BIO NEWS

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1．知的障害・神経発達障害 研究のための新しいマウスモデル

2017 年 9 月 29 日

カリフォルニア大学サンディエゴ校医学部の研究者らは、Upf3b 遺伝子を欠く最初のマウスを開発、これが知的障害・神経発達障害における基礎的な役割を研究するための新しいモデルとなる、としている。
この研究は、9 月 26 日に *Molecular Psychiatry* 誌に掲載された。

英文記事：
https://www.sciencedaily.com/releases/2017/09/170929125053.htm

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New mouse model replicates an underlying cause of intellectual disability

Model will help researchers determine how abnormalities in RNA processing can lead to learning and memory impairment

Date:

September 29, 2017

Source:

University of California - San Diego

Summary:

Researchers have developed the first mice that lack the Upf3b gene, providing a new model for studying its underlying role in intellectual disabilities and neurodevelopmental disorders.

FULL STORY

Researchers at University of California San Diego School of Medicine have developed the first mice that lack the Upf3b gene, providing a new model for studying its underlying role in intellectual disabilities and neurodevelopmental disorders. The study published September 26 in *Molecular Psychiatry*.

In humans, mutations in the UPF3B gene cause intellectual disability and are strongly associated with autism spectrum disorder, attention deficit hyperactivity disorder and schizophrenia. This gene plays a role in nonsense-mediated RNA decay (NMD), a supervisory system cells use as "volume control" on many genes.

"These observations about UPF3B made us wonder if NMD is important for mammalian brain development," said senior author Miles Wilkinson, PhD, professor of reproductive medicine at UC San Diego School of Medicine.

NMD acts on messenger RNAs (mRNAs), which carry the blueprints encoded by the genome. These blueprints are translated into the proteins essential for life. NMD was initially thought to serve only as a quality control mechanism -- degrading irregular mRNAs that encode potentially harmful proteins. But it has more recently become clear that NMD also degrades normal mRNAs in specific cell types and situations when they are not needed.

NMD plays an important part in several biological processes, including fetal and neonatal development -- a time when cells must be especially careful about how they coordinate and time the production of mRNAs (and the proteins they encode).

Wilkinson's team found that Upf3b-deficient mice differed from normal mice in a number of cellular and behavioral ways. For example, their neural stem cells were impaired in their ability to specialize into functional neurons. The neurons they did have were deficient in their ability to form dendrites and dendritic spines, structures critical for neuron-neuron communication. These Upf3b-deficient mice also exhibited defects in a specific form of memory and learning related to fear, and they were defective in sensory processing in a way often associated with schizophrenia and other brain disorders.

To investigate how Upf3b influences these cellular and behavioral features, the researchers compared the RNA sequences they found in the frontal cortex region of the brains of normal and Upf3b-deficient mice. They determined that Upf3b regulates RNAs, including direct NMD targets, that encode proteins necessary for neurons to develop and mature.

"In many ways, the behavioral impairments in mice lacking Upf3b mimicked those found in human patients with UPF3B mutations," Wilkinson said. "This new model will be critical in determining precisely how defects in NMD can lead to specific learning and sensory processing defects."

Co-authors of this study also include: Eleen Shum, Sam H. Jones, Chih-Hong Lou, Jennifer Dumdie, Haeuk Kim, Josh Espinoza, David M. Skarbrevik, Mimi H. Phan, Heiid Cook-Andersen, Neal R. Swerdlow, UC San Diego; Amanda J Roberts, The Scripps Research Institute; Lachlan A Jolly, and Jozef Gecz, University of Adelaide, and South Australian Health and Medical Research Institute.

Story Source:

Materials provided by **University of California - San Diego**. Original written by Heather Buschman. *Note: Content may be edited for style and length.*

Journal Reference:

1. L Huang, E Y Shum, S H Jones, C-H Lou, J Dumdie, H Kim, A J Roberts, L A Jolly, J L Espinoza, D M Skarbrevik, M H Phan, H Cook-Andersen, N R Swerdlow, J Gecz, M F Wilkinson. **A Upf3b-mutant mouse model with behavioral and neurogenesis defects**. *Molecular Psychiatry*, 2017; DOI: 10.1038/mp.2017.173

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University of California - San Diego. "New mouse model replicates an underlying cause of intellectual disability: Model will help researchers determine how abnormalities in RNA processing can lead to learning and memory impairment." ScienceDaily. ScienceDaily, 29 September 2017. <www.sciencedaily.com/releases/2017/09/170929125053.htm>.

University of California - San Diego. (2017, September 29). New mouse model replicates an underlying cause of intellectual disability: Model will help researchers determine how abnormalities in RNA processing can lead to learning and memory impairment. *ScienceDaily*. Retrieved October 3, 2017 from www.sciencedaily.com/releases/2017/09/170929125053.htm

University of California - San Diego. "New mouse model replicates an underlying cause of intellectual disability: Model will help researchers determine how abnormalities in RNA processing can lead to learning and memory impairment." ScienceDaily. www.sciencedaily.com/releases/2017/09/170929125053.htm (accessed October 3, 2017).

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2. 金ナノ粒子が DMD マウスモデルに CRISPR を効果的に送達

2017 年 10 月 5 日

CRISPR-Case9 は近年遺伝病に対抗する有望な兵器として浮上してきている。しかし、癌の様な有害な副作用を引き起こす可能性のあるオフターゲットの遺伝子編集には、安全性に関する懸念もある。CRISPR の 3 つの成分、Case9 酵素、ガイド RNA、ドナーDNA は、最も一般的にはアデノ随伴ウィルス（AAV）を用いて送達されるが、酵素が一旦導入されると Case9 発現を制御する方法がないため、編集完了後も突然変異を引き起こす可能性がある、とされる。
そこで、UC バークレーのバイオエンジニアリングのチームが開発した技術が CRISPR-Gold で、DNA と結合した金ナノ粒子でできている。研究者らは、デュシェンヌ型筋ジストロフィーのマウスモデルに CRISPR-Gold を筋肉注射により送達、単回注射から 2 週間後、突然変異したジストロフィン遺伝子を修正し、マウスの筋肉組織におけるジストロフィンたんぱく質の発現を回復させた、としている。
この研究は、*Nature Biomedical Engineering* 誌に掲載されている。

英文記事：
http://www.fiercebiotech.com/research/gold-nanoparticles-effectively-deliver-crispr-to-mice

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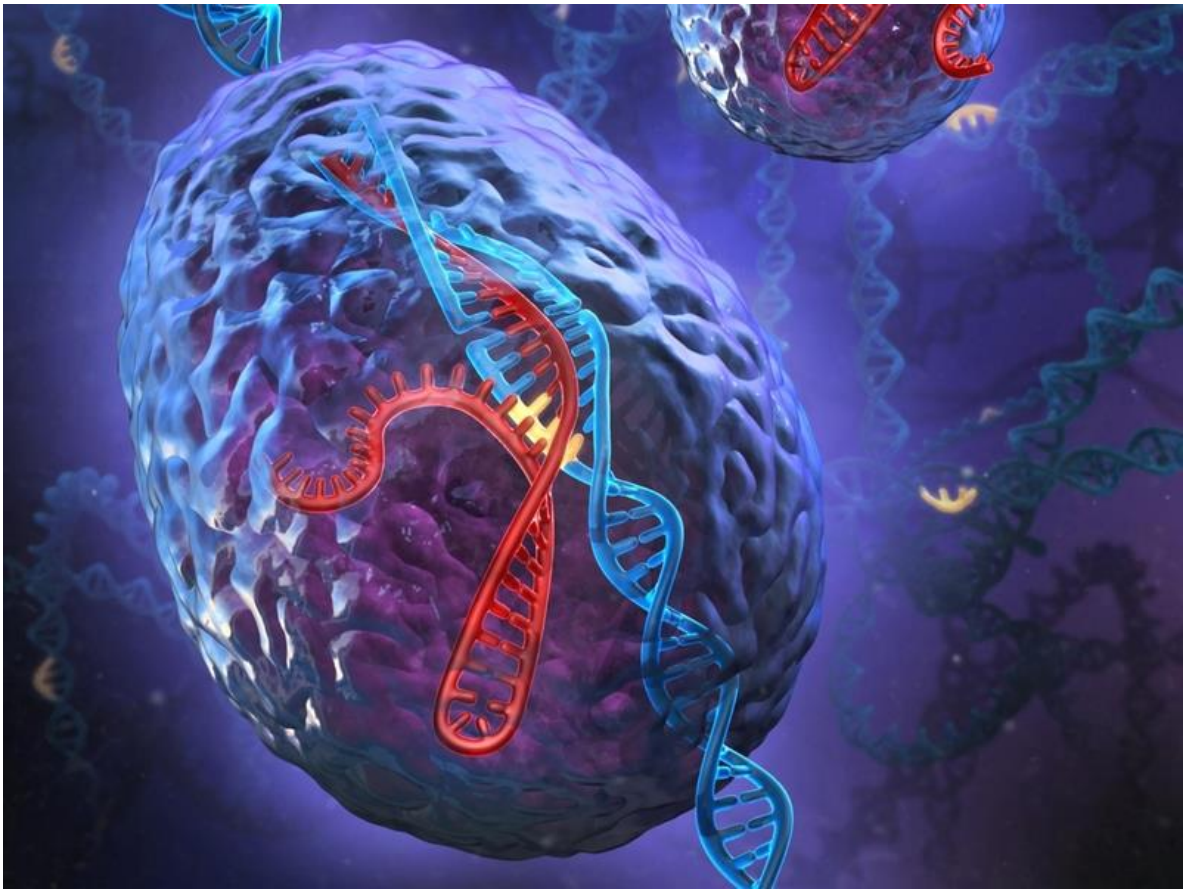
Gold nanoparticles effectively deliver CRISPR to mouse models of DMD

by Amirah Al Idrus | Oct 5, 2017 8:40am



GenEdit's nanoparticle delivery vehicle for CRISPR contains all three CRISPR components and has minimal off–target effects.Gut bacteria that 'talk' to human cells may lead to new treatments

CRISPR-Cas9 has emerged in recent years as a promising weapon against genetic disease. But it comes with some safety concerns, namely, off-target gene editing that may bring about harmful side effects such as cancer. A team at UC Berkeley is investigating the possibility that nanoparticles can address these problems.

The three components of CRISPR—the Cas9 enzyme, a guide RNA and donor DNA—are delivered using a viral vector, most commonly an adeno-associated virus (AAV). While this is the most advanced method of CRISPR delivery, it allows the Cas9 enzyme to persist in the cells, as there is no way to

control Cas9 expression once the enzyme is in the cells, said Niren Murthy, a professor of bioengineering at UC Berkeley.

So, even after editing is complete, the Cas9 will be "chewing up" parts of the genome, which can cause mutations, Murthy said. Additionally, AAVs are too small to fit all three CRISPR components, so at least two viruses must be used. A large dose of viruses—higher than what is clinically recommended—must be injected in order to get the intended effect, he said.

RELATED: RNA-targeting CRISPR could yield treatments for Huntington's, ALS

Murthy worked on a study investigating the use of a nonviral, nanoparticle delivery vehicle for CRISPR, developed by GenEdit. The technology, dubbed CRISPR-Gold, is made up of gold nanoparticles combined with DNA. This is complexed with all three CRISPR components, as well as a polymer that helps the nanoparticle penetrate into cells.

The researchers delivered CRISPR-Gold to mouse models of Duchenne muscular dystrophy via intramuscular injection. They injected the three CRISPR components without a delivery vehicle into another group of mice, which served as a negative control. They chose Duchenne because it lacks effective treatments and because it affects skeletal muscle, an area into which gene therapy can be easily injected, said GenEdit CEO Kunwoo Lee.

RELATED: Shortened telomeres linked to heart damage in Duchenne muscular dystrophy

Two weeks after a single injection, CRISPR-Gold corrected the mutated dystrophin gene and restored the expression of the dystrophin protein in the mice's muscle tissue with minimal off-target effects, according to the study. Specifically, the treatment corrected 5.4% of the dystrophin gene in the mice, a promising result, the team believes. In additional experiments, mice treated with CRISPR-Gold showed better strength and agility than mice treated in the negative control group. The findings appear in the journal Nature Biomedical Engineering.

Other research on safer CRISPR focuses on using proteins as an "off switch" for gene editing. Scientists from the University of Toronto and the University of Massachusetts identified three families of proteins that bind to the Cas9 enzyme, halting its activity. And a team from UC Berkeley and UC San Francisco

applied an anti-CRISPR protein to a CRISPR-Cas9 molecule that reduced off-target effects fourfold without compromising the desired gene editing.

While Sarepta's Duchenne drug earned FDA approval last year, it is only effective in a narrow group of patients. CRISPR could become a treatment for the approximately 30% of Duchenne patients whose disease is caused by single-base mutations or small deletions, the Berkeley researchers said.

Read more on gene editing, Duchenne muscular dystrophy (DMD), nanoparticles, drug safety, side effects, University of California Berkeley, UC San Francisco, University of Massuchusetts, CRISPR-Cas9

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3. 癌細胞を自滅させる新化合物 -マウス実験

2017 年 10 月 9 日

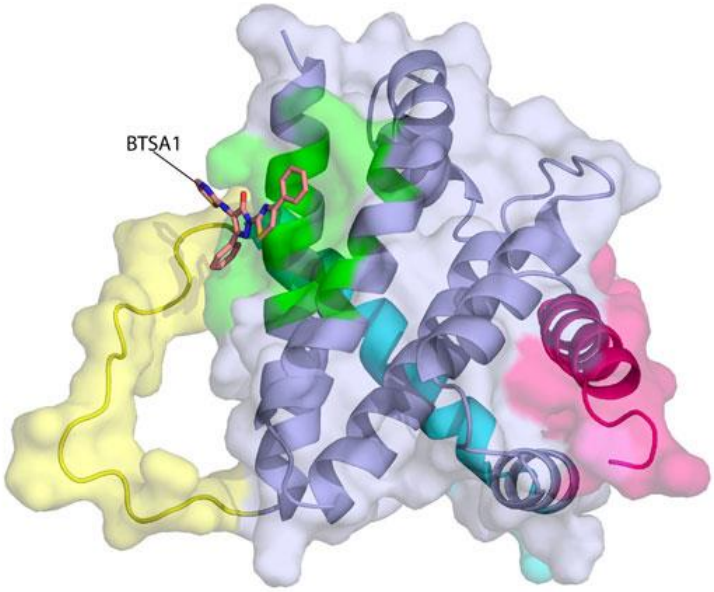
アルバートアインシュタイン医科大学の研究者チームは、健康細胞を守りながら癌細胞を自滅させる最初の化合物を発見した。新しい治療法は急性骨髄性白血病(AML) 細胞に対するものだが、他のタイプの癌にも効く可能性がある、としている。
新たに発見された「BASA1 (BAX トリガーサイトアクティベーター1 の略)」と呼ばれる化合物は、いくつかの異なるヒト AML 細胞株に加えられた時、迅速かつ広範なアポトーシスを引き起こす最も強力な BAX アクティベーターであり、この BTSA1 は患者の AML 細胞においてアポトーシスを誘導したが、患者の健康な血液形成幹細胞には影響しなかった。
研究者らは、ヒト AML 細胞をマウスに移植することによって AML の動物モデルを作製、BTSA1 を AML マウスに処置、これらのマウスは未処置のマウスよりも生存期間が長く、毒性の証拠もなかった。研究者らは、BTSA1 が他のタイプの癌の動物モデルでも同様の効果を発揮するかどうか、確認する計画をしている。
この研究は、*Cancer Cell* 誌に掲載されている。

英文記事：
https://scitechdaily.com/researchers-discover-a-new-compound-that-makes-cancer-cells-self-destruct/

Researchers Discover a New Compound That Makes Cancer Cells Self-Destruct

TOPICS:Albert Einstein College of MedicineBiochemistryCancerHealthMedicine

OCTOBER 9, 2017



This image depicts the structure of the BAX protein (purple). The activator compound BTSA1 (orange) has bound to the active site of BAX (green), changing the shape of the BAX molecule at several points (shown in yellow, magenta and cyan). BAX, once in its final activated form, can home in on mitochondria and puncture their outer membranes, triggering apoptosis (cell death). Credit: Albert Einstein College of Medicine

A team of researchers at the Albert Einstein College of Medicine reveals the first compound that directly makes cancer cells commit suicide while sparing healthy cells. The new treatment approach was directed against acute myeloid leukemia (AML) cells but may also have potential for attacking other types of cancers.

"We're hopeful that the targeted compounds we're developing will prove more effective than current anti-cancer therapies by directly causing cancer cells to self-destruct," says Evripidis Gavathiotis, Ph.D., associate professor

of biochemistry and of medicine and senior author of the study. “Ideally, our compounds would be combined with other treatments to kill cancer cells faster and more efficiently—and with fewer adverse effects, which are an all-too-common problem with standard chemotherapies.”

AML accounts for nearly one-third of all new leukemia cases and kills more than 10,000 Americans each year. The survival rate for patients has remained at about 30 percent for several decades, so better treatments are urgently needed.

The newly discovered compound combats cancer by triggering apoptosis—an important process that rids the body of unwanted or malfunctioning cells. Apoptosis trims excess tissue during embryonic development, for example, and some chemotherapy drugs indirectly induce apoptosis by damaging DNA in cancer cells.

Apoptosis occurs when BAX—the “executioner protein” in cells—is activated by “pro-apoptotic” proteins in the cell. Once activated, BAX molecules home in on and punch lethal holes in mitochondria, the parts of cells that produce energy. But all too often, cancer cells manage to prevent BAX from killing them. They ensure their survival by producing copious amounts of “anti-apoptotic” proteins that suppress BAX and the proteins that activate it.

“Our novel compound revives suppressed BAX molecules in cancer cells by binding with high affinity to BAX’s activation site,” says Dr. Gavathiotis. “BAX can then swing into action, killing cancer cells while leaving healthy cells unscathed.”

Dr. Gavathiotis was the lead author of a 2008 paper in Nature that first described the structure and shape of BAX’s activation site. He has since looked for small molecules that can activate BAX strongly enough to overcome cancer cells’ resistance to apoptosis. His team initially used computers to screen more than one million compounds to reveal those with BAX-binding potential. The most promising 500 compounds—many of them

newly synthesized by Dr. Gavathiotis' team–were then evaluated in the laboratory.

"A compound dubbed BTSA1 (short for BAX Trigger Site Activator 1) proved to be the most potent BAX activator, causing rapid and extensive apoptosis when added to several different human AML cell lines," says lead author Denis Reyna, M.S., a doctoral student in Dr. Gavathiotis' lab. The researchers next tested BTSA1 in blood samples from patients with high-risk AML. Strikingly, BTSA1 induced apoptosis in the patients' AML cells but did not affect patients' healthy blood-forming stem cells.

Finally, the researchers generated animal models of AML by grafting human AML cells into mice. BTSA1 was given to half the AML mice while the other half served as controls. On average, the BTSA1-treated mice survived significantly longer (55 days) than the control mice (40 days), with 43 percent of BTSA1-treated AML mice alive after 60 days and showing no signs of AML.

Importantly, the mice treated with BTSA1 showed no evidence of toxicity. "BTSA1 activates BAX and causes apoptosis in AML cells while sparing healthy cells and tissues–probably because the cancer cells are primed for apoptosis," says Dr. Gavathiotis. He notes that his study found that AML cells from patients contained significantly higher BAX levels compared with normal blood cells from healthy people. "With more BAX available in AML cells," he explained, "even low BTSA1 doses will trigger enough BAX activation to cause apoptotic death, while sparing healthy cells that contain low levels of BAX or none at all."

Plans call for Dr. Gavathiotis and his team to see whether BTSA1 will show similar effectiveness when tested on animal models of other types of cancer.

Publication: Denis E. Reyna, et al., "Direct Activation of BAX by BTSA1 Overcomes Apoptosis Resistance in Acute Myeloid Leukemia," Cancer Cell, 2017; doi:10.1016/j.ccell.2017.09.001

Source: Albert Einstein College of Medicine

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４．突然変異が腫瘍抑制遺伝子を過剰発現する -マウス研究

2017 年 10 月 9 日

腫瘍抑制タンパク質である p53 について、手に負えない細胞が癌腫瘍を形成することができないようにする能力は、癌研究者らの間で長い間知られていたものの、実際の戦略についてよく分かっていないままだった。
今回、スタンフォード大学医学部の研究者らは、どのようにしてこの p53 を作動させられるかを、マウス研究によって、どのようにしてそのタンパク質が膵臓癌における抗腫瘍活性を媒介するか、その明瞭な経路を示しながら着手した。
また、この研究の中で、p53 遺伝子のある突然変異が、このタンパク質の腫瘍撲滅能力を増幅し「スーパー腫瘍抑制因子」を作り出す、という予期しない結果も明らかにされた。
この研究は、*Cancer Cell* 誌、10 月 9 日のオンライン版に掲載されている。

英文記事：

https://www.sciencedaily.com/releases/2017/10/171009123207.htm

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A mutation supercharges tumor-suppressor

Date:

October 9, 2017

Source:

Stanford University Medical Center

Summary:

Stanford scientists have found an answer to one of cancer biology's toughest and most important questions: how does the body suppress tumors?

FULL STORY

Cancer researchers have long hailed p53, a tumor-suppressor protein, for its ability to keep unruly cells from forming tumors. But for such a highly studied protein, p53 has hidden its tactics well.

Now, researchers at the Stanford University School of Medicine have tapped into what makes p53 tick, delineating a clear pathway that shows how the protein mediates anti-tumor activity in pancreatic cancer. The team's research also revealed something unexpected: A particular mutation in the p53 gene amplified the protein's tumor-fighting capabilities, creating a "super tumor suppressor."

The protein functions a bit like a puppet master in the genome, guiding the activation or suppression of many cancer-relevant genes in the body. "But if you simply ask how cells with and without p53 are different, you'll see that there are at least 1,000 genes whose expression is affected by p53 status," said Laura Attardi, PhD, professor of radiation oncology and of genetics. "So, getting to the bottom of which of those many genes are critical to tumor suppression is not a trivial question."

A paper describing the work will be published online Oct. 9 in *Cancer Cell*. Attardi is the senior author. Research associate Stephano Mello, PhD, is the lead author.

Mutated for the better

Attardi began sorting out the puzzle by testing the effect of several individual p53 mutations in mice that were predisposed to pancreatic cancer. Any change in p53 activity typically points to trouble: Too little leaves the body susceptible to tumor growth, whereas too much can cause problems in development. But surprisingly, one of the p53 mutants actually kept the mice tumor-free longer, suggesting it was a super version of p53.

"What's incredible about this mutant is that it hit a sweet spot," Attardi said. "Embryos can make it through development without any obvious effects, and then adult mice show greatly enhanced resistance to tumor growth."

Mice that harbored the favorable mutation, which occurred in a transcriptional activation domain called TAD2, displayed longer, pancreatic cancer-free survival than mice with normal copies of the p53 gene. Attardi's study showed that, at 400 days old, nearly 40 percent of the mice with normal p53 function had succumbed to pancreatic cancer, whereas none of the mice with the mutant form showed signs of tumor formation.

"It's not to say that mice with the mutated version of p53 would never get cancer, but this experiment suggests that this particular mutant is really potent in limiting tumor development," Attardi said.

It turned out that the mutant hyperactivates p53, causing a subset of its downstream targets to get a surge of activity, too. But with more than 100 target genes sent into overdrive, it was critical for Attardi's team to narrow down which genes directly affected tumor suppression. Genomic data and past studies in human cancers pointed the team to the gene Ptpn14. More importantly, Ptpn14 is a known regulator of Yap, a protein that, when unchecked, turns on cancer-promoting genes in the body.

The axis of tumor super-suppression

Attardi's findings allowed her to define a pathway, or "axis," consisting of three proteins that contribute to p53-mediated tumor suppression, and it works in a linear fashion. In the chain of command, p53 ranks highest and activates Ptpn14; Ptpn14 then suppresses Yap to keep cells from turning cancerous.

In collaboration with co-author Christina Curtis, PhD, assistant professor of medicine and of genetics, and postdoctoral scholar Jose Seoane, PhD, Attardi used human cancer genomic data to extend the paradigm further, showing that when p53 is mutated in human cancer, Yap activity increases, allowing tumors to develop.

Attardi said the axis actually suggests that p53 and Ptpn14 deficiency can promote the same consequence of Yap activation.

"I think this p53-Ptpn14-Yap axis is a central mechanism," Attardi said. "P53 affects a lot of tumor-suppression processes, so if it influences a central protein like Yap, which also controls a lot of cancer processes, it can have widespread effects on cell behavior."

Attardi added that she would be hesitant to say that this is the one and only mechanism. "It would be too simplistic to think that this is absolutely the only pathway that's involved in p53-mediated suppression of pancreatic cancer, so I suspect that there will be other contributions as well."

The team's findings could inform a new type of therapeutic, mimicking the p53 super-mutant to upregulate tumor suppression. It could also inform those who are developing therapeutic Yap inhibitors.

"Clearly, Yap is a very potent oncogene," Attardi said. "And our study suggests that perhaps the focus should be on developing Yap inhibitors for tumors where p53 is gone -- maybe it's more critical in those cancers."

Now, Attardi and her team are continuing to investigate whether their newly uncovered p53 mechanism holds true for a wide range of cancers, not just pancreatic.

"We want to know if this is a tissue-specific pathway and if this really is relevant for different tumor types," Attardi said. "So we're turning to experimental models to test that."

Story Source:

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

Journal Reference:

1. Stephano S. Mello et al. **A p53 Super-tumor Suppressor Reveals a Tumor Suppressive p53-Ptpn14-Yap Axis in Pancreatic Cancer**. *Cancer Cell*, October 2017 DOI: 10.1016/j.ccell.2017.09.007

Cite This Page:

- MLA
- APA
- Chicago

Stanford University Medical Center. "A mutation supercharges tumor-suppressor." ScienceDaily. ScienceDaily, 9 October 2017. <www.sciencedaily.com/releases/2017/10/171009123207.htm>.

目次に戻る

5. 食道癌の「起源細胞」が同定された -マウス実験

2017 年 10 月 11 日

コロンビア大学医療センター（CUMC）の研究者らは、食道癌の前駆細胞であるバレット食道を生じる可能性のある上消化管内の細胞を同定した。この「起源細胞」の発見は、米国内で最も急速に増えているバレット食道および食道線癌のより正確なスクリーニング ツールおよび治療薬開発を加速させるものだとしている。
この発見は、マウスとヒトの組織で行われ、本日の *Nature* 誌オンライン版に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2017/10/171011131719.htm

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Esophageal cancer 'cell of origin' identified

In mice, basal progenitor cells give rise to Barrett's esophagus, a precursor to cancer

Date:

October 11, 2017

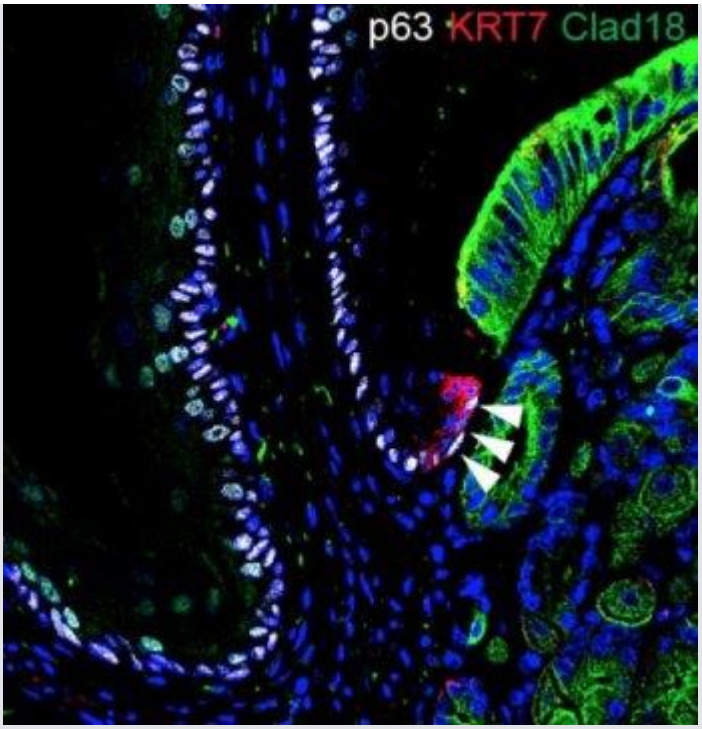
Source:

Columbia University Medical Center

Summary:

Researchers have identified cells in the upper digestive tract that can give rise to Barrett's esophagus, a precursor to esophageal cancer.

FULL STORY



Arrows point to a population of unique basal progenitor cells (p63+ KRT7+ Claudin18-) located at the equivalent of the gastroesophageal junction in a mouse model.

Credit: Lab of Jianwen Que, MD, PhD, Columbia University Medical Center

Columbia University Medical Center (CUMC) researchers have identified cells in the upper digestive tract that can give rise to Barrett's esophagus, a precursor to esophageal cancer. The discovery of this "cell of origin" promises to accelerate the development of more precise screening tools and therapies for Barrett's esophagus and esophageal adenocarcinoma, the fastest growing form of cancer in the U.S.

The findings, made in mice and in human tissue, were published in today's online edition of *Nature*.

In Barrett's esophagus, some of the tissue in the tube connecting the mouth to the stomach are replaced by intestinal-like tissue, causing heartburn and difficulty swallowing. Most cases of Barrett's stem from gastroesophageal reflux disease (GERD) -- chronic regurgitation of acid from the stomach into the lower esophagus. A small percentage of people with Barrett's esophagus develop esophageal adenocarcinoma, the most common form of esophageal cancer.

Incidence of esophageal adenocarcinoma has risen by 800 percent over the past four decades. However, there has been little progress in screening and treatment over the same period. If esophageal cancer is not detected early, patients typically survive less than a year after diagnosis.

Researchers have proposed at least five models of Barrett's esophagus, each based on a different cell type. "However, none of these experimental models mimics all of the characteristics of the condition," said study leader Jianwen Que, MD, PhD, associate professor of medicine at CUMC. "This led us to believe that there must be another, yet-to-be-discovered, cell of origin for Barrett's esophagus."

In the current study, Dr. Que and his colleague Ming Jiang, PhD, an associate research scientist in CUMC's Department of Medicine and first author of the paper, genetically altered mice to promote the development of Barrett's esophagus. His team then examined the mice's gastroesophageal junction tissue for changes. "All of the known cells in this tissue remained the same, but we found a previously unidentified zone populated by unique basal progenitor cells," he said. Progenitor cells are early descendants of stem cells that can differentiate into one or more specific cell types.

Dr. Que's team then performed a technique called lineage tracing to determine if these unique basal progenitor cells, tagged with a fluorescent protein, can give rise to Barrett's esophagus. In the tests, several mouse models were used to show that bile acid reflux or genetic changes promote expansion of these cells, leading to the development of Barrett's esophagus. The same observations were made in organoids (artificially grown masses of cells that resemble an organ) created from unique basal progenitor cells that were isolated from the gastroesophageal junction in mice and humans.

"Now that we know the cell of origin for Barrett's esophagus, the next step is to develop therapies that target these cells or the signaling pathways that are activated by acid reflux," said Dr. Que.

The study is titled, "Transitional basal cells at the squamous-columnar junction generate Barrett's oesophagus." The other contributors are: Haiyan Li (Columbia University Medical Center, New York, NY), Yongchun Zhang (CUMC), Ying Yang (CUMC), Rong Lu (CUMC), Kuancan Liu (CUMC and Fuzhou General Hospital, Fuzhou, Fujian, China), Sijie Lin (CUMC and Fuzhou General Hospital), Xiaopeng Lan (Fuzhou General Hospital), Haikun Wang (Chinese Academy of Sciences, Shanghaim, China), Han Wu (Ascendas Genomics Inc., Zhongshan, Guandong, China), Jian Zhu (University of Rochester, Rochester, NY), Zhongren Zhou (University of Rochester), Jianming Xu (Baylor College of Medicine, Houston, TX), Dong-Kee Lee (Baylor College of Medicine), Lanjing Zhang (University Medical Center of Princeton at Plainsboro, Plainsboro, NJ, and Rutgers University, Newark, NJ), Yuan-Cho Lee (CUMC), Jingsong Yuan (CUMC), Julian A. Abrams (CUMC), Timothy G. Wang (CUMC), Antonia R. Sepulveda (CUMC), Qi Wu (Tianjin Haihe Hospital, Tianjin. China), Huaiyong Chen (Tianjin Haihe Hospital), Xin Sun (Tianjin Haihe Hospital), Junjun She (Xi'an Jiaotong University, Xi'an, China), and Xiaoxin Chen (North Carolina Central University, Durham, NC).

The study was supported by grants from the National Institutes of Health (R01DK113144, R01DK100342, R01HL132996, R01CA112403, and R01CA193455), March of Dimes, Price Family Foundation, the National Key Research and Development Program of China, National Natural Science Foundation of China, the Program for the Top Young Innovative Talents of Fujian Province, and the International Collaborative Project of Fujian Province.

Story Source:

Materials

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

Journal Reference:

1. Ming Jiang, Haiyan Li, Yongchun Zhang, Ying Yang, Rong Lu, Kuancan Liu, Sijie Lin, Xiaopeng Lan, Haikun Wang, Han Wu, Jian Zhu, Zhongren Zhou, Jianming Xu, Dong-Kee Lee, Lanjing Zhang, Yuan-Cho Lee, Jingsong Yuan, Julian A. Abrams, Timothy C. Wang, Antonia R. Sepulveda, Qi Wu,

Huaiyong Chen, Xin Sun, Junjun She, Xiaoxin Chen, Jianwen Que. **Transitional basal cells at the squamous–columnar junction generate Barrett's oesophagus**. *Nature*, 2017; DOI: 10.1038/nature24269

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- MLA
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Columbia University Medical Center. "Esophageal cancer 'cell of origin' identified: In mice, basal progenitor cells give rise to Barrett's esophagus, a precursor to cancer." ScienceDaily. ScienceDaily, 11 October 2017. <www.sciencedaily.com/releases/2017/10/171011131719.htm>.
Columbia University Medical Center. (2017, October 11). Esophageal cancer 'cell of origin' identified: In mice, basal progenitor cells give rise to Barrett's esophagus, a precursor to cancer. *ScienceDaily*. Retrieved October 17, 2017 from www.sciencedaily.com/releases/2017/10/171011131719.htm
Columbia University Medical Center. "Esophageal cancer 'cell of origin' identified: In mice, basal progenitor cells give rise to Barrett's esophagus, a precursor to cancer." ScienceDaily. www.sciencedaily.com/releases/2017/10/171011131719.htm (accessed October 17, 2017).

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6. なぜ自閉症は男子に多いか -マウス研究

2017 年 10 月 17 日

なぜ自閉症スペクトラム障害（ASD）は男子に多いか、という理由を理解しようとしているアイオワ大学ヘルスケアの研究者らは、報酬習得や動機付けに関する脳のシグナル伝達経路の性別による違いを発見、雄のマウス脳は自閉症を引き起こす遺伝的グリッチに対して脆弱であり、その反対に雌のマウス脳は弾力性があるとし、本日の *Molecular Psychiatry* 誌に発表している。
この研究は、サイモンズ財団自閉症研究イニシアティブ（SFARI）の資金支援の元に行われた。

英文記事：
https://www.sciencedaily.com/releases/2017/10/171017091906.htm

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Signaling pathway may be key to why autism is more common in boys

In mice, the male brain is vulnerable and the female brain resilient to a genetic cause of autism

Date:

October 17, 2017

Source:

University of Iowa Health Care

Summary:

Researchers have discovered sex differences in a brain signaling pathway involved in reward learning and motivation that make male mice more vulnerable to an autism-causing genetic glitch.

FULL STORY

Researchers aiming to understand why autism spectrum disorders (ASD) are more common in boys have discovered differences in a brain signaling pathway involved in reward learning and motivation that make male mice more vulnerable to an autism-causing genetic glitch.

"One intriguing aspect of autism is that it predominantly affects males; four boys are affected for every one girl," says senior study author Ted Abel, PhD, director of the Iowa Neuroscience Institute at the University of Iowa Carver College of Medicine. "We don't understand what it is about this disorder that predisposes boys as compared to girls to develop autism."

This male bias is also seen in other neurodevelopmental disorders, like attention deficit hyperactivity disorder (ADHD) and specific language impairments.

Nearly one in every 200 cases of autism is caused by the deletion of a section of DNA on a particular chromosome. This type of disorder is also known as a copy number variation (CNV). The mouse model of autism used by the research team is missing the same stretch of DNA.

The researchers tested the mice for abnormalities in reward-learning behavior -- learning to associate actions with rewarding outcomes. This type of learning is mediated by a part of the brain called the striatum and is disrupted in people with autism and other neurodevelopmental disorders.

The study, published online Oct. 17 in *Molecular Psychiatry*, shows that only male mice with the autism-associated genetic deletion have abnormal reward-learning behavior. Female mice with the same genetic deletion are not affected. Moreover, these sex-specific behavioral differences are accompanied by sex differences in molecular signaling pathways in the striatum brain region.

"Problems with reward learning could explain why individuals with autism don't interact socially -- because they don't find it rewarding in the same way. It could explain why people with autism have restricted interests -- because they find only very selective things rewarding -- and it could explain the differences in language acquisition -- because the neural circuitry involved in reward learning is the same circuitry that mediates both language learning and production," says Abel, who also is the Roy J. Carver Chair in Neuroscience and UI professor of molecular physiology and biophysics.

Female protective effect

One of the genes contained in the missing section of DNA is an important signaling protein called ERK1. Activity of this protein affects the function of the striatum -- the part of the brain that's involved in reward learning and motivation. The researchers found that male mice carrying this genetic deletion have increased activation of ERK1 in the striatum coupled with decreased amounts of another protein that reduces ERK1 activity. In contrast, the female mice carrying the genetic deletion do not have overactivated ERK1. In addition, despite the genetic deletion, the female deletion mice have higher levels of ERK1 than the male deletion mice. All of these molecular differences mean that ERK1 signaling is particularly sensitive to disruption in male mice.

"This is some of the first evidence in a mouse model of autism of a 'female protective effect,' from the behavioral to the molecular level," says Nicola Grissom, first author of the study who is now an assistant professor of psychology at the University of Minnesota. "These findings shed valuable new light on the science of neurodevelopmental disorders, many of which are more common in boys. However, they also address the broader question of how sex and gender influence the neurobiology of how we learn and behave, which may be involved in the different levels of risk between women and men for developing many other neuropsychiatric conditions, as well."

The study also found that male mice carrying this genetic alteration linked to autism have increased expression of a receptor for dopamine; the D2 receptor. The level of D2 expression did not increase in the female autism mice. Abel notes that risperidone, one of very few drugs that is approved by the Food and Drug Administration to treat ASD symptoms, targets D2 dopamine receptors.

"We think we are on the right track," Abel says. "We have begun to identify what may be an underlying reason why neurodevelopmental disorders predominantly affect boys, and that involves the function of the striatum and reward learning. This has implications for how we think about the underlying behavioral differences in autism and implications for how we develop both behavioral or pharmacological therapies to improve the lives of those with autism."

The new findings are part of a bigger study where Abel and his colleagues are investigating many different mouse models of autism, in which different autism-linked genes have been disrupted. The researchers are seeking commonalities among the different models. One emerging theme, supported by the new study, is that a deficit in reward learning may be a common feature of ASD, and males are specifically deficient in this type of behavior.

Abel notes that funding from the Simons Foundation was critical to the success of the project.

"None of this would have happened without the support of the Simons Foundation Autism Research Initiative (SFARI). The impact they have had on autism research has been tremendous," he says.

Story Source:

Materials provided by **University of Iowa Health Care**

. *Note: Content may be edited for style and length.*

Journal Reference:

1. N M Grissom, S E McKee, H Schoch, N Bowman, R Havekes, W T O'Brien, E Mahrt, S Siegel, K Commons, C Portfors, T Nickl-Jockschat, T M Reyes, T Abel. **Male-specific deficits in natural reward learning in a mouse model of neurodevelopmental disorders**. *Molecular Psychiatry*, 2017; DOI: 10.1038/MP.2017.184

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- Chicago

University of Iowa Health Care. "Signaling pathway may be key to why autism is more common in boys: In mice, the male brain is vulnerable and the female brain resilient to a genetic cause of autism." ScienceDaily. ScienceDaily, 17 October 2017. <www.sciencedaily.com/releases/2017/10/171017091906.htm>.

目次に戻る

7. 野生マウスの腸内細菌が実験用マウスの健康を増殖

2017 年 10 月 19 日

野生マウスの腸内細菌を投与された実験用マウスは、自分自身の腸内細菌しか持たない実験用マウスに比べてはるかにうまく、致命的なインフルエンザ ウィルス感染から生き残り、結腸直腸癌と戦うことができる、と 10 月 19 日の *Cell* 誌で報告された。
NHI 国立糖尿病免疫病肝臓病研究所（NIDDK）の研究者らによって行われたこの研究では、実験用マウスに欠けている自然と共に進化した野生マウスの腸内微生物叢を実験用マウスに与えるために、メリーランド州とワシントン DC の 8 か所で 800 匹以上の野生マウスを捕獲、次にその野生マウスの腸内微生物（腸内細菌叢の集合ゲノム）と C57BL/6 と呼ばれる実験用マウスの共通株を比較し、C57BL/6 マウスが野生マウスとは異なる腸内微生物を有することを確認した。研究者らは更に、野生マウスの微生物を妊娠した無菌の C57BL/6 マウスに移植、比較の為に通常の C57BL/6 マウスからの微生物を妊娠した別の無菌マウスグループにも移植して、上記の結果を導き出した。

英文記事：
https://www.sciencedaily.com/releases/2017/10/171019143012.htm

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Gut bacteria from wild mice boost health in lab mice

Date:

October 19, 2017

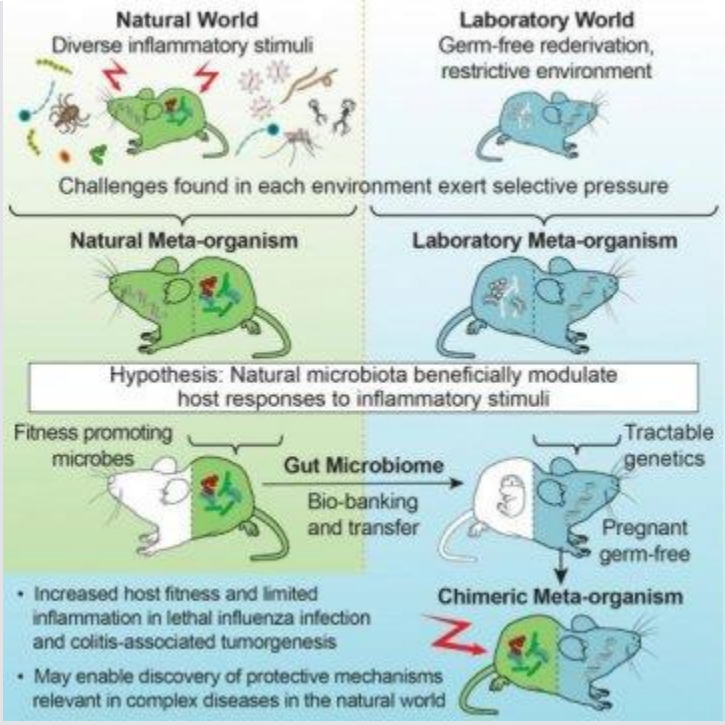
Source:

Cell Press

Summary:

Laboratory mice that are given the gut bacteria of wild mice can survive a deadly flu virus infection and fight colorectal cancer dramatically better than laboratory mice with their own gut bacteria, researchers report.

FULL STORY



This is a visualization of the process of transferring gut microbiota from wild mice to laboratory mice.

Credit: Rosshart et al.

Laboratory mice that are given the gut bacteria of wild mice can survive a deadly flu virus infection and fight colorectal cancer dramatically better than laboratory mice with their own gut bacteria, researchers report October 19 in the journal *Cell*.

The immunological benefits from the wild mice's gut bacteria may, in part, explain a persistent problem in disease research: Why disease experiments in lab mice, such as vaccine studies, turn out very differently in humans or other animals.

"We think that by restoring the natural 'microbial identity' of laboratory mice, we will improve the modeling of complex diseases of free-living mammals, which includes humans and their diseases," said Barbara Rehermann, M.D., senior author of the paper. Rehermann is chief of the Immunology Section, Liver Diseases Branch, of the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"By being so different, natural microbiota will help us to discover protective mechanisms that are relevant in the natural world and absent in the laboratory," said Stephan Rosshart, M.D., first author of the paper and NIDDK postdoctoral fellow.

Mammals -- humans included -- depend on their microbiota, the collection of microorganisms they host in and on their bodies. Evolution shapes each animal's microbiota, favoring populations of microorganisms that help the animal survive their environment and diseases they encounter. But laboratory mice aren't random house mice plucked from a field or basement.

Laboratory mice are carefully bred, fed, and raised in tightly controlled conditions so that each mouse has predictable traits and genetics. This is a great advantage in basic biology research, but creating that predictability means that a controlled environment, and not the survival pressures of the outside world, shaped the microbiotas of laboratory mice.

"We hypothesized that this might explain why laboratory mice, while paramount for understanding basic biological phenomena, are limited in their predictive utility for modeling complex diseases of humans and other free-living mammals," said Rosshart.

So, the researchers tried to give laboratory mice back what they have lost: a naturally co-evolved wild mouse gut microbiota. The researchers trapped more than 800 wild mice from eight locations across Maryland and the District of Columbia to find healthy, suitable candidates for a gut microbiota donation.

They then tested and compared the gut microbiomes (collective genomes of the gut microbiota) of the wild mice (Mus musculus domesticus) and a common strain of laboratory mice, called C57BL/6, from multiple sources. The researchers confirmed that C57BL/6 mice had distinct gut microbiomes from wild mice.

Researchers then introduced (engrafted) the microbiota of wild mice to pregnant, germ-free C57BL/6 mice. Germ-free mice are raised in a sterile environment and don't have microbiomes of their own. For a control group comparison, the researchers also engrafted microbiota from regular C57BL/6 mice into a separate group of pregnant, germ-free mice. Four generations later, the mice still carried either the wild microbiomes or the control laboratory microbiomes passed down from their foremothers.

When exposed to a high dose of influenza virus, 92 percent of the laboratory mice with wild microbiomes survived, whereas only 17 percent of laboratory mice and mice in the control group survived. In other experiments, the laboratory mice with wild microbiomes had better outcomes in the face of induced colorectal tumors, whereas the other mice had a greater number of tumors and more severe disease. The beneficial effects of the wild microbiota were associated with reduced inflammation in both models.

The researchers note that more work and evaluation is needed for definitive results, and they hope to improve and expand upon the method of using natural microbiomes in laboratory mice.

"We are planning to create a complete microbiological fingerprint of natural microbiota and its potential trans-kingdom interaction by describing all components of the microbiome -- for example, viruses and fungi -- in parallel and at various body sites," Rehermann said.

Story Source:

Materials provided by **Cell Press**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Rosshart et al. **Wild Mouse Gut Microbiota Promotes Host Fitness and Improves Disease Resistance**. *Cell*, 2017 DOI: 10.1016/j.cell.2017.09.016

目次に戻る

8. 脂肪を溶かす貼り薬、人に応用可の期待 -マウス実験で開発

2017 年 10 月 18 日

アメリカ科学振興協会に属する研究者らが、肥満マウス、ラット、および霊長類において、体重、血流インスリン、コレステロール レベルを低下させる改変たんぱく質を作製した。
現在、1975 年以来約 3 倍にもなっている肥満治療のための肥満手術だが、この研究が早急に必要とされている別の選択肢の道を開くことになる、として期待される。
研究者らは、肥満マウス、ラットおよびヒトの全てにおいて GDF15 と呼ばれるたんぱく質の血清濃度が上昇している事実に基づいて分子由来の治療法開発に着手した。GDF15 は、血漿半減期が短く、実質的な量で生産することが困難なため、研究者らは循環器系においてより安定した 2 つの異なる融合たんぱく質を生成し、より高い収量を得た。そしてこの融合たんぱく質が、肥満マウス、ラットおよびカニクイザルの体重を効果的に減少させた、としている。
この研究は *Science Translational Medicine* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2017/10/171018151820.htm

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Obesity: Engineered proteins lower body weight in mice, rats and primates

Date:

October 18, 2017

Source:

American Association for the Advancement of Science

Summary:

Researchers have created engineered proteins that lowered body weight, bloodstream insulin, and cholesterol levels in obese mice, rats, and primates.

FULL STORY

Researchers have created engineered proteins that lowered body weight, bloodstream insulin, and cholesterol levels in obese mice, rats, and primates. Their results could pave the way for urgently needed alternatives to bariatric surgery for treating obesity in humans -- the rates of which have nearly tripled worldwide since 1975.

Based on the observation that obese mice, rats, and humans all had elevated serum concentrations of a protein called GDF15 compared to lean controls, Yumei Xiong and colleagues set out to develop therapies derived from the molecule. In multiple mouse models of diet-induced and genetic obesity, delivery of the GDF15 gene reduced body weights, food intake, and serum insulin levels in the animals.

Because GDF15 has a short plasma half-life and is difficult to produce in substantial quantities, the scientists generated two different fusion proteins that were more stable in the circulation and led to higher yields. Both fusion proteins effectively decreased body weights for obese mice and cynomolgus monkeys.

Interestingly, Xiong et al. further showed that the GDF15 regimen altered food preferences in mice -- leading the animals to opt for lower calorie chow when offered a choice between standard food and an extra-rich condensed-milk diet (untreated mice gorged themselves on the high-calorie eats).

The authors determined that GDF15 activated a population of nerve cells called AP neurons that make up a portion of the gut-brain axis, yet note that further studies to identify the protein's cellular receptor are needed as potential therapeutics make their way to the clinic.

Story Source:

Materials provided by **American Association for the Advancement of Science**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yumei Xiong, Kenneth Walker, Xiaoshan Min, Clarence Hale, Thanhvien Tran, Renee Komorowski, Jerry Yang, Jasmine Davda, Noi Nuanmanee, Dao Kemp, Xiaozhen Wang, Hantao Liu, Silke Miller, Ki Jeong Lee, Zhulun Wang, Murielle M. Véniant. **Long-acting MIC-1/GDF15 molecules to treat obesity: Evidence from mice to monkeys**. *Science Translational Medicine*, 2017; 9 (412): eaan8732 DOI: 10.1126/scitranslmed.aan8732

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- MLA
- APA
- Chicago

American Association for the Advancement of Science. "Obesity: Engineered proteins lower body weight in mice, rats and primates." ScienceDaily. ScienceDaily, 18 October 2017. <www.sciencedaily.com/releases/2017/10/171018151820.htm>.
American Association for the Advancement of Science. (2017, October 18). Obesity: Engineered proteins lower body weight in mice, rats and primates. *ScienceDaily*. Retrieved October 24, 2017 from www.sciencedaily.com/releases/2017/10/171018151820.htm
American Association for the Advancement of Science. "Obesity: Engineered proteins lower body weight in mice, rats and primates." ScienceDaily. www.sciencedaily.com/releases/2017/10/171018151820.htm (accessed October 24, 2017).

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9．口内細菌、腸で増えると潰瘍誘発 治療薬開発に期待 -マウス実験

2017 年 10 月 22 日

口の中にすむ細菌が腸の中で増えると、腸に慢性の炎症が出るクローン病や潰瘍（かいよう）性大腸炎といった難病を引き起こしたり悪化させたりする可能性があると、慶応大や早稲田大などの研究チームが動物実験で確かめ、２０日付の米科学誌サイエンスに発表した。治療薬の開発に役立つ可能性があるという。

クローン病などは原因がはっきりせず根治療法がない。研究チームは、患者の唾液（だえき）を、体内に細菌がいないマウスや遺伝的に腸内に炎症が起きやすいマウスに口から投与し、腸などを分析した。マウスの腸内では「クレブシエラ属」と呼ばれる細菌が増殖して免疫細胞の一種を過剰に刺激し、炎症を起こしているとわかった。健康なマウスでは炎症は起きなかった。

この細菌は口の中や皮膚に少数いる常在菌と考えられている。研究チームの服部正平・早大教授は「腸内のほかの細菌のバランスが崩れると、この細菌が増えるのではないか。この細菌だけを攻撃する薬が開発できれば治療に役立つ可能性がある」と説明する。

研究チームの本田賢也・慶大教授は「遺伝的な背景にこの細菌が加わると、炎症性腸疾患が起き、慢性化しやすい可能性がある」と話している。（大岩ゆり）

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10. 新二重トランスジェニック齧歯類モデルで幹細胞の作用様式を同定

2017 年 10 月 31 日

幹細胞療法は、軟骨損傷の治療に大きな可能性を秘めているものの、幹細胞が再生に関与しているのか、あるいはプロセスを引き起こすだけなのかは不明であった。そこで今回 Veterinärmedizinische Universität Wien (University of Veterinary Medicine, Vienna) の研究者らは、新しい動物モデルにおける効果を追跡することでこの問題の解決に成功した。
その新しい動物モデルは、ダブルトランスジェニックで、マウスとラットの特別なドナーおよびレシピエント ラインが作成された。そのモデルは人工的に導入されたヒト細胞表面たんぱく質である胎盤アルカリフォスファターゼ（ALPP）を全ての細胞に発現させそれらの追跡を可能にした。
この研究により、幹細胞は内因性細胞の治療効果を調整するが、軟骨の再生には関与しないことが分かった。またこの突破口は、注入された細胞を追跡するのに必要な分子に対する正常な免疫反応を妨げることによって可能になった、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/10/171031085434.htm

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Stem cells conduct cartilage regeneration but are not directly involved

Date:

October 31, 2017

Source:

Veterinärmedizinische Universität Wien

Summary:

Stem cell therapy has great potential for curing cartilage damage. However, it has remained unclear whether stem cells are responsible for regeneration or whether they trigger the process. Researchers have been able to resolve this issue by tracking the effects in a new, natural model. After injection, stem cells orchestrate the healing effect of endogenous cells but are not responsible for cartilage regeneration. The breakthrough was enabled by preventing the normal immune response to the molecule required to trace the injected cells.

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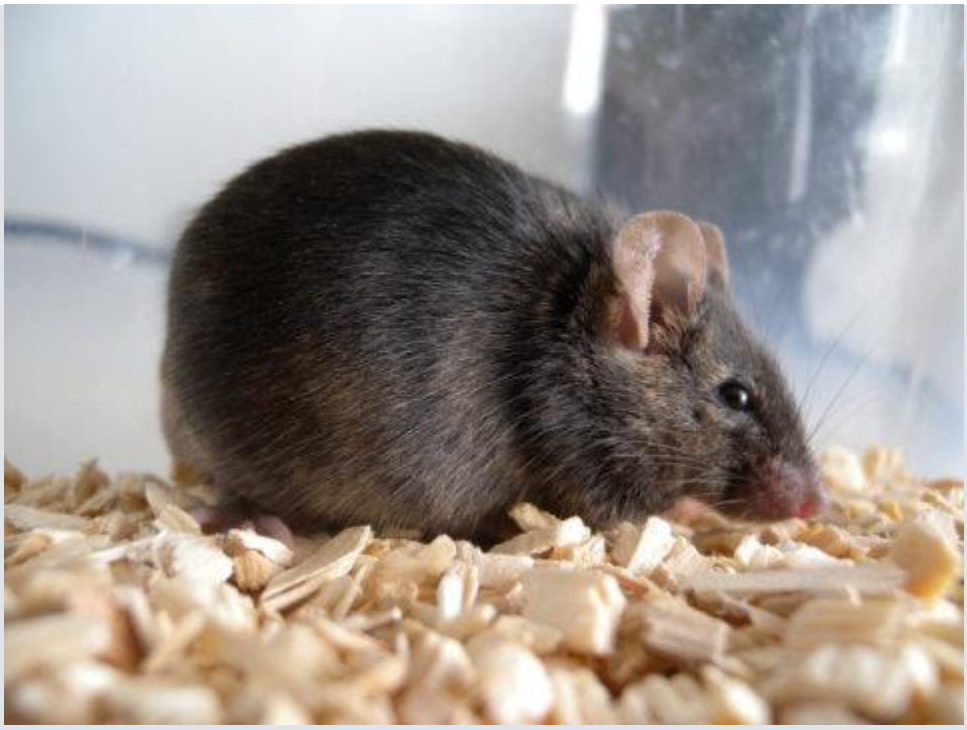
FULL STORY



New double-transgenic rodent models identified the mode of action of stem cells.

Credit: Vetmeduni Vienna

Stem cell therapy has great potential for curing cartilage damage. However, it has remained unclear whether stem cells are responsible for regeneration or whether

they trigger the process. Researchers at the Vetmeduni Vienna have been able to resolve this issue by tracking the effects in a new, natural model. After injection, stem cells orchestrate the healing effect of endogenous cells but are not responsible for cartilage regeneration. The breakthrough is published in *JCI-Insight* and was enabled by preventing the normal immune response to the molecule required to trace the injected cells.

Therapy with mesenchymal stem cells, the so-called progenitor cells of connective tissue, holds great promise for the regeneration of cartilage tissue but how stem cell therapy contributes to the healing of damaged connective tissue has been unclear. Debate has centred on whether the injected cells promote regeneration or stimulate the body's own cells to proliferate. A new strategy has now enabled researchers from the Department of Biomedical Sciences of the Vetmeduni Vienna to solve the question. The problem was that a marker protein was recognized by the immune system of the recipient as a non-self protein, leading to the rejection of the injected stem cells. The Vetmeduni Vienna scientists were able to overcome this limitation and show that progenitor cells do not participate directly in cartilage regeneration but serve to "animate" the process.

New model reveals mode of action of stem cells

"To date, it has not been possible to show what an injection of stem cells really does in an animal model," explains Reinhold Erben, the senior author of the study. "The problem is that you have to track the cells with particular proteins that the immune system of the recipient recognizes as non-endogenous and thus potentially harmful. The resulting rejection of the injected cells has prevented the validation of their mode of action."

It was thus only possible to track stem cells in immunodeficient animal models that had no reaction to the proteins due to a genetically reduced immune system. These models could not provide any clues about the mode of action of the stem cells. "We therefore worked with a 'lifelike' animal model that is immunocompetent but shows no response to our tracker molecule. This enabled us to show that stem cells have a purely modulating action in the treatment of cartilage damage," says Erben.

A new animal model

"We developed a so-called double-transgenic animal model for the purpose," notes Erben. Special donor and recipient lines of mice and rats were bred that expressed an artificially introduced human cell-surface protein, the placental alkaline phosphatase, ALPP, on all their cells to enable them to be traced. In addition, the ALPP of the recipient line differed from that of the donors at a single amino acid. As the two protein variants are almost identical, the immune system cannot distinguish the body's own cells from those of the donor. "Moreover, the mutation inactivates the otherwise heat-stable protein at high temperatures, allowing the recipient cells to be differentiated from the donor cells during the experiment," explains Erben.

New system as motivation for stem cell therapy

The idea of using a protein variant both to enable the detection of the tracking molecule and to deceive the immune system of the recipient lines can be applied in other animal models. ALPP -- like the green fluorescent protein, GFP, and luciferase -- is commonly used as a marker protein. "Unlike other tracking molecules, the two variants represent the perfect combination for stem cell research," says Erben.

The use of a double transgenic system without the loss of immunocompetence should support stem cell research in fields other than cartilage regeneration. "Our results contribute to our understanding of stem cell therapy, as they show for the first time that therapy stimulates the body's own cells to promote the regeneration of damaged connective tissue, such as cartilage," concludes Erben.

Story Source:

Materials provided by **Veterinärmedizinische Universität Wien**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Daniela Zwolanek, María Satué, Verena Proell, José R. Godoy, Kathrin I. Odörfer, Magdalena Flicker, Sigrid C. Hoffmann, Thomas Rülicke, Reinhold G. Erben. **Tracking mesenchymal stem cell contributions to regeneration in an immunocompetent cartilage regeneration model**. *JCI Insight*, 2017; 2 (20) DOI: 10.1172/jci.insight.87322
