TOKYO MEDICAL AND DENTAL UNIVERSITY

Research Activities 2020-2021

TMDU - Committed to
Pioneering Medical Research

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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.

1 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 educational institution for dentistry 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."

2021

Today, TMDU is still located in Ochanomizu / Yushima area 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.

The 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.

2 TMDU: Did you know...?

QS World University Rankings 2020 by Subject (Medicine and Dentistry)

	Medicine	Dentistry
National Rank	4	1
World Rank	101 - 150	6

SOURCE: QS World University Ranking by Subject 2020

THE World University Rankings by Subject 2021 (Clinical & Health)

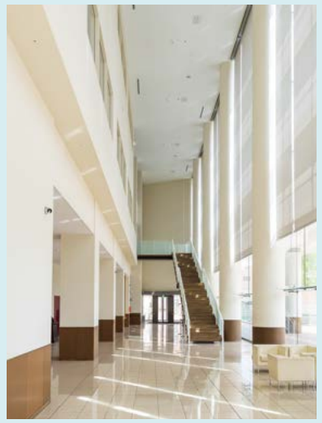
Ranked **No.3** in Japan

and **No.79** in the World

SOURCE: THE World University Ranking by Subject 2021

University Hospitals Promoting Our Research

	Beds	Outpatients Per Year
Medical Hospital	753	541,451
Dental Hospital	60	387,340



International Students

	No. of Intl. Students	No. of Countries
Graduate Schools	314	33

About **21%** of graduate school students are **International Students**

Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/president/index.html

3 Message from the President

3 Policies of TMDU Research

Yujiro Tanaka

President

Hello!
My name is Yujiro Tanaka, president of Tokyo Medical and Dental University (TMDU).
As we all know, 2020 has been the year of COVID-19. The virus has severely infected many people in Tokyo, as well.

Our hospital staff have been on the front lines in this crisis. In addition, our many researchers have assisted in PCR testing to support our hospital staff, while at the same time producing new research and published papers. I'm very proud of the great effort made by so many of our staff at TMDU to help alleviate this severe crisis.

During the COVID-19 outbreak, we have made video clips showing the scope of research activities at our university. The video clips will be posted on the university website. We hope you enjoy learning more about TMDU research activities.

Research at TMDU has 3 key aspects:

1. Academic Freedom.
This means that our researchers are given the autonomy to conduct challenging, innovative research.

2. Academic Integrity.
We make every effort to protect the integrity of scientific research by ensuring the reliability of all published papers.

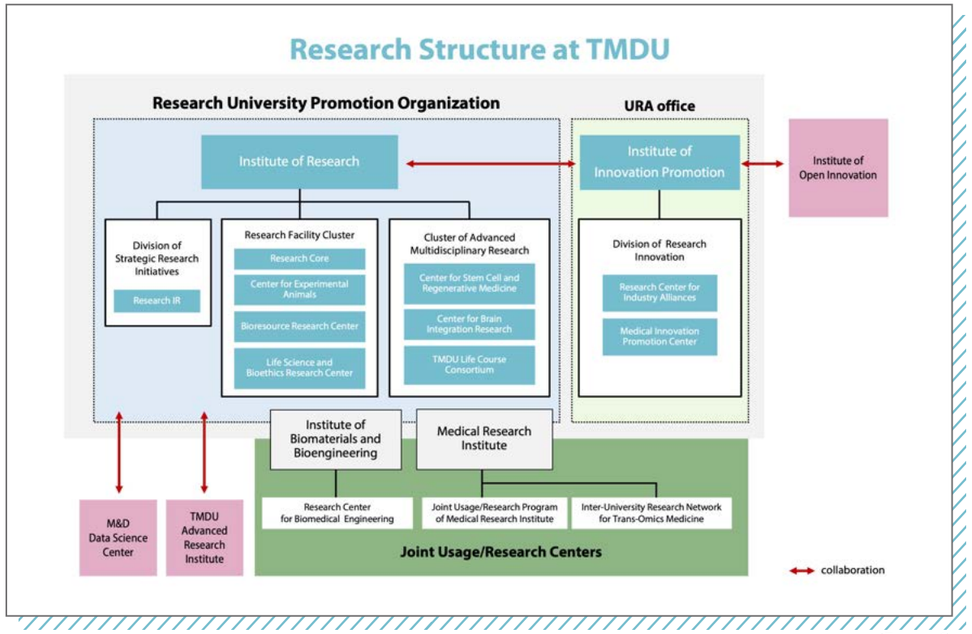
3. Contribution to Total Healthcare.
The focus of our university is Total Healthcare.
I encourage our researchers to conduct their research always asking whether their research will have a positive impact on Total Healthcare.

4 Message from the Executive Director (Research)

Akinori Kimura

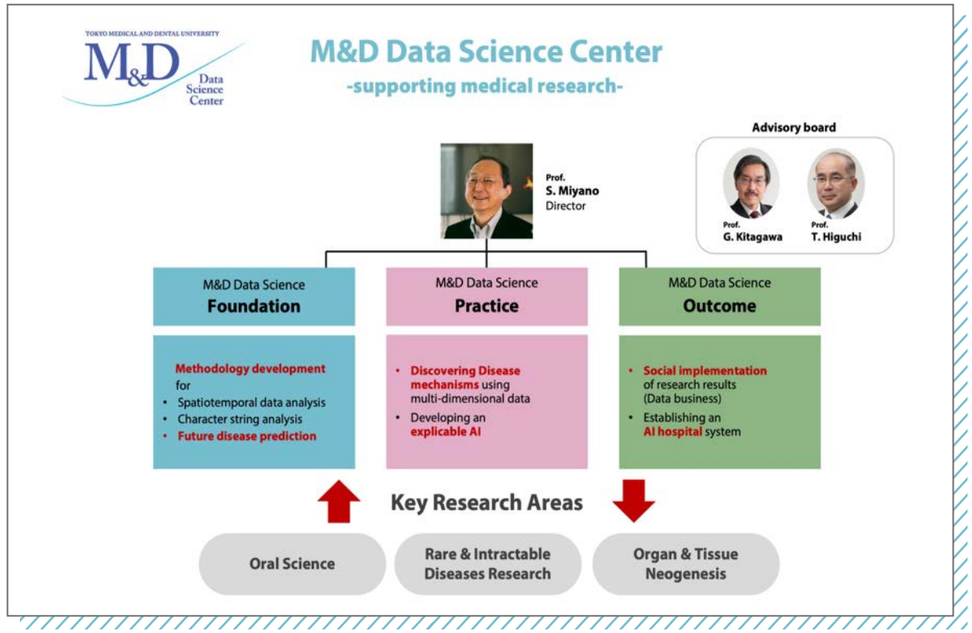
Executive Director /
Executive Vice President of Research,
Accreditation and Evaluation

Welcome to this page.
I am Akinori Kimura, the Executive Director and Vice President in charge of research. Here, I will introduce research at Tokyo Medical and Dental University (TMDU).
Our university is a national university with two faculties, Faculty of Medicine and Faculty of Dentistry, two graduate schools, Graduate School of Medical and Dental Sciences and Graduate School of Health Care Sciences, and two research institutes,Institute of Biomaterials and Bioengineering and Medical Research Institute, along with several research centers.
In 2013, TMDU was adopted as the program for promoting the enhancement of research universities by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), together with 18 other universities in Japan, and thereafter TMDU has established a system to strengthen research capabilities. Specifically, as shown in this figure, we have established two Institutes, one is the Institute of Research and the other is the Institute of Innovation Promotion. (Figure 1)



(Figure 1)

Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/executivedirector/index.html



(Figure 2)

The Institute of Research has implemented research support, promoted advanced multidisciplinary research in the biomedical field, and enhanced research in the priority area such as organ and tissue regeneration. On the other hand, the Institute of Innovation Promotion launched in 2020 has focused on collaborative research with industry, academia, and government by co-operating with the Institute of Open Innovation. Using these systems, we are now developing various methods and technologies in the medical, dentistry, biological, and engineering fields as a system to promote both basic and clinical research.

The topics of research in TMDU are disseminated both domestically and internationally. Of particular note was an English press release by Professor Takanori Takebe, who belongs to the Institute of Research. His group has developed a risk assessment system for drug-induced liver injury by using iPS cell-derived liver organoids, as reported in the Nature Medicine.

In addition, we established the M&D Data Science Center and invited Professor Satoru Miyano, a top runner of medical data science, as the director of the center, engaging for promotion of biomedical research based on multidimensional information to strengthen the data science research in the field of medicine and dentistry. (Figure 2)

We are currently facing the global epidemic of SARS-CoV-2 infection and are accepting many COVID-19 patients at our university hospital. At the same time, both basic and clinical research to overcome COVID-19 is underway. At present, over 80 projects are in progress. In addition to research related to the development of diagnosis and treatment for COVID-19 as individual research, several teams are participating in nation-wide clinical research such as therapeutic trials and COVID-19 sequelae research. As well, TMDU researchers have participated as leading members in a nation-wide collaborative research, so-called Joint Research Coronavirus Task Force, to elucidate the genetic factors related to the COVID-19 pathogenesis. The task force has also developed international joint research in collaboration with the COVID-19 Host Genetics Initiative, an international consortium.

Under these backgrounds, TMDU will set up an infectious disease platform and will promote both clinical and basic research to overcome or control various infectious diseases including COVID-19.

Lastly, TMDU will be a Designated National University from the fiscal year of 2022. We will continue to strengthen our research capabilities toward the realization of Total Healthcare in both nation-wide and world-wide scale.
Thank you for your attention.

5

Introducing the M&D Data Science Center

A center of gravity for biomedical data science in the world

Satoru Miyano

Director
M&D Data Science Center

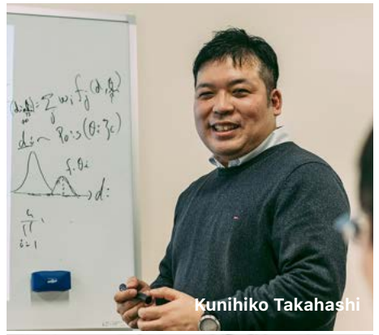

Satoru Miyano

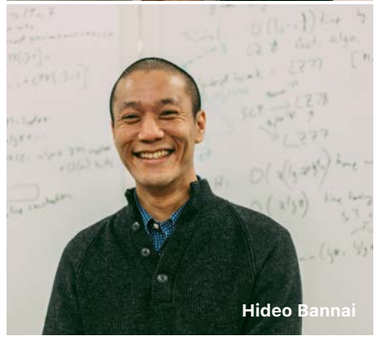
Approximately 900,000 patients are treated at Tokyo Medical and Dental University (TMDU) every year. It has amassed an enormous trove of clinical data with untapped potential to advance biomedical knowledge and improve the quality and efficacy of healthcare.
On a mission of digital transformation to mine its wealth of data for biomedical insights, M&D Data Science Center was established in April 2020 as Japan's new hub for AI-driven biomedical data science center.
When I started trying to headhunt experts to lead the medical and dental data science, I found there are very few data scientists and statisticians with the right background and skills to explore biomedical data using AI. So, an important objective of the Center is AI and Data Science education to train the next generation students. TMDU is now establishing a pioneering graduate program of AI education that will serve as a model medical data science program in Japan.


World's fastest supercomputer Fugaku

©RIKEN


Heewon Park


Kunihiko Takahashi


Hideo Bannai

Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/dsc//index.html

Messages from the heads of new departments.

Heewon Park

Professor, Department of AI Technology Development

Artificial intelligence, especially, explainable AI, plays a key role in uncovering disease mechanisms based on huge amounts of complex biomedical data. Our mission is to create novel AI methodologies that attain both statistical accuracy and interpretability, simultaneously.

Kunihiko Takahashi

Professor, Department of Biostatistics

Biostatistics has a central role in medical investigations as the science of data. We aim to develop methodologies for data analysis focused on medical, dental and healthcare applications, and will collaborate on practical research.

Hideo Bannai

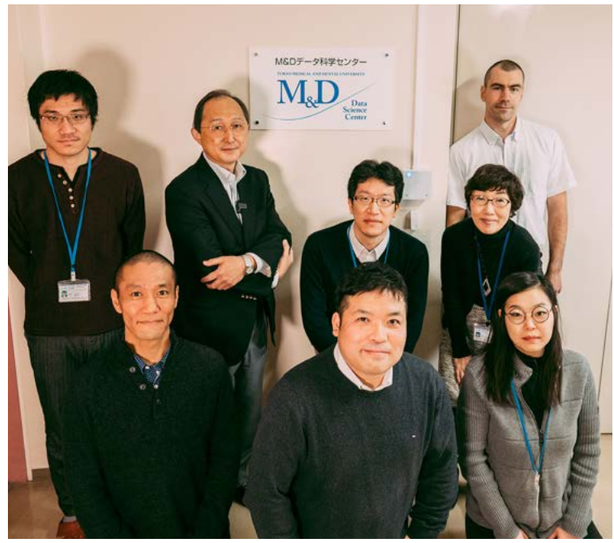
Professor, Department of Data Science Algorithm Design and Analysis

Algorithms are an essential component of data science, especially for handling large data sets. Our aim is to design algorithms and data structures that are both effective and efficient, in order to help manage and analyze various types of medical data.

The datasets are too large and complex to be analyzed by humans, so we need to use AI and powerful computing and storage platform. The Center combines state-of-the-art data infrastructure with unprecedented access to supercomputing facilities.

I previously led the University of Tokyo's Human Genome Center. M&D Data Science Center is a real opportunity to take the groundwork from the Human Genome Center's supercomputer SHIROKANE. Further, we are involved with the nearly-exascale computing power of supercomputer Fugaku. We are running "COVID-19 host whole genome project" and "the project for unravelling origin of cancer and diversity by large-scale data analysis and AI technology" on Fugaku. We have created a world-top powerful platform for biomedical data science.

We are a center of gravity for biomedical data science in the world.




Takanori Takebe

6 Features of TMDU Research

"My Medicine" with organoids - Predicting the future of liver-safe drugs

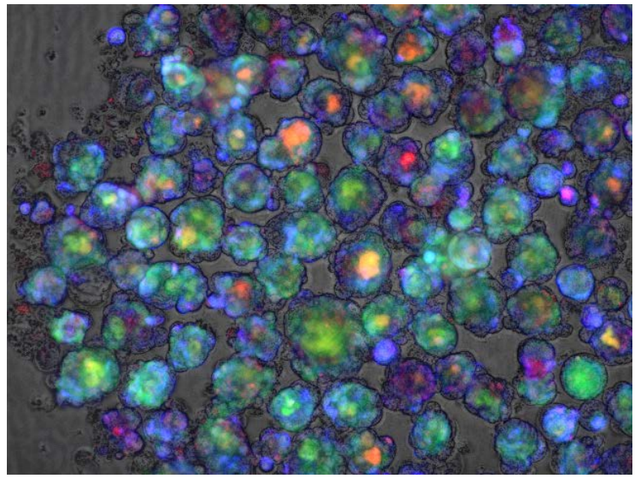
Takanori Takebe

Professor
Institute of Research, Division of Advanced Research

The ancient Romans studied the livers of sacrificial animals to read omens and make prophesies. Now researchers at Tokyo Medical and Dental University (TMDU) and Takeda-CiRA program along with a world-wide team of collaborators, have devised a polygenic risk score (PRS) based on liver genomics that can predict the likelihood of medications causing liver damage.

Introducing new drugs is a demanding process. Pharmaceutical research continually proffers potential drugs that need to be clinically trialed. These candidates are often more efficacious, but may have unacceptable or unsuspected side-effects. Unfortunately, adverse outcomes often require termination of new drug trials, and even drugs in common use may show a cumulated trend of undesired effects hitherto unpredicted; identifying patients at risk can greatly reduce this.

The liver is the primary site where most drugs, indeed any foreign potentially toxic chemical, is metabolized into an inactive form for excretion by the body. As a "frontliner" , it bears the brunt of most adverse effects that manifest as hepatocyte injury. Indeed, drug-induced-liver-injury (DILI) is the main reason why drugs are withdrawn at different stages of development, trial and usage, often after significant, and avoidable, morbidity and expense.


Color-stained confocal microscope image of multiple liver organoids used in this study
Green: Bile acid, Red: PI, Blue: ROS in human liver organoids

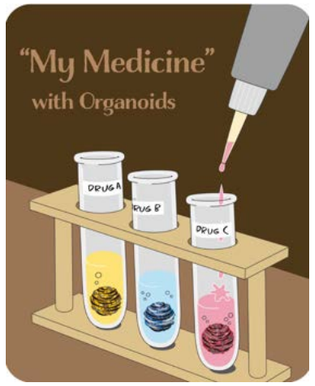


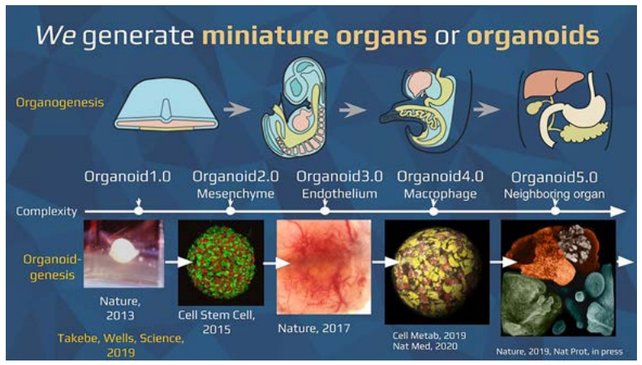
Illustration of "polygenicity in a dish" strategy

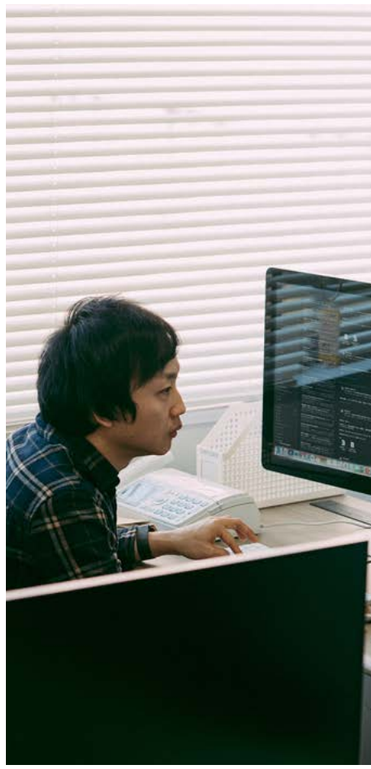
"We formulated our risk score by mathematically analyzing previous genome-wide association studies that had flagged variants likely to predict susceptibility to DILI," explains Masaru Koido, lead author. "We validated it across a spectrum of potentially hepatotoxic drugs, on genomic data, primary hepatocyte cultures and organoids from multiple donors. Noteworthy was our use of organoids—mini-organs bioengineered from three-dimensional tissue cultures derived from stem cells that replicate their microanatomy and functional complexity."

The researchers also analyzed the derived scores to delineate pathways underlying susceptibility to DILI. From the data they inferred that genetic variation at the hepatocyte level contributed to DILI susceptibility; moreover, DILI predictivity was shared across a variety of discrete drugs suggesting that the PRS related to intracellular mechanisms of hepatotoxicity.

"Our "polygenicity-in-a-dish" strategy allows safe, specific and multidimensional investigation into the pathogenesis of DILI," explains senior author Takanori Takebe. "A genetic test score will enable clinicians to tailor medication choice, dosage, and monitoring based on the patient' s estimated risk. Furthermore, drug trials could be made safer and better focused by excluding vulnerable subjects. However, further research is needed to upscale our PRS into a valid and reliable instrument for widespread screening of novel pharmaceuticals in clinical practice.

Genotyped human liver organoids will be tested to determine patients' precision against drug induced effects.





Paper Information

"Polygenic architecture informs potential vulnerability to drug-induced liver injury"

Masaru Koido, Eri Kawakami, Junko Fukumura, Yui Noguchi, Momoko Ohori, Yasunori Nio, Paola Nicoletti, Guruprasad P Aithal, Ann K Daly, Paul B Watkins, Hisashi Anayama, Yvonne Dragan,Tadahiro Shinozawa, Takanori Takebe

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/takebe/index.html

Nothing but the truth in the fight against cancer

Hiroshi Asahara

Professor
Systems BioMedicine, Graduate School of Medical and Dental Sciences

Ryota Kurimoto

Assistant Professor
Systems BioMedicine, Graduate School of Medical and Dental Sciences

The development and progression of cancer is a complicated process that occurs when cells in the body grow out of control. Many different mechanisms and pathways that directly affect cell proliferation have been uncovered. Researchers from Tokyo Medical and Dental University (TMDU) have made an additional discovery; a unique anti-cancer function for an enzyme previously believed to only influence RNA molecule structure.

In a report published in The EMBO Journal, a group of researchers from TMDU detail the identification of the protein TruB1 as a regulator of the microRNA (miRNA) let-7, which has significant implications for the fight against various cancers.

MiRNAs are small RNA molecules that serve as a sort of molecular brakes. They work by blocking certain gene expression messages from being formed into proteins. Let-7 was one of the first of over 1,500 miRNAs to be discovered and is present in the cells of many species, including humans. Previous work has shown that many tumor cells have fewer let-7 molecules than normal cells, and therefore this miRNA may be important in cancer development. Because of this, the researchers at TMDU were curious if there were any cellular proteins that could help increase the amount of let-7 present in cells.

“Let-7 is a very important miRNA in human cells that can affect many processes from development to tumor suppression,” says lead author of the study Ryota Kurimoto. “However, it is still unclear how levels of let-7 in cells are controlled, so we wanted to investigate this further.”

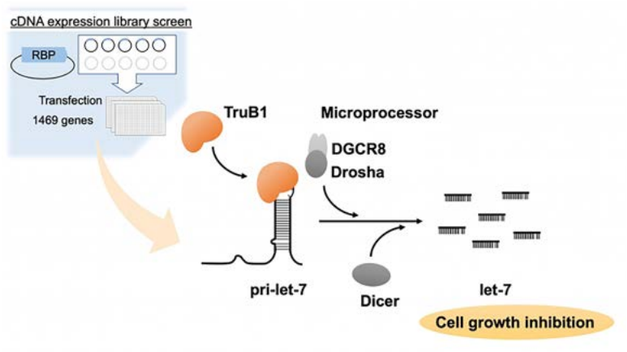
To do this, the researchers performed a cell-based screening of proteins that can bind to RNA molecules. They did this with a system called a luciferase assay, which helped them identify proteins that could assist with increasing let-7 levels.

“Our main finding was quite unexpected,” describes Hiroshi Asahara, senior author. “The protein TruB1 significantly promoted maturation of let-7 in our experiments.”

The results were mainly surprising because TruB1 had previously only been characterized as a protein that participates in a process called RNA modification.

“When binding to let-7, TruB1 didn’t perform the modification it had always been known for,” says Kurimoto. “In fact, TruB1 helped other proteins bind to let-7, which enhanced expression levels of this miRNA.”

Additionally, through regulation of let-7, TruB1 could suppress growth and division of cells. This is quite significant because it implies that TruB1 has an anti-cancer role in cells. This study provides crucial information that will be critical for the development of novel cancer therapeutics.



TruB1 promotes the maturation of let-7
A cell-based screening for novel let-7 regulators identified a tRNA pseudouridine synthase, TruB1. TruB1 directly binds to the stem - loop structure of pri - let-7 and promotes the maturation steps of let-7, selectively.

Paper Information

“The tRNA pseudouridine synthase TruB1 regulates the maturation of let-7 miRNA”

Ryota Kurimoto, Tomoki Chiba, Yoshiaki Ito, Takahide Matsushima, Yuki Yano, Kohei Miyata, Yuka Yashiro, Tsutomu Suzuki, Kozo Tomita, Hiroshi Asahara

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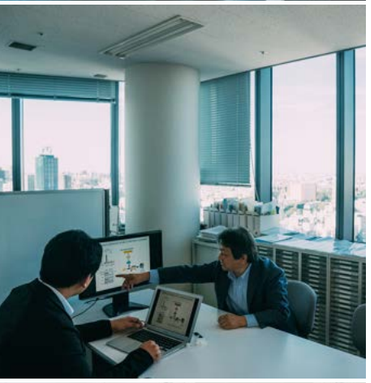
Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/asahara/index.html


Shigeomi Shimizu



How cells decide the way they want to recycle their content

Shigeomi Shimizu

Professor
Pathological Cell Biology, Medical Research Institute

Satoru Torii

Junior Associate Professor
Pathological Cell Biology, Medical Research Institute

Autophagy is a housekeeping process through which cells remove dysfunctional contents to balance energy sources during times of stress. Now, researchers from Tokyo Medical and Dental University (TMDU) identified a novel molecular mechanism by which a type of autophagy, called alternative autophagy, is activated. In a new study published in Nature Communications, they showed how a specific phosphorylation site of the protein Unc51-like kinase 1 (Ulk1) is essential for the cell to go down the alternative autophagy path.

As living structures, cells ensure homeostasis by carrying out specific processes by which they build and degrade their contents. Particularly at times of stress, for example during exposure to toxins, autophagy helps to ensure an orderly turnover process by which cells can recycle their contents to survive. Interestingly, the process of autophagy can take place by several distinct molecular mechanisms, two of which are canonical and alternative autophagy. While the protein Ulk1 is known to initiate both types of autophagy, the mechanism by which Ulk1 differentially regulates them has remained unclear.

"Autophagy is a very elaborate process by which cells recycle their contents," says the corresponding author of the study Shigeomi Shimizu. "The goal of our study was to understand how Ulk1 that has control over two types of autophagy, differentially regulates them."

To achieve their goal, the researchers used mouse embryonic fibroblasts (MEFs) deficient in the protein Atg5 to turn off canonical autophagy. By exposing them to etoposide, a DNA-damaging reagent, they then induced alternative autophagy. Using mass spectrometry, the researchers found that Ulk1 carried an additional phosphoryl group at its amino acid serine in position 746 (Ser746; p-Ulk1746), also called phosphorylation, when exposed to etoposide but not when left untreated. By developing a new antibody against p-Ulk1746, the researchers then showed that the protein localized to the Golgi complex within the cells. The Golgi complex is an organelle participating in many cellular processes, including alternative autophagy.

"While these were already exciting findings, our goal was to understand whether the specific phosphorylation of Ulk1 at the serine 746 site is required for alternative autophagy and which kinase is responsible for this phosphorylation step," says lead and the corresponding author of the study Satoru Torii.

To analyze the causal relationship between Ulk1 Ser746 phosphorylation and alternative autophagy, the researchers used a fluorescent tandem protein consisting of red fluorescent protein (RFP) and green fluorescent protein (GFP). Because GFP does not fluoresce within acidic environments, the tandem protein made autolysosomes, cellular compartments that are created during autophagy, become red. While the red fluorescence appeared after etoposide treatment, it was not generated in cells producing Ulk1 nonphosphorylated mutant, indicating that p-Ulk1746 is required for alternative autophagy. Next, the researchers demonstrated that receptor-interacting protein kinase 3 (RIPK3), a protein that phosphorylates other proteins involved in necroptosis, is responsible for the generation of p-Ulk1746 by showing that p-Ulk1746 and alternative autophagy occurred in normal cells but not in cells deficient in RIPK3. Intriguingly in MEFs that expressed Atg5, canonical autophagy was not affected by RIPK3-deficiency, indicating that p-Ulk1746 is not involved in canonical autophagy.

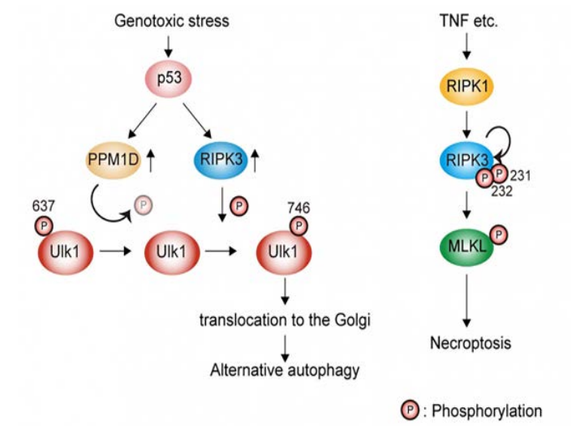


Figure : Elucidation of regulatory mechanism of Ulk1 in alternative autophagy. Genotoxic stress induces Ulk1 dephosphorylation at Ser637 in a p53/PPM1D-dependent manner. The dephosphorylated Ulk1 is then phosphorylated at Ser746 by a necroptosis initiator, RIPK3, and translocates to the Golgi, which results in alternative autophagy (left). TNF signaling induces necroptosis but not alternative autophagy (right).

"These are striking results that shed new light on how cells regulate the complex process of autophagy," says Shimizu. "We hope that our findings will be helpful in understanding the role of alternative autophagy in normal biology and disease."


Satoru Torii

Paper Information

"Identification of a phosphorylation site on Ulk1 required for genotoxic stress-induced alternative autophagy"

Satoru Torii, Hirofumi Yamaguchi, Akira Nakanishi, Satoko Arakawa, Shinya Honda, Kenta Moriwaki, Hiroyasu Nakano, Shigeomi Shimizu

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/shimizu/index.html


Fumitoshi Ishino

Generation of three-dimensional heart organoids

Fumitoshi Ishino

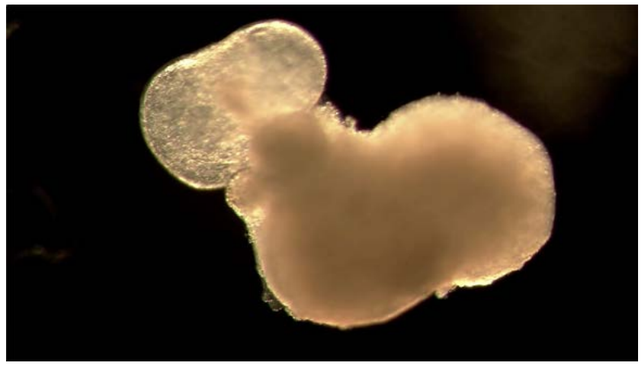
Professor
Epigenetics, Medical Research Institute

Jiyoung Lee

Associate Professor
Epigenetics, Medical Research Institute


Jiyoung Lee

Heart organoid generated from mouse ES cells



This heart organoid has atria- and ventricle-like structures and also exhibits beating movement.

Heart development as it happens in vivo, or in a living organism, is a complex process that has traditionally been difficult to mimic in vitro, or in the laboratory. In a new study, researchers from Tokyo Medical and Dental University (TMDU) developed three-dimensional functional heart organoids from mouse embryonic stem cells that closely resemble the developing heart.

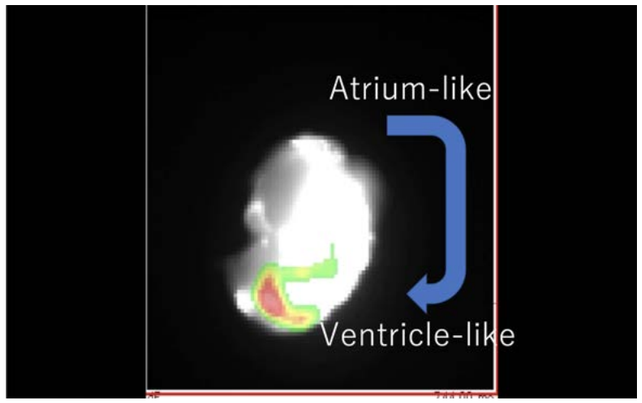
The heart consists of multiple layers of tissue including many different cell types, including working heart muscle, connective tissue cells, and cells that make up blood vessels. These cells work together to ensure a proper functioning of the heart and thus the constant supply of fresh, oxygenated blood to the rest of the body. Studying all forms of heart disease in the laboratory and developing novel drugs to treat these diseases require disease models that closely resemble the actual heart. While effort has been made to generate heart muscle cells in vitro, these cells present as clumps without the tissue organization seen in vivo.

“Despite its seemingly simple function, the heart is a complex organ with an even more complex structure,” say corresponding authors of the study Professors Jiyoung Lee and Fumitoshi Ishino. “To achieve that level of structural complexity, during development the heart is exposed to a myriad of signals. We wanted to capitalize on our knowledge of the signaling molecules during heart development and generate heart organoids that resemble the developing heart more closely than current techniques.”

To achieve their goal, the researchers looked into the factors involved in heart development in vivo and speculated that the protein fibroblast growth factor 4 (FGF4) and a complex consisting of the proteins laminin and entactin (LN/ET complex), all of which are known are expressed in the embryonic heart, are necessary and sufficient to enable structural similarity between the heart organoids and the actual embryonic heart. Indeed, mouse embryonic stem cells exposed to FGF4 and LN/ET showed considerable similarity to the developing heart based on structural as well as molecular analyses.

Intriguingly, the process of development in the heart organoids closely reflected the morphological changes during embryonic heart development in vivo. A closer look at the cellular components making up the heart organoids revealed that cells of the embryonic heart, including cells of all four chambers as well as of the conduction system, were present in the structural organization seen during embryonic development. Importantly, the heart organoids possessed functional properties close to their in vivo-counterpart.

“These are striking results that show how our method provides a biomimetic model of the developing heart using a rather simple protocol. This tool could be helpful in studying the molecular processes during heart development, and in developing and testing novel drugs against heart disease,” say Professors Lee and Ishino.



Paper Information

“In vitro generation of functional murine heart organoids via FGF4 and extracellular matrix”

Jiyoung Lee, Akito Sutani, Rin Kaneko, Jun Takeuchi, Tetsuo Sasano, Takashi Kohda, Kensuke Ihara, Kentaro Takahashi, Masahiro Yamazoe, Tomohiro Morio, Tetsushi Furukawa, Fumitoshi Ishino

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/ishino/index.html

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/katagiri/index.html

How poor oral hygiene may result in metabolic syndrome

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Masahiro Hatasa

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Periodontal or gum disease is known to be a significant risk factor of metabolic syndrome, a group of conditions increasing the risk for heart disease and diabetes. In a new study, researchers from Tokyo Medical and Dental University (TMDU) discovered that infection with Porphyromonas gingivalis, the bacterium causing periodontal disease, causes skeletal muscle metabolic dysfunction, the precursor to metabolic syndrome, by altering the composition of the gut microbiome.

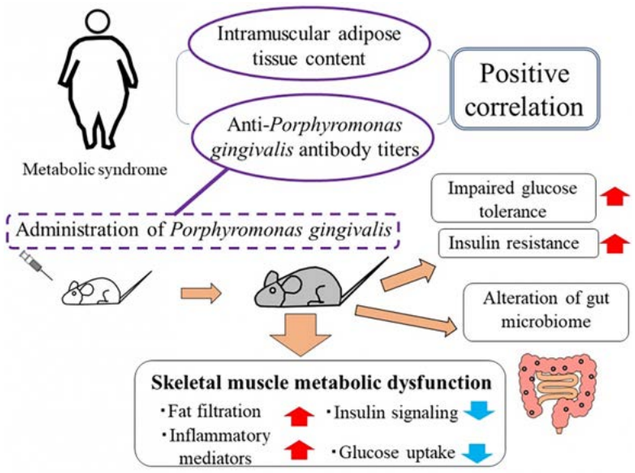
Periodontal bacteria have long been known to cause inflammation within the oral cavity, but also systemically increase inflammatory mediators. As a result, sustained infection with periodontal bacteria can lead to increases in body weight and lead to increased insulin resistance, a hallmark of type 2 diabetes. The function of insulin is to help shuttle glucose from the blood into tissues, most importantly to skeletal muscle, where one quarter of all glucose in stored. Unsurprisingly, insulin resistance plays a key role in the development of metabolic syndrome, a group of conditions including obesity, altered lipid metabolism, high blood pressure, high blood glucose levels, and systemic inflammation. Although skeletal muscle plays a key role in decreasing blood glucose levels, a direct connection between periodontal bacterial infection and the metabolic function of skeletal muscle has not been established yet.

“Metabolic syndrome has become a widespread health problem in the developed world,” says first author of the study Kazuki Watanabe. “The goal of our study was to investigate how periodontal bacterial infection might lead to metabolic alterations in skeletal muscle and thus to the development of metabolic syndrome.”

To achieve their goal, the researchers first investigated antibody titers to Porphyromonas gingivalis in the blood of patients with metabolic syndrome and found a positive correlation between antibody titers and increased insulin resistance. These results showed that patients with metabolic syndrome were likely to have undergone infection with Porphyromonas gingivalis and thus have mounted an immune response yielding antibodies against the germ. To understand the mechanism behind the clinical observation, the researchers then turned to an animal model. When they gave mice that were fed a high-fat diet (a pre-requisite to developing metabolic syndrome) Porphyromonas gingivalis by mouth, the mice developed increased insulin resistance, and fat infiltration and lower glucose uptake in the skeletal muscle compared with mice that did not receive the bacteria.

But how was this bacterium capable of causing systemic inflammation and metabolic syndrome? To answer this question, the researchers focused on the gut microbiome, the network of bacteria present in the gut and with which the organism co-exists symbiotically. Intriguingly, the researchers found that in mice administered with Porphyromonas gingivalis the gut microbiome was significantly altered, which might decrease insulin sensitivity.

“These are striking results that provide a mechanism underlying the relationship between infection with the periodontal bacterium Porphyromonas gingivalis and the development of metabolic syndrome and metabolic dysfunction in skeletal muscle,” says corresponding author of the study Professor Sayaka Katagiri.



Summary of the study

Anti-Porphyromonas gingivalis antibody titers positively correlated with intramuscular adipose tissue content in metabolic syndrome patients. Administration of P. gingivalis impaired glucose tolerance and insulin resistance, altered the gut microbiome. Skeletal muscle of recipients of P. gingivalis exhibited fat infiltration and lower glucose uptake with higher inflammatory mediators and lower insulin signaling.

Paper Information

“Porphyromonas gingivalis impairs glucose uptake in skeletal muscle associated with altering gut microbiota”

Kazuki Watanabe, Sayaka Katagiri, Hirokazu Takahashi, Naoki Sasaki, Shogo Maekawa, Rina Komazaki, Masahiro Hatasa, Yoichiro Kitajima, Yusuke Maruyama, Takahiko Shiba, Keiji Komatsu, Yujin Ohsugi, Kenichi Tanaka, Ayumi Matsuzawa, Tomomitsu Hirota, Haruka Tohara, Yuichiro Eguchi, Keizo Anzai, Atsuhiko Hattori, Takanori Iwata

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Publication Date : Epub 2020 Nov 16.
DOI : 10.1096/fj.202001158R

Link to the Paper
https://doi.org/10.1096/fj.202001158R

“Endotoxemia by Porphyromonas gingivalis alters endocrine functions in brown adipose tissue”

Masahiro Hatasa, Yujin Ohsugi, Sayaka Katagiri, Sumiko Yoshida, Hiromi Niimi, Kazuki Morita, Yosuke Tsuchiya, Tsuyoshi Shimohira, Naoki Sasaki, Shogo Maekawa, Takahiko Shiba, Tomomitsu Hirota, Haruka Tohara, Hirokazu Takahashi, Hiroshi Nitta and Takanori Iwata

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Publication Date : 19 January 2021.
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Reversible stickiness is something to smile about

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Nobuhiko Yui

Atsushi Tamura

Everyone who has had tooth cavities filled knows that the best dental materials stay where the dentist puts them. The adhesion of currently available dental materials to tooth surfaces continues to improve, but what about short-term treatments that are not supposed to adhere indefinitely? Tokyo Medical and Dental University (TMDU) researchers have developed a method of making dental materials easier to remove; their findings are published in ACS Applied Polymer Materials.

The continual improvement of long-lasting caries treatments can be regarded a triumph of dental material research. However, there are dental procedures that require non-permanent adhesion to the tooth surface, such as the fixing of orthodontic brackets. Removing adhered materials after such procedures generally requires mechanical detachment that can damage tooth enamel.

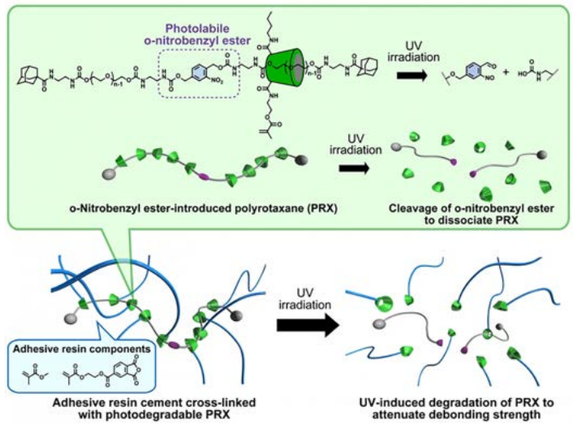
Efforts to improve removal processes have produced materials that are weakened by triggers, such as heat or electric currents. However, approved sources of these stimuli are not readily available in standard dental clinics. The researchers therefore focused on UV light-responsive materials that can be triggered by the UV sources widely used by dentists to cure resin cements and composites.

The toughness of many dental cements is a result of mixing them with a cross-linker that locks the cement molecules to each other to form a stable network. The researchers have introduced a chemical 'switch' into a new cross-linker that opens when UV light is shined on it.

"The cross-linker structure resembles rings threaded onto a piece of string with bulky stoppers at each end," study lead author Atsushi Tamura explains. "We have added a section to the string—an o-nitrobenzyl ester group—that breaks under UV light causing the rings to slide off. This has a significant effect on the stability of the cement material the cross-linker is holding in place."

The researchers used their cross-linker to stabilize a commercially available resin cement that was used to stick two polymer blocks together, or to attach a polymer block to a bovine tooth. After shining UV light on the cross-linked cement for just 2 minutes, the cement showed a significant reduction in adhesion strength in both tests, meaning separation of the bonded materials was easier following UV treatment.

"We are very encouraged by the initial findings using our cross-linker," study corresponding author Nobuhiko Yui explains. "Although the UV wavelength used to disrupt the material was not clinically appropriate in this case, we intend to develop the chemistry of our internal switch so that it can provide a facile and readily accessible method of removing adhesives in the clinic."



UV light-embrittled dental resin cement containing photodegradable polyrotaxane cross-linkers.
To facilitate the debonding of dental restorative materials adhered on tooth surfaces, UV light-embrittled dental resin cement containing photodegradable polyrotaxane (PRX) cross-linkers was developed. PRX is a supramolecular interlocked polymer composed of α-cyclodextrin threaded on a linear polymer chain capped with bulky stopper molecules. The photodegradable PRXs containing photolabile o-nitrobenzyl ester was newly designed and used as a cross-linker of dental resin cements. The UV irradiation cleaves o-nitrobenzyl ester and the PRXs are dissociated, leading to decreasing the adhesive force of the dental resin cements. The plastic block was adhered on to the surface of bovine dentin using adhesive resin cement cross-linked with photodegradable PRXs, and the adhesive strength between plastic and dentin was clinically acceptable value. By contrast, the adhesive force was decreased by approximately 60% through the irradiation of UV light for 2 min, due to the photodegradation of PRX cross-linkers. This result suggests that the adhesive resin cement containing photodegradable PRX cross-linkers is a promising candidate for facilitating the debonding of dental materials from tooth surfaces via UV light irradiation.

Paper Information

"Light-Embrittled Dental Resin Cements Containing Photodegradable Polyrotaxane Cross-Linkers for Attenuating Debonding Strength"

Satomi Matsunaga, Atsushi Tamura, Mayu Fushimi, Hokuto Santa, Yoshinori Arisaka, Toru Nikaido, Junji Tagami Nobuhiko Yui

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/yui/index.html

Tetsuro Watabe

Shintaro Sakakitani

6 Features of TMDU Research

β-AR agonist therapy puts the brakes on oral cancer progression

Tetsuro Watabe

Professor
Biochemistry, Graduate School of Medical and Dental Sciences

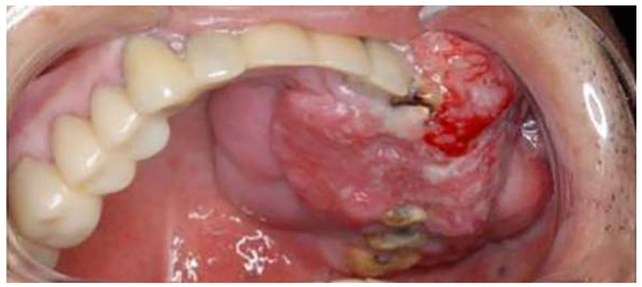
Affecting almost 600,000 people worldwide every year, and with only a 50% survival rate, oral squamous cell carcinoma (OSCC) is one of the more common and deadly forms of cancer. The poor prognosis of OSCC patients is mainly attributed to a lack of therapies that block the metastasis, or spread, of cancer cells from the primary tumor to other sites in the body.

Prior to metastasis, cancer cells undergo a series of changes that cause them to become motile and more invasive. This process, called epithelial - mesenchymal transition (EMT), equips cancer cells with everything they need to travel through the lymphatic system and form secondary tumors. Furthermore, recent reports imply that EMT also confers cancer cells with tumor initiation activity and drug resistance.

Working on the theory that disrupting EMT should prevent cancer progression and therefore reduce OSCC mortality rates, researchers from Tokyo Medical and Dental University (TMDU) screened a panel of small chemical compounds for their ability to reverse the process of EMT in oral cancer cells. The results, published this month in Cancer Science, may represent an exciting new avenue for the treatment of OSCC.

"We identified a β2 - adrenergic receptor (β2 - AR) agonist called isoxsuprine that effectively interfered with EMT," says lead author of the study Shintaro Sakakitani. "Interestingly, previous studies have provided conflicting results regarding the involvement of β-ARs in tumorigenesis—some reports suggest that β-AR signaling is important in tumor progression, while others point to a protective role for β-AR induction."

After treating a range of oral cancer cell types with isoxsuprine, the researchers found that the resulting increase in β2-AR expression significantly



Katarzyna A. Podyma - Inoue

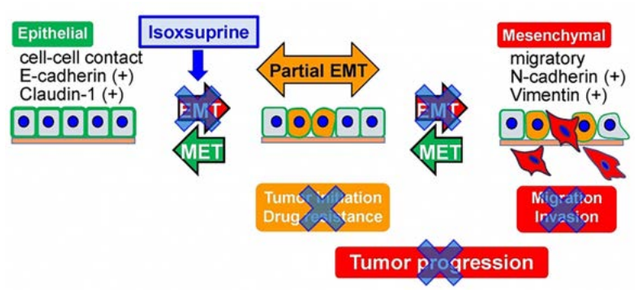
Assistant Professor
Biochemistry, Graduate School of Medical and Dental Sciences

impaired EMT and reduced cell motility. A non-selective agonist called isoprenaline, which enhances the expression of all types of β- adrenergic receptor not just β2, produced a similar result.

Confirming the protective role of β-AR activation, the researchers then pre-treated cells with a chemical that prevents receptor expression, resulting in enhanced EMT. Further, deletion of the gene coding for β2 - AR completely abolished the protective effects of isoxsuprine.

As a further test of treatment efficacy, the researchers established tumors in mice and provided daily treatment with either isoxsuprine or a placebo. Not surprisingly, at the end of the treatment period, mice that received isoxsuprine had significantly smaller tumors compared with the placebo group, confirming the tumor-suppressive effects of isoxsuprine.

"These results are hugely encouraging," says senior author Katarzyna Anna Podyma-Inoue. "The efficacy of β-AR-agonist therapy in both the in vitro and in vivo models suggests that this group of compounds may be the answer to preventing metastasis in OSCC and could potentially even inhibit tumor growth, offering a much better prognosis for OSCC patients worldwide."



Activation of β2-adrenergic receptor signals inhibit progression of oral cancer by suppressing mesenchymal phenotypes

In this study we identified isoxsuprine, a β2-adrenergic receptor agonist as an effective inhibitor of mesenchymal phenotypes and migration of oral squamous cell carcinoma cells suggesting that β2-adrenergic receptor signal is a new promising therapeutic target for treatment of oral cancer.

Katarzyna A. Podyma - Inoue

Paper Information

"Activation of β2-adrenergic receptor signals suppresses mesenchymal phenotypes of oral squamous cell carcinoma cells"

Shintaro Sakakitani Katarzyna A. Podyma-Inoue Rina Takayama Kazuki Takahashi Mari Ishigami-Yuasa Hiroyuki Kagechika Hiroyuki Harada Tetsuro Watabe

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/watabe/index.html


Kohsuke Imai


Tzu-WenYeh

Human lifelong immunity depends on APRIL

Kohsuke Imai

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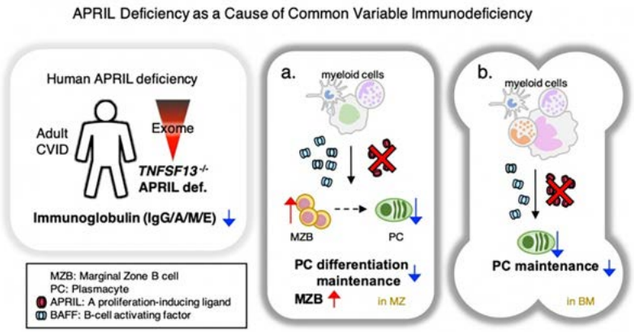
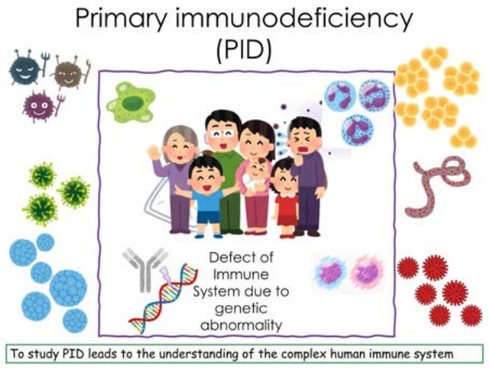


The first APRIL deficiency was found in an adult common variable immunodeficiency patient. We performed whole exome sequencing in the patient and found the homozygous deletion mutation in TNFSF13. Based on the findings in the APRIL-deficient patient, APRIL is critical for life-long maintenance of plasmacytes to produce immunoglobulins in humans. We assumed that the functional defect in B cells due to APRIL deficiency occurs at a) plasmacyte differentiation from memory/MZ B cells, and b) life-long maintenance in the bone marrow.

The immune system depends on a complex interaction between various cells for proper functioning. In a new study, researchers from Tokyo Medical and Dental University (TMDU) discovered that an absence of the protein APRIL in humans results in the underdevelopment of antibody-producing plasmacytes causing common variable immunodeficiency (CVID), a condition which is characterized by increased susceptibility to infections of affected patients.

Plasmacytes, whose lifelong task is to keep producing immunoglobulins, are a key component of the immune system. They develop when B cells, a type of immune cell, are activated by T cells and other blood cells, called myeloid cells, and switch from producing low-quality to high-quality antibodies. Because each plasmacyte produces one specific antibody, their development is closely regulated and thus depends on a complex interaction between B cells and myeloid cells. A protein that is part of this process is APRIL (A PRolif-eration-Inducing Ligand), which is produced by myeloid cells to induce the development of plasmacytes from B cells. Could defects in APRIL result in immunodeficiency in humans? Until now this was unknown.



"There are countless components within the complex immune system machinery," says corresponding author Kohsuke Imai. "Disrupting one of them can severely decrease the immune system's ability to fight infections. The goal of our study was to understand how a deficiency of APRIL affects the human immune system."

To achieve their goal, the researchers sequenced all protein-coding part of DNA of a patient with CVID and found a mutation in the gene encoding APRIL, resulting in an absence of APRIL in the patient's blood. Upon closer investigation of the makeup of the patient's blood cells, the researchers found that the patient had increased levels of marzinal zone B cells and reduced levels of plasmacytes and immunoglobulins.

"These findings suggest that a deficiency of APRIL disrupts the development of immunoglobulin-producing plasmacytes," says lead author Tzu-Wen Yeh. "Our next goal was to determine if APRIL not only correlates with, but also causes immunodeficiency."

The researchers isolated blood cells from the patient and reprogrammed them to become induced pluripotent stem cells (iPSCs), which have the capability of producing any cell of the body. Because the patient had a genetic mutation in the gene encoding APRIL, the iPSCs did so too. The researchers then differentiated the iPSCs to monocyte-derived dendritic cells(iPSC-moDCs), which induce plasmacyte differentiation from B cells. When the patient derived iPSC-moDCs were cocultured with B cells from healthy controls the researchers found that plasmacyte differentiation was impaired, again showing that APRIL plays an important role in plasmacyte development. However, when the researchers added recombinant APRIL to the coculture, plasmacyte development was rescued, demonstrating that the absence of APRIL was the cause in the patient's CVID.

"These are striking results that show how APRIL has an essential function in the proper functioning of the immune system," says Kohsuke Imai. "Our findings provide new insights into plasmacyte maintenance and immunoglobulin production. To our knowledge, our study provides the first report to show that deficiency in APRIL is linked to common variable immunodeficiency in humans. Substitution of recombinant APRIL in congenital or acquired APRIL deficiency might even be a potential novel treatment for the immunodeficiency due to hypogammaglobulinemia."

Paper Information

"APRIL-dependent lifelong plasmacyte maintenance and immunoglobulin production in humans"

Tzu-WenYeh, Tsubasa Okano, Takuya Naruto, Motoi Yamashita, Miko Okamura, Kay Tanita, Likun Du, Qiang Pan-Hammarström, Noriko Mitsui, Satoshi Okada, Hirokazu Kanegane, Kohsuke Imai, Tomohiro Morio

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Link to the Video
http://www.tmd.ac.jp/english/research_activities/Vol-6/imai/index.html


Koju Kamoi

The natural artistry of disease: a wintry landscape in the eye

Koju Kamoi

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Kyoko Ohno-Matsui

Professor
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Leukemias and lymphomas are life-threatening malignancies affecting white blood cells and the immune system; fortunately, radiotherapy and chemotherapy, combined with stem cell therapy, can improve survival significantly. Now, Japanese researchers report one such patient who presented with an intriguing and rare delayed ocular complication descriptively named frosted branch angiitis.

A Japanese woman in her early fifties was diagnosed with acute-type adult T-cell leukemia-lymphoma associated with human T-cell lymphotropic virus type 1 (HTLV-1). She was managed with whole body irradiation and anti-cancer drugs, followed by allogeneic (donor) human stem cell transplant (HSCT). HSCT allows physicians to use higher doses of chemoradiotherapy as the patient gets an infusion (transplant) of blood-forming stem cells to restore collaterally damaged bone marrow. The patient went into remission and had no complications for several years.

Over four years after HSCT, she developed blurred vision and was referred for further examination. A slit-lamp biomicroscope, which shines a thin sheet of light into the eye for inspection, revealed cellular infiltrates in both segments. Junior Associate Professor Koju Kamoi, lead / corresponding author, describes the remarkably picturesque fundoscopy findings. "Along the retinal blood vessels, a translucent sheath was visible resembling the icy branches of a tree in winter. We recognized this as frosted branch angiitis (Figure A), a rare presentation of florid retinal vasculitis."

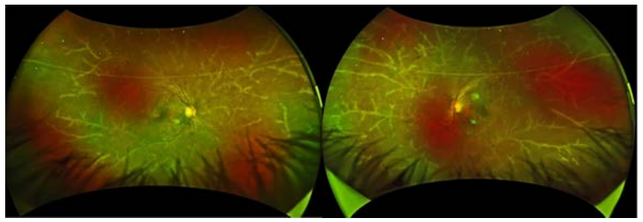


Figure A
Widefield imaging of frosted branch angiitis

The medical team ran a battery of tests to rule out recurrence, other autoimmune disease, and bacterial, viral or fungal infections. Therefore, the physicians concluded that the frosted branch angiitis resulted from immune activation following HSCT. First described in the Japanese literature by Ito in 1976 occurring in a six-year-old child, frosted branch angiitis is very rare, with most cases reported from Japan and sporadically from other countries.

The patient was treated with corticosteroids to suppress inflammation. After six months the lesion regressed but steroids were continued for over a year. Surprisingly, a month after stopping systemic steroids, the patient developed a skin rash (Figure B) and dryness of both eyes. "This sequence of events suggests that frosted branch angiitis was likely the first sign of systemic inflammation," explains Dr Kamoi. "Steroids could have suppressed the slower skin and eye-surface changes that were expressed following discontinuation."

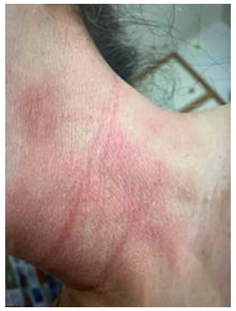
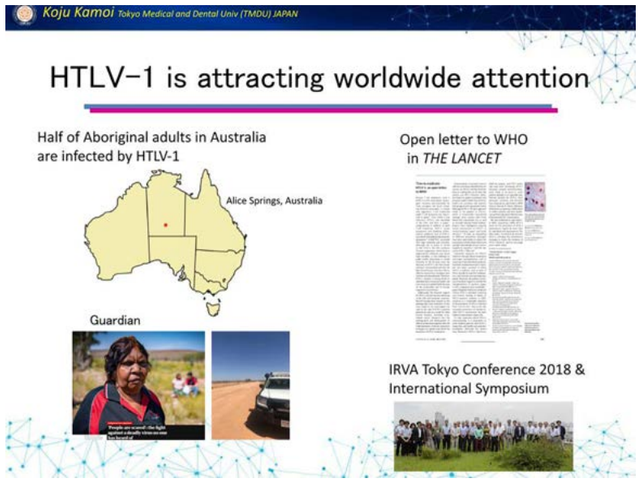


Figure B
A skin rash around her neck

"Though HSCT is beneficial in many situations, it may activate the immune system adversely," warns Professor Kyoko Ohno-Matsui, senior author. "Frosted branch angiitis could serve as early warning sign of inflammation elsewhere in the body. Therefore, intraocular monitoring is warranted in these patients."




Kyoko Ohno-Matsui

Paper Information

"Frosted branch angiitis after allogeneic haematopoietic stem cell transplantation in adult T-cell leukaemia-lymphoma"

Koju Kamoi, Seiko Kato, Kaoru Uchimaru, Arinobu Tojo, Kyoko Ohno-Matsui

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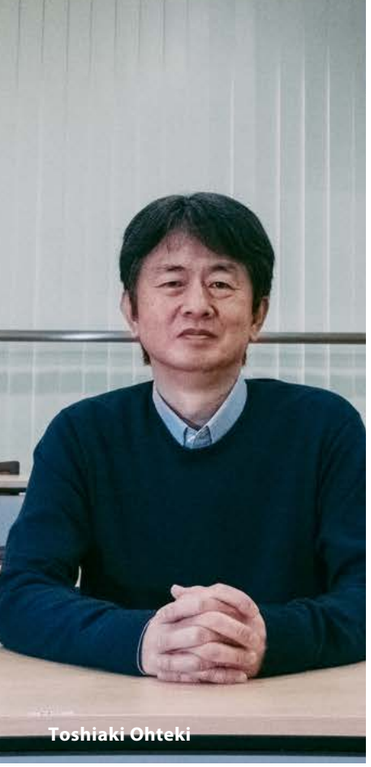
Toshiaki Ohteki

A new molecular guardian of intestinal stem cells

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Taku Sato

Junior Associate Professor
Biodefense Research, Medical Research Institute

Intestinal stem cells keep a fine balance between two potential forms: remaining as stem cells, or developing into intestinal epithelial cells. In a new study, researchers from Tokyo Medical and Dental University (TMDU) discovered a novel molecular mechanism that regulates this balance and preserves the stemness of intestinal stem cells—that is, their ability to develop into any intestinal epithelial cell type.

The inner lining of intestines, the intestinal epithelium, ensures adequate digestion and adsorption of nutrients. It is made up of several different cell types, all of which fulfill a specific function. Intestinal stem cells ensure proper functioning of the intestines, which requires constantly replacing old and damaged cells with young cells, by developing, or differentiating, into one of the different intestinal epithelial cell types when needed. Because there is a constant demand for new cells, intestinal stem cells have the ability to self-renew, thereby providing a constant supply of stem cells as well. However, little is known about the mechanisms that regulate this balance between self-renewal and differentiation.

"Just like any other type of stem cell, intestinal stem cells have the ability to differentiate into any cell within their lineage," says corresponding author of the study Professor Toshiaki Ohteki. "But they have to do it in a regulated manner, only differentiating when needed. The goal of our study was to understand the regulatory mechanism that preserves the stemness of intestinal stem cells."

To achieve their goal, Taku Sato, a main contributor of this project, and collaborators focused on a molecular signaling pathway that they had previously shown to preserve the stemness of hematopoietic stem cells (HSCs) that give rise to blood cells. Interferons are molecules that are produced especially during viral and bacterial infections, but more recently it was also shown that they are present even in the absence of infections to regulate various biological processes. In either case, interferons induce the expression of certain genes, a process that is regulated by the protein interferon regulatory factor-2 (IRF2) to ensure that the actions of interferons are balanced. In the case of HSCs, IRF2 turned out to be a critical factor for their stemness.

In the current study, the researchers found that IRF2 is produced throughout the intestinal epithelium and that IRF2-deficient mice had normal anatomical structure during homeostasis (the absence of an infection or any other damaging factor). However, in the presence of 5-fluorouracil, which is known to damage the intestinal epithelium, normal mice were able to regenerate completely, but IRF2-deficient mice showed a blunted regenerative response (Figure 1), indicating that intestinal stem cells were not able to function properly in the absence of IRF2. Interestingly, immature Paneth cells, which are specialized secretory cells, were highly abundant in IRF2-deficient mice. The researchers had the same finding in normal mice exposed to lymphocytic choriomeningitis virus (LCMV), which causes chronic infection.

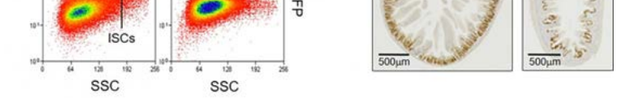

Figure 1. An IRF2 deficiency reduces intestinal stem cells (ISCs) and attenuates crypt regeneration after injury.
A. Flow cytometric analysis revealed that the number of ISCs was reduced in Irf2–/– mice compared with control mice. Lgr5-GFP: reporter fluorescence of ISCs.
B. Sections of the jejunum from control (left) and Irf2–/– (right) mice, 6 days after the induction of epithelial injury by 5-fluorouracil administration, were stained with Ki67. The number of Ki67-stained regenerated crypts were substantially reduced in Irf2–/– mice compared with control mice.

"These are striking results that show how excess interferon signaling in the absence of IRF2 impairs the ability to self-renew and directs intestinal stem cells towards the secretory cell lineage (Figure 2). Our findings provide new insight into the biology of intestinal stem cells and show that regulated interferon signaling is a means to preserve the stemness of intestinal stem cells," says Professor Ohteki.

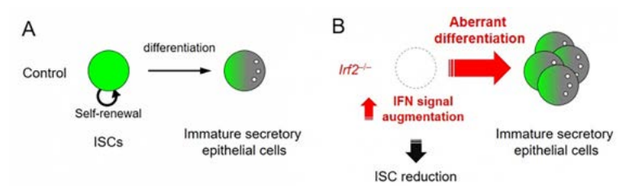

Figure 2. Aberrant differentiation of ISCs in Irf2–/– mice.
A. ISCs undergo self-renewal and have the capacity to produce more differentiated epithelial cells, such as immature secretory epithelial cells. The balance between self-renewal and differentiation is strictly maintained in ISCs.
B. In Irf2–/– mice, augmented IFN signaling causes aberrant differentiation of ISCs into immature secretory epithelial cells, that causes ISC reduction.


Taku Sato

Paper Information

"Regulated IFN signalling preserves the stemness of intestinal stem cells by restricting differentiation into secretory-cell lineage"

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Research Activities 2020-2021

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