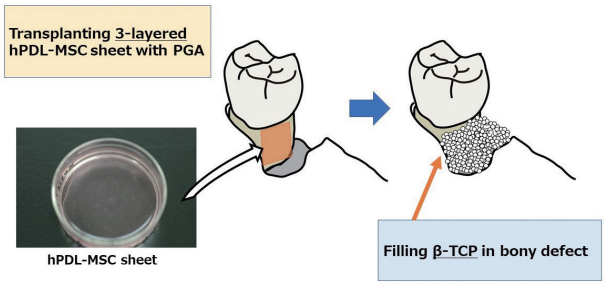
by Takanori Iwata

Conventional dissection therapy cannot regenerate periodontal tissue at all. In addition, recent studies have revealed the increase of peri-implantitis. Therefore, I think we have to regenerate the periodontium around natural teeth. In fact, regenerative therapies have been conducted, and many of the products are commercially available.



Recently, cytotherapy using living mesenchymal stem cells (MSCs) are studied for periodontal regeneration all over the world. For cell transplantation, we introduced a special cell cultureware, where a temperature responsive polymer named poly N isopropylacrylamide is grafted. The polymer' s character is hydrophobic at 37 degrees, in contrast, hydrophilic at 20 degrees and it' s reversible. Cells can attach and proliferate in hydrophobic condition at 37 degrees. After they become confluency, cells detach spontaneously just by reducing the temperature. You can harvest intact cells and ECM as a sheet.
Using this cultureware, you can retrieve transplantable cell sheets with intact cell-cell interaction and ECMs.

Our strategy is transplantation of 3 layered PDL derived MSC sheets to the root surface, then bony defects were filled with beta TCP. This movie shows the transplantation of autologous PDL cell sheets. After the debridement, the root was conditioned with EDTA for 2 minutes.



After washing with saline sufficiently, three-layered autologous PDL-derived cell sheets were trimmed to the defect size and placed on the denuded root surface and the bony defect was filled with beta-tricalcium phosphate (β-TCP) granules.

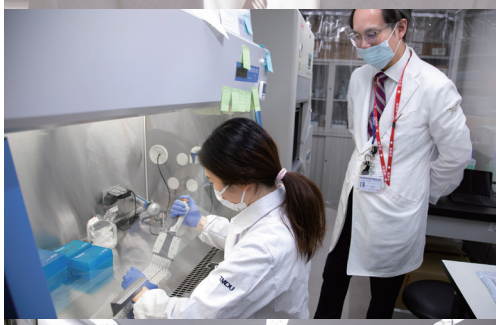
We have experienced 10 cases of autologous PDL cell sheets transplantation in this clinical study, and no adverse reaction has been observed over 6 years.

The clinical and radiographic parameters were improved by the transplantation of PDL cell sheets combined with β-TCP granules.

Our final goal is to bring this product to the patients.

Now we are collaborating with the company and plan to perform a clinical trial.

Takanori Iwata



Paper Information

Periodontal regeneration with autologous periodontal ligament-derived cell sheets – A safety and efficacy study in ten patients

Takanori Iwata, Masayuki Yamato, Kaoru Washio, Toshiyuki Yoshida, Yuka Tsumanuma, Azusa Yamada, Satoru Onizuka, Yuichi Izumi, Tomohiro Ando, Teruo Okano and Isao Ishikawa

Publication: Regenerative Therapy, 2018 Dec; 9: 38–44.
Publication Date: 24 August 2018
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Link to the Video
https://www.tmd.ac.jp/english/research_activities/Vol-7/iwata/

Shinsuke Yasuda

Mari Kamiya

Targeting Necroptosis for Inflammatory Myopathies

by Shinsuke Yasuda and Mari Kamiya

A new study has suggested that treatment to target necroptosis in muscle fibers using a necroptosis inhibitor lessens myositis-induced muscle weakness as well as muscle cell death and inflammation in the muscles. This has been shown to be a promising strategy for treating polymyositis.

Polymyositis (PM) is a chronic inflammatory myopathy wherein muscle weakness is the most common symptom, leading to progressive and persistent disability. Its pathophysiology is assumingly the injury of muscle fibers by autoaggresive cytotoxic T lymphocytes (CTLs). Current treatments of PM depend on nonspecific immunosuppressants including glucocorticoids and immunosuppressive agents. However, some patients fail to respond to the immunosuppressive therapies, and some also suffer from infectious diseases during the treatment. In addition, muscle weakness persists in more than half of the patients despite reduction in muscle inflammation.

It is clear that a better therapeutic strategy that not only suppresses muscle inflammation but also prevents muscle weakness and at the same time avoiding an increasing risk of infection is needed.

The study hypothesized that the injured muscle fibers in PM release pro-inflammatory molecules, and that the inhibition of the cell death of muscle fibers could be a novel therapeutic strategy to suppress both muscle injury and inflammation.

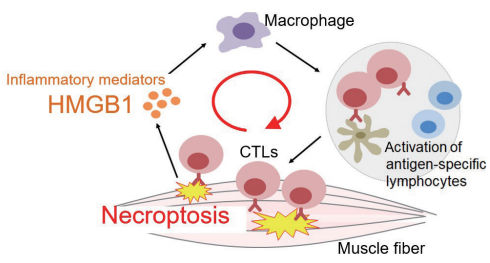
In a study published in Nature Communications, researchers from Tokyo Medical and Dental University (TMDU) found that the pattern of cell death in muscle fibers is necroptosis. This was done using an integrative analysis including histological imaging of human muscle biopsy samples from PM/dermatomyositis (DM; another subset of inflammatory myopathies) patients and functional studies with models of PM. The injured muscle fibers undergo necroptosis and release high levels of HMGB1 which lead to further acceleration of muscle inflammation and subsequent muscle injury in PM. This indicates that muscle cells are not merely passive responders, but rather are aggressors that actively promote muscle inflammation in PM.

In the treatment of PM, it is important to promote muscle regeneration to help recover from muscle weakness in addition to the suppression of muscle injuries by CTLs. A speedy improvement in this was actually observed during treatment which suggests an improvement of muscle fiber functions due to the inhibition of necroptosis. HMGB1 acts as a potent regenerative factor in muscles and so therefore the long-term blocking of HMGB1 in the chronic phase of the disease seems to interfere with muscle strength in PM patients. Considering the therapeutic effect of necroptosis inhibition to suppress muscle fiber death and subsequent release of HMGB1, inhibition of necroptosis may be seen as providing a good therapeutic option in the acute phase of the disease.

Inflammatory myopathies are systemic diseases which can affect the skin, lung, heart, joint, and gastro-intestinal tract. Given the involvement of necroptosis in inflammatory diseases of various organs and the efficacy of necroptosis inhibitions in corresponding animal models such as dermatitis, acute respiratory distress syndrome, cardiomyositis, arthritis, and colitis, systemic inhibition of necroptosis could also be a potential therapy for the extramuscular involvement of inflammatory myopathies.

Conclusively, inhibition of necroptosis in muscle fibers would be a novel therapeutic strategy to recover muscle strength through suppressing muscle cell death and inflammation in PM. Since this type of muscle cell-directed therapy does not directly suppress immune cells or inflammatory mediators, it is a promising alternative to current immunosuppressive therapies for PM with potentially less infectious complications.

Clinical trials to test the therapeutic and side effects of necroptosis inhibition are awaited in PM, given the promising therapeutic effects in these pre-clinical studies.



Visual abstract

Muscle fiber necroptosis and subsequent release of HMGB1 aggravate inflammation in PM.

Paper Information

Targeting necroptosis in muscle fibers ameliorates inflammatory myopathies

Mari Kamiya, Fumitaka Mizoguchi, Kimito Kawahata, Dengli Wang, Masahiro Nishibori, Jessica Day, Cynthia Louis, Ian P. Wicks, Hitoshi Kohsaka and Shinsuke Yasuda

Publication: Nature Communications, 2022 Jan 10;13(1):166.
Publication Date: 10 January 2022
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Seeing Lipids More Deeply with Mass Spectrometry

by Takehiko Sasaki and Shin Morioka

The development of new scientific ways to see more deeply into the building blocks of nature on a cellular level has led to some of the greatest advances in medicine over the last century. Now, new research into phosphoinositides, which are a family of membrane lipids essential for many biological and pathological processes and which represent one of the most functionally versatile membrane lipid families involved in human health and disease, has seen further developments in the use of mass spectrometry in continuing to push back the barriers leading to new treatments for many diseases.

In the past, due to various reasons related to their complexity and their low intracellular concentrations, the profiling of these lipids and the linking of a specific acyl variant to biological change has been difficult. However, a new system called PRMC-MS (Phosphoinositide Regioisomer Measurement by Chiral column chromatography and Mass Spectrometry) has now enabled the characterization of the dynamics of phosphoinositide acyl variants both in intracellular and extracellular environments.

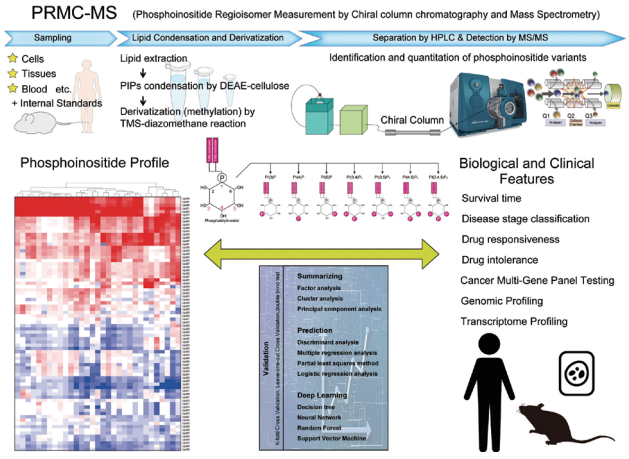
Previous methods of measuring and profiling phosphoinositides have produced results that cannot be easily applied to clinical or pathological samples from experimental animals. Even newer methods involving the use of mass spectrometry which have made advances in some areas still reflect the problem of how to simultaneously quantify the acyl variants of individual regioisomers in biological samples.

The PRMC-MS method now solves this problem and points the way to an understanding of how these lipids influence cell functions. Using PRMC-MS, it is now possible to simultaneously measure all eight classes of phosphoinositides in a single sample. The highly sensitive nature of PRMC-MS allows for the detection of tiny but important changes in intracellular phosphoinositide levels, yielding data that shows that it can be applied to blood samples to track phosphoinositide signatures potentially related to disease states.

PRMC-MS enables the comprehensive analysis of phosphoinositide acyl variants in various types of biological samples, including surgical specimens, which can be used to shed light on previously unrecognized disturbances of phosphoinositide fatty acyl profiles in cancerous tissue and to monitor their extracellular mobilization. Further study of the differing acyl variants and their conferring of protein binding properties could possibly also reveal how they activate a signaling pathway that favors cancer cell growth and survival and emerge as a target for cancer therapy. Thus, PRMC-MS may well illuminate the role played by phosphoinositides in the pathogenesis of cancers and inflammatory diseases.

In addition, the use of PRMC-MS in the evaluation of phosphoinositide signatures at the acyl variant level in tissue and liquid biopsies may reveal biomarkers suitable for a wide variety of clinical applications.

In the future, applications such as the above may greatly facilitate drug development strategies based on the devising of a therapeutic agent that pinpoints a specific pathogenic phosphoinositide acyl variant, and thus open the way for much more accurate therapeutic methods and cures for patients suffering from a range of diseases that have proven difficult in the past.



Phospholipid analysis for disease diagnosis and therapy

PRMC-MS enables in-depth profiling of phosphoinositides and paves the way for medical applications of bioactive phospholipids.

Takehiko Sasaki

Shin Morioka

Paper Information

A mass spectrometric method for in-depth profiling of phosphoinositide regioisomers and their disease-associated regulation

Shin Morioka, Hiroki Nakanishi, Toshiyoshi Yamamoto, Junya Hasegawa, Emi Tokuda, Tomoya Hikita, Tomoko Sakihara, Yuuki Kugii, Chitose Oneyama, Masakazu Yamazaki, Akira Suzuki, Junko Sasaki and Takehiko Sasaki

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/sasaki/

Yuta Kochi

Predicting the Progression of Rheumatoid Arthritis

by Yuta Kochi

Predicting the future may be beyond our grasp, but what about predicting disease progression? Researchers in Japan have delved into the human genome to investigate a predictive tool for the progression of rheumatoid arthritis (RA), an inflammatory autoimmune disease showing progressive joint damage.

In a study published in Arthritis & Rheumatology, researchers led by Tokyo Medical and Dental University (TMDU) used data from a genome-wide association study (GWAS) of RA susceptibility to construct a polygenic risk score (PRS). They evaluated the PRS' s ability to predict radiographic progression—progressive anatomical damage assessed by radiographic imaging—in individuals with RA.

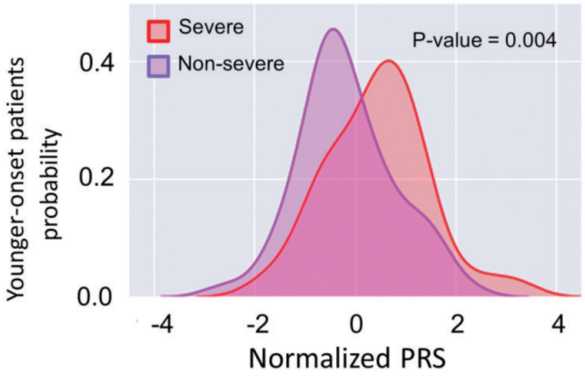
In a GWAS, genomic analysis of a group of individuals is performed to identify genetic variants that may be associated with a certain trait or disease. A PRS can be generated from a GWAS dataset and represents an individual' s risk of developing a specific disease based on a summation of the genetic variants associated with that disease. Previous studies have identified genetic factors associated with radiographic progression of RA, including the presence of anti-citrullinated protein antibodies (ACPAs) and variants located in the human leukocyte antigen (HLA) region of the human chromosome that contribute to regulating the immune system. However, the predictive accuracy of these factors is not robust. Therefore, the TMDU-led research team set out to evaluate the ability of the PRS to predict radiographic progression in people with RA.

"We generated the PRS using summary statistics from a GWAS analysis of RA susceptibility and evaluated radiographic joint damage retrospectively from patient medical records," explains lead author Suguru Honda.

The researchers then conducted statistical analysis to assess whether there is an association between PRS and severity of radiographic progression. Additionally, the research team performed a multivariable analysis to evaluate the association between radiographic progression and the combination of PRS and other factors such as sex, age of onset, and presence of ACPAs or HLA region variants.

"Our analyses revealed an association between PRS and radiographic progression," says senior author Yuta Kochi. "The PRS significantly differed between severe and non-severe progression groups."

The researchers found that patients with a higher PRS had a higher risk of severe progression, particularly among younger-onset individuals. Furthermore, the multivariable analysis revealed that the association of the PRS with radiographic progression is not influenced by other clinical factors. Thus, PRS' s could be used to predict radiographic progression. These findings highlight the potential applications of genetic profiling in the development of precision medicine approaches for the treatment of RA.



Distribution of PRS in rheumatoid arthritis patients

PRS of patients with severe radiographic progression was significantly higher than that of patients with non-severe progression.

Paper Information

Polygenic risk scores are associated with radiographic progression in patients with rheumatoid arthritis

Suguru Honda, Katsunori Ikari, Koichiro Yano, Chikashi Terao, Eiichi Tanaka, Masayoshi Harigai and Yuta Kochi

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Link to the Video

https://www.tmd.ac.jp/english/research_activities/Vol-7/yasuda/

Drilling into the Dental Secrets of Edo-era Japanese Bacterial Genomes

by Takeaki Sudo and Takahiko Shiba

Your teeth are like tiny time capsules—they have the potential to provide a wealth of information to scientists centuries in the future. For example, if you allow your plaque to harden into dental calculus (also known as tartar), it could preserve the genetic material of your oral microbiome: the bacteria that call your mouth home.

In a new study published in Frontiers in Cellular and Infection Microbiology, a research team from Tokyo Medical and Dental University (TMDU) investigated the teeth of 12 human skeletons from Edo-era Japan (1603–1867), collected in 1955 from a former graveyard in Tokyo.

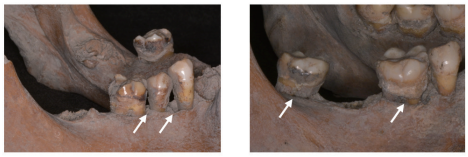
The goals of this study were to identify signs of periodontitis (commonly called gum disease) in these ancient skeletons, analyze the bacterial genomes preserved in the dental calculus, and compare the Edo-era oral microbiomes to their equivalents in modern samples.

To investigate relationships between the identified bacteria and periodontitis, the researchers developed a new method to diagnose periodontal disease in ancient skeletons. Study first author Takahiko Shiba explains, “Previously, teeth would need to be extracted from the jawbone to determine the root length and quantify bone loss as an indicator of periodontal disease. However, with advancements in micro-computed tomography technology, we were able to accurately quantify bone loss without removing teeth from the skeletons.”

Unexpectedly, the researchers detected periodontal disease in 5 of the 12 Edo-era skeletons (42%), thus the prevalence of gum disease among individuals in the Edo era appears to have been similar to that in the modern era; 37.3% of Japanese people in their forties were found to suffer from gum disease in 2005.

However, despite this similarity in the prevalence of periodontal disease, important differences were also identified between the bacterial genomes of the ancient dental calculus and those of modern Japanese samples. For example, a trio of bacterial species associated with severe periodontal disease known as the “red complex” was not found among these ancient bacterial genomes. Different bacterial species appear to be the main pathogens responsible for periodontal disease in Edo-era Tokyo.

According to another corresponding author, Hiroaki Kobayashi, “The Edo era of Japan is noted for its strict isolationist foreign policy, with very little interaction between Japanese people and foreigners. This policy appeared to be reflected in the oral microbiomes we studied, which were distinct from modern and ancient Western counterparts. Thus, our study sheds new light on the evolution of the oral microbiome and on periodontal pathogenesis.”



Bone resorption due to periodontal disease

Dental calculus deposits

Figure 1. Periodontal disease observed in skeletons from the Edo period.

Periodontal bone defects and dental calculus were observed in skeletons and several teeth from the Edo period, respectively.

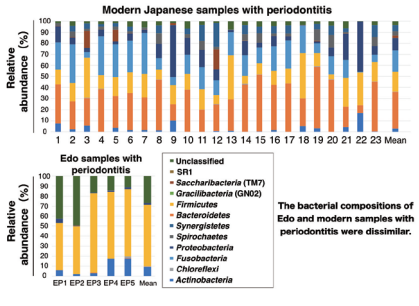


Figure 2. Bacterial composition at the phylum level based on 16S rDNA sequencing in Edo and modern samples with periodontitis.

The 16S rDNA sequencing revealed that the bacterial composition of Edo and modern samples with periodontitis were different. Interestingly, several bacteria observed in modern samples were not detected in the Edo samples.

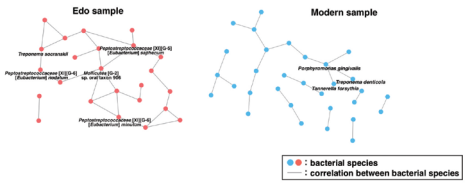


Figure 3. Bacterial networks based on the co-occurrence relationships among bacterial species.

The structure of the bacterial networks differed between Edo and modern samples, suggesting that the relationships among bacterial species differed between the two sets of samples. Porphyromonas gingivalis, better known as causative bacteria of periodontitis, was a core species in the bacterial network of the modern samples. In contrast, Eubacterium, Mollicutes, and Treponema socranskii might have been important in the bacterial network of the Edo samples.

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Paper Information

Comparison of Periodontal Bacteria of Edo and Modern Periods Using Novel Diagnostic Approach for Periodontitis With Micro-CT

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