BIO NEWS

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(参考) サンフランシスコ南部 Oyster Point に準備中のバイオテック集積地 Gateway of Pacific
http://www.gatewayofpacific.com/

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https://www.sciencemag.org/news/2018/11/crispr-bombshell-chinese-researcher-claims-have-created-gene-edited-twins?utm_campaign=news_daily_2018-11-27&et_rid=375979900&et_cid=2513468
・Roche の子会社 Genentech が Jecure Therapeutics を買収（11/28）
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1．米国の研究で使用されるサルの数が過去最高に

2018 年 11 月 2 日

米国農務省（USDA）が 9 月下旬に発表したデータによると、米国の生物医学研究で使用されたサルの数が過去最高を記録した。これはヒト以外の霊長類が、マウスなど他の動物よりも有用であると考える科学者からの要求が高まっていることを反映しているのでは、としている。また同時に、これは実験動物の使用を減らそうとしているグループを失望させる結果にもなっている。
科学者は、昨年の研究で、75,825 頭の非ヒト霊長類を使用したが、これは 2015 年に比べて 22%も増加している。反対に、ネコ、イヌ、ウサギ、モルモットに関してはいずれも 10 年前よりも低い数字となっている。ただし、USDA からの報告はないものの、米国の生物医学研究に使用される動物の 95%はマウスであり、非ヒト霊長類はわずか 0.5%である。
研究におけるサル使用の上昇は、「科学の状態と非ヒト霊長類の重要性の両方を表している」と NIH は声明で述べた。又、代理店が支援する非ヒト霊長類のほぼ 3 分の 2 はカニクイザル（15%）、ヒヒ（6%）、残りの 12 種のサル種がアカゲザルである。 アカゲザルに対する需要の高まりは、9 月に発表された NIH の報告書によると、HIV/エイズ、脳、アルツハイマー病、および中毒を研究する研究者によって引き起こされていると思われる。

英文記事：
https://www.sciencemag.org/news/2018/11/record-number-monkeys-being-used-us-research?utm_campaign=news_daily_2018-11-02&et_rid=375979900&et_cid=2465506

Rhesus macaques are among the most popular nonhuman primates used in biomedical research.

AP Photo/Brennan Linsley

Record number of monkeys being used in U.S. research

By **David Grimm**Nov. 2, 2018 , 9:00 AM

The number of monkeys used in U.S. biomedical research reached an all-time high last year, according to data released in late September by the U.S. Department of Agriculture (USDA).

The uptick (see graph below)—to nearly 76,000 nonhuman primates in 2017—appears to reflect growing demand from scientists who believe nonhuman primates are more useful than other animals, such as mice or dogs, for testing drugs and studying diseases that also strike humans.

“I think the numbers are trending up because these animals give us better data. … We need them more than ever,” says Jay Rappaport, director of the Tulane National Primate Research Center in Covington, Louisiana, which houses about

5000 monkeys. The increase also comes amidst a surge in funding from the National Institutes of Health (NIH), which supports much of the nonhuman primate research in the United States.

The figures have surprised and disappointed groups seeking to reduce the use of lab animals. The biomedical community has said it is committed to reducing the use of research animals by finding replacements and using these animals more selectively, says Thomas Hartung, director of Johns Hopkins University's Center for Alternatives to Animal Testing in Baltimore, Maryland. But the new numbers suggest "people are just blindly running toward the monkey model without critically evaluating how valuable it really is."

Nonhuman primate research has faced intensifying scrutiny. **Harvard University closed its national primate research center**—one of only eight in the country—in 2015, after a federal investigation into the deaths of four of its animals. That same year, **NIH ended its support of all invasive chimpanzee studies**, citing a report that found these animals were no longer essential to biomedical research. And in 2016, Congress directed NIH to hold a **workshop** on the utility and ethics of monkey research.

Monkeys on the rise

Trends in the use of various research animals as a percentage change over their 2008 numbers

-40-30-20-1001020MonkeysCatsDogsGuinea pigsRabbits
2008Percent2009201020112012201320142015201620172017

J. YOU/*SCIENCE*

Public opposition to animal research has been rising—with a recent Pew Research Center poll finding that a record **52% of Americans oppose such studies**. And importing monkeys to the United States has become increasingly difficult as almost **all commercial air carriers now refuse to fly the animals**.

Yet according to the new USDA figures, **scientists used 75,825 nonhuman primates for research last year**, up 22% since 2015 and 6% since 2008. In contrast, the number of cats, dogs, rabbits, and other animals recorded by USDA are all being used at lower numbers than they were a decade ago. (Nonhuman primates constitute just 0.5% of all animals used in U.S. biomedical research; about 95% are rats and mice, which are not reported by USDA.) The total number of monkeys in labs—which also includes those bred in colonies and those not currently being used in research—has remained fairly steady for the past decade, with about 110,000 recorded last year (see second graph, below).

The uptick in monkey research "represents both the state of the science and the importance of nonhuman primates," NIH said in a statement. Nearly two-thirds of the nonhuman primates the agency supports are rhesus macaques, with cynomolgus macaques (15%), baboons (6%), and a dozen other monkey species making up the remainder. The rising demand for rhesus macaques appears to be driven by researchers studying HIV/AIDS, the brain, Alzheimer's disease, and addiction, according to an **NIH report** released in September.

The rise might also reflect the agency's expanding investment in these studies. NIH gave 249 grants in 2017 that supported nonhuman primate research, up from 171 in 2013. And the agency expects the number of nonhuman primates it supports to continue to grow in coming years.

Growing demand

The total number of monkeys in research labs has not changed much in the past few years, but more are being used in studies.

Number of nonhuman primates2008200920102011201220132014201520162017
050,000100,000150,000 Bred and housed Experimented

J. YOU/*SCIENCE*

That forecast frustrates Hartung, who says NIH should launch a review of the need for monkeys, similar to the one that led it to **end its support for chimpanzee research**. He challenges the idea, for instance, that nonhuman primates are more

useful for drug testing than rats or mice. Nonhuman primates are more genetically variable than rodents, he argues, and researchers typically use relatively few monkeys for studies of drug efficacy and safety. As a result, those experiments could yield skewed data on how the drugs will act in humans. Scientists embracing monkey experiments, he says, are at risk of "repeating the mistakes of the past."

Other animal advocates hope the new statistics will move members of Congress to put greater pressure on U.S. agencies to reduce nonhuman primate use. "I think when Congress sees these numbers, things are going to come to a head," says Mike Ryan, director of policy and government affairs at the New England Anti-Vivisection Society in Boston. This week, Representative Brendan Boyle (D–PA)—reacting to an **investigation into the Food and Drug Administration** (FDA) by the Washington, D.C.–based animal activist White Coat Waste Project—sent a bipartisan letter to FDA asking it to review all studies involving the more than 300 nonhuman primates it oversees. "Painful primate testing is shameful, and it has no place in the 21st century," Boyle tells *Science*. "It's clear that federal agencies are still not doing enough to curb this appalling practice."

In the meantime, Rappaport says nonhuman primate facilities like his are simply struggling to meet the demand. Some scientists are reporting that they have delayed studies by at least 6 months because they can't obtain animals, the NIH report notes. The growing demand could sharpen the tensions surrounding animal research. "The public wants more cures, but fewer animals," says Cindy Buckmaster, board chair of the Washington, D.C.–based Americans for Medical Progress, which supports animal studies. "They can't have it both ways."

doi:10.1126/science.aav9290

David Grimm

David is the Online News Editor of *Science*.

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2. 生分解性の足場を用いた幹細胞療法の進歩

2018 年 11 月 5 日

ラトガース大学の科学者らは、幹細胞を移植して薬物を送る為の生分解性の小さな足場を作ることに成功した。中枢神経系疾患の治療薬として期待されている幹細胞移植は、細胞生存率が低く、細胞の不完全な分化や神経結合の限られた成長によって妨げられてきたが、この研究成果が、アルツハイマー病およびパーキンソン病、老化脳変性、脊髄損傷および外傷性脳損傷の治療に役立つ可能性が出てきた。

Nature Communications 誌に掲載されたこの研究によると、科学者らが自然の組織を模倣して作ったこのナノサイズの足場は、試験管やマウスでは良好な結果を出しており、今後神経科学者や臨床医と協力して、より大きな動物のナノ足場を試験し、最終的には脊髄損傷の治療のための臨床試験に移行する予定だ、としている。

英文記事：

https://www.sciencedaily.com/releases/2018/11/181105081710.htm

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Advance stem cell therapy with biodegradable scaffold

New technology is aimed at central nervous system diseases and injuries

Date:

November 5, 2018

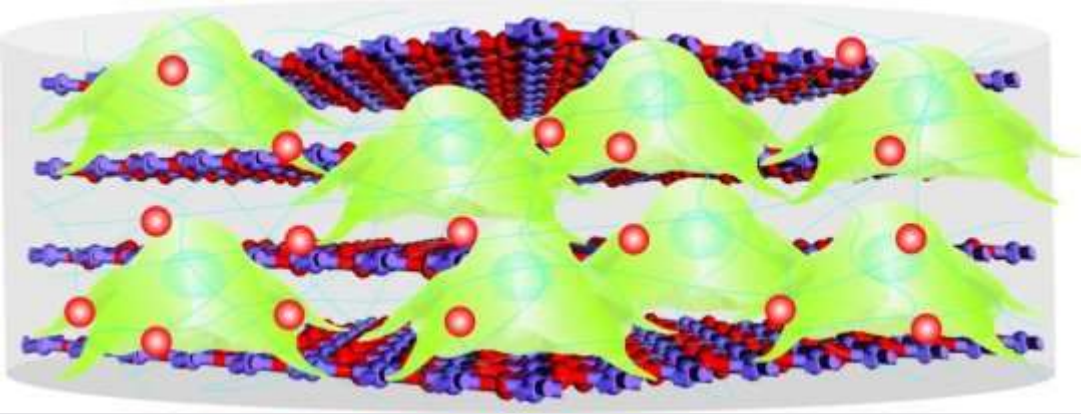
Source:

Rutgers University

Summary:

Scientists have created a tiny, biodegradable scaffold to transplant stem cells and deliver drugs, which may help treat Alzheimer's and Parkinson's diseases, aging brain degeneration, spinal cord injuries and traumatic brain injuries. Stem cell transplantation, which shows promise as a treatment for central nervous system diseases, has been hampered by low cell survival rates, incomplete differentiation of cells and limited growth of neural connections.

FULL STORY



A biodegradable inorganic nano-scaffold, consisting of stem cells, proteins and drugs, for advanced stem cell therapy and drug delivery.

Credit: KiBum Lee, Letao Yang and Sy-Tsong Dean Chueng.

Rutgers scientists have created a tiny, biodegradable scaffold to transplant stem cells and deliver drugs, which may help treat Alzheimer's and Parkinson's diseases, aging brain degeneration, spinal cord injuries and traumatic brain injuries.

Stem cell transplantation, which shows promise as a treatment for central nervous system diseases, has been hampered by low cell survival rates, incomplete differentiation of cells and limited growth of neural connections.

So, Rutgers scientists designed bio-scaffolds that mimic natural tissue and got good results in test tubes and mice, according to a study in *Nature Communications*. These nano-size scaffolds hold promise for advanced stem cell transplantation and neural tissue engineering. Stem cell therapy leads to stem cells becoming neurons and can restore neural circuits.

"It's been a major challenge to develop a reliable therapeutic method for treating central nervous system diseases and injuries," said study senior author KiBum Lee, a professor in the Department of Chemistry and Chemical Biology at Rutgers University-New Brunswick. "Our enhanced stem cell transplantation approach is an innovative potential solution."

The researchers, in cooperation with neuroscientists and clinicians, plan to test the nano-scaffolds in larger animals and eventually move to clinical trials for treating spinal cord injury. The scaffold-based technology also shows promise for regenerative medicine.

Story Source:

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

Journal Reference:

1. Letao Yang, Sy-Tsong Dean Chueng, Ying Li, Misaal Patel, Christopher Rathnam, Gangotri Dey, Lu Wang, Li Cai, Ki-Bum Lee. **A biodegradable hybrid inorganic nanoscaffold for advanced stem cell therapy**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-05599-2

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Rutgers University. "Advance stem cell therapy with biodegradable scaffold: New technology is aimed at central nervous system diseases and injuries." ScienceDaily. ScienceDaily, 5 November 2018. <www.sciencedaily.com/releases/2018/11/181105081710.htm>.

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3. ASD と統合失調症の両方にリンクする「マスターキー」遺伝子

2018 年 11 月 5 日

統合失調症や自閉症スペクトラム障害（ASD）など複雑な脳疾患における最近の研究では、脳機能にとって重要な遺伝子ネットワークの中心になるリスク遺伝子がいくつかの「マスターキー」であることが確認されている。エモリー大学と中国科学アカデミーの研究者らは、MIR-137 と呼ばれるこれらのマスターキーを部分的に欠くマウスを作成し分析した結果、これらのマウスが学習および記憶障害、反復行動および社会性障害を示した、としている。また、この変異マウスを、マウスの上昇する酵素 Pde10a（ホスホジエステラーゼ 10a）の阻害剤である血管拡張薬パパベリンで治療することによって、マウスの性能を向上できた、としている。
ちなみに、変異マウスを作製するために、北京の中国科学アカデミーの科学者らに協力を仰いだが、MIR-137 を完全に欠くマウスは発達に問題があって出生直後に死亡する為、この技術的に困難なマウスを作製するには数年かかる、としている。

英文記事：
https://medicalxpress.com/news/2018-11-master-key-gene-links-asd.html

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'Master key' gene has links to both ASD and schizophrenia

November 5, 2018, Emory University

Credit: CC0 Public Domain

Recent studies of complex brain disorders such as schizophrenia and autism spectrum disorder (ASD) have identified a few "master keys," risk genes that sit at the center of a network of genes important for brain function. Researchers at Emory and the Chinese Academy of Sciences have now created mice partially lacking one of those master keys, called MIR-137, and have used them to identify an angle on potential treatments for ASD.

The results are scheduled for publication in *Nature Neuroscience*.

Mice partially lacking MIR-137 display learning and memory deficits, repetitive behaviors and impaired sociability. MIR-137 encodes a microRNA, which regulates hundreds of other genes, many of which are also connected to schizophrenia and autism spectrum disorder.

By treating mutant mice with papaverine, a vasodilator discovered in the 19th century, scientists could improve the performance of the mice on maze navigation and social behavior tests. Papaverine is an inhibitor of the enzyme Pde10a (phosphodiesterase 10a), which is elevated in mutant mice.

Other Pde10a inhibitors have been tested in schizophrenia clinical trials, but the new results suggest this group of compounds could have potential for some individuals with ASD, says senior author Peng Jin, Ph.D., professor of human genetics at Emory University School of Medicine.

Having just the right level of MIR-137 function is important. Previous studies of people with genetic deletions show that a loss of MIR-137 is **connected with intellectual disability and autism spectrum disorder**. The reverse situation, in which a genetic variation increases MIR-137 levels, appears to contribute to schizophrenia.

"It's interesting to think about in the context of precision medicine," Jin says. "Individuals with a partial loss of MIR137—either genomic deletions or reduced expression—could potentially be candidates for treatment with Pde10a inhibitors."

To create the mutant mice, Jin's lab teamed up with Dahua Chen, Ph.D. and Zhao-Qian Teng, Ph.D. scientists at the State Key Laboratories of Stem Cell and Reproductive Biology and Membrane Biology, part of the Institute of Zoology, Chinese Academy of Sciences in Beijing. Jin says that generating mice with a heritable disruption of MIR-137 was technically challenging, taking several years. Mice completely lacking MIR-137 have problems with development and die soon after birth. The effect is similar if the deletion is restricted to the nervous system. Other "knockouts" of microRNA genes have not displayed such distinct post-natal effects, Jin notes. However, the scientists wanted to study animals that had one copy intact—a situation analogous to the humans with ASD.

"Several studies had shown an association between MIR-137 and both ASD and schizophrenia, but it was very important to show that causal relationship," Jin says.

Mice with one copy of MIR-137 disrupted in the brain learn to navigate mazes with more difficulty than controls. They also display increased repetitive behaviors (self-grooming and marble-burying) and show a limited preference to socialize with another mouse rather than an object, and do not discriminate familiar mice from strangers.

The brains of mutant mice have a higher density of dendritic spines, indicating that they have impaired synaptic pruning, a process other researchers have observed is altered in schizophrenia and autism.

Analyzing the genes in brain cells whose activities were most altered by MIR-137 loss allowed the researchers to pinpoint Pde10a. Treating mutant mice with papaverine improved their ability to learn mazes, although it did not restore their performance to that of control mice. In addition, papaverine treatment significantly increased the amounts of time mutant mice interacted with other mice.

Explore further: **Mouse model of intellectual disability isolates learning gene**

More information: Ying Cheng et al, Partial loss of psychiatric risk gene Mir137 in mice causes repetitive behavior and impairs sociability and learning via increased Pde10a, *Nature Neuroscience* (2018). **DOI: 10.1038/s41593-018-0261-7**

Journal reference: Nature Neuroscience

Provided by: Emory University

目次に戻る

４．自己免疫と心臓病のリンクをマウスで説明

2018 年 11 月 8 日

乾癬、狼瘡および関節リウマチのような自己免疫疾患を有する人は、心臓血管疾患を発症する危険性が高い。具体的には、乾癬および狼瘡の人は、これらの疾患のない人よりも心臓発作を患う可能性が 2～8 倍高く、慢性関節リウマチを患う若年および中年の成人では、心臓血管疾患が死因のトップとなっている。
現在、セントルイスのワシントン大学医学部の研究者らは、この自己免疫疾患と心血管疾患との関連性を理解し始めており、11 月 8 日の *Cell Metabolism* 誌にその研究成果を発表している。
乾癬様のマウスを研究した研究者らは、マウスの血管が堅いことを発見。更にマウスに高コレステロール食を 3 週間与えたところ、実験的乾癬群のマウスは、通常のマウスと比較して、血管内に有意に大きなコレステロール沈着を発症した。コレステロールは通常、血液と組織の間を自由に循環するが、これらのマウスでは柔軟性のない血管壁が壁にコレステロールを閉じ込め、心臓発作や脳卒中を引き起こす可能性があるプラークを促進した、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/11/181108130543.htm

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Link between autoimmune, heart disease explained in mice

Immune cells cause cholesterol to be trapped in blood vessels

Date:

November 8, 2018

Source:

Washington University School of Medicine

Summary:

Autoimmune diseases such as psoriasis, lupus and rheumatoid arthritis more than double the risk of cardiovascular disease. A new study shows that immune cells that arise during autoimmune disease cause cholesterol to become trapped inside blood vessels.

FULL STORY

Gwendalyn Randolph, PhD, (above) prepares samples for a human study on the link between autoimmune and cardiovascular diseases. She recently published an animal study showing that immune cells that arise during autoimmune disease cause cholesterol to become trapped inside blood vessels.

Credit: Matt Miller

People with autoimmune diseases such as psoriasis, lupus and rheumatoid arthritis are at high risk of developing cardiovascular disease, even though none of these conditions seem to target the cardiovascular system directly. Now, researchers at Washington University School of Medicine in St. Louis believe they have begun to understand the link between the two.

Researchers studying mice with a psoriasis-like condition found that the mice's blood vessels were stiff. Cholesterol normally circulates freely between the blood and the tissues, but in these mice the inflexible vessel walls trapped cholesterol in their walls, promoting plaques that can cause heart attacks and strokes.

"For decades it's been known that the trapping of cholesterol drives disease, and now we have a mechanism for how certain immune responses typical of autoimmune diseases might make that worse," said senior author Gwendalyn Randolph, PhD, the Emil R. Unanue Distinguished Professor of Immunology and a professor of medicine. "In the mouse, the signs of cardiovascular disease scarcely arose when we neutralized these immune components. In people, it's hard to be sure, but we would predict it would be preventable, too."

The findings are published Nov. 8 in *Cell Metabolism*.

People with psoriasis and lupus are two to eight times more likely to suffer a heart attack than people without these diseases. For young and middle-aged adults with rheumatoid arthritis, cardiovascular disease is the top cause of death.

Psoriasis is characterized by patches of red, thickened, scaly skin. The thickening is partly due to an excess of collagen, the main protein in connective tissues such as skin and blood vessels -- and also the key ingredient in some beauty products designed to plump lips and erase wrinkles. In people with psoriasis, the excess collagen isn't confined to the rash area; it can be found in seemingly normal, healthy skin, too.

Randolph and first author Li-Hao "Paul" Huang, PhD, an instructor in pathology, suspected that the walls of blood vessels also might be webbed with too much collagen. They created a light-sensitive form of high-density lipoprotein (HDL) -- the molecular carrying case for cholesterol -- that fluoresces when hit with a laser beam, and inserted it into mice. The researchers then induced a psoriasis-like disease in the mice by painting their ears with imiquimod, an inflammatory compound that activates the same kinds of immune cells that play a role in human psoriasis.

By following the fluorescent cholesterol carrier, the researchers could see that HDL cholesterol was delayed in getting out of the bloodstream in the mice that received the compound. This was true not only in the skin, but in internal arteries near the heart. In addition, the skin and blood vessels were more densely interlaced with collagen and more resistant to stretching.

Further, when the researchers fed mice a high-cholesterol diet for three weeks while also painting their ears, the mice in the experimental psoriasis group developed significantly larger cholesterol deposits in their blood vessels.

"The skin-driven immune response can drive systemic changes," Randolph said. "Once immune cells are programmed by reactions to the inflamed skin, they move around the body to other skin sites and arteries to be ready for the next insult, enhancing the collagen density wherever they go."

An immune cell type called Th17 cells multiplies robustly in autoimmune diseases such as psoriasis, lupus and rheumatoid arthritis, releasing copious amounts of the immune molecule IL-17. When the researchers neutralized IL-17 in mice with psoriasis-like disease, using an antibody, collagen density went down and cholesterol deposits shrank.

Drugs that target IL-17 already are approved to treat psoriasis, marketed under brand names such as Cosentyx and Taltz, and other anti-IL-17 therapies are in the pipeline.

"It'll take a few years before we know for sure, but we predict that the anti-IL-17 antibodies that already are being used to treat autoimmune diseases will be effective at reducing risk of cardiovascular disease," Randolph said. "This would be important because some other drugs on the market seem to improve the skin disease but not reduce cardiovascular risk."

Story Source:

Materials provided by **Washington University School of Medicine**. Original written by Tamara Bhandari. *Note: Content may be edited for style and length.*

Journal Reference:

1. Li-Hao Huang, Bernd H. Zinselmeyer, Chih-Hao Chang, Brian T. Saunders, Andrew Elvington, Osamu Baba, Thomas J. Broekelmann, Lina Qi, Joseph S. Rueve, Melody A. Swartz, Brian S. Kim, Robert P. Mecham, Helge Wiig, Michael J. Thomas, Mary G. Sorci-Thomas, Gwendalyn J. Randolph. **Interleukin-17 Drives Interstitial Entrapment of Tissue Lipoproteins in Experimental Psoriasis**. *Cell Metabolism*, 2018; DOI: 10.1016/j.cmet.2018.10.006

目次に戻る

5. アレルギー性ショックがどのようにして迅速に起きるか、マウス実験で明らかに

2018 年 11 月 8 日

誰かが重度のアレルギーを持っている場合、アナフィラキシーショック反応は、どのようにして素早く起きるのか？11 月 9 日号の *Science* 誌に掲載されたデューク大学医療センターの研究者らによる研究は、アナフィラキシーショック中に免疫細胞がどのようにして誘発されるか追跡するためにマウスモデルを用いている。
彼らが説明するのは、以前は知られていなかったメカニズムで、これによると、この新しく同定された免疫細胞（樹状細胞）が樹状突起を用いてアレルゲンを探し血管を採掘し、侵入者を連続的にサンプリングする。血液媒介アレルゲンが感知されると、樹状細胞の表面から芽を出したマイクロビーズを介してアレルゲンをマスト細胞に迅速に送達するという通常にはないメカニズムだ、としている。

英文と記事：
https://www.eurekalert.org/pub_releases/2018-11/dumc-umd103018.php

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PUBLIC RELEASE: 8-NOV-2018

Using mice, Duke researchers identify how allergic shock occurs so quickly

A newly identified immune cell mines the blood for allergens to directly trigger inflammation

Duke University Medical Center

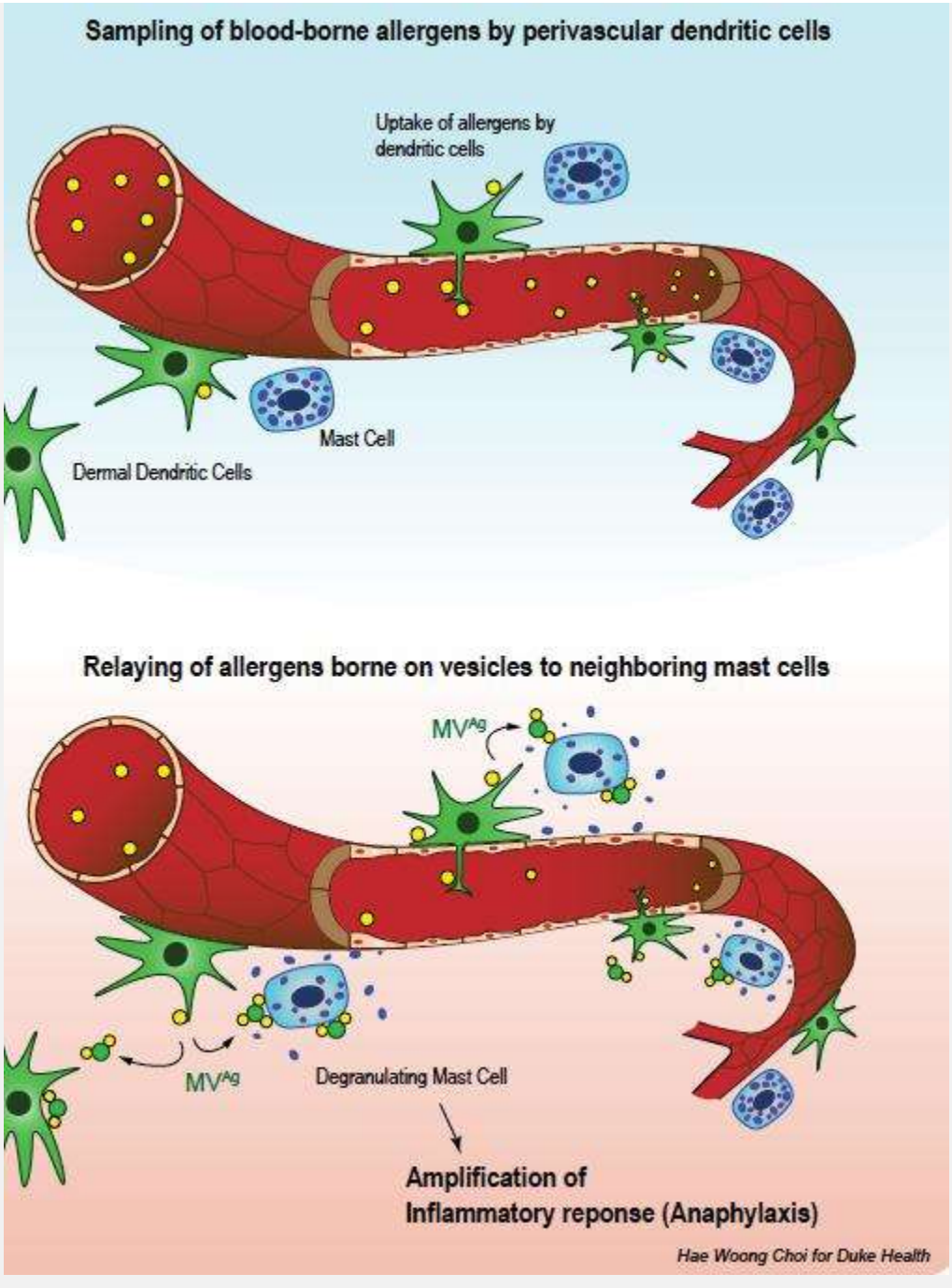

IMAGE: A newly identified subset of dendritic cells on the exterior of blood vessels use dendrites to drill into the blood vessels and continuously sample for foreign invaders. When allergens are... **view more**

Credit: Hae Woong Choi for Duke Health

DURHAM, N.C. - When someone has a severe allergy, the life-threatening effects of an exposure are nearly instantaneous - skin rash, fainting, labored breathing, weak pulse, racing heart.

This response -- anaphylactic shock -- has a straightforward cause and effect. But underlying that process has been a physiological puzzler: How does this massive reaction happen so quickly?

Researchers at Duke Health, publishing in the Nov. 9 issue of the journal *Science*, used mouse models to track how immune cells are triggered during anaphylactic shock. They describe a previously unknown mechanism in which a newly identified immune cell basically mines the blood vessels for allergens and then utilizes an unusual mechanism for rapidly delivering the blood-borne allergens to mast cells. The finding potentially opens innovative lines of attack to shut down this deadly over-reaction that afflicts one in 50 people a year in the United States.

"The central finding is that dendritic cells, which are key players in allergy development, also play a direct role in triggering anaphylactic shock," said senior author Soman N. Abraham, Ph.D., professor in Duke's Departments of Pathology, Immunology and Molecular Genetics & Microbiology, and member of the Program in Emerging Infectious Diseases, Duke-National University of Singapore, Singapore.

It is understood that mast cells are the main actors in anaphylactic reactions as they engage in what's called degranulation -- the release of histamines and other inflammatory substances into the blood stream, leading to systemic shock. But it was previously unknown how mast cells, which are located outside of the vascular system, were alerted to an allergen circulating in the blood stream.

What Abraham and colleagues observed was a newly identified subset of dendritic cells located on the exterior surface of blood vessels. Using probe-like protrusions called dendrites that drill into the blood vessels, these cells continuously sample the blood for foreign invaders.

When the dendrites sense blood-borne allergens, dendritic cells alert the neighboring mast cells to the presence of the invader. This communication is unusual, involving a time-saving process of

handing over the allergen through micro-vesicles, little allergen-coated bubbles, which bud off from the surface of the dendritic cells.

"In addition to their well-known capacity to internalize, process and present antigens to immune cells, dendritic cells now appear to actively distribute antigens they have acquired to surrounding immune cells even before they are internalized," said first author, Hae Woong Choi.

As these allergen-bearing vesicles make contact with mast cells throughout the vasculature of the body, a torrent of inflammatory mediators are released into the blood stream, quickly resulting in anaphylactic shock.

To further demonstrate the dendritic cell's critical role in promoting anaphylactic shock, the researchers were able to deplete these dendritic cells in mice, curbing the allergic reaction. This new observation could lead to the development of new therapeutics targeting dendritic cells.

Additional research is needed to explore whether this newly described activity of dendritic cells has an unknown benefit.

"While it's detrimental in the context of allergens, this function might be needed to fight diseases and actually be helpful," Abraham said. "Maybe these dendritic cells are designed to detect blood-borne parasites, viruses or bacteria, so we need to understand any other circumstances that activate them before contemplating shutting them down or impeding their activity."

###

In addition to Abraham and Choi, study authors include Jutamas Suwanpradid, Il Hwan Kim, Herman F. Staats, Muzlifah Haniffa and Amanda S. MacLeod.

The work received funded from the National Institutes of Health (U01-AI082107; 620 R01-AI096305; R56-DK095198; R21-AI128727).

目次に戻る

6.「長寿タンパク質」が老いたマウスの筋肉治癒を活性化

2018 年 11 月 23 日

老化の欠点の１つは、骨格筋が傷害後癒す能力を失うことである。今週の *Nature Communications* 誌に掲載されたピッツバーグ大学の新たな研究では、いわゆる「長寿タンパク質」クロソ（Klotho）が若いマウスでは筋肉の損傷後急増するのに対して、老いたマウスでは平らなままであることが示されている。又、老いたマウスのクロソのレベルを上げること、あるいは、クロソ不足の負の効果を軽減することによって、損傷後の筋肉再生を回復することができた、としている。又、クロソの投与については、時期、量、経路など、更なる研究が必要だ、ともしている。

英文記事：
https://www.sciencedaily.com/releases/2018/11/181123135030.htm

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'Longevity protein' rejuvenates muscle healing in old mice

Date:

November 23, 2018

Source:

University of Pittsburgh Schools of the Health Sciences

Summary:

A protein found in healing muscles of younger mice helps older animals bounce back from injury.

FULL STORY

One of the downsides to getting older is that skeletal muscle loses its ability to heal after injury. New research from the University of Pittsburgh implicates the so-called "longevity protein" Klotho, both as culprit and therapeutic target.

The paper, published this week in *Nature Communications*, showed that, in young animals, Klotho expression soars after a muscle injury, whereas in old animals, it remains flat. By raising Klotho levels in old animals, or by mitigating downstream effects of Klotho deficiency, the researchers could restore muscle regeneration after injury.

"We found that we were able to rescue, at least in part, the regenerative defect of aged skeletal muscle," said lead author Fabrisia Ambrosio, Ph.D., director of rehabilitation for UPMC International, associate professor of physical medicine and rehabilitation at Pitt, and core faculty at the McGowan Institute of Regenerative Medicine. "We saw functional levels of muscle regeneration in old animals that paralleled those of their young counterparts, suggesting that this could potentially be a therapeutic option down the road."

Suspecting that Klotho acts through mitochondria dysfunction, the researchers gave Klotho-deficient animals a mitochondria-targeting drug called SS-31, which currently is in phase III clinical trials. Treated animals grew more new muscle tissue at the site of injury compared to untreated controls, and their strength after recovery rivaled that of genetically normal mice.

Similarly, injecting Klotho into older animals a few days after injury resulted in greater muscle mass and better functional recovery than their saline-treated counterparts. Normal, healthy mice did not benefit from SS-31 after injury.

Clinically, these findings could translate to older adults who either sustained a muscle injury or underwent muscle-damaging surgery. Giving them Klotho at the appropriate timepoint could boost their muscle regeneration and lead to a more complete recovery.

Ambrosio cautions that the timing, dosage and route of administration will require future research.

"If you just bombard the muscle with Klotho, we do not expect to observe any functional benefit," Ambrosio said. "We've found that mimicking the timing profile we see in young animals seems to be critical. We think that this gives some insight into the therapeutic window."

Story Source:

Materials provided by **University of Pittsburgh Schools of the Health Sciences**. *Note: Content may be edited for style and length.*

Journal Reference:

1. A. Sahu, H. Mamiya, S. N. Shinde, A. Cheikhi, L. L. Winter, N. V. Vo, D. Stolz, V. Roginskaya, W. Y. Tang, C. St. Croix, L. H. Sanders, M. Franti, B. Van Houten, T. A. Rando, A. Barchowsky, F. Ambrosio. **Age-related declines in α-Klotho drive progenitor cell mitochondrial dysfunction and impaired muscle regeneration**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-07253-3

Cite This Page:

- MLA
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University of Pittsburgh Schools of the Health Sciences. "'Longevity protein' rejuvenates muscle healing in old mice." ScienceDaily. ScienceDaily, 23 November 2018. <www.sciencedaily.com/releases/2018/11/181123135030.htm>.
University of Pittsburgh Schools of the Health Sciences. (2018, November 23). 'Longevity protein' rejuvenates muscle healing in old mice. *ScienceDaily*. Retrieved November 27, 2018 from www.sciencedaily.com/releases/2018/11/181123135030.htm

University of Pittsburgh Schools of the Health Sciences. "'Longevity protein' rejuvenates muscle healing in old mice." ScienceDaily. www.sciencedaily.com/releases/2018/11/181123135030.htm (accessed November 27, 2018).

目次に戻る

7. 脂肪を「褐色」に変える薬が肥満と戦う助けに -マウス実験

2018 年 11 月 26 日

我々の身体には 2 種類の脂肪があって、「白色脂肪」はカロリーを蓄積し、「褐色脂肪」はエネルギーを消費し体重減少に役立つ。
今回ケンブリッジ大学の研究者らは、この白色脂肪を“褐色化”させ褐色脂肪の効率を高める方法を発見し、その成果が *Nature Communications* 誌に掲載されている。
褐色脂肪内の細胞はミトコンドリアに富んでおり、身体に酸素と栄養を供給できるようより多くの血管が通っている。褐色細胞が完全に活性化されると、100g の褐色細胞だけで 1 日 3,400 カロリーを燃やすことができ、これはほとんどの人間の日々の食物からの摂取カロリーよりも高く、肥満と戦うのに充分とされる。我々が年をとるにつれて体内の褐色脂肪の量も減少する。
今現在分かっている褐色脂肪を活性化させる唯一の方法は、寒さの中で冬眠のような状態を起こすことであり、これは辛く不快であるばかりでなく、非現実的な方法である。
2012 年にケンブリッジ大学は、脳と身体の組織両方において褐色脂肪活性を制御する BMP8b と呼ばれる分子を同定、このタンパク質を産生する遺伝子をマウスで欠損させた場合、褐色脂肪が機能しなくなることを示したが、今回はマウスで BMP8b の量を増やすと、褐色脂肪の機能が向上すること、又白色脂肪の一部が褐色脂肪に変化することを示した。

英文記事：
https://www.sciencedaily.com/releases/2018/11/181126123416.htm

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Study in mice suggests drug to turn fat 'brown' could help fight obesity

Date:

November 26, 2018

Source:

University of Cambridge

Summary:

Our bodies contain two types of fat: white fat and brown fat. While white fat stores calories, brown fat burns energy and could help us lose weight. Now, scientists have found a way of making the white fat 'browner' and increasing the efficiency of brown fat. While their study was carried out in mice, they hope that this finding will translate into humans and provide a potential new drug to help fight obesity.

FULL STORY

Our bodies contain two types of fat: white fat and brown fat. While white fat stores calories, brown fat burns energy and could help us lose weight. Now, scientists at the University of Cambridge have found a way of making the white fat 'browner' and increasing the efficiency of brown fat.

While their study was carried out in mice, they hope that this finding will translate into humans and provide a potential new drug to help fight obesity.

Obesity is a condition in which individuals accumulate more and more fat until their fat stops functioning. This can lead to diseases such as diabetes. However, not all fat tissue is bad: the fat that accumulates in obesity is known as 'white fat', but a second form of fat known as 'brown fat' could be used to treat obesity.

Both brown and white fat are made up of fat cells known as adipocytes, but in brown fat, these cells are rich in mitochondria -- the 'batteries' that power our bodies -- which give the tissue its

brown colour. Brown fat also contains more blood vessels to allow the body to provide it with oxygen and nutrients.

While white fat stories energy, brown fat burns it in a process known as 'thermogenesis'. When fully activated, just 100g of brown fat can burn 3,400 calories a day -- significantly higher than most people's daily food intake and more than enough to fight obesity.

We all have some brown fat -- or brown adipose tissue, as it is also known -- in our bodies, but it is found most abundantly in newborns and in hibernating animals (where the heat produced by brown fat enables them to survive even in freezing temperatures). As we age, the amount of brown fat in our bodies decreases.

Just having more brown fat alone is not enough -- the tissue also needs to be activated. Currently, the only ways to activate brown fat are to put people in the cold to mimic hibernation, which is both impractical and unpleasant, or to treat them with drugs known as adrenergic agonists, but these can cause heart attacks. It is also necessary to increase the number of blood vessels in the tissue to carry nutrients to the fat cells and the number of nerve cells to allow the brain to 'switch on' the tissue.

In 2012, a team led by Professor Toni Vidal-Puig from the Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, identified a molecule known as BMP8b that regulates the activation of brown fat in both the brain and the body's tissues. They showed that deleting the gene in mice that produces this protein stopped brown fat from functioning.

Now, in a study published today in the journal *Nature Communications*, Professor Vidal-Puig has led an international team of researchers which has shown that increasing how much BMP8b mice can produce increases the function of their brown fat. This implies that BMP8b, which is found in the blood, could potentially be used as a drug to increase the amount of brown fat amount in humans as well as making it more active. Further research will be necessary to demonstrate if this is the case.

To carry out their research, the team used mice that had been bred to produce higher levels of the protein in adipose tissue. As anticipated, they found that increasing BMP8b levels changed some of the white fat into brown fat, a process known as beiging and thus increased the amount of energy burnt by the tissue.

They showed that higher levels of BMP8b make the tissue more sensitive to adrenergic signals from nerves -- the same pathway target by adrenergic agonist drugs. This may allow lower doses of these drugs to be used to activate brown fat in people, hence reducing their risk of heart attack.

Unexpectedly, but importantly, the team also found that the molecule increased the amount of blood vessels and nerves in brown fat.

"There have been a lot of studies that have found molecules that promote brown fat development, but, simply increasing the amount of brown fat will not work to treat disease -- it has to be able to get enough nutrients and be turned on," says Professor Vidal-Puig, lead author of the study.

Co-author Dr Sam Virtue, also from the Institute of Metabolic Science, adds: "It's like taking a one litre engine out of a car and sticking in a two litre engine in its place. In theory the car can go quicker, but if you only have a tiny fuel pipe to the engine and don't connect the accelerator pedal it won't do much good. BMP8b increases the engine size, and fits a new fuel line and connects up the accelerator!"

Story Source:

Materials provided by **University of Cambridge**. The original story is licensed under a Creative Commons License. *Note: Content may be edited for style and length.*

Journal Reference:

1. Vanessa Pellegrinelli, Vivian J. Peirce, Laura Howard, Samuel Virtue, Dénes Türei, Martina Senzacqua, Andrea Frontini, Jeffrey W. Dalley, Antony R. Horton, Guillaume Bidault, Ilenia Severi, Andrew Whittle, Kamal Rahmouni, Julio Saez-Rodriguez, Saverio Cinti, Alun M. Davies, Antonio Vidal-Puig. **Adipocyte-secreted BMP8b mediates adrenergic-induced remodeling of the neuro-vascular network in adipose tissue**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-07453-x

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University of Cambridge. "Study in mice suggests drug to turn fat 'brown' could help fight obesity." ScienceDaily. ScienceDaily, 26 November 2018. <www.sciencedaily.com/releases/2018/11/181126123416.htm>.

目次に戻る

8. 希少遺伝病に対する免疫制御物質を同定 -マウス実験

2018 年 11 月 27 日

Scripps 研究所の科学者らは、癌および慢性ウィルス感染を治療するときに主な標的となる重要な免疫系制御タンパク質を発見した。又、このタンパク質 ABHD12 の機能を明らかにし、11 月 12 日の *Nature Chemical Biology* 誌で発表している。
彼らは、ABHD12 ノックアウトマウスおよび ABHD12 阻害剤で治療したマウスには、ウイルスを浄化するためにはるかに激しく効果的な免疫反応があり、ABHD12 欠損または阻害後のクローン 13 感染マウスでは、死亡率および肺病変の亢進が顕著であった。
この知見は、将来の研究で調査するいくつかの可能性を示唆しており、ABHD12 を標的とし、その活性を低下させ、免疫系を刺激する治療は、より広範な用途を有するかもしれない、としている。

英文記事：
https://medicalxpress.com/news/2018-11-trail-rare-genetic-disease-scientists.html

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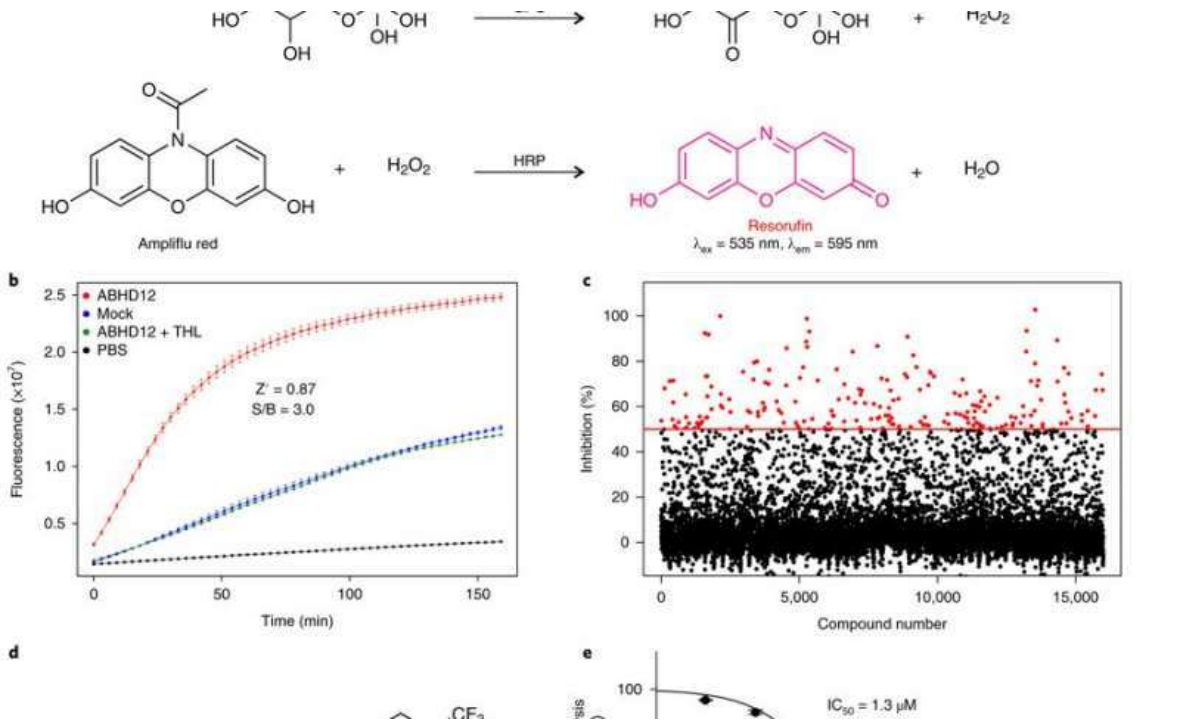
On the trail of rare genetic disease, scientists uncover key immune regulator

November 27, 2018,
The Scripps Research Institute



a, An enzyme-coupled assay that begins with ABHD12-mediated hydrolysis of 17:0 lyso-PA, which is followed by glycerol-3-phosphate oxidase (GPO)-mediated generation of H2O2, and culminates in the horseradish peroxidase (HRP)-mediated …**more**

Scientists at Scripps Research have found an important immune system-regulating protein that in principle could be targeted to treat cancers and chronic viral infections.

The scientists, in a study published November 12 in *Nature Chemical Biology*, set out to determine the function of a protein, ABHD12, whose absence causes a rare genetic disease featuring a host of brain and nerve problems.

The researchers found that ABHD12 normally acts as a powerful "brake" on the immune system to keep it from becoming harmfully overactive. Mice engineered without the protein have signs of elevated inflammation, and their immune systems are more likely to overreact to a viral infection.

The discovery suggests that the absence of ABHD12 in people with mutant versions of its gene may cause neurological disease at least in part via excessive immune activity. It also indicates that ABHD12 may be a useful target for drugs that boost the immune system—for example against cancers and viruses that normally persist by shutting down people's immune defenses.

"This is a good example of how the study of a rare genetic disease can reveal a pathway that plays a key role in human biology," says study co-senior author Benjamin Cravatt, professor and chair of the Department of Chemical Physiology at Scripps Research.

The rare disease in this case is a mix of progressive brain, peripheral nerve, and eye problems that scientists have given the acronym PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract). Since 2010, researchers have known that PHARC is caused by gene mutations that prevent ABHD12 from being made. But the normal function—or functions—of ABHD12, and the precise reasons its absence causes disease, have been unclear.

The Cravatt laboratory, in a 2013 study, engineered "knockout" mice that lack the ABHD12 gene, and determined that the ABHD12 protein is an enzyme that normally breaks down lysophospholipids—fat-related molecules that include lyso-PS, an important stimulator of immune activity. In the new study, Cravatt's team collaborated with researchers at Abide Therapeutics to extend their work on ABHD12 by developing a compound that selectively inhibits the enzyme's function.

"The idea was to use this inhibitor to disrupt ABHD12 in otherwise normal adult mice, and compare the effects to what we see in the ABHD12-knockout mice that never have a working copy of the enzyme," Cravatt says.

The team found that in adult mice, reducing ABHD12 activity with the inhibitor led to a rise in lyso-PS in immune cells called macrophages, as well as in brain tissue. The rise wasn't as great as that seen in the ABHD12-knockout mice, and even four weeks of treatment with the inhibitor appeared to cause only slight hearing defects—nothing like the profound defects experienced by PHARC patients.

However, in further experiments conducted by the laboratory of study co-senior author John Teijaro, an assistant professor in the Department of Immunology and Microbiology at Scripps Research, it was clear that the reduction in ABHD12 activity had a big effect on the mouse immune system.

Teijaro's team infected the inhibitor-treated mice with a virus called lymphocytic choriomeningitis virus (LCMV) clone 13, which can deactivate elements of the immune system to establish a persistent infection in its hosts. Ordinary mice infected with LCMV clone 13 typically have minor symptoms but take a long time to clear the infection.

Teijaro and colleagues found that the ABHD12-knockout mice, as well as the mice treated with the ABHD12 inhibitor, had immune responses that were much more vigorous and effective in clearing the virus, often excessively so.

"The enhanced mortality and lung pathology were striking in clone-13 infected mice following ABHD12 inhibition or deletion," Teijaro says.

The findings suggest several possibilities to investigate with future research. For example, the enhanced immune activity in the knockout and inhibitor-treated mice hints that the signs and symptoms of PHARC may have an immunological basis.

"It is now known that the immune system plays a big role in many brain diseases, including neurodegenerative diseases such as Alzheimer's and Parkinson's," Cravatt notes. "There have also been hints of immune involvement in developmental brain disorders such as autism and schizophrenia."

He adds that if PHARC turns out to be caused in part by chronic brain and nerve inflammation, it might be treatable, if caught early enough, with anti-inflammatory or immune-suppressing drugs.

At the same time, treatments that target ABHD12, reducing its activity and stimulating the immune system, might have even broader use.

"The enhanced killer-T-cell activity we saw following ABHD12 deletion in the LCMV-infected mice suggests that blocking ABHD12 may enhance T-cell responses in immune suppressive environments such as chronic viral infections and cancers," Teijaro says.

"We're certainly eager to explore those possibilities," Cravatt says.

Explore further: Researchers discover possible new target for treating brain inflammation

More information: Daisuke Ogasawara et al, Selective blockade of the lyso-PS lipase ABHD12 stimulates immune responses in vivo, *Nature Chemical Biology* (2018). **DOI: 10.1038/s41589-018-0155-8**

Journal reference: Nature Chemical Biology

Provided by: The Scripps Research Institute

目次に戻る

9. ナノスケールの血液検査技術で癌の発見

2018 年 11 月 28 日

マンチェスター大学の科学者らによって、がん患者の血液から従来よりも多くの情報を得る手法が開発された。この発見は、早期診断を加速し、創薬をスピードアップし、個別化医療の進歩を導く可能性がある。Cancer Research UK が資金を提供するこの研究は、今日（11 月 28 日）の *Advanced Materials* 誌に掲載されている。
CAELYX®と呼ばれる化学療法薬は、リポソームと呼ばれる柔らかい脂質ベースのナノ粒子に含まれ、これが副作用を最小限に抑えるための血管として働く。今回マンチェスター大学の科学者らは、この CAELYX®を投与された進行卵巣癌の女性の血液サンプルを採取し、注入されたリポソームを抽出しそのリポソーム表面に付着した様々な生体分子を検出し、そこから多くの情報が得られた、としている。
彼らはこの技術をマウスに使用して、病気の初期段階で癌を特定するための最良のバイオマーカーパターンを見つけたいと考えている。

英文記事：
https://www.sciencedaily.com/releases/2018/11/181128082737.htm

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Nanoscale blood test technique set to springboard cancer discoveries

Date:

November 28, 2018

Source:

Cancer Research UK

Summary:

A technique to get more information from the blood of cancer patients than previously possible has been developed. The discovery could potentially accelerate early diagnosis, speed up drug discovery and lead to advancements in personalized medicines.

FULL STORY

A technique to get more information from the blood of cancer patients than previously possible has been developed.

The discovery could potentially accelerate early diagnosis, speed up drug discovery and lead to advancements in personalised medicines. The Cancer Research UK-funded study is published in *Advanced Materials* today (Wednesday).

The scientists, from the University of Manchester, collected blood samples from women with advanced ovarian cancer who were treated with a type of chemotherapy called CAELYX®. This chemotherapy drug is contained in a soft, lipid-based nanoparticle, called a liposome, which acts as a vessel to help minimise side effects.

Women gave a sample of blood, following an injection of CAELYX® over a course of 90 minutes as part of their treatment. By extracting the injected liposomes, the scientists were able to detect a wide variety of biomolecules that stuck to the surface of the liposome -- called the 'biomolecule corona'.

Professor Kostas Kostarelos, lead author from the University of Manchester, said: "We're astonished at how rich the information was on the surface of the liposomes taken from the blood. We hope this technique could be a springboard for further research, from monitoring disease progression or recurrence, to identifying which treatment is best for each patient and potentially finding new biomarkers for early diagnosis."

This is a step forward in developing a better technique to gather information from patients' blood -- a 'halo effect' of biomolecules sticking to the liposomes has been seen before, but only after dipping the nanoparticles in blood samples in a tube outside the patient's body.

Dr Marilena Hadjidemetriou, study author from the University of Manchester, said: "The blood is a potential goldmine of information, but there's a challenge to amplify cancer signals that would otherwise be buried within the 'noise'.

"More abundant proteins mask rarer and smaller molecules that could be significant in helping us to understand disease progression or finding potential new drug targets. This technique overcomes this challenge."

Professor Caroline Dive, Cancer Research UK's expert in liquid biopsies, said: "Finding a test to help diagnose, track and treat cancer is something many scientists are pursuing. Liquid biopsies are quicker, cheaper and less invasive than many other tests, and this technique is an important early step in developing such a test. Further work will reveal what the information captured using liposomes can tell us about the disease."

The researchers now hope to use this technique in mice to help find the best patterns of biomarkers to identify cancers in the early stages of disease as part of their Cancer Research UK Pioneer Award, which funds innovative ideas from any discipline that could revolutionise our understanding of cancer.

Story Source:

Materials provided by **Cancer Research UK**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Marilena Hadjidemetriou, Sarah McAdam, Grace Garner, Chelsey Thackeray, David Knight, Duncan Smith, Zahraa Al-Ahmady, Mariarosa Mazza, Jane Rogan, Andrew Clamp, Kostas Kostarelos. **The Human In Vivo Biomolecule Corona onto PEGylated Liposomes: A Proof-of-Concept Clinical Study**. *Advanced Materials*, 2018; DOI: 10.1002/adma.201803335

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- APA
- Chicago

Cancer Research UK. "Nanoscale blood test technique set to springboard cancer discoveries." ScienceDaily. ScienceDaily, 28 November 2018. <www.sciencedaily.com/releases/2018/11/181128082737.htm>.