BIO NEWS

June, 2017

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1．骨を透かして骨幹細胞の内部を把握 –マウス実験

2017 年 4 月 26 日

カリフォルニア工科大学（Caltech）の研究者らは、Bone CLARITY（**C**lear **L**ipid-exchanged **A**crylamide-hybridized **R**igid **I**maging/**I**mmunostaining/**I**n situ hybridization–compatible **T**issue h**Y**drogel）と呼ばれる骨を透明にする新しい方法を開発、これによって骨粗しょう症のような骨関連疾患治療を可能にする、としている。
この研究では、死後のトランスジェニックマウスから採取した骨が使用された。これらのマウスは、容易に画像化できるように、幹細胞が赤色に蛍光発色するように遺伝子操作されていた。
又、Caltech チームは、Amgen 社が骨量を増加させるとして開発した新化合物について、この技術を用いて試験したことも報告している。
この研究論文は、*Science Translational Medicine* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2017/04/170426141716.htm

Bare bones: Making bones transparent

Transparent bones enable researchers to observe the stem cells inside

Date:

April 26, 2017

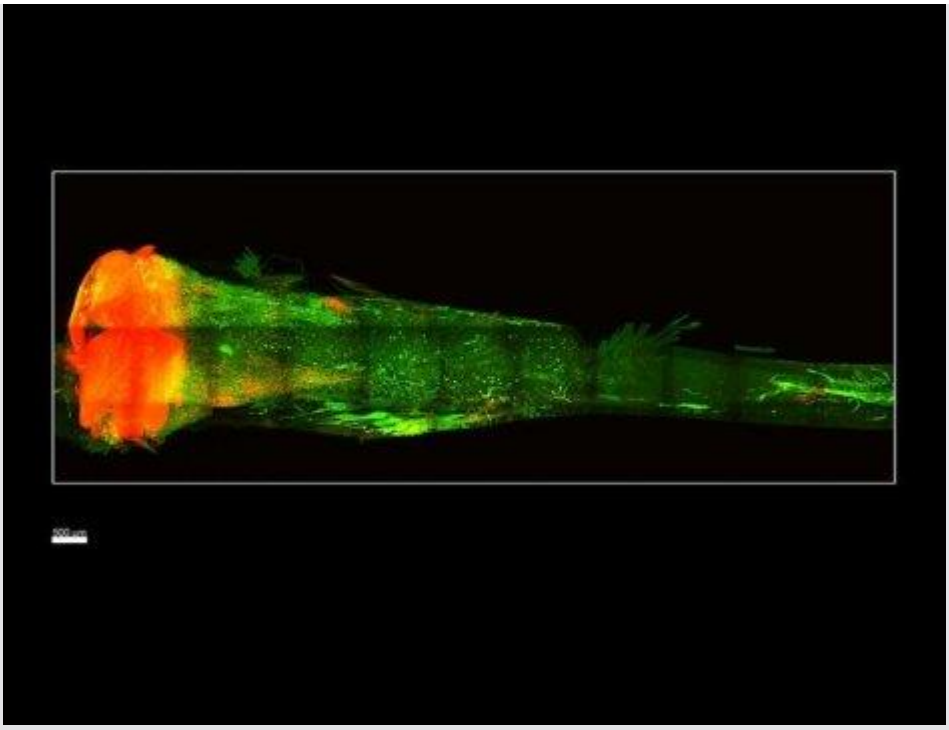
Source:

California Institute of Technology

Summary:

A new bone clearing technique is a breakthrough for testing osteoporosis drugs. The technique has promising applications for understanding how bones interact with the rest of the body.

FULL STORY



A mouse tibia that has been rendered transparent with Bone CLARITY. Stem cells appear distributed throughout the bone in red. The ability to see bone stem cell behavior is crucial for testing new osteoporosis treatments.

Credit: Science Translational Medicine, Greenbaum, Chan, et al; Gradinaru laboratory/Caltech

Ten years ago, the bones currently in your body did not actually exist. Like skin, bone is constantly renewing itself, shedding old tissue and growing it anew from stem cells in the bone marrow. Now, a new technique developed at Caltech can render intact bones transparent, allowing researchers to observe these stem cells within their environment. The method is a breakthrough for testing new drugs to combat diseases like osteoporosis.

The research was done in the laboratory of Viviana Gradinaru (BS '05), assistant professor of biology and biological engineering and a Heritage Medical Research Institute Investigator. It appears in a paper in the April 26 issue of *Science Translational Medicine*.

In healthy bone, a delicate balance exists between the cells that build bone mass and the cells that break down old bone in a continual remodeling cycle. This process is partially controlled by stem cells in bone marrow, called osteoprogenitors, that develop into osteoblasts or osteocytes, which regulate and maintain the skeleton. To better understand diseases like osteoporosis, which occurs when loss of bone mass leads to a high risk of fractures, it is crucial to study the behavior of stem cells in bone marrow. However, this population is rare and not distributed uniformly throughout the bone.

"Because of the sparsity of the stem cell population in the bone, it is challenging to extrapolate their numbers and positions from just a few slices of bone," says Alon Greenbaum, postdoctoral scholar in biology and biological engineering and co-first author on the paper. "Additionally, slicing into bone causes deterioration and loses the complex and three-dimensional environment of the stem cell inside the bone. So there is a need to see inside intact tissue."

To do this, the team built upon a technique called CLARITY, originally developed for clearing brain tissue during Gradinaru's postgraduate work at Stanford University. CLARITY renders soft tissues, such as brain, transparent by removing opaque molecules called lipids from cells while also providing structural support by an infusion of a clear hydrogel mesh. Gradinaru's group at Caltech later expanded the method to make all of the soft tissue in a mouse's body transparent. The team next set out to develop a way to clear hard tissues, like the bone that makes up our skeleton.

In the work described in the new paper, the team began with bones taken from postmortem transgenic mice. These mice were genetically engineered to have their stem cells fluoresce red so that they could be easily imaged. The team examined the femur and tibia, as well as the bones of the vertebral column; each of the samples was about a few centimeters long. First, the researchers removed calcium from the bones: calcium contributes to opacity, and bone tissue has a much higher amount of calcium than soft tissues. Next, because lipids also provide tissues with structure, the team infused the bone with a hydrogel that locked cellular components like proteins and nucleic acids into place and preserved the architecture of the samples. Finally, a gentle detergent was flowed throughout the bone to wash away the lipids, leaving the bone transparent to the eye. For imaging the cleared bones, the team built a custom

light- sheet microscope for fast and high-resolution visualization that would not damage the fluorescent signal. The cleared bones revealed a constellation of red fluorescing stem cells inside.

The group collaborated with researchers at the biotechnology company Amgen to use the method, named Bone CLARITY, to test a new drug developed for treating osteoporosis, which affects millions of Americans per year.

"Our collaborators at Amgen sent us a new therapeutic that increases bone mass," says Ken Chan, graduate student and co-first author of the paper. "However, the effect of these therapeutics on the stem cell population was unclear. We reasoned that they might be increasing the proliferation of stem cells." To test this, the researchers gave one group of mice the treatment and, using Bone CLARITY, compared their vertebral columns with bones from a control group of animals that did not get the drug. "We saw that indeed there was an increase in stem cells with this drug," he says. "Monitoring stem cell responses to these kinds of drugs is crucial because early increases in proliferation are expected while new bone is being built, but long-term proliferation can lead to cancer."

The technique has promising applications for understanding how bones interact with the rest of the body.

"Biologists are beginning to discover that bones are not just structural supports," says Gradinaru, who also serves as the director of the Center for Molecular and Cellular Neuroscience at the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech. "For example, hormones from bone send the brain signals to regulate appetite, and studying the interface between the skull and the brain is a vital part of neuroscience. It is our hope that Bone CLARITY will help break new ground in understanding the inner workings of these important organs."

Story Source:

Materials provided by **California Institute of Technology**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Alon Greenbaum, Ken Y. Chan, Tatyana Dobreva, David Brown, Deepak H. Balani, Rogely Boyce, Henry M. Kronenberg, Helen J. Mcbride and Viviana Gradinaru. **Bone CLARITY: Clearing, imaging, and computational analysis of osteoprogenitors within intact bone marrow**. *Science Translational Medicine*, April 2017 DOI: 10.1126/scitranslmed.aah6518

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2. マウスの歯が示す組織再生の新しい洞察

2017 年 4 月 27 日

幹細胞研究者らは、幹細胞を使うことによって、傷病を治癒したり、損傷した心臓組織にパッチを当てたり、腎臓や他の移植可能な器官をゼロから増殖させる日の到来を目指している。この夢は毎年現実に近づいているのだが、研究者らにとっての永続的な悩みの 1 つは、傷ついたり老化した組織を再生する為に、これらの細胞がいかにして自ら数を増やしたり成熟した成人細胞に変わるべき時を知るのか、ということだ。
そこでこの重要な意思決定プロセスへの答えが、マススの前歯にあるかもしれないと考えたカリフォルニア大学サンフランシスコ校（UCSF）の研究者らは、周囲の組織からのシグナルが、歯科幹細胞が通常の休眠状態を保ったり、歯を成長させるベルトコンベヤー上を飛び跳ねて成熟した歯の組織に変化する過程を開始させたりする役割をしていることを発見し、4 月 27 日の *Cell Steam Cell* 誌に発表した。

英文記事：
https://www.eurekalert.org/pub_releases/2017-04/uoc--mtp042717.php?platform=hootsuite

PUBLIC RELEASE: 27-APR-2017

Mouse teeth providing new insights into tissue regeneration

Basic research has implications from lab-grown teeth to cancer research

UNIVERSITY OF CALIFORNIA - SAN FRANCISCO

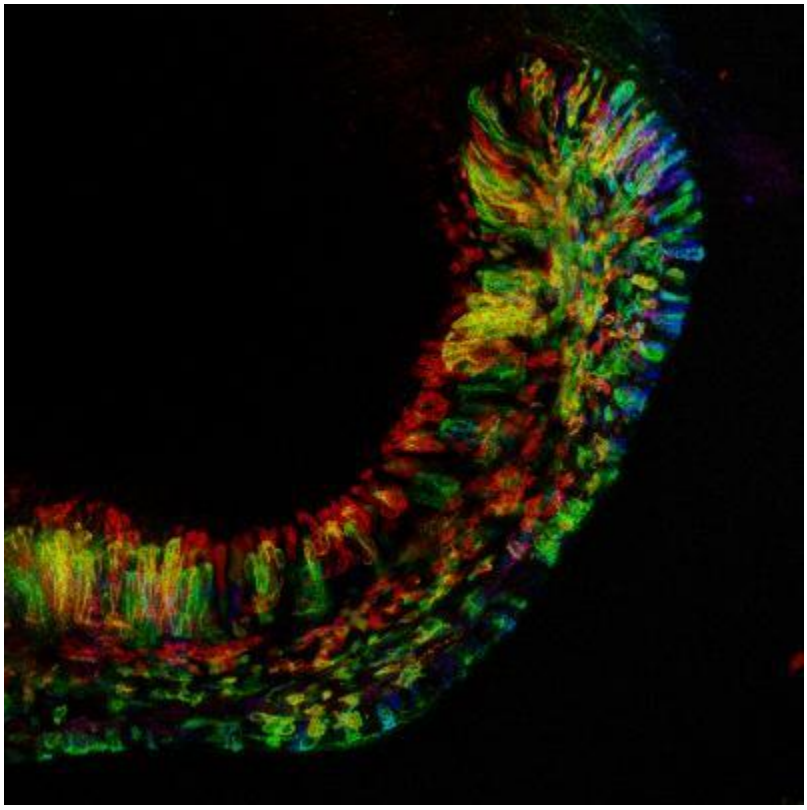

IMAGE: This image shows the 'cervical loop', the zone at the back of the mouse incisor where dental stem cells live and generate new tooth tissue. Klein and his lab caused... view more

Credit: Klein Lab / UCSF

Researchers hope to one day use stem cells to heal burns, patch damaged heart tissue, even grow kidneys and other transplantable organs from scratch. This dream edges closer to reality every year, but one of the enduring puzzles for stem cell researchers is how these remarkable cells know when it's time for them to expand in numbers and transform into mature, adult cells in order to renew injured or aging tissue.

The answer to this crucial decision-making process may lie in a most remarkable organ: the front tooth of the mouse.

Constantly growing incisors are the defining feature of all rodents, which rely on these sharp, chisel-like gnashers for burrowing and self-defense as well as gnawing food. Inside the jaw, a mouse's incisors look more like a walrus's tusks or the teeth of a saber-toothed tiger, with only the sharpened tips showing through the gums at the front of the mouth.

As the front of the tooth gets ground down, a pool of stem cells deep inside the jaw, at the very inner part of the tooth, is constantly building up the back of each incisor and pushing the growing tooth forward -- a bit like the lead of a mechanical pencil.

"As we grow older our teeth start to wear out, and in nature, once you don't have your teeth anymore, you die. As a result, mice and many other animals - from elephants to some primates - can grow their teeth continuously," said UC San Francisco's Ophir Klein, MD, PhD, a professor of orofacial sciences in UCSF's School of Dentistry and of pediatrics in the School of Medicine. "Our lab's objective is to learn the rules that let mouse incisors grow continuously to help us one day grow teeth in the lab, but also to help us identify general principles that could enable us to understand the processes of tissue renewal much more broadly."

In a new study, published online April 27, 2017, in *Cell Stem Cell*, Jimmy Hu, PhD, a postdoctoral researcher in the Klein laboratory, has discovered that signals from the surrounding tissue are responsible for triggering these dental stem cells to leave their normal state of dormancy, hop on the conveyor belt of the growing tooth, and begin the process of transforming into mature tooth tissue.

"We usually think of stem cells responding to chemical signals to start proliferating and differentiating, but here there's an exciting interaction between the physical environment and the cells that can prompt them to meet the demands of the growing tooth," Hu said.

In their study, Hu and colleagues discovered that integrins, proteins that sit in cell membranes and link the internal skeleton of cells to the larger protein scaffolding of the surrounding tissue, trigger a newly described signaling cascade within the stem cells that causes them to begin rapidly multiplying - a process called "proliferation."

It's not clear yet exactly what external signals are responsible for triggering the stem cells to proliferate, the authors say, but they propose that the cells could be detecting that they have moved into a region where the back of the tooth needs to actively produce more cells based on changes in local tissue stiffness or the physical forces pulling and pushing on the cells.

"Our data clearly show that as stem cells move into their designated proliferating space, they ramp up integrin production. These integrins allow the cells to interact with extracellular molecules and become triggered to expand in numbers before eventually producing a large pool of mature dental cells," Hu said.

Of additional interest to the researchers is the fact that both integrins and YAP - one of the molecules involved in the newly discovered integrin-triggered signaling cascade - have previously been implicated in the growth of certain types of tumors, which are thought to share some features of stem cell biology. This finding adds evidence to a growing sense among cancer researchers that interactions between cancer cells and the surrounding tissue may be a key step in triggering tumor growth.

"Integrins and YAP had been implicated in cancer before, but our work connects the two in an organ as opposed to in a Petri dish," Klein said. "Wouldn't it be nice if the same insights that let us learn to grow new tissues in the lab also lead to improved therapies to prevent the growth of tumors in patients?"

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Additional authors on the study were Wei Du, PhD, of UCSF and Sichuan University in China; Samuel J. Shelton, PhD, and Michael C. Oldham, PhD, of UCSF; and C. Michael DiPersio, PhD, of Albany Medical College in New York. The work was funded by the National Institutes Dental and Craniofacial Research of the National Institutes of Health (R01-DE024988, R35-DE026602, F32-DE023705, K99-DE025874).

About UCSF: UC San Francisco (UCSF) is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy; a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences; and a preeminent biomedical research enterprise. It also includes UCSF Health, which comprises three top-ranked hospitals, UCSF Medical Center and UCSF Benioff Children's Hospitals in San Francisco and Oakland, and other partner and affiliated hospitals and healthcare providers throughout the Bay Area. Please visit http://www.ucsf.edu/news.

目次に戻る

3. 非ヒト霊長類遺伝子編集で米国初の成功

2017 年 5 月 1 日

マウスは我々の医学進歩のために便利な基礎モデルであり、将来的にもこの状況が続くと思われる。が、そのサイズと生理的な相違点のいくつかは、神経学や生殖に関する研究を含む人間の医学の重要な領域に欠けているのも事実である。
今回、ミシガン州立大学率いる研究で、CRISPR/Cas9 と呼ばれる技術を用いた遺伝子編集が、アカゲザル胚において非常に効果的であることが示され、アメリカでは初めて実証され、*Human Molecular Genetics* 誌に掲載された。

英文記事：
https://www.sciencedaily.com/releases/2017/05/170501112525.htm

First US success of nonhuman primate gene editing

Date:

May 1, 2017

Source:

Michigan State University

Summary:

Scientists have shown that gene editing using CRISPR/Cas9 technology can be quite effective in rhesus monkey embryos -- the first time this has been demonstrated in the US.

FULL STORY

Mice have been and will continue to be good base models for human medicinal advances. However, their size and some of their physiological differences leave them lacking in important areas of human medicine, including neurological and reproductive research.

In a study led by Michigan State University, scientists have shown that gene editing using CRISPR/Cas9 technology can be quite effective in rhesus monkey embryos ¬- the first time this has been demonstrated in the U.S.

The results, published in the current issue of *Human Molecular Genetics*, open the door for pursuing gene editing in nonhuman primates as models for new therapies, including pharmacological, gene- and stem cell-based therapies, said Keith Latham, MSU animal science professor and lead author of the study.

"Our paper is the first in the U.S. to publish on the use of this technology in nonhuman primate embryos," he said. "Using nonhuman primate embryos is important because the closer we can approximate the human condition in the animal model, the better the chances of developing successful treatments as well as limiting risks that may be encountered in clinical trials."

While mice are mammals, they bear litters rather than individual offspring. Their anatomy and physiology differ in many respects from humans. While many advances in understanding diseases have been made first using mouse models, making the leap from a successful mouse study to clinical trials can be difficult or impossible for some areas of research.

"If scientists want to test drugs for dementia, Alzheimer's or autism, ideal models would react similarly to humans in regards to the reduction of symptoms, outbreak of side effects, such as enduring the same lesions as humans do, or exhibiting similar behavioral characteristics," said Latham, who's with the College of Agriculture and Natural Resources and an MSU AgBioResearch scientist.

"Nonhuman primates are much better models for such diseases. And in terms of some surgical procedures, implants, developing prosthetics, or other therapies, nonhuman primates can prove better suited than rodents."

CRISPR has opened the door to do gene editing in many species other than mice. Developing this technology in nonhuman primates in the U.S. would allow more scientists in this country to incorporate these models into their research, he added.

The advances will allow scientists to move forward and tackle some of the technical barriers related to the research. Other issues that may be later resolved are the commitment to increased costs and longer waiting times when using nonhuman primates.

Fruit flies, often used in genetic studies, reproduce in two weeks. Rodents, with pre-disposed genetic characteristics, can be easily ordered and shipped to laboratories within days. Committing to raising nonhuman primates can cost around $15,000 and can take as long as 4-6 years to have a mature monkey with the desired genetic characteristics.

The high-efficiency of gene editing that scientists are now able to achieve makes it worth the cost and the wait, Latham said.

To conduct the research, Latham partnered with the California National Primate Research Center, where the monkey embryos were produced, in collaboration with his co-investigator Dr. Catherine VandeVoort, an expert in nonhuman primate reproduction. Dr. Daniel Bauer, at Harvard Medical School, Boston Children's Hospital and Dana-Farber Cancer Institute also collaborated on the study.

The resources offered by the CNPRC were crucial for this work, Latham said.

"Extreme amounts of care go into maintaining the well-being of the monkeys," he said. "They follow strict protocols to ensure this is a priority. So being able to conduct the science here at Michigan State while partnering with the center is the best combination of science and animal welfare."

Story Source:

Materials provided by **Michigan State University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Uros Midic, Pei-hsuan Hung, Kailey A Vincent, Benjamin Goheen, Patrick G. Schupp, Diane D. Chen, Daniel E. Bauer, Catherine A VandeVoort, Keith E. Latham. **Quantitative assessment of timing, efficiency, specificity, and genetic mosaicism of CRISPR/Cas9 mediated gene editing of hemoglobin beta gene in rhesus monkey embryos.**. *Human Molecular Genetics*, 2017; DOI: 10.1093/hmg/ddx154

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- APA
- Chicago

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Michigan State University. (2017, May 1). First US success of nonhuman primate gene editing. *ScienceDaily*. Retrieved May 9, 2017 from www.sciencedaily.com/releases/2017/05/170501112525.htm
Michigan State University. "First US success of nonhuman primate gene editing." ScienceDaily. www.sciencedaily.com/releases/2017/05/170501112525.htm (accessed May 9, 2017).

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４．結腸癌の研究をスピードアップさせる新モデル

2017 年 5 月 3 日

MIT の研究者らは、CRISPR として知られる遺伝子編集システムを用いて、ヒト腫瘍に非常によく似た結腸腫瘍をマウス内に生成できることを示した。 この進歩によって、今後この疾患がどのように進行するか、科学者らがそれについてより多くを学び新治療法の試験を可能にするはずだ。
CRISPR ベースの技術は、癌研究の多くの側面に革命を起こし始めており、この疾患を持つマウスモデルをより速くより正確に構築することもその一つである。ここ最近の成果としては、MIT の Koch 研究所の研究者らによって肺腫瘍および肝腫瘍がマウス内に構築されている。
この研究は、*Nature Biology* 誌の 5 月 1 日号に掲載されている。

英文記事：
http://www.technology.org/2017/05/03/new-model-could-speed-up-colon-cancer-research/

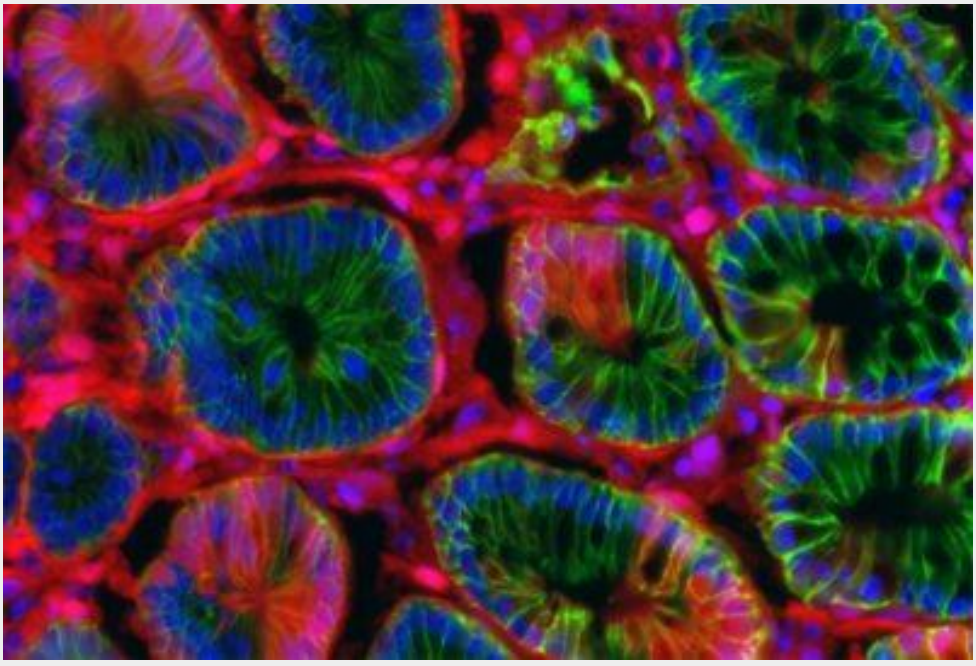
New model could speed up colon cancer research

Posted ***May 3, 2017***

Using the gene-editing system known as CRISPR, MIT researchers have shown in mice that they can generate colon tumors that very closely resemble human tumors. This advance should help scientists learn more about how the disease progresses and allow them to test new therapies.

Once formed, many of these experimental tumors spread to the liver, just like human colon cancers often do. These metastases are the most common cause of death from colon cancer.

“That’s been a missing piece in the study of colon cancer. There is really no reliable method for recapitulating the metastatic progression from a primary tumor in the colon to the liver,” says Omer Yilmaz, an MIT assistant professor of biology, a member of MIT’s Koch Institute for Integrative Cancer Research, and the lead senior author of the study, which appeared in the journal *Nature Biotechnology*.



MIT researchers created this colon tumor by delivering RNA encapsulated in lipid nanoparticles to the colon. The RNA can activate or delete specific genes, leading to tumor growth. Image courtesy of the researchers

The study builds on recent work by Tyler Jacks, the director of the Koch Institute, who has also used CRISPR to generate lung and liver tumors in mice.

“CRISPR-based technologies have begun to revolutionize many aspects of cancer research, including building mouse models of the disease with greater speed and greater precision. This study is a good example of both,” says Jacks, who is also an author of the *Nature Biotechnology* paper.

The paper's lead authors are Jatin Roper, a research affiliate at the Koch Institute and a gastroenterologist at Tufts Medical Center, and Tuomas Tammela, a research scientist at the Koch Institute.

Mimicking human tumors

For many years, cancer biologists have taken two distinct approaches to modeling cancer. One is to grow immortalized human cancer cells known as cancer cell lines in a lab dish. "We've learned a lot by studying these two-dimensional cell lines, but they have limitations," Yilmaz says. "They don't really reproduce the complex in vivo environment of a tumor."

Another widely used technique is genetically engineering mice with mutations that predispose them to develop cancer. However, it can take years to breed such mice, especially if they have more than one cancer-linked mutation.

Recently, researchers have begun using CRISPR to generate cancer models. CRISPR, originally discovered by biologists studying the bacterial immune system, consists of a DNA-cutting enzyme called Cas9 and short RNA guide strands that target specific sequences of the genome, telling Cas9 where to make its cuts. Using this process, scientists can make targeted mutations in the genomes of living animals, either deleting genes or inserting new ones.

To induce cancer mutations, the investigators package the genes for Cas9 and the RNA guide strand into viruses called lentiviruses, which are then injected into the target organs of adult mice.

Yilmaz, who studies colon cancer and how it is influenced by genes, diet, and aging, decided to adapt this approach to generate colon tumors in mice. He and members of his lab were already working on a technique for growing miniature tissues known as organoids — three-dimensional growths that, in this case, accurately replicate the structure of the colon.

In the new paper, the researchers used CRISPR to introduce cancer-causing mutations into the organoids and then delivered them via colonoscopy to the colon, where they attached to the lining and formed tumors.

“We were able to transplant these 3-D mini-intestinal tumors into the colon of recipient mice and recapitulate many aspects of human disease,” Yilmaz says.

More accurate modeling

Once the tumors are established in the mice, the researchers can introduce additional mutations at any time, allowing them to study the influence of each mutation on tumor initiation, progression, and metastasis.

Almost 30 years ago, scientists discovered that colon tumors in humans usually acquire cancerous mutations in a particular order, but they haven’t been able to accurately model this in mice until now.

“In human patients, mutations never occur all at once,” Tammela says. “Mutations are acquired over time as the tumor progresses and becomes more aggressive, more invasive, and more metastatic. Now we can model this in mice.”

To demonstrate that ability, the MIT team delivered organoids with a mutated form of the APC gene, which is the cancer-initiating mutation in 80 percent of colon cancer patients. Once the tumors were established, they introduced a mutated form of KRAS, which is commonly found in colon and many other cancers.

The scientists also delivered components of the CRISPR system directly into the colon wall to quickly model colon cancer by editing the APC gene. They then added CRISPR components to also edit the gene for P53, which is commonly mutated in colon and other cancers.

“These new approaches reduce the time frame to develop genetically engineered mice from two years to just a few months, and involve very basic gene engineering with CRISPR,” Roper says. “We used P53 and KRAS to demonstrate the principle that

the CRISPR editing approach and the organoid transplantation approach can be used to very quickly model any possible cancer-associated gene."

In this study, the researchers also showed that they could grow tumor cells from patients into organoids that could be transplanted into mice. This could give doctors a way to perform "personalized medicine" in which they test various treatment options against a patient's own tumor cells.

Fernando Camargo, a professor of stem cell and regenerative biology at Harvard University, says the study represents an important advance in colon cancer research.

"It allows investigators to have a very flexible model to look at multiple aspects of colorectal cancer, from basic biology of the genes involved in progression and metastasis, to testing potential drugs," says Camargo, who was not involved in the research.

Yilmaz' lab is now using these techniques to study how other factors such as metabolism, diet, and aging affect colon cancer development. The researchers are also using this approach to test potential new colon cancer drugs.

Source: MIT, written by Anne Trafton

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5. 慢性的な痛みを改善するにはより多くの睡眠を

睡眠不足のマウスでは覚醒状態を促進するカフェインやその他の薬が鎮痛剤よりも高効果

2017 年 5 月 8 日

NHI の新プログラムの一環としてサポートされている、ボストン小児病院と Beth Israel Deaconess Medical Center (BIDMC) の新しい共同研究で、慢性的な睡眠不足は痛みに対する敏感さを増すことが示されている。この研究は、慢性的な痛みを持つ患者がより多くの睡眠をとることによって救済されることを示唆しているが、同時にカフェインのような覚醒を促進する薬物の服用によっても救済を得ることができる、ともしている。
5 月 8 日の *Nature Medicine* 誌に掲載されたこの厳密なマウス研究によると、両方のアプローチが標準的な鎮痛剤よりも優れていた、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/05/170508112447.htm

To improve chronic pain, get more sleep (coffee helps too)

In sleep-deprived mice, caffeine and other drugs to promote wakefulness ease pain better than analgesics

Date:

May 8, 2017

Source:

Boston Children's Hospital

Summary:

New research shows that chronic sleep loss increases pain sensitivity. It suggests that chronic pain sufferers can get relief by getting more sleep, or, short of that, taking medications to promote wakefulness such as caffeine.

FULL STORY

New research from Boston Children's Hospital and Beth Israel Deaconess Medical Center (BIDMC) shows that chronic sleep loss increases pain sensitivity. It suggests that chronic pain sufferers can get relief by getting more sleep, or, short of that, taking medications to promote wakefulness such as caffeine. Both approaches performed better than standard analgesics in a rigorous study in mice, described in the May 8, 2017 issue of *Nature Medicine*.

Pain physiologist Alban Latremoliere, PhD, of Boston Children's and sleep physiologist Chloe Alexandre, PhD, of BIDMC precisely measured the effects of acute or chronic sleep loss on sleepiness and sensitivity to both painful and non-painful stimuli. They then tested standard pain medications, like ibuprofen and morphine, as well as wakefulness-promoting agents like caffeine and modafinil. Their findings reveal an unexpected role for alertness in setting pain sensitivity.

Keeping mice awake, through custom entertainment

The team started by measuring normal sleep cycles, using tiny headsets that took electroencephalography (EEG) and electromyography (EMG) readings. "For each mouse, we have exact baseline data on how much they sleep and what their sensory sensitivity is," says Latremoliere, who works in the lab of Clifford Woolf, PhD, in the F.M. Kirby Neurobiology Center at Boston Children's.

Next, unlike other sleep studies that force mice to stay awake walking treadmills or falling from platforms, Alexandre, Latremoliere and colleagues deprived mice of sleep in a way that mimics what happens with people: They entertained them.

"We developed a protocol to chronically sleep-deprive mice in a non-stressful manner, by providing them with toys and activities at the time they were supposed to go to sleep, thereby extending the wake period," says Alexandre, who works in the lab of Thomas Scammell, MD, at BIDMC. "This is similar to what most of us do when we stay awake a little bit too much watching late-night TV each weekday."

To keep the mice awake, researchers kept vigil, providing the mice with custom-made toys as interest flagged while being careful not to overstimulate them. "Mice love nesting, so when they started to get sleepy (as seen by their EEG/EMG pattern) we would give them nesting materials like a wipe or cotton ball," says Latremoliere. "Rodents also like chewing, so we introduced a lot of activities based around chewing, for example, having to chew through something to get to a cotton ball."

In this way, they kept groups of six to 12 mice awake for as long as 12 hours in one session, or six hours for five consecutive days, monitoring sleepiness and stress hormones (to make sure they weren't stressed) and testing for pain along the way.

Pain sensitivity was measured in a blinded fashion by exposing mice to controlled amounts of heat, cold, pressure or capsaicin (the agent in hot chili peppers) and then measuring how long it took the animal to move away (or lick away the discomfort caused by capsaicin). The researchers also tested responses to non-painful stimuli, such as jumping when startled by a sudden loud sound.

"We found that five consecutive days of moderate sleep deprivation can significantly exacerbate pain sensitivity over time in otherwise healthy mice," says Alexandre. "The response was specific to pain, and was not due to a state of general hyperexcitability to any stimuli."

Analgesics vs. wake-promoting agents

Surprisingly, common analgesics like ibuprofen did not block sleep-loss-induced pain hypersensitivity. Even morphine lost most of its efficacy in sleep-deprived mice. These observations suggest that patients using these drugs for pain relief might have to increase their dose to compensate for lost efficacy due to sleep loss, thereby increasing their risk for side effects.

In contrast, both caffeine and modafinil, drugs used to promote wakefulness, successfully blocked the pain hypersensitivity caused by both acute and chronic sleep loss. Interestingly, in non-sleep-deprived mice, these compounds had no analgesic properties.

"This represents a new kind of analgesic that hadn't been considered before, one that depends on the biological state of the animal," says Woolf, director of the Kirby Center at Boston Children's. "Such drugs could help disrupt the chronic pain cycle, in which pain disrupts sleep, which then promotes pain, which further disrupts sleep."

A new approach to chronic pain?

The researchers conclude that rather than just taking painkillers, patients with chronic pain might benefit from better sleep habits or sleep-promoting medications at night, coupled with daytime alertness-promoting agents to try to break the pain cycle. Some painkillers already include caffeine as an ingredient, although its mechanism of action isn't yet known. Both caffeine and modafinil boost dopamine circuits in the brain, so that may provide a clue.

"This work was supported by a novel NIH program that required a pain scientist to join a non-pain scientist to tackle a completely new area of research," notes Scammel, professor of neurology at BIDMC. "This cross-disciplinary collaboration enabled our labs to discover unsuspected links between sleep and pain with actionable clinical implications for improving pain management."

"Many patients with chronic pain suffer from poor sleep and daytime fatigue, and some pain medications themselves can contribute to these co-morbidities," notes Kiran Maski, MD, a specialist in sleep disorders at Boston Children's. "This study suggests a novel approach to pain management that would be relatively easy to implement in clinical care. Clinical research is needed to understand what sleep duration is required and to test the efficacy of wake-promoting medications in chronic pain patients."

Story Source:

Materials provided by **Boston Children's Hospital**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Chloe Alexandre, Alban Latremoliere, Ashley Ferreira, Giulia Miracca, Mihoko Yamamoto, Thomas E Scammell, Clifford J Woolf. **Decreased alertness due to sleep loss increases pain sensitivity in mice**. *Nature Medicine*, 2017; DOI: 10.1038/nm.4329

目次に戻る

6. ＜アマミトゲネズミ＞iPS から卵子と精子　絶滅対策に期待

2017 年 5 月 13 日

ｉＰＳ細胞から卵子と精子の作製に成功したアマミトゲネズミ＝北海道大の黒岩麻里教授提供

絶滅危惧種・アマミトゲネズミの体細胞で作ったｉＰＳ細胞（人工多能性幹細胞）から卵子と精子を作り出すことに成功したと、宮崎大の本多新（あらた）研究員（発生生物学）らの研究チームが１２日付の米科学誌電子版に発表した。ラットとマウス以外のｉＰＳ細胞からできたのは世界初といい、希少種の絶滅防止対策に役立つ可能性があるという。

【写真特集】絶滅危惧種の生き物たち

アマミトゲネズミは体長約１２～１５センチの哺乳類。鹿児島県の奄美大島にのみ生息する国の天然記念物のため、通常は実験で使えない。チームは、保護のため捕獲しようとした時に偶然切れ落ちた雌の尾の細胞から、さまざまな組織や臓器に変化するｉＰＳ細胞を作製。これをマウスの受精卵（胚）に注入して雌マウスの子宮に移植して出産させた。すると、生まれた雌マウスはアマミトゲネズミの卵子、雄マウスはその精子をもっていた。

ヒトなど哺乳類の雌雄を決める性染色体は２本あるが、アマミトゲネズミは他の哺乳類では雌になるためのＸ染色体しかない。進化の過程で雄になるためのＹ染色体を失ったとされるが、それがなくても雄も生まれ、どのように性別が決まるのか分かっていない。本多研究員は今回の成果について、「他の哺乳類も含め、性別が決まる過程の解明にもつながる」と話した。【斎藤有香】

最終更新:5/13(土) 8:58

毎日新聞

記事：
http://www.miyazaki-u.ac.jp/public/files/685d665965b49bafd50354a301a0d5d4.pdf
詳しくは上の URL を参照して下さい。

目次に戻る

7. 青少年の主要死亡原因 -WHO 報告

2017 年 5 月 16 日

WHO が報告した健康調査によると、毎年 120 万人以上の青年が死亡していることが判明し、その多くは予防可能なものであった。
結果を簡単に見てみると、世界中の 10 歳から 19 歳の青年の主要死亡原因トップは道路上での事故で、毎年約 11 万 5 千人が亡くなり、その大部分は歩行、自転車、またはオートバイによる。その他一般的な上位死亡原因は、呼吸器感染症、自殺、下痢症、溺死。
また、10 歳から 19 歳の男性では、対人暴力で毎年 4 万 2 千人以上が死亡、15 歳から 19 歳の女性では、労働および安全でない中絶による合併症が主な死因となっている。若い女性は肺炎など呼吸器感染症での死亡も多く、これは安全でない燃料を使っての調理が原因と考えられる、としている。

英文記事：
http://www.who.int/mediacentre/news/releases/2017/yearly-adolescent-deaths/en/

More than 1.2 million adolescents die every year, nearly all preventable

News release

WHO and partners recommend actions to improve adolescent health

16 May 2017 / *GENEVA* – More than 3000 adolescents die every day, totalling 1.2 million deaths a year, from largely preventable causes, according to a new report from

WHO and partners. In 2015, more than two-thirds of these deaths occurred in low- and middle-income countries in Africa and South-East Asia. Road traffic injuries, lower respiratory infections, and suicide are the biggest causes of death among adolescents.

Most of these deaths can be prevented with good health services, education and social support. But in many cases, adolescents who suffer from mental health disorders, substance use, or poor nutrition cannot obtain critical prevention and care services – either because the services do not exist, or because they do not know about them.

In addition, many behaviours that impact health later in life, such as physical inactivity, poor diet, and risky sexual health behaviours, begin in adolescence.

"Adolescents have been entirely absent from national health plans for decades," says Dr Flavia Bustreo, Assistant Director-General, WHO. "Relatively small investments focused on adolescents now will not only result in healthy and empowered adults who thrive and contribute positively to their communities, but it will also result in healthier future generations, yielding enourmous returns."

Data in the report, *Global accelerated action for the health of adolescents (AA-HA!): Guidance to support country implementation*, reveal stark differences in causes of death when separating the adolescent group by age (younger adolescents aged 10–14 years and older ones aged 15–19 years) and by sex. The report also includes the range of interventions – from seat-belt laws to comprehensive sexuality education – that countries can take to improve their health and well-being and dramatically cut unnecessary deaths.

Road injuries top cause of death of adolescents, disproportionately affecting boys

In 2015, road injuries were the leading cause of adolescent death among 10–19-year-olds, resulting in approximately 115 000 adolescent deaths. Older adolescent boys aged 15–19 years experienced the greatest burden. Most young people killed in road crashes are vulnerable road users such as pedestrians, cyclists and motorcyclists.

However, differences between regions are stark. Looking only at low- and middle-income countries in Africa, communicable diseases such as HIV/AIDS, lower respiratory infections, meningitis, and diarrhoeal diseases are bigger causes of death among adolescents than road injuries.

Lower respiratory infections and pregnancy complications take toll on girls' health

The picture for girls differs greatly. The leading cause of death for younger adolescent girls aged 10–14 years are lower respiratory infections, such as pneumonia – often a result of indoor air pollution from cooking with dirty fuels. Pregnancy complications, such as haemorrhage, sepsis, obstructed labour, and complications from unsafe abortions, are the top cause of death among 15–19-year-old girls.

Adolescents are at very high risk of self-harm and suicide

Suicide and accidental death from self-harm were the third cause of adolescent mortality in 2015, resulting in an estimated 67 000 deaths. Self-harm largely occurs among older adolescents, and globally it is the second leading cause of death for older adolescent girls. It is the leading or second cause of adolescent death in Europe and South-East Asia.

A vulnerable population in humanitarian and fragile settings

Adolescent health needs intensify in humanitarian and fragile settings. Young people often take on adult responsibilities, including caring for siblings or working, and may be compelled to drop out of school, marry early, or engage in transactional sex to meet their basic survival needs. As a result, they suffer malnutrition, unintentional injuries, pregnancies, diarrhoeal diseases, sexual violence, sexually-transmitted diseases, and mental health issues.

Interventions to improve adolescent health

"Improving the way health systems serve adolescents is just one part of improving their health," says Dr Anthony Costello, Director, Maternal, Newborn, Child and Adolescent Health, WHO. "Parents, families, and communities are extremely important, as they have the greatest potential to positively influence adolescent behaviour and health."

The *AA-HA! Guidance* recommends interventions across sectors, including comprehensive sexuality education in schools; higher age limits for alcohol consumption; mandating seat-belts and helmets through laws; reducing access to and misuse of firearms; reducing indoor air pollution through cleaner cooking fuels; and increasing access to safe water, sanitation, and hygiene. It also provides detailed explanations of how countries can deliver these interventions with adolescent health programmes.

Top 5 causes of death for all adolescents aged 10–19 years in 2015

Cause of death	Number of deaths
1. Road traffic injury	115 302
2. Lower respiratory infections	72 655
3. Self-harm	67 149
4. Diarrhoeal diseases	63 575
5. Drowning	57 125

Top 5 causes of death for males aged 10–19 years in 2015

Cause of death	Number of deaths
1. Road traffic injury	88 590
2. Interpersonal violence	42 277
3. Drowning	40 847
4. Lower respiratory infections	36 018
5. Self-harm	34 650

Top 5 causes of death for females aged 10–19 years in 2015

Cause of death	Number of deaths
1. Lower respiratory infections	36 637
2. Self-harm	32 499
3. Diarrhoeal diseases	32 194
4. Maternal conditions	28 886
5. Road traffic injury	26 712

Notes to editors

The *AA-HA! Guidance* was produced by WHO in collaboration with UNAIDS, UNESCO, UNFPA, UNICEF, UN Women, World Bank, the Every Woman, Every Child initiative and The Partnership for Maternal, Newborn , Child & Adolescent Health. The document will be launched at the Global Adolescent Health Conference: Unleashing the Power of a Generation, on 16 May in Ottawa, Canada.

The report helps countries implement the *Global strategy for women's, children's and adolescents' health (2016–2030)* by providing comprehensive information needed to decide what to do for adolescent health, and how to do it. The Global strategy, which was launched in 2015 to support the Sustainable Development Goals (SDGs), provides an opportunity to improve adolescent health and to respond more effectively to adolescents' needs.

- Global strategy for women's, children's and adolescents' health (2016–2030)

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8. 核移植技術でアレルギーマウス誕生

－アレルギー疾患の原因解明と治療に期待－

2017 年 5 月 12 日

理化学研究所（理研）バイオリソースセンターは、核移植クローン技術を用いて高感受性アレルギーモデルマウスを作り出すことに成功した。また、この研究で開発した高感受性アレルギーモデルマウス系統は、正常な繁殖能力を持ち、研究室で容易に飼育・維持できる。今後、アレルギーが起こる原因を解明したり、予防・治療法を開発するのに役立つと期待できる、としている。この研究成果は 5 月 2 日の *EMBO Reports* 誌に掲載されている。

記事：
http://www.riken.jp/pr/press/2017/20170512_2/

2017 年 5 月 12 日

理化学研究所

核移植技術でアレルギーマウス誕生

－アレルギー疾患の原因解明と治療に期待－

要旨

理化学研究所（理研）バイオリソースセンター遺伝工学基盤技術室の小倉淳郎室長、井上貴美子専任研究員、神沼修客員研究員、佐伯真弓客員研究員、塩野義製薬株式会社創薬疾患研究所癌・免疫部門の形

山和史免疫・炎症グループ長らの共同研究グループ※は、核移植クローン技術を用いて高感受性アレルギーモデルマウスを作り出すことに成功しました。

花粉や食物など特定の抗原に対するアレルギーは、多くの人の健康を脅かす病気です。生体に侵入したさまざまな抗原は、CD4 陽性 T 細胞[1]と呼ばれるリンパ球の表面にある受容体（T 細胞受容体[2]、TCR）に結合して、生体防御を目的としたさまざまな反応を引き起こします。アレルギー患者の体内では、この抗原反応性 CD4 陽性 T 細胞が増殖し、過剰な反応が起きるためにアレルギー症状が現れます。アレルギーが起こる原因の解明と予防・治療法の開発には、実験動物モデルが大きな役割を果たします。

今回、共同研究グループは、アレルギー誘発抗原として知られる、ダニ抗原や卵白抗原を注射したマウスから取り出した抗原反応性 CD4 陽性 T 細胞を用いて、核移植クローン[3]を行い、クローンマウスを作出しました。この CD4 陽性 T 細胞の TCR は、アレルギー誘発抗原に反応するように遺伝子の再構成[4]を受けているため、クローンマウスの体内では、CD4 陽性 T 細胞のほぼ全てが同じ抗原反応性 TCR を持っています。つまり、クローンマウスの体内はあたかもアレルギー患者のように、抗原反応性 CD4 陽性 T 細胞が多く存在する状態になっています。共同研究グループが、生まれたクローンマウスを正常なマウスと交配すると、抗原反応性 TCR の遺伝子が子孫に遺伝し、クローンマウス由来のマウス系統を樹立することができました。これらのマウスにダニ抗原や卵白抗原を投与したところ、1～2 週間以内

に、しかもわずか数回の投与で、気管支喘息やアレルギー性鼻炎に似た重篤なアレルギー症状が起こることが分かりました。

本研究で開発した高感受性アレルギーモデルマウス系統は、正常な繁殖能力を持ち、研究室で容易に飼育・維持できます。今後、アレルギーが起こる原因を解明したり、予防・治療法を開発するのに役立つと期待できます。

本研究成果は、欧州の科学雑誌『*EMBO Reports*』（5 月 2 日付け）に掲載されました。

本研究は、日本学術振興会 科学研究費補助金 新学術領域研究「生殖細胞のエピゲノムダイナミクスとその制御」ならびに基盤研究「抗原特異的モノクローナル T 細胞レセプターを介する免疫機構の解明」の支援および塩野義製薬（株）資金提供による共同研究（理研、東京都医学総合研究所、塩野義製薬）により行われました。

背景

花粉や食物など特定の抗原に対するアレルギーは、多くの人の健康を脅かす疾患であり、社会的にも大きな問題となっています。生体に侵入したさまざまな抗原は、抗原提示細胞[5]に取り込まれたのち、CD4 陽性 T 細胞と呼ばれるリンパ球の表面にある受容体（T 細胞受容体、TCR）に結合して、さまざまな反応を引き起こします。この反応は生体防御に必要ですが、CD4 陽性 T 細胞が過剰に反応すると、抗

原に対する反応も過剰になり、結果としてアレルギー症状を引き起こします。このようなアレルギーの発症機構を解明し、その予防・治療法を開発するためには、モデルとなる実験動物が欠かせません。しかし、アレルギー患者の体内で生じている特定の抗原反応性 CD4 陽性 T 細胞の増加状態を、実験動物の体内で再現することは困難でした。

これまでアレルギー症状を起こすマウスを作るには、マウスに数週間にわたって十数回以上も抗原を投与したり、あらかじめ体内に免疫応答を活性化する物質と共に抗原溶液を注射するなど、長期間の煩雑な作業が必要でした。最近では、抗原反応性 TCR の遺伝子を導入したトランスジェニック（TCR-Tg）マウス[6]が開発され、抗原特異的な T 細胞の反応を容易に誘発できるようになりましたが、その TCR の発現は自然経過で発現した TCR とは異なり、人工的に挿入された遺伝子調節領域によって制御されているため、TCR-Tg マウスの T 細胞の反応が、生体が自然に獲得した抗原反応性 T 細胞の反応を正確に反映するか確証はありませんでした。

そこで共同研究グループは、核移植クローン技術に着目しました。核移植クローン技術を用いると、生まれてきたクローン動物は全身の細胞がドナー細胞と同じ遺伝子型を持ちます。このため、特定の抗原に反応するよう TCR 遺伝子が再構成された CD4 陽性 T 細胞に由来するクローン動物では、ほぼ全ての CD4 陽性 T 細胞が、同じように再構成された TCR 遺伝子を保持します。これらの TCR 遺伝子は、T 細

胞本来の調節領域による発現制御を受けるため、TCR-Tg マウスよりも自然に近い反応の観察が期待できます。

研究手法と成果

共同研究グループは、マウスにダニ抗原あるいは卵白抗原を注射して抗原に敏感な状態にし（抗原感作）、抗原に特異的に反応する T 細胞のみが活性化されて増殖する性質を利用して、抗原感作マウスのリンパ節から取り出した細胞から目的の CD4 陽性 T 細胞を増殖させました。しかし、核移植クローン実験には増殖していない静止期の細胞が必要なため、いったん増殖させた抗原反応性 T 細胞を静止期に誘導するよう工夫しました。

このようにして得られた CD4 陽性 T 細胞を核ドナー細胞として核移植クローンを行った結果、これまでに 18 匹のクローンマウスが生まれ、そのうち 11 匹が成体に成長しました。これらのクローンマウスから T 細胞を取り出して、ドナーT 細胞の培養に用いた抗原と一緒に培養したところ、そのうち 8 匹の T 細胞が抗原を認識して活性化されたことを確認しました。これらのマウスを正常マウスと交配すると、抗原反応性 TCR 遺伝子は子孫に伝達され、クローンマウス由来のマウス系統を樹立できました。

次にこれらのマウスに対し、ダニ抗原あるいは卵白抗原を投与しました。すると 1～2 週間以内に、しかもわずか数回の投与で、気管支喘息やアレルギー性鼻炎に似た重篤なアレルギー症状が起きました。

ダニ抗原反応性 CD4 陽性 T 細胞由来のクローンマウス系統では、ダニ抗原の投与によって気管支肺胞領域に強い炎症が生じ、気道上皮の肥厚およびリンパ球や好酸球[7]の浸潤が観察されたほか、気道過敏性[8]の亢進がみられました。卵白抗原反応性 CD4 陽性 T 細胞由来のクローンマウス系統では、卵白抗原の投与によって鼻粘膜にリンパ球や好酸球が浸潤し、鼻粘膜過敏性[8]の亢進がみられました。

なお、TCR はα鎖とβ鎖が二量体を作ることによって初めて抗原反応性を示すとされていましたが、クローンマウス系統では、抗原反応性 TCRα鎖またはβ鎖のどちらかだけを発現するマウスでも、アレルギー症状が強まることが分かりました。さらに、核移植に用いた T 細胞に発現する抗原反応性 TCR の違いによって T 細胞の反応性やサイトカイン産生パターンが異なり、その結果引き起こされるアレルギー・免疫反応が異なることも分かりました（図 1）。

今後の期待

本研究では、抗原特異的 CD4 陽性 T 細胞をドナー細胞に用いることにより、高感受性アレルギーモデルマウスの作出に成功しました。これらのマウスは、さまざまな免疫学的実験で使用される近交系[9]BALB/c マウスへ戻し交配[10]しています。また、今回はダニ抗原と卵白抗原を特異抗原に用いましたが、同様にスギ花粉など他の抗原でも特異的クローンマウスを作出できます。

本成果は今後、アレルギー疾患の発症機構を解明し、その予防・治療法の開発への貢献が期待できます。また、抗原特異的 TCRα鎖および TCRβ鎖を別々に発現する個体・細胞を得ることが可能になったことにより、TCR を介した T 細胞の活性化や分化機構の解明にも大きく貢献できると考えられます。

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補足説明

1. CD4 陽性 T 細胞

リンパ球の一種である T 細胞の中で、細胞表面に CD4 と呼ばれる特徴的な分子を発現するもの。CD8 を発現する CD8 陽性 T 細胞が、ウイルス感染細胞やがん細胞を殺傷する役割を果たすのに対し、CD4 陽性 T 細胞は外界から体内に侵入した抗原物質に反応して活性化し、生体防御を目的としたさまざまな免疫応答を引き起こす。

2. T 細胞受容体

T 細胞の細胞膜上に発現し、抗原物質を認識して細胞内に活性化刺激を伝える受容体。多くはα鎖とβ鎖の二量体から構成される。それぞれの TCR 遺伝子が胸腺内でランダムに再構成されるため、個々の成熟 T 細胞に発現する TCR は多様性に富む。その結果、個体レベルではさまざまな抗原に対する免疫応答が可能となる。

3. 核移植クローン

染色体を除いた卵子にドナー細胞核を移植することにより、胚として発生させる技術。本研究のようにドナー細胞に体細胞を用いることで、体細胞クローン動物を作出できる。

4. 遺伝子の再構成

胸腺における T 細胞発生の過程で TCR 遺伝子に起きる不可逆的な編集現象。TCRα鎖およびβ鎖それぞれの遺伝子領域に存在するセグメント候補群（α鎖では Vαと Jα遺伝子，β鎖では Vβと

Dβと Jβ遺伝子）から、ランダムに各セグメントが選ばれて遺伝子が構成された後、各 T 細胞につき 1～2 種類の TCRα、β鎖が転写、翻訳されて細胞表面に発現する。

5. 抗原提示細胞

抗原を細胞内に取り込み処理して T 細胞に提示することで、T 細胞を活性化させる機能を持つ細胞群で、樹状細胞やマクロファージなどが含まれる。抗原提示細胞に取り込まれた抗原は、アミノ酸数が 10 個程度の抗原ペプチドに分解され、自己 MHC（主要組織適合遺伝子複合体）との複合体として細胞の表面に発現することで、T 細胞が認識できるような形となり、T 細胞に提示される。

6. TCR トランスジェニクマウス（TCR-Tg マウス）

再構成された抗原特異的 TCR の遺伝子を、遺伝子操作によって人工的に導入したマウス。同じ抗原特異的 TCR が、生体内のほぼ全ての T 細胞に発現する。

7. 好酸球

白血球の中の顆粒球の一種。顆粒中に種々の細胞障害性タンパクを貯留しており、寄生虫感染時には脱顆粒によってそれらのタンパク質を放出し、生体を防御する役割を担う。アレルギー患者の患部にも多くの集積がみられ、障害性タンパクによる組織障害によって炎症の増悪や組織のリモデリングが引き起こされる。

8. 気道過敏性、鼻粘膜過敏性

気管支喘息患者では、発作時に気道が狭くなり呼吸困難症状が起きるが、気道局所に集積した好酸球などにより組織障害が起きた結果、誘発抗原だけでなく、さまざまな非特異的刺激に反応して気管支平滑筋が収縮しやすくなり、喘息発作を起こしやすくなる。この状態を気道過敏性の亢進という。アレルギー性鼻炎患者では、同様の現象が鼻粘膜でみられ、非特異的刺激に反応してくしゃみ、鼻漏などが起きやすくなる鼻粘膜過敏性の亢進が引き起こされる。

9. 近交系

兄妹交配を 20 世代以上継続して維持している系統。理論上、系統内の全ての個体は同じ遺伝子組成を持つ。

10. 戻し交配

親あるいは親と同じ系統･品種と交配すること。戻し交配を繰り返すことにより、遺伝的背景を均一化した子孫を得ることができる。

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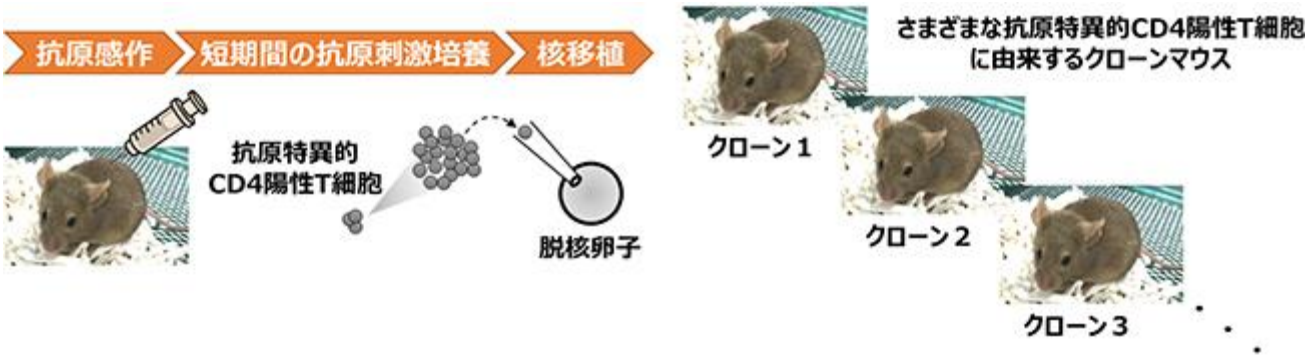

図 1　抗原特異的 CD4 陽性 T 細胞の核移植によるクローンマウス作製

マウスにダニや卵白などの抗原を注射して、抗原に敏感な状態にする（抗原感作）。感作したマウスのリンパ節から CD4 陽性 T 細胞を集め、抗原と一緒に短期間培養することで増殖させる（短期間の抗原刺激培養）。その CD4 陽性 T 細胞の核を、染色体を除いたマウスの卵子に移植する（核移植）。それを胚として発生させ、クローンマウスを作出する。生まれたクローンマウスは、核移植に用いた T 細胞に発現する抗原反応性 TCR の違いによって、引き起こされるアレルギー・免疫反応が異なる。

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目次に戻る

9. 患者本人の細胞から血液細胞を作成 -マウス実験

2017 年 5 月 17 日

ボストン小児病院の研究者らは、事実上体内のあらゆる細胞型を作り出すことができる多能性幹細胞を用いて、マウス実験により血液を形成する幹細胞の作成に初めて成功した。この進歩は、血液患者の根本原因の研究、および患者本人の細胞を使用することによって免疫性の合致した血液細胞を作成する新たな道を切り開く、としている。
1998 年にヒト胚性幹（ES）細胞が単離されて以来、血液幹細胞を造血に使用する試みはほとんどなされていない。 iPS 細胞は後に、ニューロンや心臓細胞など複数のヒト細胞型を生成するために使用されたが、血液形成幹細胞についてははまだ分かっていなかった。そういった意味では 10 年以上にわたる目標へやっと近づいた、と言える。
この研究論文の筆頭著者 Ryohichi Sugiura 氏はボストン小児病院 Daley Lab の所属（大阪大学医学部出身）で、この論文は *Nature* 誌に掲載された。

英文記事：
https://www.sciencedaily.com/releases/2017/05/170517132609.htm

Approaching a decades-old goal: Making blood stem cells from patients' own cells

New technique raises possibility of making all types of blood cells to treat disease

Date:

May 17, 2017

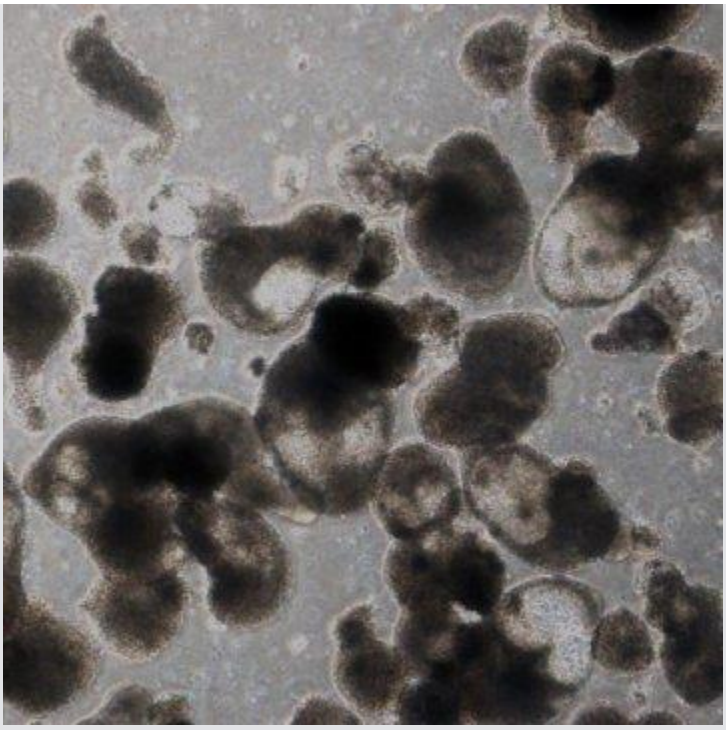
Source:

Boston Children's Hospital

Summary:

For the first time, researchers have generated blood-forming stem cells in the lab using pluripotent stem cells, which can make virtually every cell type in the body. The advance opens new avenues for research into the root causes of blood diseases and to creating immune-matched blood cells for treatment purposes, derived from patients' own cells.

FULL STORY



Sugimura, Daley and colleagues made a mix of blood progenitor cells (shown here) and blood stem cells. Both types of cells are able to generate multiple kinds of blood cells (red blood cells, lymphocytes, etc.).

Credit: Courtesy Daley Lab

Researchers at Boston Children's Hospital have, for the first time, generated blood-forming stem cells in the lab using pluripotent stem cells, which can make virtually every cell type in the body. The advance, published in the journal *Nature*, opens new avenues for research into the root causes of blood diseases and to creating immune-matched blood cells for treatment purposes, derived from patients' own cells.

"We're tantalizingly close to generating bona fide human blood stem cells in a dish," says senior investigator George Daley, MD, PhD, who heads a research lab in Boston Children's Hospital's Stem Cell Program and is dean of Harvard Medical School. "This work is the culmination of over 20 years of striving."

Although the cells made from the pluripotent stem cells are a mix of true blood stem cells and other cells known as blood progenitor cells, they proved capable of generating multiple types of human blood cells when put into mice.

"This step opens up an opportunity to take cells from patients with genetic blood disorders, use gene editing to correct their genetic defect and make functional blood cells," says Ryohichi (Rio) Sugimura, MD, PhD, the study's first author and a postdoctoral fellow in the Daley Lab. "This also gives us the potential to have a limitless supply of blood stem cells and blood by taking cells from universal donors. This could potentially augment the blood supply for patients who need transfusions."

Combining two approaches to achieve a breakthrough

Since human embryonic stem (ES) cells were isolated in 1998, scientists have been trying, with little success, to use them to make blood-forming stem cells. In 2007, three groups (including the Daley lab) generated the first induced pluripotent stem (iPS) cells from human skin cells through genetic reprogramming. iPS cells were later used to generate multiple human cell types, such as neurons and heart cells -- yet blood-forming stem cells remained elusive.

Sugimura, Daley and colleagues combined two previous approaches. First, they exposed human pluripotent stem cells (both ES and iPS cells) to chemical signals that direct stem cells to differentiate into specialized cells and tissues during normal embryonic development. This generated hemogenic endothelium, an early embryonic tissue that eventually gives rise to blood stem cells, although the transition to blood stem cells had never been achieved in a dish.

In the second step, the team added genetic regulatory factors (called transcription factors) to push the hemogenic endothelium toward a blood-forming state. Starting with 26 transcription factors identified as likely candidates, they eventually came down to just five (RUNX1, ERG, LCOR, HOXA5 and HOXA9) that were both necessary and sufficient for creating blood stem cells. They delivered the factors into the cells with a lentivirus, as used in some forms of gene therapy.

Finally, they transplanted the genetically engineered hemogenic endothelial cells into mice. Weeks later, a small number of the animals carried multiple types of human blood cells in their bone marrow and blood circulation. These included red blood cell precursors, myeloid cells (precursors of monocytes, macrophages, neutrophils, platelets and other cells), and T and B lymphocytes. Some mice were able to mount a human immune response after vaccination.

ES cells and iPS cells were similarly good at creating blood stem and progenitor cells when the technique was applied. But the researchers are most interested in iPS cells, which offer the added ability to derive cells directly from patients and model disease.

"We're now able to model human blood function in so-called 'humanized mice,'" says Daley. "This is a major step forward for our ability to investigate genetic blood disease."

What is a blood stem cell?

The researchers' technique produced a mixture of blood stem cells and so-called hematopoietic progenitor cells, which also give rise to blood cells. Their ultimate goal is to expand their ability to make true blood stem cells in a way that's practical and safe, without the need for viruses to deliver the transcription factors, and to introduce gene-editing techniques like CRISPR to correct genetic defects in pluripotent stem cells before blood cells are made.

One challenge in making bona-fide human blood stem cells is that no one's been able to fully characterize these cells.

"It's proved challenging to 'see' these cells," says Sugimura. "You can roughly characterize blood stem cells based on surface markers, but even with this, it may not be a true blood stem cell. And once it starts to differentiate and make blood cells, you can't go back and study it -- it's already gone. A better characterization of human blood stem cells and a better understanding of how they develop would give us clues to making bona-fide human blood stem cells."

Story Source:

Materials provided by **Boston Children's Hospital**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ryohichi Sugimura et al. **Haematopoietic stem and progenitor cells from human pluripotent stem cells**. *Nature*, May 2017 DOI: 10.1038/nature22370

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10. 毛髪の成長メカニズム新発見 -マウス実験

2017 年 5 月 25 日

UC サンフランシスコの研究者らは、マウス実験で、炎症制御に関わる免疫細胞の一種である制御性 T 細胞(Tregs -“tee-regs”と発音)が幹細胞を直接刺激して健康な育毛を促進することを発見した。また、これらの免疫細胞と一緒でなければ、幹細胞は毛包を再生することができず、これが脱毛症に繋がる、としている。
5 月 26 日の *Cell* 誌オンライン版に掲載されたこの新しい研究は、Tregs の欠陥が自己免疫疾患としての脱毛症の原因となるばかりでなく、男性型脱毛症を含む他の形態の脱毛症にも関係している可能性があると示唆している。

英文記事：
https://www.sciencedaily.com/releases/2017/05/170525125626.htm

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New hair growth mechanism discovered

Faulty immune cells may play role in alopecia, other forms of baldness

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Source:

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Summary:

Regulatory T cells (Tregs; pronounced 'tee-regs'), a type of immune cell generally associated with controlling inflammation, directly trigger stem cells in the skin to promote healthy hair

growth, researchers have discovered. Without these immune cells as partners, the researchers found, the stem cells cannot regenerate hair follicles, leading to baldness.

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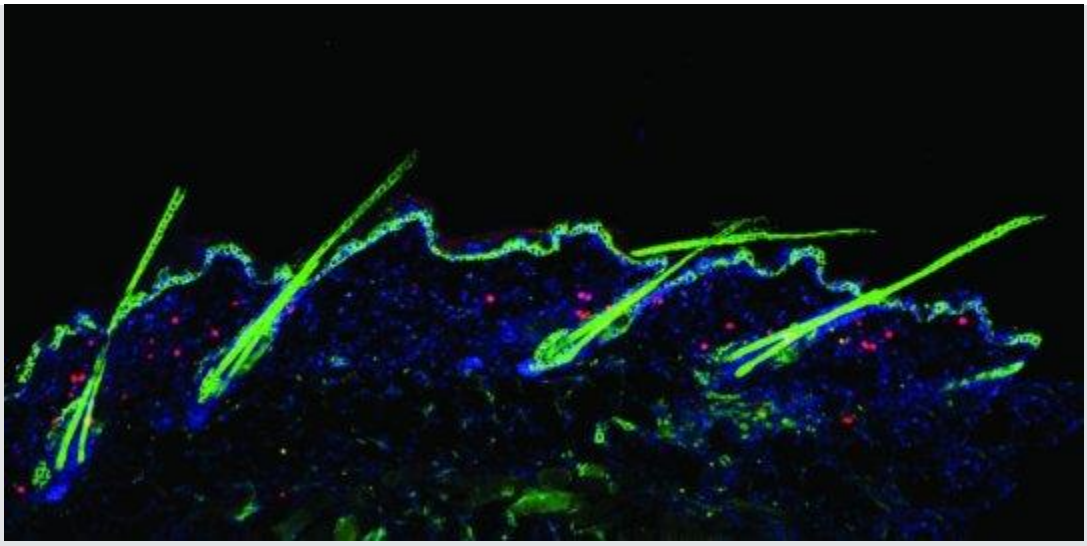

In a highly magnified cross section of mouse skin, fluorescent Tregs (red) are seen clustered around hair follicles and hairs (green).

Credit: Rosenblum lab/UCSF

In experiments in mice, UC San Francisco researchers have discovered that regulatory T cells (Tregs; pronounced "tee-regs"), a type of immune cell generally associated with controlling inflammation, directly trigger stem cells in the skin to promote healthy hair growth. Without these immune cells as partners, the researchers found, the stem cells cannot regenerate hair follicles, leading to baldness.

"Our hair follicles are constantly recycling: when a hair falls out, the whole hair follicle has to grow back," said Michael Rosenblum, MD, PhD, an assistant professor of dermatology at UCSF and senior

author on the new paper. "This has been thought to be an entirely stem cell-dependent process, but it turns out Tregs are essential. If you knock out this one immune cell type, hair just doesn't grow."

The new study -- published online May 26 in *Cell* -- suggests that defects in Tregs could be responsible for alopecia areata, a common autoimmune disorder that causes hair loss, and could potentially play a role in other forms of baldness, including male pattern baldness, Rosenblum said. Since the same stem cells are responsible for helping heal the skin after injury, the study raises the possibility that Tregs may play a key role in wound repair as well.

Anti-inflammatory immune cells directly activate skin stem cells

Normally Tregs act as peacekeepers and diplomats, informing the rest of the immune system of the difference between friend and foe. When Tregs don't function properly, we may develop allergies to harmless substances like peanut protein or cat dander, or suffer from autoimmune disorders in which the immune system turns on the body's own tissues.

Like other immune cells, most Tregs reside in the body's lymph nodes, but some live permanently in other tissues, where they seem to have evolved to assist with local metabolic functions as well as playing their normal anti-inflammatory role. In the skin, for example, Rosenblum and colleagues have previously shown that Tregs help establish immune tolerance to healthy skin microbes in newborn mice, and these cells also secrete molecules that help with wound healing into adulthood.

Rosenblum, who is both an immunologist and a dermatologist, wanted to better understand the role of these resident immune cells in skin health. To do this, he and his team developed a technique for temporarily removing Tregs from the skin. But when they shaved patches of hair from these mice to make observations of the affected skin, they made a surprising discovery. "We quickly noticed that the shaved patches of hair never grew back, and we thought, 'Hmm, now that's interesting,'" Rosenblum said. "We realized we had to delve into this further."

In the new research, led by UCSF postdoctoral fellow and first author Niwa Ali, PhD, several lines of evidence suggested that Tregs play a role in triggering hair follicle regeneration.

First, imaging experiments revealed that Tregs have a close relationship with the stem cells that reside within hair follicles and allow them to regenerate: the number of active Tregs clustering around follicle stem cells typically swells by three-fold as follicles enter the growth phase of their regular cycle of rest

and regeneration. Also, removing Tregs from the skin blocked hair regrowth only if this was done within the first three days after shaving a patch of skin, when follicle regeneration would normally be activated. Getting rid of Tregs later on, once the regeneration had already begun, had no effect on hair regrowth.

Tregs' role in triggering hair growth did not appear related to their normal ability to tamp down tissue inflammation, the researchers found. Instead, they discovered that Tregs trigger stem cell activation directly through a common cell-cell communication system known as the Notch pathway. First, the team demonstrated that Tregs in the skin express unusually high levels of a Notch signaling protein called Jagged 1 (Jag1), compared to Tregs elsewhere in the body. They then showed that removing Tregs from the skin significantly reduced Notch signaling in follicle stem cells, and that replacing Tregs with microscopic beads covered in Jag1 protein restored Notch signaling in the stem cells and successfully activated follicle regeneration.

"It's as if the skin stem cells and Tregs have co-evolved, so that the Tregs not only guard the stem cells against inflammation but also take part in their regenerative work," Rosenblum said. "Now the stem cells rely on the Tregs completely to know when it's time to start regenerating."

Study could lead to new treatments for autoimmune hair loss

Rosenblum said the findings may have implications for alopecia areata, an autoimmune disease that interferes with hair follicle regeneration and causes patients to lose hair in patches from their scalp, eyebrows, and faces. Alopecia is among the most common human autoimmune diseases -- it's as common as rheumatoid arthritis, and more common than type 1 diabetes -- but scientists have little idea what causes it.

After his team first observed hair loss in Treg-deficient mice, Rosenblum learned that the genes associated with alopecia in previous studies are almost all related to Tregs, and treatments that boost Treg function have been shown to be an effective treatment for the disease. Rosenblum speculates that better understanding Tregs' critical role in hair growth could lead to improved treatments for hair loss more generally.

The study also adds to a growing sense that immune cells play much broader roles in tissue biology than had previously been appreciated, said Rosenblum, who plans to explore whether Tregs in the skin also play a role in wound healing, since the same follicle stem cells are involved in regenerating skin following injury.

"We think of immune cells as coming into a tissue to fight infection, while stem cells are there to regenerate the tissue after it's damaged," he said. "But what we found here is that stem cells and immune cells have to work together to make regeneration possible."

Story Source:

Materials provided by **University of California - San Francisco**. Original written by Pete Farley. *Note: Content may be edited for style and length.*

Journal Reference:

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