BIO NEWS

March, 2019

In-Vivo Science International Inc.

1230 Bordeaux Drive

Sunnyvale, CA 94089, USA

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Evolus の眉間のしわを取り薬 JEUVEAU（prabotulinumtoxinA）が米国 FDA に承認され、Allergan の昨年売り上げ 35 億 8,000 万ドルの BOTOX より 20-25%ほど安く利用可能になる。ネスレの Dysport（abobotulinumtoxinA）や Merz Pharma の Xeomin（incobotulinumtoxinA）などのしわ取り薬はより繁く投与する必要があり、BOTOX に太刀打ちできない。一方、Revance Therapeutics のボツリヌス毒素しわ取り薬 RT002（DaxibotulinumtoxinA for Injection）は BOTOX より長く効くことが試験で示されている。

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昨年の売り上げ 35 億 8,000 万ドルのしわ取り薬 BOTOX を売る Allergan とその提携会社 Medytox が、FDA に最近承認された韓国 Daewoong Pharmaceuticals の競合品 Jeuveau（DWP-450）の製造に盗んだ工程が使われているとしてその輸入禁止を求めている。

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1. BIO CEO & Investor 会議

2019 年 2 月 1 日

2 月 11、12 日にニューヨークで開催される BIO CEO & Investor 会議は、既存のバイオテック企業、新興の上場および選り抜きの非上場バイオテック企業に焦点を当てた最大の投資家会議の 1 つで、投資機会について広く偏りのない見解を示す。この会議では、問題志向の本会議、治療分野や重要なビジネス上の問題に焦点を当てた教育セッション、企業のプレゼンテーション、1 対 1 のパートナーシップ会議、およびネットワーキングの会議が提供される。

英文記事：
https://www.bio.org/events/bio-ceo-investor-conference?utm_medium=3pp&utm_source=newsletter-mp-stat&utm_campaign=ceo2019-mediapartners&utm_source=STAT+Newsletters&utm_campaign=71ef9278a1-Weekend_Reads_COPY_01&utm_medium=email&utm_term=0_8cab1d7961-71ef9278a1-150065641

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2. 免疫系をハイジャックして皮膚癌が広がる -マウス実験

2019 年 1 月 31 日

Cancer Research UK が資金援助したロンドンのクイーンメアリー大学の科学者らによるマウス研究で、浸潤性皮膚癌によって放出され、健康な免疫細胞を再プログラミングして癌が広がるのを助ける分子が発見された。これらの分子を阻害薬で標的化することによって、この攻撃的な皮膚癌治療後の再発防止に役立つとして、この知見が今日の *Cell* 誌に掲載されている。
研究者らは、マウスとヒトの腫瘍サンプルの浸潤性メラノーマの端からの細胞に注目し、それらが作り出すミシオン II と呼ばれるたんぱく質の効果を調査した。すると、これらの細胞中の高レベルのミシオン II が細胞をより可動性にするだけでなく、免疫系を再プログラミングする化学物質の放出も引き起こすことを発見した。これらの化学物質はマクロファージと呼ばれる周囲の健康な免疫細胞に影響を及ぼし、それらの自然な癌殺傷能力をハイジャックする。また、これらの化学物質の中には血管に小さな穴を開けて、癌細胞が血流や体の新しい領域に逃げるのを可能にするものもある。
研究者らは、阻害剤を他の標的療法と併用できるかどうか特定することで、将来的には黒色腫が再発するリスクを減らせる可能性がある、としている。

英文記事：
https://medicalxpress.com/news/2019-01-skin-cancer-mice-hijacking-immune.html

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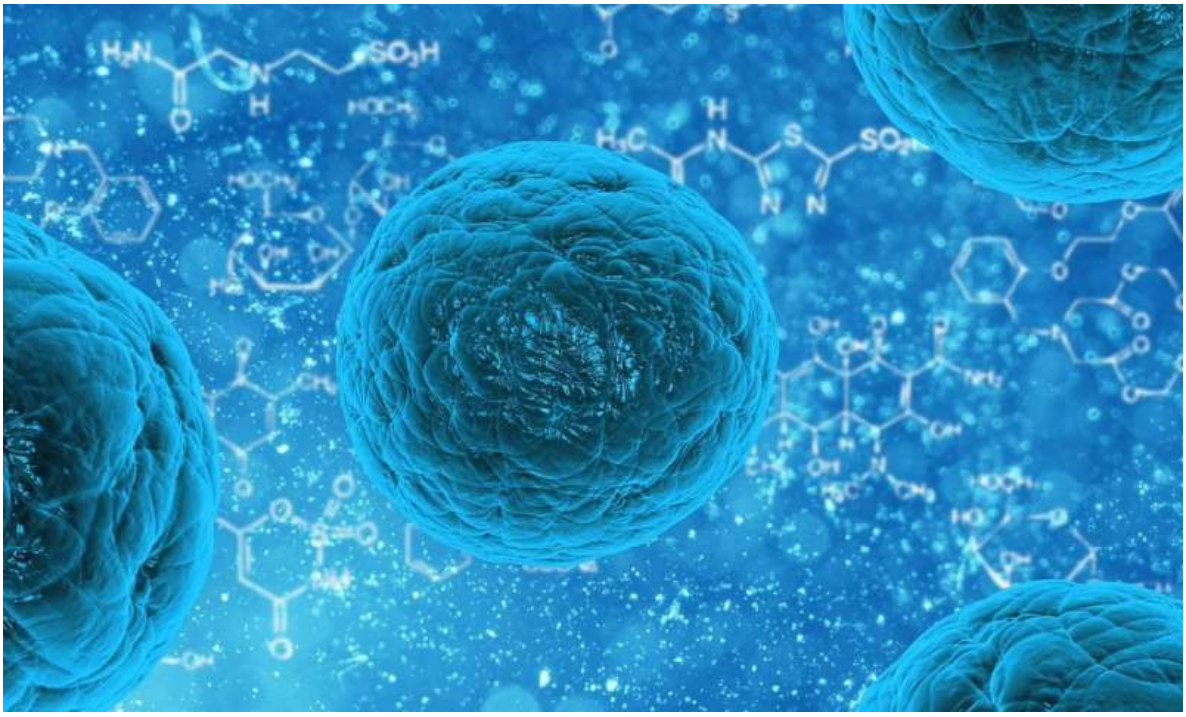
JANUARY 31, 2019

Skin cancer can spread in mice by hijacking the immune system

by Cancer Research UK



Credit: CC0 Public Domain

Scientists have uncovered molecules released by invasive skin cancer that reprogram healthy immune cells to help the cancer to spread.

Targeting these molecules with inhibiting drugs could help to prevent this aggressive skin cancer coming back after treatment.

The findings of the Cancer Research UK-funded study are published in *Cell*, today.

Researchers from Queen Mary University of London looked at cells from the edges of invasive melanomas in mice and human tumour samples, to investigate the effects of a protein they produce—called Myosin II.

They found that high levels of Myosin II in these cells not only makes them more mobile, but also triggers the release of chemicals that reprogram the immune system.

These chemicals affect the surrounding healthy immune cells, called macrophages, and hijack their natural cancer-killing abilities. This means that instead of attacking the cancer cells, they end up helping them to survive.

Some of these chemicals also make tiny holes in the blood vessels, allowing cancer cells to escape into the bloodstream and to new areas of the body.

Professor Vicky Sanz-Moreno, Cancer Research UK-funded lead author from Barts Cancer Institute, Queen Mary University of London, said: "This study highlights how cancer cells interact with and influence their surrounding environment to grow and spread. Developing treatments that target the chemicals that alter the immune system could help to prevent the spread of the disease."

Researchers also found that one of the chemicals released by Myosin II-rich cells, called interleukin 1A, was key for making cancer cells more invasive. By blocking Myosin II activity with different drugs, they reduced the amount of interleukin 1A produced by melanoma cells in mice and human tumour samples.

Professor Sanz-Moreno explains: "By using therapeutic drugs that block either Myosin II activity or the release of interleukin 1A, we can make the tumour less invasive and slow its growth, making it easier to treat."

Drugs that block Myosin II activity are already being used to treat diseases such as glaucoma, a progressive disease of the eye. Researchers are planning further lab studies to investigate whether drugs that block Myosin II could be combined with existing melanoma treatments.

Sanz-Moreno adds "We are excited to find out whether inhibitor drugs could be used in combination with other targeted therapies. By identifying effective treatment combinations, we hope that in the future Myosin II and interleukin 1A inhibitors could be used to improve patient outcomes and reduce the risk of melanoma coming back."

Professor Richard Marais, director of the Cancer Research UK Manchester Institute and melanoma expert, said: "These exciting findings show how the basic research that Cancer Research UK funds

is helping us to understand cancer biology and develop effective treatments for cancer patients."

"When melanoma is removed, there's always a chance that some cells could remain. What this study shows is that we may be able to develop treatments to stop those remaining cells from spreading after surgery, helping patients to survive for longer."

Explore further

Molecule predicts patient's ability to survive melanoma

More information: *Cell* (2019). www.cell.com/cell/fulltext/S0092-8674(18)31652-0

Provided by Cancer Research UK

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3. マウスから移植可能な B 細胞生成

2019 年 2 月 7 日

マウス胚性幹細胞由来の機能性 B-1 細胞は、長期間の生着が可能であり、マウスへの移植後天然の抗体を分泌する、として研究者らが 2 月 7 日に *Stem Cell Reports* 誌で報告した。
この研究の上席著者は、UT Health in Houston の McGovern Medical School、幹細胞および再生医療センターの吉本ももこ女史（京大出身）、マウス胚性幹細胞から移植可能な免疫細胞を作ることは困難なため、マウス胚性幹細胞から移植可能な機能性 B-1 細胞を得ることは、この分野における大きな進歩だと、語っている。そして、この細胞が広範囲の免疫学的疾患の治療薬として試験できる、としている。

英文記事：
https://medicalxpress.com/news/2019-02-scientists-functional-transplantable-cells-mice.html

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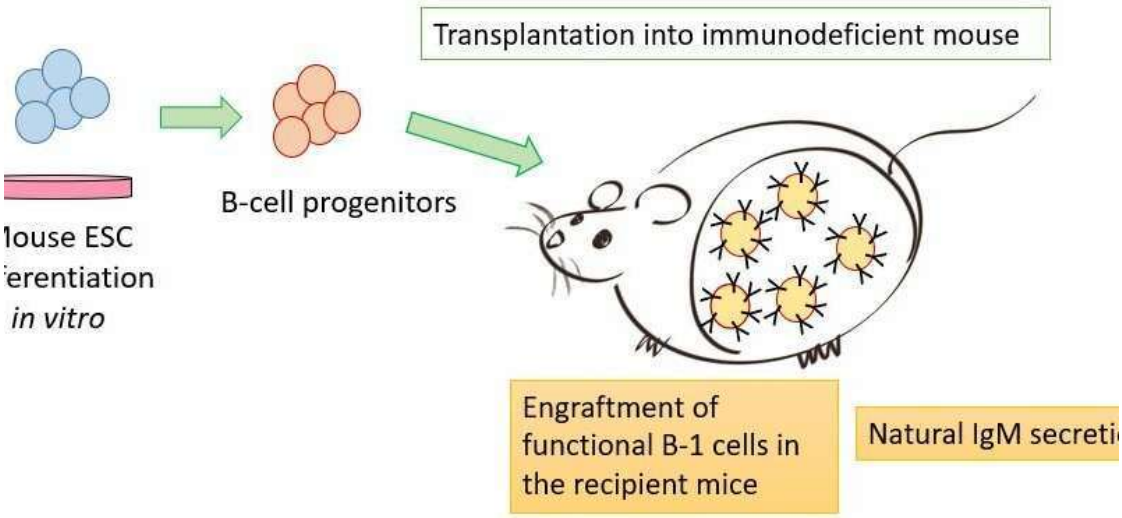
FEBRUARY 7, 2019

Scientists generate functional, transplantable B cells from mice

by Cell Press



This figure illustrates the process by which researchers generated functional, transplantable B cells from mice.
Credit: Momoko Yoshimoto

Functional B-1 cells derived from mouse embryonic stem cells are capable of long-term engraftment and secrete natural antibodies after transplantation in mice, researchers report February 7th in the journal *Stem Cell Reports*. Scientists are interested in B-1 cells generated from pluripotent stem cells because they could be tested as a therapeutic for a broad range of immunological disorders.

"It is still challenging to produce transplantable immune cells from mouse embryonic stem cells, so obtaining transplantable functional B-1 cells from mouse embryonic stem cells is a significant advance in

the field," says senior study author Momoko Yoshimoto of the Center for Stem Cell & Regenerative Medicine at the McGovern Medical School at UTHealth in Houston. "The take-home message is that a portion of immune cells may be replaced by cell therapies utilizing pluripotent stem cells in the future."

Hematopoietic stem cells in the adult bone marrow—the soft, sponge-like tissue in the center of most bones—provide various blood cells throughout life. Hematopoietic stem cell transplants are now routinely used to treat patients with cancers and other disorders of the blood and immune systems. But with current in vitro methods, it is challenging to produce hematopoietic stem cells that recapitulate the properties of cells in living organisms without gene manipulation.

In particular, bone marrow transplantation may fail to reconstitute some immune cells called B-1 cells, which produce immunoglobulin M (IgM) antibodies—the first type of antibody the immune system makes to fight a new infection. In addition to patients who receive stem cell transplants, IgM deficiency also occurs in individuals with some cancers, autoimmune diseases, allergic diseases, and gastrointestinal diseases, increasing the risk for life-threatening infections.

In the new study, Yoshimoto and her colleagues demonstrated that functional, transplantable B-1 cells can be generated from mouse embryonic stem cells without gene modifications. The researchers

overcame previous barriers preventing this feat by using high-quality cell lines to support B cell development. After being transplanted into recipient mice, stem cell-derived B progenitors matured into B-1 cells that were maintained for more than 6 months and secreted natural IgM antibodies.

"Producing functional B-1 progenitors in vitro from mouse embryonic stem cells is an important step to develop a cell therapy to provide natural IgM and innate B-1 cells that may not be provided by bone marrow transplantation," Yoshimoto says.

In future studies, the researchers will attempt to generate B cells from human induced pluripotent stem cells, which may be used for cell therapy to treat patients with immunological disorders. "This is just a first step in a long process to translate our findings to humans," Yoshimoto says.

More information: *Stem Cell Reports*, Lin et al.: "Long-Term Engraftment of ESC-Derived B-1 Progenitor Cells Supports HSC-Independent Lymphopoiesis" http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(19)30007-4, DOI: 10.1016/j.stemcr.2019.01.006

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４．運動がアルツハイマー病から身を守る -マウス実験

2019 年 2 月 8 日

コロンビア大学 Irving 医療センターなどの共同研究によって、運動がどのようにしてアルツハイマー病の危険性を減らすのか、その理由が示された。
数年前に、運動中に循環系に放出されるイリシンと呼ばれるホルモンが発見された。最初は、このイリシンが主にエネルギー代謝における役割を担っている、とされていたが、更なる研究で、このホルモンが、学習と記憶にとって重要な領域である海馬のニューロンの成長を促進もするかもしれないことが発見された。
そこで、イリシンが脳内で何をするか調べる為に、研究チームはマウス実験を行い、健康なマウスの海馬でイリシンを無効にすると、シナプスと記憶が弱まることを発見、脳のイリシンレベルを高めることで、マウスの記憶が保護されることを示した。また、運動がイリシンと脳に及ぼす影響については、5 日間ほぼ毎日泳いだマウスが、βアミロイドの注入を受けても記憶障害を発症しなかった、としている。
これらの調査結果は、イリシンがヒトの認知症を予防または治療するための新しい治療法発見のために利用できる可能性があることを示唆している。又、研究チームは現在、このホルモンの脳内濃度を上昇させるか、またはその作用を模倣することができる医薬化合物を探している。

英文記事：
https://www.sciencedaily.com/releases/2019/02/190208173511.htm

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How exercise may protect against Alzheimer's

Date:

February 8, 2019

Source:

Columbia University Irving Medical Center

Summary:

A hormone called irisin -- produced during exercise -- may protect neurons against Alzheimer's disease.

FULL STORY

Athletes know a vigorous workout can release a flood of endorphins: "feel-good" hormones that boost mood. Now there's evidence that exercise produces another hormone that may improve memory and protect against Alzheimer's disease, according to a study co-led by Ottavio Arancio, MD, PhD, a researcher at Columbia University's Vagelos College of Physicians and Surgeons and Taub Institute for Research on Alzheimer's Disease and the Aging Brain.

The study was published in *Nature Medicine*.

Physical activity is known to improve memory, and studies suggest it may also reduce the risk of Alzheimer's disease. But researchers don't understand why.

A few years ago, exercise researchers discovered a hormone called irisin that is released into the circulation during physical activity. Initial studies suggested that irisin mainly played a role in energy metabolism. But newer research found that the hormone may also promote neuronal growth in the brain's hippocampus, a region critical for learning and memory.

"This raised the possibility that irisin may help explain why physical activity improves memory and seems to play a protective role in brain disorders such as Alzheimer's disease" says Arancio, who is a professor of pathology and cell biology and of medicine at Columbia University Vagelos College of Physicians and Surgeons.

Irisin is reduced in brains of people with Alzheimer's

In the new study, Arancio and his colleagues at the Federal University of Rio de Janeiro in Brazil and Queens University in Canada first looked for a link between irisin and Alzheimer's in people.

Using tissue samples from brain banks, they found that irisin is present in the human hippocampus and that hippocampal levels of the hormone are reduced in individuals with Alzheimer's.

To explore what irisin does in the brain, the team turned to mice. These experiments show that irisin, in mice, protects the brain's synapses and the animals' memory: When irisin was disabled in the hippocampus of healthy mice, synapses and memory weakened. Similarly, boosting brain levels of irisin improved both measures of brain health.

Swimming boosts irisin, protects memory in mice

The researchers then looked at the effect of exercise on irisin and the brain. In the study's most compelling experiments, the researchers found that mice who swam nearly every day for five weeks did not develop memory impairment despite getting infusions of beta amyloid -- the neuron-clogging, memory-robbing protein implicated in Alzheimer's.

Blocking irisin with a drug completely eliminated the benefits of swimming, the researchers also found. Mice who swam and were treated with irisin-blocking substances performed no better on memory tests than sedentary animals after infusions with beta amyloid.

Together the findings suggest that irisin could be exploited to find a novel therapy for preventing or treating dementia in humans, Arancio says. His team is now searching for pharmaceutical compounds that can increase brain levels of the hormone or can mimic its action.

"In the meantime, I would certainly encourage everyone to exercise, to promote brain function and overall health," he said. "But that's not possible for many people, especially those with age-related conditions like heart disease, arthritis, or dementia. For those individuals, there's a particular need for drugs that can mimic the effects of irisin and protect synapses and prevent cognitive decline."

Story Source:

Materials provided by **Columbia University Irving Medical Center**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Mychael V. Lourenco, Rudimar L. Frozza, Guilherme B. de Freitas, Hong Zhang, Grasielle C. Kincheski, Felipe C. Ribeiro, Rafaella A. Gonçalves, Julia R. Clarke, Danielle Beckman, Agnieszka Staniszewski, Hanna Berman, Lorena A. Guerra, Letícia Forny-Germano, Shelby Meier, Donna M. Wilcock, Jorge M. de Souza, Soniza Alves-Leon, Vania F. Prado, Marco A. M. Prado, Jose F. Abisambra, Fernanda Tovar-Moll, Paulo Mattos, Ottavio Arancio, Sergio T. Ferreira, Fernanda G. De Felice. **Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models**. *Nature Medicine*, 2019; 25 (1): 165 DOI: 10.1038/s41591-018-0275-4

Cite This Page:

- MLA
- APA
- Chicago

Columbia University Irving Medical Center. "How exercise may protect against Alzheimer's." ScienceDaily. ScienceDaily, 8 February 2019. <www.sciencedaily.com/releases/2019/02/190208173511.htm>.

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5. 新しいマウスモデルがⅠ型糖尿病のなぞを解き明かす

2019 年 2 月 12 日

推定で 125 万人のアメリカ人がⅠ型糖尿病を患っているとされる。この病気をインスリンで管理することはできるが、治療法を見付けることはできていない。その理由としては、ヒトのⅠ型糖尿病全般を真似た信頼できる動物モデルがいなかいことがあげられる。
今回トレド大学の研究者らは、実験用マウスでⅠ型糖尿病の発症と進行を再現する新しい方法を発見した。開発されたヒト化マウスモデルは、以前は不可能だった方法でこの慢性疾患の研究方法を再構築する可能性を秘めた画期的な手段だとしている。このマウスモデルを使用した最初の査読研究は、2 月 7 日の *Scientific Reports* 誌に掲載されている。

英文と記事：
https://www.sciencedaily.com/releases/2019/02/190212092611.htm

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A new mouse model may unlock the secrets of type I diabetes

Date:

February 12, 2019

Source:

University of Toledo

Summary:

Finding new treatments or a cure for type I diabetes has been elusive in part because scientists have not had a reliable animal model that mimics the full scope of human type I

diabetes. A research team has now developed a humanized mouse model that spontaneously develops Type I diabetes and the full range of complications experienced by diabetes patients. That allows study of the disease and its natural progression in a way not previously possible.

FULL STORY

Researchers at The University of Toledo have found a new way to replicate in lab mice the development and progression of Type I diabetes, a breakthrough that has the potential to reshape how the chronic disease is studied.

An estimated 1.25 million Americans are living with Type I diabetes. While the condition can be managed with insulin, finding a treatment or cure for the disease has been elusive -- in part because scientists have not had a reliable animal model that mimics the full scope of human Type I diabetes.

"We see these patients every day. We see them come to the hospital, we see how they struggle," said Dr. Juan Jaume, professor of medicine in UT's College of Medicine and Life Sciences and senior author of the new invention. "Unfortunately, research has been held back because the scientific community didn't have a good model to study the disease and its progression. Now we do. We have developed a mouse model that is a step forward toward finding a cure."

The first peer-reviewed study using the UT-developed mouse model was published Feb. 7 in the natural sciences journal *Scientific Reports*.

In that study, Jaume, who is also chief of the Division of Endocrinology and director of UT's Center for Diabetes and Endocrine Research, and co-collaborator Dr. Shahnawaz Imam, a senior researcher in the Departments of Medicine and an associate member of the Center for Diabetes and Endocrine Research, looked at how a certain protein can influence T-cells in the pancreas to delay the onset of diabetes.

While the study adds to the overall knowledge about diabetes, it is the mouse model that holds the real potential.

In the new model, mice spontaneously develop Type I diabetes and, importantly, the full range of complications experienced by diabetes patients. That allows study of the disease and its natural progression in a way not previously possible.

"Our model is showing exactly the same physiopathology that humans with diabetes suffer," Imam said. "Our mice are getting eye problems, they are getting kidney problems and also neuropathy. That's a very important part of this -- they have the same human complications that all diabetes patients have, not just those with Type I."

The laboratory mice were developed through a series of selective breeding experiments and genetic modification that included adding human genes to the mice.

A provisional patent on the Spontaneous Type I Diabetes Mouse Model was filed last year.

Type I diabetes, formerly known as juvenile diabetes, results from an autoimmune attack on cells in the pancreas that produce insulin. Without insulin, the body cannot process the sugars in food, leading to dangerously high blood sugar.

Though many species develop diabetes, Jaume said the process of Type I diabetes seems to be unique to humans. And while scientists have frequently used other specially bred mice, including what's known as the non-obese diabetic mouse, to study diabetes and test treatments, those lab animals don't mimic the exact human pathophysiology of the disease.

"The existing non-obese diabetic mouse model does not completely resemble the human condition," Jaume said. "There are more than 125 different therapies that cure Type I diabetes in non-obese diabetic mice. Clinical trials were developed because of that model, but none have worked in humans. Everybody has been searching for a better model."

Jaume and Imam have been working on their model for more than a decade. It is already showing research promise.

Using the same idea behind CAR T-cell therapy for cancer, in which certain immune system cells are taken from a patient and paired with an artificial receptor that once reintroduced into the body homes in on the tumor, the team is developing cellular therapies for diabetes that uses the mice's regulatory cells to cool down the immune response.

The University has also filed a provisional patent on the treatment method, and Jaume and Imam will soon begin a more in-depth study of its effectiveness.

Story Source:

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

Journal Reference:

1. Shahnawaz Imam, R. Prathibha, Pervaiz Dar, Khalil Almotah, Ahmed Al-Khudhair, Syed Abdul-Moiz Hasan, Nancy Salim, Talha Naser Jilani, Raghavendra G. Mirmira, Juan Carlos Jaume. **eIF5A inhibition influences T cell dynamics in the pancreatic microenvironment of the humanized mouse model of Type 1 Diabetes**. *Scientific Reports*, 2019; 9 (1) DOI: 10.1038/s41598-018-38341-5

Cite This Page:

- MLA
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- Chicago

University of Toledo. "A new mouse model may unlock the secrets of type I diabetes." ScienceDaily. ScienceDaily, 12 February 2019. <www.sciencedaily.com/releases/2019/02/190212092611.htm>.

目次に戻る

6. ”古い”精子がより健康な子孫を産む -ゼブラフィッシュで実験

2019 年 2 月 14 日

今まで、どの精子が卵子を授精させるかはあまり問題ではないと考えられてきた。しかし、今回スウェーデンのイーストアングリア大学とウプサラ大学のゼブラフィッシュを使った研究によって、精子によってそれらが子孫に与える影響に大きな違いがあることが示された。
この研究によると、卵子を授精する前により長く生きている -古い- 精子の方がより健康な子孫を産みだし、更にこれらの子孫はより長くより健康な寿命を持ち、より多くのより健康な子孫を産みだす、としている。
欧州研究評議会によって資金提供されたこの研究の成果は、今日の *Evolution Letters* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2019/02/190214084646.htm

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'Old' sperm produces healthier offspring

Date:

February 14, 2019

Source:

University of East Anglia

Summary:

Research shows that sperm that live for longer before fertilizing an egg produce healthier offspring. What's more, these offspring go on to have longer, healthier lifespans -- and in turn produce more and healthier offspring themselves. It was assumed that it doesn't matter which sperm fertilizes an egg. But this shows that there are massive differences

between sperm and how they affect offspring. The research was carried out in zebrafish but may have implications for human fertility.

FULL STORY

Sperm that live for longer before fertilising an egg produce healthier offspring -- according to new research from the University of East Anglia and Uppsala University in Sweden.

New research published today shows that longer-lived sperm in an ejaculate of a zebrafish male produce offspring with longer and healthier lifespans -- who in turn produce more and healthier offspring themselves -- than the shorter-lived sperm in the same ejaculate.

The findings may have important implications for human reproduction and fertility, particularly in the context of assisted fertilisation technologies.

Lead researcher Dr Simone Immler, from UEA's School of Biological Sciences, said: "One male produces thousands to millions of sperm in a single ejaculate but only very few end up fertilizing an egg.

"The sperm within an ejaculate vary not only in their shape and performance, but also in the genetic material that each of them carries.

"Until now, there was a general assumption that it doesn't really matter which sperm fertilises an egg as long as it can fertilise it.

"But we have shown that there are massive differences between sperm and how they affect the offspring."

The research team performed in vitro fertilisations by collecting gametes from males and females. They then split the ejaculate of a male into two halves.

In one half, they selected for shorter-lived sperm and in the other for longer lived sperm. They then added the sperm to two half clutches from a female to fertilise the eggs and reared the offspring into adulthood.

They then monitored their lifespan and their reproductive output for two years.

Dr Immler said: "We found that when we select for the longer-lived sperm within the ejaculate of male zebrafish, the resulting offspring is much fitter than their full siblings sired by the shorter-lived sperm of the same male.

"More specifically, offspring sired by longer-lived sperm produce more and healthier offspring throughout their life that age at a slower rate.

"This is a surprising result, which suggests that it is important to understand how sperm selection may contribute to the fitness of the next generations."

The researchers are currently in the process of identifying the genes underlying their findings.

"This research has important implications for evolutionary biology and potentially beyond into areas that use assisted fertilization technologies, for example in livestock rearing or IVF in humans," added Dr Immler.

The research was funded by the European Research Council.

Story Source:

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

Journal Reference:

1. Ghazal Alavioon, Andrea Cabrera Garcia, Magali LeChatelier, Alexei A. Maklakov, Simone Immler. **Selection for longer lived sperm within ejaculate reduces reproductive ageing in offspring**. *Evolution Letters*, 2019; DOI: 10.1002/evl3.101

Cite This Page:

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- APA
- Chicago

University of East Anglia. "'Old' sperm produces healthier offspring." ScienceDaily. ScienceDaily, 14 February 2019. <www.sciencedaily.com/releases/2019/02/190214084646.htm>.

目次に戻る

7. DNA の 3D 配置が種の存続にいかにして役立つか

– 父親の子孫産出能力における重要な発達期間が明らかに

2019 年 2 月 18 日

父親から子供まで、遺伝情報の伝達には精子中の DNA の綿密なパッキングが必要である。しかし、子孫を準備するに当たって、自然がどのようにこの DNA をパッケージするのかは明らかにされていない。

シンシナティ小児病院医療センターの科学者らは、男性の生殖細胞が成熟する際の DNA の 3 次元組織を明らかにする新しい技術を用いて、父親が遺伝情報をどのようにして後世に伝えるのか説明するのに役立つ発達段階における重要な時期を明らかにした。

研究には雄マウスの成熟しつつある生殖細胞が使用され、これによると、その期間は、減数分裂と呼ばれる雄の精子の発達段階であり、生殖細胞が雌の卵子を受精させることができる精子に成熟し、子供の全ての細胞を作る基礎を築くときであった。実際に受精可能な精子になるまでに、遺伝物質は緊密に配置され、細胞の遺伝的コントロールセンターである核内に正確な 3D 組織を持っており、この 3D 組織が次の世代を生み出すのに必要である、としている。

この研究の主任研究員は、日本人の Satoshi Namekawa 博士で、この研究は *Nature Structural & Molecular Biology* 誌に掲載されている。

英文記事：

https://www.sciencedaily.com/releases/2019/02/190218123205.htm

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How 3D arrangement of DNA helps perpetuate the species

Study reveals crucial developmental period for father's ability to produce offspring

Date:

February 18, 2019

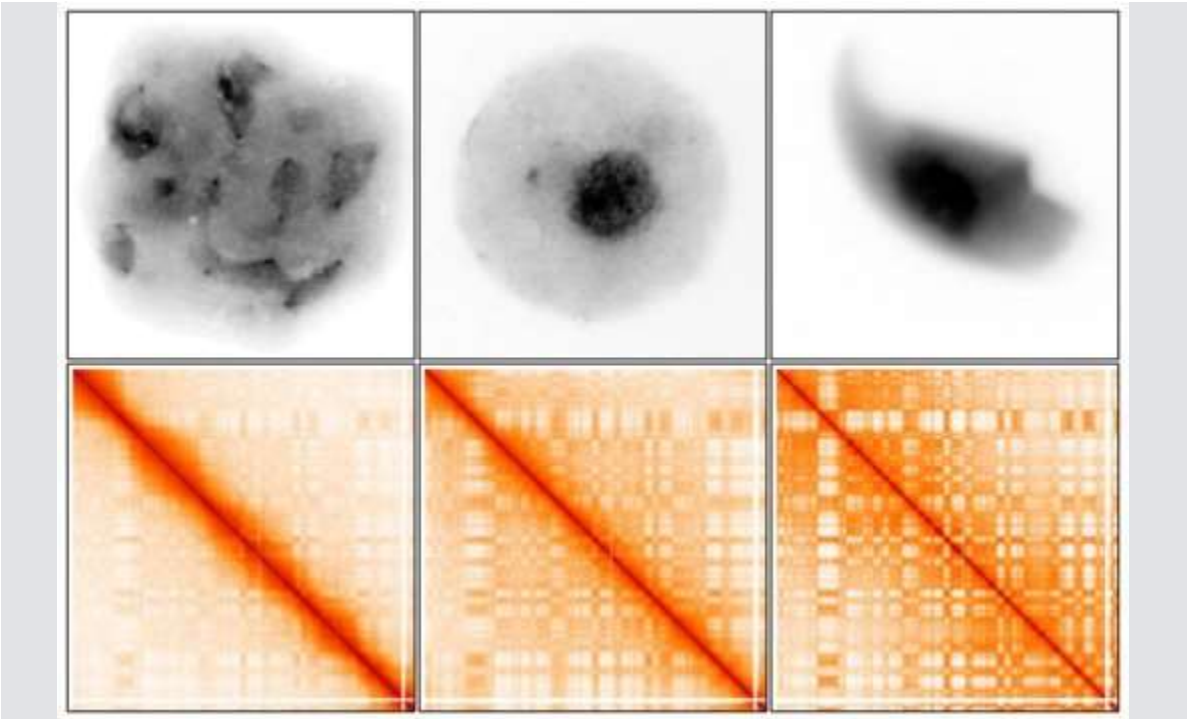
Source:

Cincinnati Children's Hospital Medical Center

Summary:

From fathers to children, the delivery of hereditary information requires the careful packing of DNA in sperm. But just how nature packages this DNA to prepare offspring isn't clear. Using new technology to reveal the 3D organization of DNA in maturing male reproductive cells, scientists revealed a crucial period in development that helps explain how fathers pass on genetic information to future generations.

FULL STORY



The top row of images show genetic material (shaded in grey) in male reproductive germ cells from mice, starting from left to right with pachytene stage spermatocytes, then round spermatid, and finally sperm. Called chromatin, the material comprises massive polymers of DNA spooled around proteins. The bottom row shows, from left to right, Hi-C heat maps for a specific chromosome in the nucleus of germ cells at different developmental stages. The heat maps essentially are snapshots of chromatin interactions, shown in various shades of orange. The deeper the orange, the more interactions there are. The images are from a study in Nature Structural and Molecular Biology.

Credit: Cincinnati Children's

From fathers to children, the delivery of hereditary information requires the careful packing of DNA in sperm. But just how nature packages this DNA to prepare offspring isn't clear. Using new technology to reveal the 3D organization of DNA in maturing male reproductive cells, scientists revealed a crucial period in development that helps explain how fathers pass on genetic information to future generations.

The period was captured during a stage of male sperm development called meiosis. This is when reproductive cells, called germ cells, are maturing into sperm that can fertilize a female egg, laying the foundation to make all the cells of a child. Publishing their findings in *Nature Structural & Molecular Biology*, reproductive biologists at Cincinnati Children's Hospital Medical Center say nature prepares the 3D organization of DNA before packing it into sperm.

By the time the germ cells actually become fertile sperm, the genetic material is tightly arranged. The male germ cell's hereditary material has precise 3D organization in the cell's genetic control center, the nucleus. Researchers report that this 3D organization is necessary for a male to help produce the next generation of life.

"We propose that male sperm is not just a carrier of DNA. Our data suggest that the three-dimensional organization in the cell nucleus helps establish a molecular foundation that can reproduce a complete zygote capable of becoming the next generation," said Satoshi Namekawa PhD, a principal investigator on the study and member of the Division of Reproductive Sciences.

The findings open the possibility of new research to investigate how the 3D organization of genetic material affects fertility and issues such as premature birth or stillbirth. Also collaborating on the study was the laboratory of Noam Kaplan, PhD at Technion Israel Institute of Technology, in Haifa, Israel.

Nature's Way

Using the maturing germ cells of male mice for their study, the researchers honed in on meiosis, the stage when male germ cells shed half of their chromosomes while shuffling around genetic material. This is part of nature's rule that male and female mammals each contribute half of their genetic material to generate a genetically whole but diverse member of the next generation. Humans have a total 46 chromosomes, with mother and father each contributing 23.

Using a technology called Hi-C, researchers were able to show the 3D organization and interactions of chromosomes, as well as the genes in the nucleus of meiotic male germ cells. The authors propose that preparing 3D organization in meiosis is vital for genes that allow germ cells to regain their ability to produce all the cells of the body after fertilizing a female egg.

"In meiosis, gene expression is extremely high and diverse," said Kris Alavattam, the study's first author and member of the Namekawa laboratory. "Many of these genes are essential for germ cells to develop, and many are expressed nowhere else but germ cells and at no other time."

During this time, the hereditary material in germ cells is organized in spatially related compartments called genomic compartments. In meiotic male germ cells, the researchers noticed genomic compartments are weaker than those in other cells of the body. This weakness helps facilitate what they call a global reprogramming of 3D chromatin organization. This organization of chromatin -- the packaging of DNA with DNA-binding proteins -- promotes essential gene expression and germ cell development. After meiosis, genomic compartments of chromatin become stronger and stronger, packing DNA in a highly organized manner as cells ready for procreation.

In order to gain more insight about possible contributions to reproductive health problems in people, the scientists now want to use their laboratory modeling systems to understand how the disruption of 3D chromatin organization may harm fertility.

Story Source:

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

Journal Reference:

1. Kris G. Alavattam, So Maezawa, Akihiko Sakashita, Haia Khoury, Artem Barski, Noam Kaplan, Satoshi H. Namekawa. **Attenuated chromatin compartmentalization in meiosis and its maturation in sperm development**. *Nature Structural & Molecular Biology*, 2019; DOI: 10.1038/s41594-019-0189-y

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Cincinnati Children's Hospital Medical Center. "How 3D arrangement of DNA helps perpetuate the species: Study reveals crucial developmental period for father's ability to produce offspring." ScienceDaily. ScienceDaily, 18 February 2019. <www.sciencedaily.com/releases/2019/02/190218123205.htm>.

目次に戻る

8. CRISPR/Cas9 療法でマウスの老化抑制、健康増進、寿命延長が可能に

2019 年 2 月 19 日

ソーク研究所の研究者らは、老化プロセスを減速させる新しい遺伝子治療を開発した。2 月 18 日の *Nature Medicine* 誌に掲載された所見では、希少遺伝病であるハッチンソン-ギルフォード プロジェリア症候群のマウスで観察される老化促進を抑制することができる新たな CRISPR/Cas9 ゲノム編集療法に焦点があてられている。
老化は、心臓病、癌、アルツハイマー病を含む多くの衰弱状態に対する主要危険因子であるから、この新たな遺伝子治療は、抗老化療法として必要性に迫られるものである、としている。

英文記事：
https://www.sciencedaily.com/releases/2019/02/190219111747.htm

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CRISPR/Cas9 therapy can suppress aging, enhance health and extend life span in mice

Date:

February 19, 2019

Source:

Salk Institute

Summary:

Researchers have developed a new gene therapy to help decelerate the aging process. The findings highlight a novel CRISPR/Cas9 genome-editing therapy that can suppress the accelerated aging observed in mice with Hutchinson-Gilford progeria syndrome, a rare genetic disorder that also afflicts humans.

FULL STORY

This image shows two mice of the same age with progeria. The larger and healthier mouse on the left received the gene therapy, while the mouse on the right did not.

Credit: Salk Institute

Aging is a leading risk factor for a number of debilitating conditions, including heart disease, cancer and Alzheimer's disease, to name a few. This

makes the need for anti-aging therapies all the more urgent. Now, Salk Institute researchers have developed a new gene therapy to help decelerate the aging process.

The findings, published on February 18, 2019 in the journal *Nature Medicine*, highlight a novel CRISPR/Cas9 genome-editing therapy that can suppress the accelerated aging observed in mice with Hutchinson-Gilford progeria syndrome, a rare genetic disorder that also afflicts humans. This treatment provides important insight into the molecular pathways involved in accelerated aging, as well as how to reduce toxic proteins via gene therapy.

"Aging is a complex process in which cells start to lose their functionality, so it is critical for us to find effective ways to study the molecular drivers of aging," says Juan Carlos Izpisua Belmonte, a professor in Salk's Gene Expression Laboratory and senior author of the paper. "Progeria is an ideal aging model because it allows us to devise an intervention, refine it and test it again quickly."

With an early onset and fast progression, progeria is one of the most severe forms of a group of degenerative disorders caused by a mutation in the LMNA gene. Both mice and humans with progeria show many signs of aging, including DNA damage, cardiac dysfunction and dramatically shortened life span. The LMNA gene normally produces two similar proteins inside a cell: lamin A and lamin C. Progeria shifts the production of lamin A to progerin. Progerin is a shortened, toxic form of lamin A that accumulates with age and is exacerbated in those with progeria.

"Our goal was to diminish the toxicity from the mutation of the LMNA gene that leads to accumulation of progerin inside the cell," says co-first author Hsin-Kai Liao, a staff researcher in the Izpisua Belmonte lab. "We reasoned that progeria could be treated by CRISPR/Cas9-targeted disruption of both lamin A and progerin."

The researchers utilized the CRISPR/Cas9 system to deliver the gene therapy into the cells of the progeria mouse model expressing Cas9. An adeno-associated virus (AAV) was injected containing two synthetic guide RNAs and a reporter gene. The guide RNA ushers the Cas9 protein to a specific location on the DNA where it can make a cut to render lamin A and progerin nonfunctional, without disrupting lamin C. The reporter helps researchers track the tissues that were infected with the AAV.

Two months after the delivery of the therapy, the mice were stronger and more active, with improved cardiovascular health. They showed decreased degeneration of a major arterial blood

vessel and delayed onset of bradycardia (an abnormally slow heart rate) -- two issues commonly observed in progeria and old age. Overall, the treated progeria mice had activity levels similar to normal mice, and their life span increased by roughly 25 percent.

"Once we improve the efficiency of our viruses to infect a wide range of tissues, we are confident that we will be able to increase life span further," says Pradeep Reddy, a postdoctoral fellow in the Izpisua Belmonte lab and an author of the paper.

Taken together, the results suggest that targeting lamin A and progerin using a CRISPR/Cas9 system can dramatically improve the physiological health and life span of progeria mice. These results provide a significant new understanding of how scientists may eventually be able to target molecular drivers of aging in humans.

Future efforts will focus on making the therapy more effective and will refine it for human use. Currently, there is no cure for progeria, so the symptoms are managed and complications are treated as they arise.

"This is the first time a gene editing therapy has been applied to treat progeria syndrome," says Izpisua Belmonte, holder of the Roger Guillemin Chair. "It will need some refinements, but it has far fewer negative effects compared to other options available. This is an exciting advancement for the treatment of progeria."

Story Source:

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

Journal Reference:

1. Ergin Beyret, Hsin-Kai Liao, Mako Yamamoto, Reyna Hernandez-Benitez, Yunpeng Fu, Galina Erikson, Pradeep Reddy, Juan Carlos Izpisua Belmonte. **Single-dose CRISPR–Cas9 therapy extends lifespan of mice with Hutchinson–Gilford progeria syndrome**. *Nature Medicine*, 2019; DOI: 10.1038/s41591-019-0343-4

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Salk Institute. "CRISPR/Cas9 therapy can suppress aging, enhance health and extend life span in mice." ScienceDaily. ScienceDaily, 19 February 2019. <www.sciencedaily.com/releases/2019/02/190219111747.htm>.

目次に戻る

9. 筋ジストロフィーマウスの CRISPR ゲノム編集治療の効果が長く保たれた

2019 年 2 月 18 日

デューク大学の研究者らは、CRISPR ゲノム編集機能を担うアデノ随伴ウイルス（AAV）の 1 回きりの投与でデュシェンヌ型筋ジストロフィー（DMD）マウスのジストロフィン回復が免疫反応誘発や意図せぬゲノム/転写変化にもかかわらず長く（1 年以上）保たれることを示した。この研究は *Nature Medicine* 誌の 2 月 18 日オンライン版で発表されている。

英文記事：
https://medicalxpress.com/news/2019-02-crispr-treatment-long-term-benefits-mice.html

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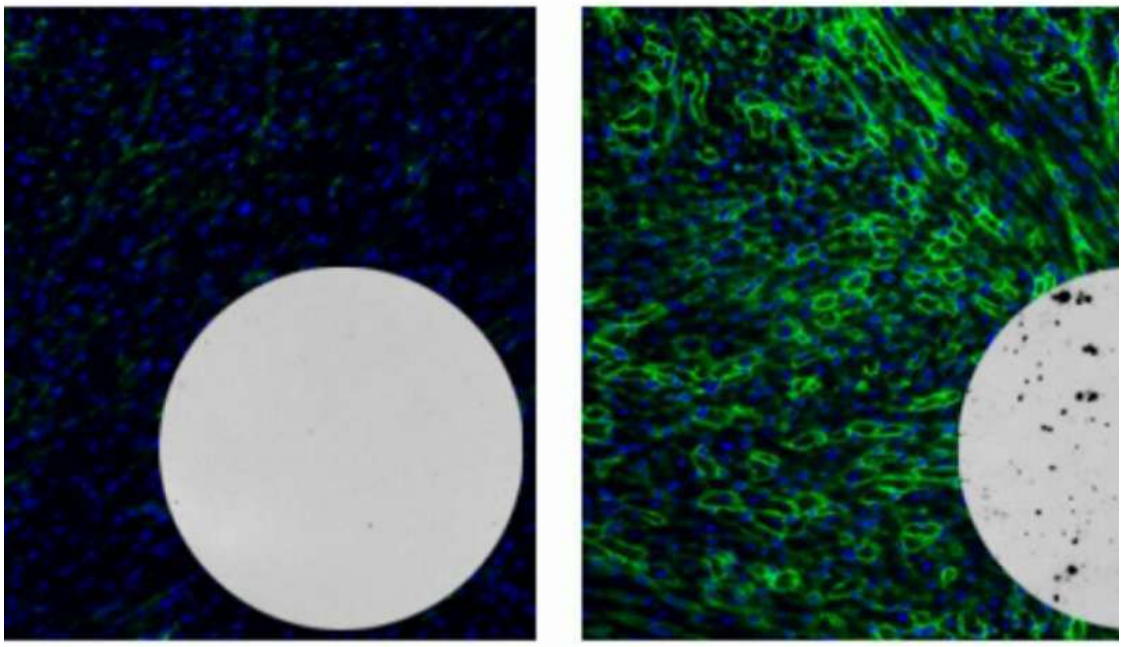
FEBRUARY 18, 2019

Single CRISPR treatment provides long-term benefits in mice

by Duke University



These images highlight the stark contrast between mouse models of untreated Duchenne muscular dystrophy (left) and those treated with a CRISPR-based genetic therapy after one year (right). On the right, green indicates a higher level of dystrophin gene expression. The dark spots in the inset show T cells from these mice responding to the bacterial Cas9 protein, indicating the presence of an immune response to the therapy. Credit: Charles Gersbach, Duke University

Researchers at Duke University have shown that a single systemic treatment using CRISPR genome editing technology can safely and stably correct a genetic disease—Duchenne muscular dystrophy (DMD)—for more than a year in mice, despite observed immune responses and alternative gene editing outcomes.

The study appears online on February 18 in the journal *Nature Medicine*.

In 2016, Charles Gersbach, the Rooney Family Associate Professor of Biomedical Engineering at Duke, published one of the first successful uses of CRISPR to treat an animal model of genetic disease with a strategy that has the potential to be translated to human therapy. Many additional examples have since been published, and several genome editing therapies targeting human diseases are currently in clinical trials, with more on the way.

Gersbach's latest research focuses on a mouse model of DMD, which is caused by the body's inability to produce dystrophin, a long protein chain that binds the interior of a muscle fiber to its surrounding support structure.

Dystrophin is encoded by a gene containing 79 protein-coding regions, called exons. If one or more exons are disrupted or deleted by an inherited mutation, the chain does not get built, causing muscle to slowly shred and deteriorate. Most patients are wheelchair-bound by age 10 and don't live beyond their 20s or early 30s.

Gersbach has been working on potential genetic treatments for Duchenne since 2009. His lab was one of the first to begin focusing on CRISPR/Cas9, a modified version of a bacterial defense system that targets and slices apart the DNA of invading viruses. His approach uses CRISPR/Cas9 to snip out dystrophin exons around the genetic mutation, leaving the body's natural DNA repair system to

stitch the remaining gene back together to create a shortened—but functional—version of the dystrophin gene.

"As we continue to work to develop CRISPR-based genetic therapies, it is critical to test our assumptions and rigorously assess all aspects of this approach," Gersbach said. "A goal of our experiments was to test some ideas being discussed in the field, which will help us understand the potential of CRISPR to treat genetic diseases in general and Duchenne muscular dystrophy in particular. This includes monitoring the long-term durability of the response in the face of potential immune responses against the bacterial Cas9 protein."

The first eight-week study demonstrated that functional dystrophin was restored and muscle strength increased. It did not, however, explore the long-term durability of the treatment.

"It is widely believed that gene editing leads to permanent gene correction," Gersbach said. "However, it's important to explore theoretical possibilities that could undermine the effects of gene editing, such as losing treated cells or an immune response."

The goal of the new study was to explore factors that could alter the long-term effects of CRISPR/Cas9-based gene editing.

Christopher Nelson, the post-doctoral fellow in Gersbach's lab who led the work, administered a single dose of the CRISPR therapy

intravenously to both adult and newborn mice carrying a defective dystrophin gene. Over the course of the following year, researchers measured how many muscle cells were successfully edited and what types of genetic alterations were made, as well as the generation of any immune response against the bacterial CRISPR protein, Cas9, which acts as the "scissors" that makes cuts to the genome.

Other studies have reported that the mouse immune system can mount a response to Cas9, which could potentially interfere with the benefit of CRISPR therapies. Several groups have also reported that some people have preexisting immunity to Cas9 proteins, likely because of previous exposure to the bacterial host.

"The good news is that even though we observed both antibody and T cell responses to Cas9, neither appeared to result in any toxicity in these mice," said Nelson. "The response also did not prevent the therapy's ability to successfully edit the dystrophin gene and produce long-term protein expression."

The results also suggested approaches to address potential challenges, should they arise in the future. For example, the researchers observed that when two-day-old mice without fully developed immune systems were treated intravenously, no immune response was detected. The CRISPR genome editing remained stable and, in some cases, even strengthened over the course of a year. One could imagine delivering the therapy to infants as a method of circumventing or modulating an unwanted immune response.

Gersbach and Nelson acknowledge, however, that the mouse immune system often functions quite differently from the human immune system. And newborn screening for DMD is not currently widely performed; most Duchenne diagnoses occur when children are three to five years old. To address this challenge, Gersbach said suppressing the immune system during treatment may be a viable approach.

The researchers are also investigating potential strategies to restrict the expression or delivery of Cas9 to only the muscle cells for short durations, which may lessen immune detection.

"We were pleased to observe that all the mice were doing well a year after treatment, but our results show that there needs to be more focus on the immune response as we move toward larger animal models," Nelson said.

Nelson and Gersbach have previously investigated the potential of off-target editing by CRISPR/Cas9 to unintentionally modify other sites in the genome and reported minimal activity at likely off-target sites. Other recent studies, however, have reported that CRISPR can sometimes make genetic edits at the correct site but not in the intended manner. For example, some studies have shown that CRISPR can cut out genetic sections much larger than intended or that pieces of DNA can embed at the site of the cut. These types of edits had previously been unreported in genome editing studies because the methods being used only detected the intended edit.

To comprehensively map all the edits occurring in the dystrophin gene, Nelson used a DNA sequencing approach that agnostically reports any type of edit. Surprisingly, there were many types of edits being made in addition to the intended removal of the targeted exon, including a high level of insertion of DNA sequences from the viral vector encoding the CRISPR/Cas9 system.

Depending on the type of tissue and the dosage of CRISPR delivered, as many as half of the on-target edits resulted in these alternative sequence changes. Although this result was surprising, the unintended sequence changes do not appear to impact the safety or efficacy of this CRISPR/Cas9 gene editing approach for DMD.

"None of these edits would necessarily be a cause for concern in this case because the dystrophin gene is already defective," said Nelson. "That being said, any unintended results could potentially take away from the efficiency of the gene editing you're trying to achieve, which supports the importance of designing ways to objectively identify and mitigate alternative edits in future studies."

"Previous studies suggested that some of these other types of edits could happen," Gersbach said. "But this is one of the first comprehensive measurements of these events in an animal model using a therapeutically relevant approach. Moving forward, this phenomenon needs to be monitored carefully and better understood. Methods that avoid these alternative edits and increase

the frequency of the intended edit will be important to maximizing the potential of genome editing to treat disease."

Explore further

Researchers overcome hurdle in CRISPR gene editing for muscular dystrophy

More information: Long-term evaluation of AAV-CRISPR genome editing for Duchenne muscular dystrophy, *Nature Medicine* (2019). DOI: 10.1038/s41591-019-0344-3

Provided by Duke University

目次に戻る

10. 免疫系がいかにして健康な腸内微生物叢を維持するか

2019 年 2 月 26 日

国際的研究チームは、腸内の微生物に対する免疫反応を制御する重要なメカニズムを発見した。この研究結果は、慢性炎症性腸疾患の新しい治療法の開発に貢献する可能性があるとして、*Nature Immunology* 誌に掲載されている。
免疫系は腸内の病原菌の拡散を防ぎ、同時にそれは有益な微生物の定着を可能にもする。逆に、腸内の微生物の組成、いわゆる微生物叢は、免疫反応の質に影響を与える。
研究者らは、マウスにおける免疫系と微生物叢の相互作用の分子制御剤、いわゆる制御性 T 細胞に焦点を当て、腸内の特定の制御性 T 細胞の発達と機能に不可欠の分子 c-Maf を特定した。無傷の c-Maf 依存性制御性 T 細胞を持つマウスに変化した微生物叢を移植した時、マウスは腸の免疫系に過剰反応を示した、としている。
チームは、これから、腸内細菌と免疫系との間の確立された病理学的相互作用が患者においてどのように不安定化され、そして元の状態に回復され得るかを研究したい、としている。

英文記事：
https://www.sciencedaily.com/releases/2019/02/190226112241.htm

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How the immune system maintains a healthy gut microbiota

Date:

February 26, 2019

Source:

Charité - Universitätsmedizin Berlin

Summary:

Researchers have uncovered a critical mechanism that controls immune reactions against microorganisms in the intestine. The results of the international study may contribute to the development of new therapies for chronic inflammatory bowel disease.

FULL STORY

Researchers from the Cluster of Excellence "Precision Medicine in Chronic Inflammation" in Kiel and Charité -- Universitätsmedizin Berlin have uncovered a critical mechanism that controls immune reactions against microorganisms in the intestine. The results of the international study may contribute to the development of new therapies for chronic inflammatory bowel disease. They have been published in the journal *Nature Immunology*.

The immune system protects against the spread of pathogenic germs in the intestine. At the same time, it allows the colonisation of beneficial microorganisms. Conversely, the composition of the microorganisms in the intestine, the so-called microbiota, has an influence on the quality of the immune reaction. An international research group led by Prof. Dr. Alexander Scheffold of Kiel University (CAU) and the Cluster of Excellence "Precision Medicine in Chronic Inflammation" has uncovered a critical mechanism that establishes the balance between immune system and microbiota.

The researchers Dr. Christian Neumann (Charité), Dr. Sascha Rutz (Genentech, San Francisco), Prof. Dr. Axel Kallies (University of Melbourne and Walter and Eliza Hall Institute of Medical Research, Melbourne), Prof. Scheffold and colleagues studied molecular regulators of immune-microbiome interactions in mice. The team focused on so-called regulatory T cells. These are immune cells that prevent harmless or even useful microorganisms in the intestine from being attacked by the immune system. "We have identified a molecule, c-Maf, which is critical for the development and function of specific regulatory T cells in the gut," explains Scheffold. C-Maf prevents the immune system from attacking the microbiota. "If this molecule is missing, the gut's immune system overreacts and the microbiota composition changes considerably," added first

author Dr. Neumann of Charité's Institute of Microbiology, Infectious Diseases and Immunology. This change in composition proved remarkably stable: When the researchers transferred the altered microbiota to mice with intact c-Maf-dependent regulatory T cells, they also developed an overreaction of the intestinal immune system.

"These results show that both the immune system and the microbiota mutually contribute to establishing and maintaining the balance in the gut," emphasises Prof. Scheffold. "This could explain how a microbial imbalance can contribute to chronic inflammatory bowel disease and why the treatment often fails." These findings could lead to new therapeutic approaches that, for example in the case of inflammatory bowel disease, aim to influence and harmonize both immune response and microbiota. In the future, the team would like to study how an established pathological interaction between intestinal bacteria and the immune system can be destabilized in patients and restored to its original state.

Story Source:

Materials provided by **Charité - Universitätsmedizin Berlin**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Christian Neumann, Jonas Blume, Urmi Roy, Peggy P. Teh, Ajithkumar Vasanthakumar, Alexander Beller, Yang Liao, Frederik Heinrich, Teresita L. Arenzana, Jason A. Hackney, Celine Eidenschenk, Eric J. C. Gálvez, Christina Stehle, Gitta A. Heinz, Patrick Maschmeyer, Tom Sidwell, Yifang Hu, Derk Amsen, Chiara Romagnani, Hyun-Dong Chang, Andrey Kruglov, Mir-Farzin Mashreghi, Wei Shi, Till Strowig, Sascha Rutz, Axel Kallies, Alexander Scheffold. **c-Maf-dependent Treg cell control of intestinal TH17 cells and IgA establishes host–microbiota homeostasis**. *Nature Immunology*, 2019; DOI: 10.1038/s41590-019-0316-2

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