BIO NEWS

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・世界最強 ミノムシから産業糸（12/6)
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・認知症予防に長時間歩行 東北大研究（12/10)
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・科学研究予算 100 億円超増額へ（12/13)
・FDA がインスリン等をバイオシミラー参入可能な分類に変えると発表（12/13)
・NIH 科学者が研究用に胎児組織を手に入れることはトランプ政権が禁止（12/13)
Science 誌の調べによると、米国立衛生研究所（NIH）で働く研究者が実験のためにヒト胎児組織を手に入れることを同国トランプ政権が今年 9 月から禁じている。未公表のこの命令の影響は 2 つの研究室に及んでおり、胎児組織を使ってヒト化したマウスによる HIV 感染の仕組みを調べているモンタナ州の Rocky Mountain Laboratories（RML）と胎児網膜組織を使って眼疾患を調べている National Eye Institute の研究が支障をきたしている。
・Merck & Co、ブラジルの Instituto Butantan と組んでデングワクチンを開発（12/14)
・Allen Institute が免疫研究部門 Allen Institute for Immunology を新設（12/14)

10 月に亡くなったマイクロソフト設立者の 1 人 Paul Allen 氏によって 2003 年に設立された生命科学研究機関 Allen Institute が、同氏からの 1 億 2500 万ドルの寄附を元手に免疫研究機関 Allen Institute for Immunology を新たに設立。

・肝臓の再生 促す仕組み解明 -東北大（12/14)

・出産女性の死亡率が中国全域で速やかに低下（12/14)

・人食い細菌が免疫阻止 解明 -大阪大微生物病研究所（12/15)

・Teva がイスラエルの世界事業本丸も移転する（12/15)

・ベビーパウダーの発癌性物質アスベスト混入を J&J が長年隠蔽/Reuters（12/15)

タルク粉製品で癌を被ったという数多の訴訟で J&J はベビーパウダー製品が安全で有害物質の混入はないと主張しているが、Reuters の調べによると、同社は発癌性物質アスベストの混入を何十年も前から把握しながら隠蔽。裁判資料によると J&J の幹部や医師等はタルクのアスベスト陽性検査について 1971 年から社内で検討していたにも拘わらず、その結果を通知していなかった。

・ムーディーズ：武田薬の格付け 3 段階引き下げ、Shire 買収が影響（12/17)

ムーディーズ・ジャパンは 17 日、武田薬品工業の格付けを信用リスクが低い「Ａ２」からリスクが中程度の「Ｂａａ２」に 3 段階引き下げたと発表。総額約 7 兆円での Shire 買収で有利子負債が増加することが影響。

・エボラウイルス蛋白質に成り済ましてその複製を封じるヒト蛋白質が見つかった（12/17)

・米国の高校 3 年生の 5 人に 1 人（21%）がニコチン蒸気吸引経験あり（12/18)

米国で 44 年前から続く調査 Monitoring the Future study の今年の結果では、去年の 11%のほぼ 2 倍の 21%、すなわち約 5 人に 1 人の高校最高学年-通常 4 年生（12th-grader；12 年生）が先立つ 30 日間に加熱装置からのニコチン蒸気吸引（Nicotine Vaping）経験ありと回答。10 年生（10th-grader）と 8 年生（8th-grader）はそれぞれ 16%と 6%がニコチン蒸気吸引経験有。ここ数年に売り出された蒸気発生加熱装置 JUUL の使用は思春期の若者に急速に広まっている。

・iPS 細胞の備蓄事業、京大から独立へ 山中教授が意向(12/18)

・Sanofi、米国ケンブリッジの開発地区 Cambridge Crossing に大規模な拠点を築く（12/19)

米国東海岸ボストンのバイオテック涌出地 Kendall Square 隣接の開発地区 Cambridge Crossing に Sanofi が新たな拠点を築く。

・Tetra Discovery、認知/記憶障害薬のアジア権利を 4,000 万ドルで塩野義製薬に付与(12/19)

・GSK が Pfizer と店頭販売医療品の合弁事業を作り、3 年以内に上場させる（12/20)

・Lilly、新薬需要に支えられて来年の利益や売上はアナリスト予想を上回る見通し（12/20)

・Roivant Sciences、第一三共の手持ち品から選んで開発を受け継ぐ権利を取得（12/20)
・蛋白質の形を変えて病気を治療する薬を開発している Relay、4 億ドル調達（12/21)
・Rakuten Aspyrian、光で奮って腫瘍を撃つ抗癌剤の開発資金 1 億 3,400 万ドル調達 (12/23)
・Ionis、再来年 2020 年 1 月に CEO 交代　-現在の CEO・Stanley Crooke 氏が現在の COO・Brett Monia 氏に CEO の座を譲って会長に（12/24)
・世界の 25 歳成人の 4 人に 1 人が脳卒中をやがて発現～生活習慣や食事の改善が必要 (12/25)
・微生物薬の Vedanta が 2,700 万ドル調達（12/28)
・Perrigo、16 億 3,600 万ユーロの税金支払い不足とアイルランドが判断　(12/28)

昨年の売り上げおよそ 20 億ドル（19 億 7,310 万ドル）の多発性硬化症（MS）薬 TYSABRI (natalizumab) の権利が 2013 年に Biogen に渡ったことによる Perrigo の税金支払いが 16 億 3,600 万ユーロ（18 億 7,000 万ドル）も不足しているとアイルランドが判断。この状況を背景に Perrigo の株価は 30%近く下落。同社は不服申立ての予定。

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1. ヒト化マウスの「ワクチン・シグナチャー」で感染症を深く理解

2018 年 11 月 28 日

プリンストン大学の研究者らは、ヒト化マウスとヒトとの免疫応答を比較する為の体系的な方法を開発し、この新しい試験プラットフォームを使用して、新たに開発されたヒト化マウスが、ヒトとの有意な免疫系応答を共有することを示した。
感染症によって毎年何百万人もの人々が命を落としているが、実験用マウスはヒト免疫不全ウィルス（HIV）を含む人間のウィルスには影響を受けないという事実に妨げられている。そこで、研究者らは何十年もの間、免疫系がヒトと同様の方法で反応するように「ヒト化」されたマウスに目を向けている。
プリンストン大学率いる研究チームは、ヒト化マウスの免疫反応が実際のヒトにどのように測定されるかを評価する包括的な方法を開発し、この成果が *Nature Communications* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/11/181128153950.htm

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Vaccine signatures in humanized mice point to better understanding of infectious diseases

Date:

November 28, 2018

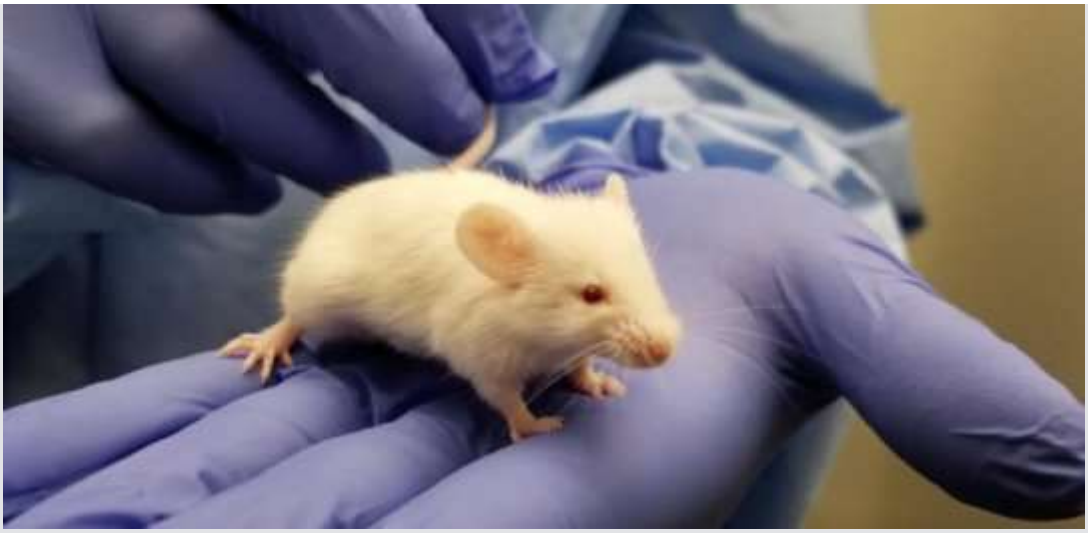
Source:

Princeton University

Summary:

Researchers have developed a systematic way to compare the immune responses of humanized mice versus humans. They used this new testing platform to show that a newly developed humanized mouse shares significant immune-system responses with humans.

FULL STORY



Researchers led by a team at Princeton University are exploring ways to make the mouse immune system more similar to that of humans, enabling mice to help in the search for new vaccines and treatments.

Credit: Alexander Ploss and Florian Douam, Princeton University

Infectious diseases kill millions of people each year, but the search for treatments is hampered by the fact that laboratory mice are not susceptible to some human viruses, including killers like human immunodeficiency virus (HIV). For decades, researchers have turned to mice whose immune systems have been "humanized" to respond in a manner similar to humans.

Now a team at Princeton University has developed a comprehensive way to evaluate how immune responses of humanized mice measure up to actual humans. The research team looked at the

mouse and human immune responses to one of the strongest vaccines known, a yellow fever vaccine called YFV-17D. The comparison of these "vaccine signatures" showed that a newly developed humanized mouse developed at Princeton shares significant immune-system responses with humans. The study was published in the journal *Nature Communications*.

"Understanding immune responses to human pathogens and potential vaccines remains challenging due to differences in the way our human immune system responds to stimuli, as compared to for example that of conventional mice, rats or other animals," said Alexander Ploss, associate professor of molecular biology at Princeton University. "Until now a rigorous method for testing the functionality of the human immune system in such a model has been missing. Our study highlights an experimental paradigm to address this gap."

Humanized mice have been used in infectious disease research since the late 1980s. Yet without rigorous comparisons, researchers know little about how well the mice predict human responses such as the production of infection-fighting cells and antibodies.

To address this issue, researchers exposed the mice to the YFV-17D vaccine, which is made from a weakened, or attenuated, living yellow fever virus. Vaccines protect against future infection by provoking the production of antibodies and immune-system cells.

In previous work, the researchers explored the effect of YFV-17D on conventional humanized mice. But the researchers found that the mice responded only weakly. This led them to develop a mouse with responses that are more similar to those of humans.

To do so, the researchers introduced additional human genes for immune system components -- such as molecules that detect foreign invaders and chemical messengers called cytokines -- so that the complexity of the engrafted human immune system reflected that of humans. They found that the new mice have responses to YFV-17D that are very similar to the responses seen in humans. For example, the pattern of gene expression that occurs in response to YFV-17D in the mice shared significant similarities to that of humans. This signature gene expression pattern, reflected in the "transcriptome," or total readout of all of the genes of the organism, translated into better control of the yellow fever virus infection and to immune responses that were more specific to yellow fever.

"Many vaccines have been generated empirically without profound knowledge of how they induce immunity," Douam said. "The next generation of mouse models, such as the one we introduced in

our study, offer unprecedented opportunities for investigating the fundamental mechanisms that define the protective immunity induced by live-attenuated vaccines."

Mice bearing human cells or human tissues have the potential to aid research on treatments for many diseases that infect humans but not other animals, such as -- in addition to HIV -- Epstein Barr Virus, human T-cell leukemia virus, and Karposi sarcoma-associated herpes virus.

"Our study highlights the importance of human biological signatures for guiding the development of mouse models of disease," said Ploss. "It also highlights a path toward developing better models for human immune responses."

The study involved contributions from Florian Douam, Carly G. K. Ziegler, Gabriela Hrebikova, Bruno Fant, Robert Leach, Lance Parsons, Wei Wang, Jenna M. Gaska, Benjamin Y. Winer, Brigitte Heller, Alex K. Shalek and Alexander Ploss.

Funding for this study was provided by the National Institutes of Health, the National Institute of General Medical Sciences, the Bill & Melinda Gates Foundation and the New Jersey Commission on Cancer Research.

Story Source:

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

Journal Reference:

1. Florian Douam, Carly G. K. Ziegler, Gabriela Hrebikova, Bruno Fant, Robert Leach, Lance Parsons, Wei Wang, Jenna M. Gaska, Benjamin Y. Winer, Brigitte Heller, Alex K. Shalek, Alexander Ploss. **Selective expansion of myeloid and NK cells in humanized mice yields human-like vaccine responses**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-07478-2

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2. 上海の「Pharma Valley」は、中国版「Kendall 広場」

2018 年 12 月 3 日

上海にあるファーマバレー（Pharma Valley）と呼ばれるエリアは、米国マサチューセッツ州ケンブリッジの Kendall 広場に相当し、現在急速に成長している。
ファーマバレーは、政府が設立した張江ハイテクパーク内に位置し、10 平方キロメートルクラスターには 500 社以上のバイオテクノロジー企業が集まっている。国家医療製品管理局（NMPA）が承認した 3 つの医薬品のうち 1 つが開発された場所でもあり、Roche や Novartis のような多国籍企業も、歩いて数分の距離にある。
Hutchison China MediTech（Chi-Med）の CEO であるクリスチャン・ホッグ氏によると、現在、中国の革新的なバイオファーマ活動の 70～80%がこのファーマバレーで発生している、とのことである。

英文記事：
https://www.statnews.com/2018/12/03/pharma-valley-chinas-kendall-square/?utm_source=STAT+Newsletters&utm_campaign=4091a45013-Cancer_Briefing&utm_medium=email&utm_term=0_8cab1d7961-4091a45013-150065641

Pharma Valley, China's equivalent of Kendall Square, is expanding rapidly

By YI-LING LIU

DECEMBER 3, 2018

Photos by ELKE SCHOLIERS FOR STAT

Pharma Valley employees often meet to discuss their work at a Starbucks.

SHANGHAI — Harbour BioMed opened its first office in a Shanghai industrial park in 2016, with a team of eight people. Just two years later, it has become a global biotech company, with offices in Boston and Rotterdam, Netherlands, and more than 150 employees. Here in China, they're spread among three new labs, and a new office is under construction in walking distance to a cancer hospital. Even so, in Harbour's original lab, scientists work shoulder to shoulder, sharing limited bench space.

That sort of explosive growth is not all that remarkable here: This is China's Kendall Square, the epicenter of the country's biotech industry, where scaffolding sprouts like weeds.

Harbour is only one of more than 500 biotech companies that have flocked to a 10-square-kilometer cluster known as "Pharma Valley," with roughly 30 companies opening in each of the last two years, according to a drug company in the park.

Christian Hogg, CEO of Chi-Med

Located within the government-established Zhangjiang Hi-Tech Park, Pharma Valley is where one in three medicines approved by the China National Medical Products Administration (NMPA) has been developed. Multinational companies such as Roche and Novartis are a minute's walk away from the glossy laboratories of contract research organizations and smaller, home-grown startups. Young professionals in sneakers bike through the tree-lined, campus-like streets and congregate at the Pharma Valley cafeteria at lunch hour over noodle bowls. At a Starbucks across the street, CEOs fuel up on coffee, tap away on IBM ThinkPads, and make deals.

"If we need to have a discussion on a collaboration [with another company], our team is just a holler away," said Dr. Jingsong Wang, the CEO and founder of Harbour BioMed.

Although Pharma Valley lags its Boston prototype in capital, entrepreneurial talent, and scientific firepower, its biotech ecosystem is growing rapidly. When Christian

Hogg, CEO of Hutchison China MediTech (Chi-Med) arrived 15 years ago, there was only a handful of buildings in the entire park. Since then, two new subway stations have opened in the area to ease traffic tie-ups, and office rents are now surging by roughly 10 percent a year.

Today, 70 to 80 percent of innovative biopharma activity in China occurs in Pharma Valley, Hogg said recently.

Kendall Square's mature biotech ecosystem — with nearby world-class hospitals, a sophisticated network of investors, and abundant talent in both academia and entrepreneurship — will be difficult to replicate in China, Wang said. But what the Chinese biotech industry lacks, he added, it makes up for with unprecedented expansion.

目次に戻る

3. 好きなだけ食べても太らせない遺伝子

2018 年 12 月 4 日

そんなに調子の良い話はない、と思うだろう。しかし、好きなだけ食べても太らない、そんな斬新なアプローチが近い将来現実になるかもしれない。
オーストラリアのフリンダース大学の研究によると、RCAN1 として知られる 21 番染色体の遺伝子は熱発生を抑制、これがマウスから除去された時、いくら長期間高脂肪食を与えて飼育しても、マウスが体重を増やすことはなかった、といている。
また、肥満を特徴の一つとするダウン症の人は余分に有する 21 番染色体に位置する RCAN1 遺伝子が ATP を減らす方向の発熱の仕組み 2 つを抑制しているらしい、ともしている。
この研究の背後にある国際チームは、この遺伝子を阻害する同様のアプローチがヒトにも有効であることを期待して研究を進める。
この研究は、*EMBO reports* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181204095412.htm

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Gene that lets you eat as much as you want holds promise against obesity

Date:

December 4, 2018

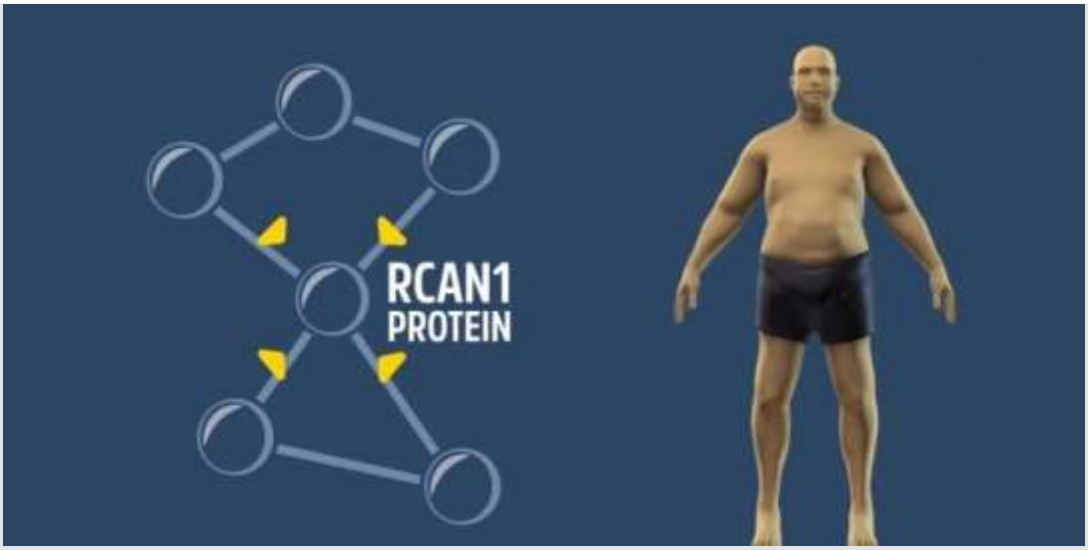
Source:

Flinders University

Summary:

It sounds too good to be true, but a novel approach that might allow you to eat as much as you want without gaining weight could be a reality in the near future. When a single gene known as RCAN1 was removed in mice and they were fed a high fat diet, they failed to gain weight, even after gorging on high fat foods for prolonged periods.

FULL STORY



When a single gene known as RCAN1 was removed in mice and they were fed a high fat diet, they failed to gain weight, even after gorging on high fat foods for prolonged periods. The international team behind the study are hopeful a similar approach that inhibits this gene will also be effective with humans.

Credit: Flinders University

It sounds too good to be true, but a novel approach that might allow you to eat as much food as you want without gaining weight could be a reality in the near future.

When a single gene known as RCAN1 was removed in mice and they were fed a high fat diet, they failed to gain weight, even after gorging on high fat foods for prolonged periods.

The international team behind the study are hopeful a similar approach that inhibits this gene will also be effective with humans to combat obesity and serious diseases like diabetes.

Led by Professor Damien Keating at Flinders University, the study used a huge genetic screen in rodents to identify novel genetic candidates that may cause obesity, potentially paving the way for new drug therapies.

"We know a lot of people struggle to lose weight or even control their weight for a number of different reasons. The findings in this study could mean developing a pill which would target the function of RCAN1 and may result in weight loss," Professor Keating says.

Obesity is a major global health epidemic, resulting in increased risk of serious diseases like type 2 diabetes, and heart disease, but avenues for effective therapeutic treatments are lacking.

There are two types of fat in the human body- brown fat burns energy, while white fat stores energy.

Professor Keating says blocking RCAN1 helps to transform unhealthy white fat into healthy brown fat, presenting a potential treatment method in the fight against obesity.

"We have already developed a series of drugs that target the protein that this gene makes, and we are now in the process of testing them to see if they inhibit RCAN1 and whether they might represent potential new anti-obesity drugs,"

"In light of our results, the drugs we are developing to target RCAN1 would burn more calories while people are resting. It means the body would store less fat without the need for a person to reduce food consumption or exercise more."

Two thirds of Australian adults and a quarter of children are either overweight or obese, and the statistics are just as concerning in Britain and the US.

"We looked at a variety of different diets with various timespans from eight weeks up to six months, and in every case we saw health improvements in the absence of the RCAN1 gene."

The researchers say these findings open up a potentially simple treatment but further studies are required to determine if they translate the same results to humans.

"Our research is focused on understanding how cells send signals to each other and how this impacts health and the spread of disease."

"We really want to pursue this, it's exciting and we have research funding from the Australian government through the National Health and Medical Research Council to continue to explore viable options. These results show we can potentially make a real difference in the fight again obesity."

Story Source:

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

Journal Reference:

1. David Rotter, Heshan Peiris, D Bennett Grinsfelder, Alyce M Martin, Jana Burchfield, Valentina Parra, Christi Hull, Cyndi R Morales, Claire F Jessup, Dusan Matusica, Brian W Parks, Aldons J Lusis, Ngoc Uyen Nhi Nguyen, Misook Oh, Israel Iyoke, Tanvi Jakkampudi, D Randy McMillan, Hesham A Sadek, Matthew J Watt, Rana K Gupta, Melanie A Pritchard, Damien J Keating, Beverly A Rothermel. **Regulator of Calcineurin 1 helps coordinate whole-body metabolism and thermogenesis**. *EMBO reports*, 2018; e44706 DOI: 10.15252/embr.201744706

Cite This Page:

- MLA
- APA
- Chicago

Flinders University. "Gene that lets you eat as much as you want holds promise against obesity." ScienceDaily. ScienceDaily, 4 December 2018. <www.sciencedaily.com/releases/2018/12/181204095412.htm>.

目次に戻る

４．メチルマロン酸血症は、あるホルモンの上昇度で肝障害の度合いを判断 -マウス実験

2018 年 12 月 6 日

メチルマロン酸血症（MMA)は、食物タンパク質および特定の脂肪酸を分解する能力を損なうゲノム疾患である。米国で生まれる 5 万人に 1 人の子供に影響を及ぼし、新生児スクリーニングによって検出できる。
研究者らは、マウス研究で、希少疾患であるこの MMA 患者が肝臓移植を受けるべき時期を医者が判断材料として使用するのに大変役立つホルモンを発見し、12 月 6 日の *JCI Insight* 誌で発表している。
国立衛生研究所の一部である国立ヒトゲノム研究所（NHGRI）の研究者らは、深刻なゲノム障害である MMA 患者と同じ状態を模倣する肝臓病のマウスにおいて、線維芽細胞増殖因子 21（FGF21）と呼ばれるホルモンが著しく上昇することを発見した。この知見に基づいて、MMA 患者を治療する医療チームは FGF21 レベルを測定して患者の肝臓がどれほど重度に影響を受けているか予測できる、としている。又、この発見は、脂肪肝疾患、肥満および糖尿病のような一般的な疾患を明らかにする可能性もある、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181206114812.htm

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Elevated hormone flags liver problems in mice with methylmalonic acidemia

Study findings can immediately be applied to human patients with the disease

Date:

December 6, 2018

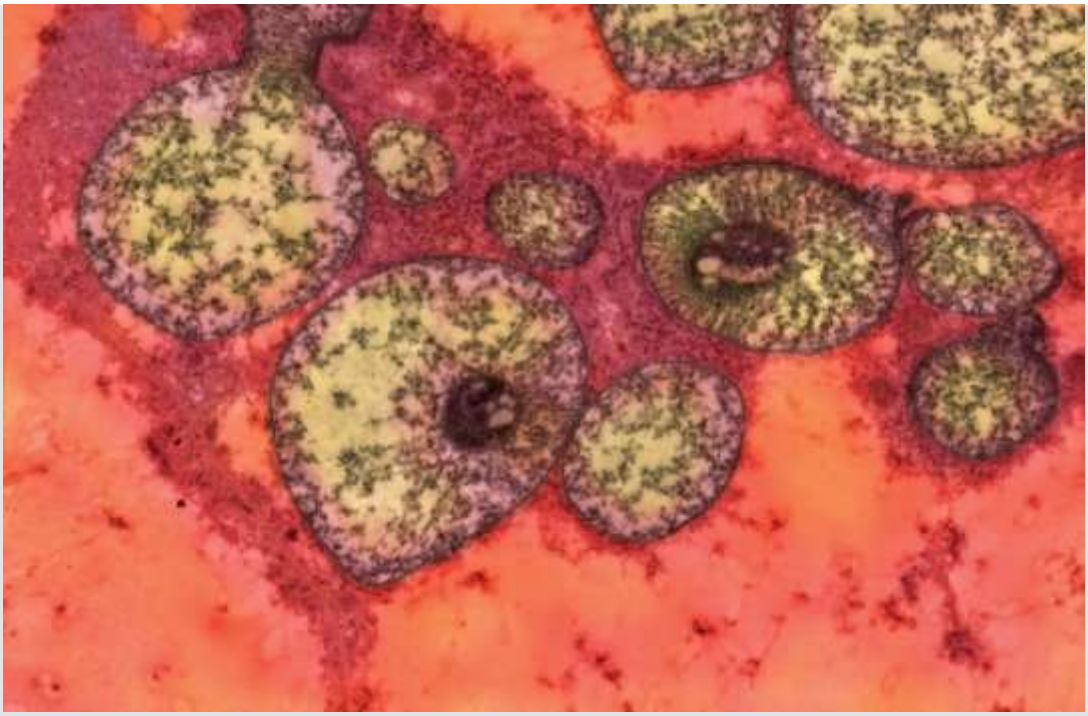
Source:

NIH/National Human Genome Research Institute

Summary:

Researchers have discovered a hormone in a mouse study that can be used immediately to can help doctors predict how severely patients with the rare disease methylmalonic acidemia are affected and when to refer them for liver transplants. The findings also might shed light on more common disorders such as fatty liver disease, obesity and diabetes.

FULL STORY



The figure is an electron micrograph showing abnormally shaped and structured mitochondria in the liver of a mutant mouse that models methylmalonic acidemia.

Credit: Patricia M. Zerfas, NIH Office of Research Services

Researchers have discovered that a hormone, fibroblast growth factor 21 (FGF21), is extremely elevated in mice with liver disease that mimics the same condition in patients with methylmalonic acidemia (MMA), a serious genomic disorder. Based on this finding, medical teams treating patients with MMA will be able to measure FGF21 levels to predict how severely patients' livers are affected and when to refer patients for liver transplants. The findings also might shed light on more common disorders such as fatty liver disease, obesity and diabetes by uncovering similarities in how MMA and these disorders affect energy metabolism and, more specifically, the function of mitochondria, the cells' energy powerhouses.

The study, conducted by researchers at the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health, was published December 6 in *JCI Insight*.

"Findings from mouse studies usually take years to translate into health care treatment, but not in this case," said Charles P. Venditti, M.D., Ph.D., senior author and senior investigator in the NHGRI Medical Genomics and Metabolic Genetics Branch. "We can use this information today to ensure that patients with MMA are treated before they develop severe complications."

MMA is a genomic disease that impairs a person's ability to break down food proteins and certain fatty acids. The condition affects roughly 1 in 50,000 children born in the United States and can be detected through newborn screening. Children with MMA suffer from frequent life-threatening metabolic crises when they encounter a minor viral illness or other stressors like trauma, dietary imbalance or surgery. They must adhere to a special low-protein diet and take various supplements their entire lives.

The NHGRI team created a new mouse model and used it to discover key pathways that were affected during a fasting challenge to model a metabolic crisis in a patient with MMA. It enabled them to identify markers that they could then measure in MMA patients to assess the severity of the dysfunction in their mitochondria, specifically in the liver.

The MMA mice also allowed them to study the response to liver-directed gene therapy and to compare the findings in patients after liver transplant surgery. Liver transplants give patients with MMA a missing enzyme and ease some of the symptoms, but do not cure the disease. Kidney transplantation, on the other hand, is necessary when these patients reach terminal stages of renal failure, an expected chronic complication of MMA. Selecting which patients would benefit from a liver or combined liver/kidney transplant as opposed to just a kidney transplant is an important clinical decision for families and their clinicians.

"We found that having MMA, whether in a mouse or person, causes stress pathways to be chronically activated and can impair their ability to respond to acute stress," said Irini Manoli, M.D., Ph.D., lead author and associate investigator in NHGRI's Medical Genomics and Metabolic Genetics Branch. "Our new markers can accurately predict how effective a therapy, whether cellular or genomic, might be for the patients."

The NHGRI team will use FGF21 measurements along with other tests presented in the study in the design of upcoming gene-based clinical trials that the lab has worked on for many years. The NHGRI team will next assess the role of FGF21 pathways in other symptoms seen in MMA. Since 2003, Dr. Venditti and his team have conducted research on patients with MMA and are following 200 patients with MMA, the world's largest cohort. Their goals are to understand what defines the vulnerability to stress in MMA to better diagnose life-threatening metabolic crises that occur in patients, test new genomic therapies and find treatments that work for every patient.

NHGRI is the driving force for advancing genomics research at the National Institutes of Health. By conducting and funding world-class genomics research, training the next generation of genomics experts, and collaborating with diverse communities, NHGRI accelerates scientific and medical breakthroughs that improve human health. Learn more at genome.gov.

Story Source:

Materials provided by **NIH/National Human Genome Research Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Irini Manoli, Justin R. Sysol, Madeline W. Epping, Lina Li, Cindy Wang, Jennifer L. Sloan, Alexandra Pass, Jack Gagné, Yiouli P. Ktena, Lingli Li, Niraj S. Trivedi, Bazoumana Ouattara, Patricia M. Zerfas, Victoria Hoffmann, Mones Abu-Asab, Maria G. Tsokos, David E. Kleiner, Caterina Garone, Kristina Cusmano-Ozog, Gregory M. Enns, Hilary J. Vernon, Hans C. Andersson, Stephanie Grunewald, Abdel G. Elkahloun, Christiane L. Girard, Jurgen Schnermann, Salvatore DiMauro, Eva Andres-Mateos, Luk H. Vandenberghe, Randy J. Chandler, Charles P. Venditti. **FGF21 underlies a hormetic response to metabolic stress in methylmalonic acidemia**. *JCI Insight*, 2018; 3 (23) DOI: 10.1172/jci.insight.124351

目次に戻る

5. 幼児虐待と親のような保護的行動を制御する感覚スイッチ -マウス実験

2018 年 12 月 13 日

多くの哺乳類は、ヒトと同様に、幼児に対して育成的な保護行動を示し、時に代理親としても機能する。しかし、若年の雄は、自己遺伝子を繁殖させる戦略として幼児虐待・殺害に従事する傾向がある。このように相反する社会的行動はどのように制御されているのか？
12 月 13 日に *Cell* 誌に掲載されたハーバード大学とセインズベリーウエルカムセンター （UCL: University College London）の研究では、マウスにおけるこのような極端な行動の切り替えは、新生児から発せられるフェロモンとマルチ感覚の合図が両方合わさって決定されることが示されている。
研究者らは、雌と雄のマウスが幼児をどのように認識して社会的行動を起こすのか決定するために、シリコンのダミー赤ちゃんマウスを用いてフェロモンのシグナル伝達を遺伝子操作（鋤鼻器官（VNO）の受容体の特定のサブタイプを遺伝子的に欠失させた）した。
VNO 機能をノックアウトすると攻撃的な行動は消滅、ただ親的な行動はノックアウトされなかった。他の感覚的合図が幼児として認識することに寄与するか、異なるダミーの形で調べた結果、雄は最も現実的な形にしか反応しなかった。
研究者らの次の課題は、同じ雄が父親になった時脳内でどのような変化が起きるのか調べることである、としている。

英文と記事：
https://phys.org/news/2018-12-neuroscientists-uncover-sensory-infanticide-parental.html

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Neuroscientists uncover sensory switches controlling infanticide and parental behavior

December 13, 2018, Sainsbury Wellcome Centre

Hybrid on the left and pup-shaped on the right. Credit: © Sainsbury Wellcome Centre

Many species of mammals have evolved what appear to be paradoxical behaviours towards their young. Like humans, most exhibit nurturing, protective behaviours, and in some circumstances even act as surrogate parents. However, virgin males often engage in infanticide as a strategy to propagate their own genes. How are these conflicting social behaviours controlled?

Research published today in *Cell* demonstrates that the switch between such extreme behaviours in mice is determined by a mixture of pheromones and multisensory cues emanating from newborn pups.

Researchers at Harvard University and the Sainsbury Wellcome Centre, UCL have used novel silicone pup dummies and genetically manipulated pheromonal signalling to determine how male and female mice recognise pups and generate social behaviours. The study explored whether the same signals or different phenomena elicit parental behaviour in parents and infanticide in virgin males.

By genetically deleting specific subtypes of receptors in the vomeronasal organ (VNO), a specialised olfactory system in mice that senses pheromones involved in social behaviours, Isogai et al. convert virgin males that normally attack pups into nurturing adults.

"Interestingly, knocking out the VNO function only abolishes aggressive behaviour and does not knock out parental behaviour. This means the mice still have access to cues that elicit parental behaviours and so even though the cues for infanticide and parental behaviour may be overlapping, there are differences" commented Yoh Isogai, Group Leader at the Sainsbury Wellcome Centre.

Initially, the researchers proposed that pheromones specific to pups would be triggers for specific adult behaviours; however, a systematic search failed to uncover any such compounds. This is consistent with the fact that virgin males do not exhibit aggression when presented with pup pheromones alone. Their behavioural assay combined with mass spectrometry allowed them to identify specific molecules in female saliva and in blood as critical stimuli for the male aggression.

The team then explored whether other sensory cues might contribute to the recognition of pups. To do this they developed silicone molded dummies of differing shapes including an unnatural brick shape, a blob, a hybrid shape and a realistic pup-shaped dummy. The males reacted to only the most realistic shapes, indicating that pup features as well as pheromones confer important social cues. Simplified shapes such as the blob did not yield much of a natural response and interestingly nothing was more effective than the natural shape of a pup. The lack of movement of the silicone dummies also did not appear to be limiting, which is supported by observations that virgin males attack dead pups.

The study advances our understanding of how animals recognise social cues and process this information into socially relevant behaviours. Parental behaviours and infanticide are innate in mice and it is thought that the circuit underlying the recognition of social cues could be conserved and therefore one day might help us to understand how humans are able to recognise such a diverse range of social information in other individuals.

The next pieces of the puzzle for the Isogai Lab are to determine how the specific features emitted by an animal, such as pheromones and shape, are combined into social information by the brain. Also, the scientists hope to determine what changes in the brains of male mice when they become fathers.

Explore further: Uncovering maternal to paternal communications in mice

More information: Yoh Isogai et al, Multisensory Logic of Infant-Directed Aggression by Males, *Cell* (2018). **DOI: 10.1016/j.cell.2018.11.032**

Journal reference: Cell

Provided by: Sainsbury Wellcome Centre

目次に戻る

6. 肥満問題に CRISPR も参戦、ゲノム編集なしで肥満を解消

2018 年 12 月 13 日

体重に関する UC サンフランシスコ校の新しい研究は、CRISPR 療法が DNA を切断することなく脂肪を減らすことができることを示している。この研究は 12 月 13 日号の *Science* 誌に掲載されている。
彼らは、CRISPR の改変版 -CRISPR の目的地に赴く機能を利用して DNA を切らずに遺伝子発現を底上げする新たな仕組み CRISPRa(CRISPR-mediated activation)- を使用して、特定の遺伝子の活性度を上昇させ、極端な体重増加をしやすくする遺伝子変異を有するパプロ不全のマウスの重度の肥満を予防する方法を説明している。重要なことは、研究者らがゲノムを全く編集することなく長期間にわたる体重管理を達成したことだ、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181213142117.htm

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CRISPR joins battle of the bulge, fights obesity without edits to genome

Date:

December 13, 2018

Source:

University of California - San Francisco

Summary:

A weighty new study shows that CRISPR therapies can cut fat without cutting DNA. Researchers describe how a modified version of CRISPR was used to ramp up the activity of certain genes and prevent severe obesity in mice with genetic mutations that predispose them to extreme weight gain. Importantly, the researchers achieved long-lasting weight control without making a single edit to the genome.

FULL STORY

A weighty new study shows that CRISPR therapies can cut fat without cutting DNA. In a paper published Dec. 13, 2018, in the journal *Science*, UC San Francisco researchers describe how a modified version of CRISPR was used to ramp up the activity of certain genes and prevent severe obesity in mice with genetic mutations that predispose them to extreme weight gain. Importantly, the researchers achieved long-lasting weight control without making a single edit to the genome.

Single-Copy Mutations Drive Many Human Diseases

Though the human genome contains two copies of every gene in an individual, one from each parent, scientists know of at least 660 genes where a mutation in just one copy can lead to diseases, some of which are devastating. One such condition is severe obesity, which the authors of the new study used as a model to develop a new therapeutic approach for treating these disorders.

Mutations in a single copy of SIM1 or MC4R -- two genes critical for regulating hunger and satiety -- are the most frequently observed mutations in severely obese individuals. When both copies of these genes are functioning, people are generally able to manage their food intake. But mutations can render one copy non-functional, forcing the body to rely exclusively on a single working copy, which on its own, doesn't sufficiently signal satiation, leaving afflicted individuals with an unrelenting appetite. As a result, they can't control their food intake and end up severely obese. But recent advances in CRISPR technology may offer a solution.

"We thought that if we could increase the dosage of the existing functional copy of the gene, we could prevent many human diseases in individuals harboring these mutations," said Nadav Ahituv,

PhD, professor of bioengineering and therapeutic sciences and senior author of the new study. "We were able to accomplish this by using a novel CRISPR-based technology developed right here at UCSF."

CRISPRa Activates Appetite-Suppressing Genes

The technology in question is CRISPRa (a for activation). Developed at UCSF in the lab of Jonathan Weissman, PhD, professor of cellular and molecular pharmacology, CRISPRa differs from conventional CRISPR in that it doesn't make cuts to the genome. It retains CRISPR's guidance system, which can be programmed to home in on a particular DNA sequence, but replaces the molecular scissors with a volume control knob. When CRISPRa finds its target, it amplifies the activity of that gene. No edits are made.

Recognizing its potential, the researchers created CRISPRa systems that targeted sequences that regulate the activity of SIM1 or MC4R. They used a viral-delivery system to introduce these CRISPRa constructs into the hunger-control regions of the brain in mice that were genetically engineered to have only one functional copy of either gene.

Mice that received the CRISPRa constructs produced more SIM1 or MC4R than those that didn't. Furthermore, the amounts were comparable to what mice with two working copies of these genes normally produce. Most importantly, the increased dose was enough to prevent the mice from becoming obese.

"The results were dramatic. Mice that were missing one copy of the SIM1 gene received the CRISPRa injections at four weeks of age and maintained a healthy body weight like normal mice. Mice that didn't receive CRISPRa injections couldn't stop eating. They started gaining weight at six weeks of age, and by the time they were 10-weeks old, they were severely obese on a regular diet" said Navneet Matharu, PhD, a researcher in the Ahituv lab and lead author of the new study.

CRISPRa-treated mice were 30 to 40 percent lighter than their untreated counterparts. The effects were also long-lasting. The researchers monitored the mice for ten months -- a significant fraction of a mouse's normal lifespan -- and found that those that received a single CRISPRa treatment maintained a healthy weight for the duration of their monitoring.

"These results demonstrate that CRISPRa can be used to up the dosage of genes in diseases that result from a missing copy, providing a potential cure for certain forms of obesity as well as hundreds of other diseases," said Matharu.

CRISPRa Can Overcome the Limits of Gene Editing

The researchers believe they could have achieved similar results by using CRISPR to edit the genomes of these mice, but they argue that CRISPRa has a number of advantages over the standard version of the gene-editing technology.

"For therapeutic purposes, CRISPRa may be preferable to conventional CRISPR. It solves many of the problems associated with making permanent modifications to the genome, and it has the potential to treat a variety of genetic diseases for which gene editing isn't an option," said Christian Vaisse, MD, PhD, the Vera M. Long Endowed Chair in Diabetes Research at UCSF and co-author of the study.

Though CRISPR targets specific DNA sequences, off-target effects have been observed. With conventional CRISPR, this can lead to inadvertent but permanent changes to the genome with potentially harmful outcomes. However, off-target effects associated with CRISPRa are less likely to be damaging because no permanent changes are made. In fact, the new study shows that using CRISPRa to target promoters and enhancers -- noncoding DNA sequences that control when and where a gene is turned on -- seems to prevent off-target effects while confining the desired effects to specific tissues of interest.

The researchers also note that CRISPRa could be used to treat other kinds of genetic disease. Diseases that arise from so-called "microdeletions" -- a term that counterintuitively refers to the loss of large chromosome segments that span millions of nucleotides and multiple genes -- are currently too large for conventional CRISPR to repair. In such cases, CRISPRa could be used to compensate for the deletion by increasing the activity of several genes on the unaffected copy of the chromosome. And in cases where a gene is completely lost, CRISPRa could activate another gene with a similar function to compensate for the missing gene, the researchers said.

"Though this particular study focused on obesity, we believe our system could be applied to any situation in which having only one functional copy of a gene leads to disease," Ahituv said. "Our method demonstrates tremendous therapeutic potential for numerous diseases, and we show that we can achieve these benefits without making any edits to the genome."

Story Source:

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

Journal Reference:

1. Navneet Matharu et al. **CRISPR-mediated activation of a promoter or enhancer rescues obesity caused by haploinsufficiency**. *Science*, 2018 DOI: 10.1126/science.aau0629

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University of California - San Francisco. "CRISPR joins battle of the bulge, fights obesity without edits to genome." ScienceDaily. ScienceDaily, 13 December 2018. <www.sciencedaily.com/releases/2018/12/181213142117.htm>.

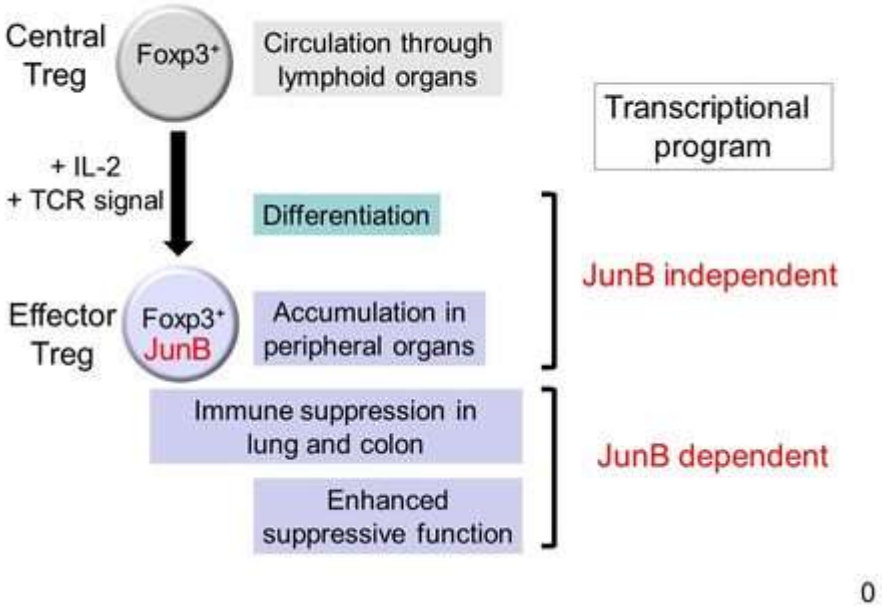
目次に戻る

7. 過剰な免疫反応を抑えるための新たなブレーキ制御メカニズムの発見 -マウス実験

2018 年 12 月 17 日

https://www.oist.jp/ja/news-center/press-releases/33433

沖縄科学技術大学院大学（OIST、沖縄県恩納村　学長ピーター・グルース）免疫シグナルユニットの小泉真一研究員らは、免疫システムの恒常性を保つために必要な新たな分子メカニズムを明らかにしました。研究チームは、転写因子※1「JunB」が免疫反応のブレーキとして働く制御性 T 細胞※2の免疫抑制機能を促進することを発見しました。また、この JunB によって促進される制御性 T 細胞の機能は、肺および大腸の過剰な炎症を抑制するために必要であることがわかりました。したがって、制御性 T 細胞の JunB をターゲットに特定の臓器における炎症を調節することは、自己免疫疾患※3・アレルギー疾患の治療だけでなく効果的ながん免疫療法※4の開発へとつながる可能性があります。制御性 T 細胞の JunB の役割を初めて明らかにした本研究成果は、2018 年 12 月 17 日発行の英科学誌 *Nature Communications* に掲載されました。



- English

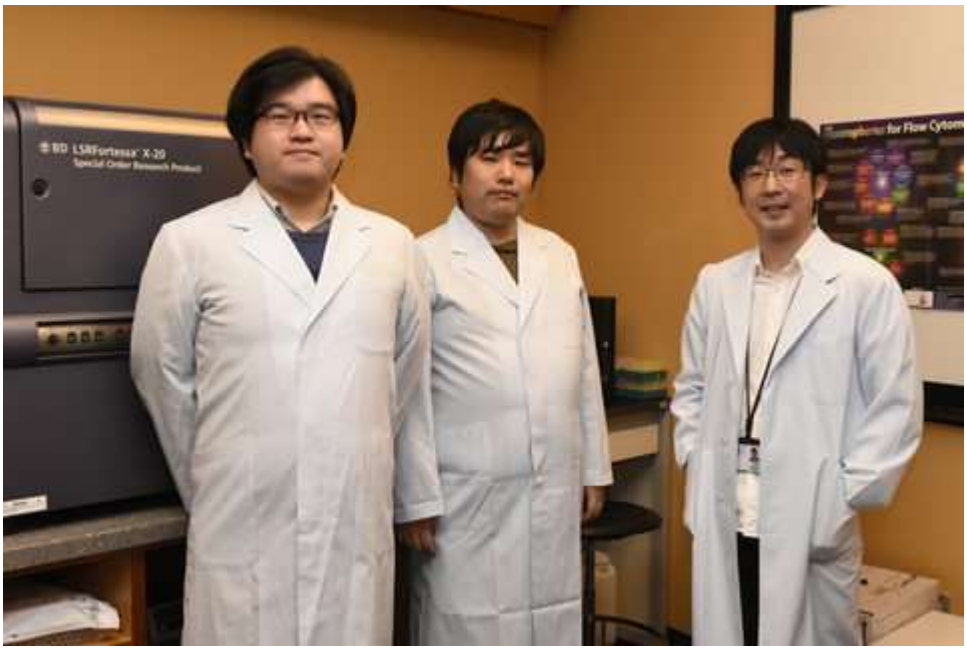
本研究で明らかになった制御性 T 細胞における JunB の役割。JunB はエフェクター型の制御性 T 細胞の大腸・肺における免疫抑制機能を促進する。FOXp3 はヒトの遺伝性免疫疾患の原因遺伝子として、2001 年に米国の研究グループにより報告された転写因子。

研究の背景と経緯

免疫システムは細菌やウイルスなどの病原体やがん細胞の排除に重要な役割を果たします。しかしながら、免疫システムが正常に働かなくなると過剰な免疫反応が自己の細胞や組織に向けられ、その結果、関節リウマチ、潰瘍性大腸炎および多発性硬化症といった自己免疫疾患を引き起こします。また、花粉などの特に害のない物質に対する免疫応答はアレルギー疾患の原因となります。

過剰な免疫反応を回避するために、免疫システムはブレーキの役割をはたすメカニズムをいくつか備えています。例えば、本年ノーベル生理学・医学賞を受賞した京都大学の本庶佑教授と米テキサス大学のジェームズ・P・アリソン教授が発見した免疫チェックポイント分子

※5PD1 と CTLA4 は、過剰な免疫反応を抑える重要なメカニズムです。これらに加えて、免役抑制機能をもつ制御性 T 細胞も自己免疫疾患やアレルギー疾患を防ぐために必須な役割を担います。一方、制御性 T 細胞が過度に働くと、がん細胞に対する免疫を抑制してしまいます。したがって、状況に応じて制御性 T 細胞の機能を適切に制御することで、自己免疫疾患やアレルギー疾患の治療だけでなく、効果的かつ副作用の少ないがん免疫療法が可能になると考えられます。しかしながら、制御性 T 細胞の免疫抑制機能を制御するメカニズムはまだ十分に解明されていません。



- English

（左から）佐々木大樹研究員、小泉真一研究員、石川裕規准教授

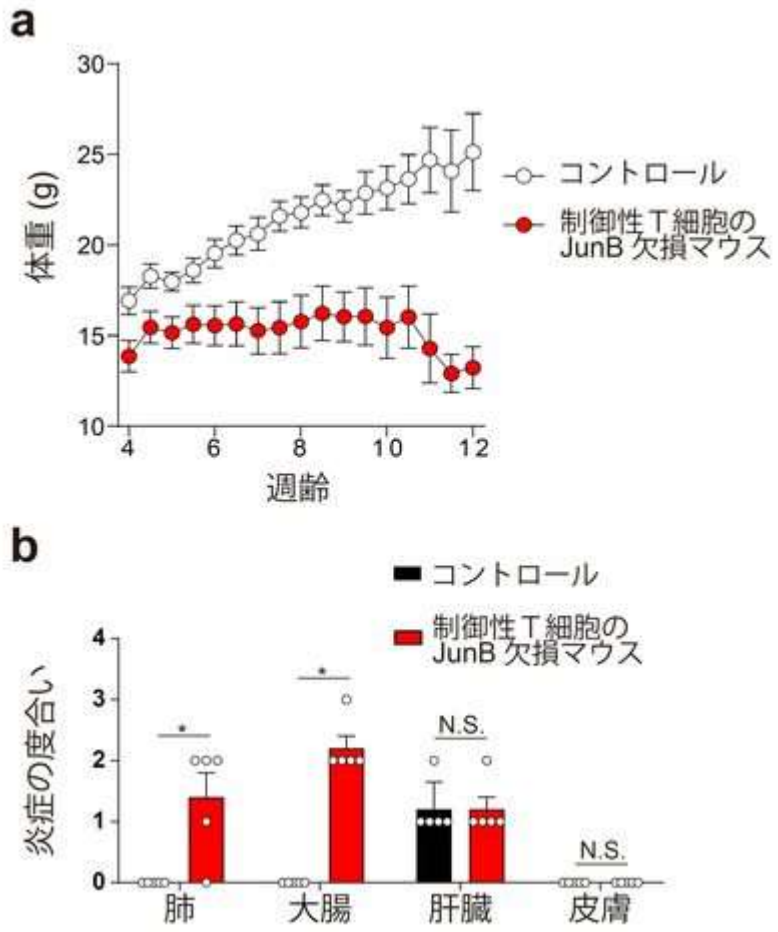
研究内容

制御性 T 細胞が正常に機能するためには、リンパ節などリンパ系組織に存在するナイーブ型の制御性 T 細胞※6が、様々な非リンパ系の臓器に移動し、強力な免疫抑制機能を示すエフェクター型の制御性 T 細胞※7へと分化する必要があります。研究チームは、エフェクター型の制御性 T 細胞の分化および機能を制御するメカニズムを理解するために、JunB という

転写因子に注目しました。同チームは昨年 JunB が自己免疫疾患を引き起こすヘルパーT 細胞[※8]の機能を調節することを報告しましたが、制御性 T 細胞における JunB の機能は分かっていませんでした。

まず、研究チームは JunB が制御性 T 細胞集団のなかでナイーブ型ではなくエフェクター型の細胞においてのみ発現することを見出しました。次に、制御性 T 細胞の JunB の機能を明らかにするために、この細胞集団において JunB を欠損するマウスを作製しました。作製したマウスは正常に生まれましたが、生後4週間には顕著な体重減少を示し、生後24週までに半数以上のマウスが死亡しました（図1a）。これらのマウスの肺と大腸においては激しい炎症が見られましたが、皮膚と肝臓ではそのような炎症は認められませんでした（図 1b）。

JunB の欠損が制御性 T 細胞へ与える影響を調べたところ、JunB はエフェクター型の制御性 T 細胞の分化には必要ありませんでしたが、その細胞数の維持、大腸への蓄積、および免疫抑制機能の亢進のために重要であることが明らかになりました。さらに、JunB の欠損により発現が変動する遺伝子を網羅的に解析したところ、免疫チェックポイント分子 CTLA4 を含むいくつかの免疫抑制機能をもつ分子の発現が JunB によって制御されることが明らかになりました（図2）。しかしながら、エフェクター型の制御性 T 細胞で高く発現する多くの遺伝子は JunB に依存せずに発現することも確認されました（図2）。これらの結果は、JunB はエフェクター型の制御性 T 細胞の特定の機能を促進することで、肺および大腸の炎症を抑制することを示唆しています。

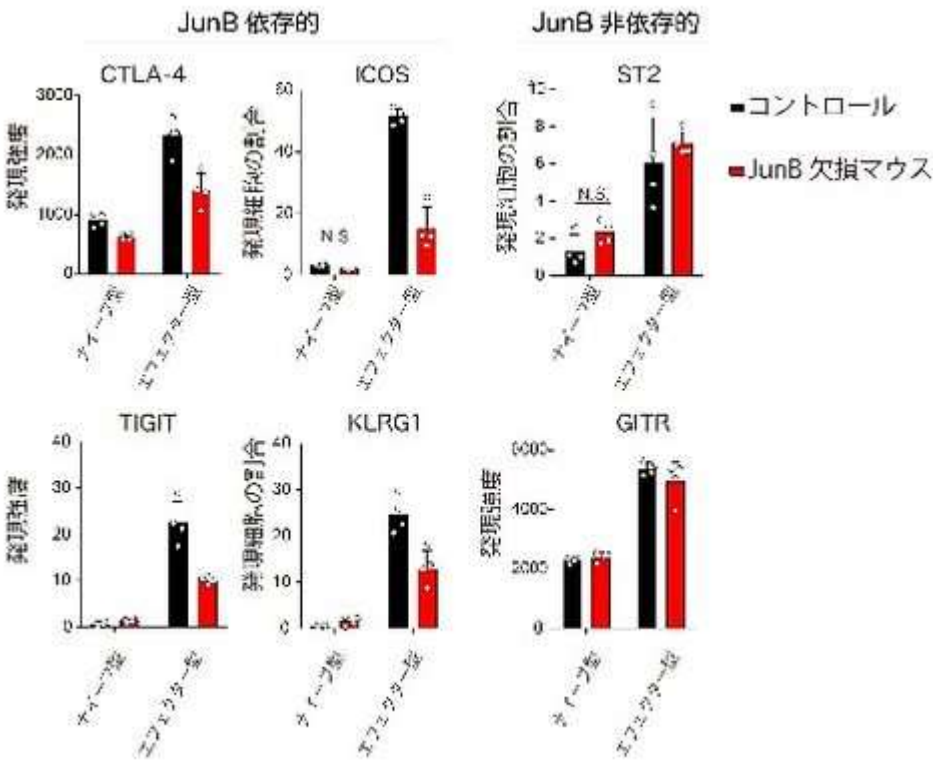


制御性 T 細胞の JunB を欠損したマウスは体重減少（a）および肺、大腸における過度の炎症（b）を伴う自己免疫疾患を発症する。

今回の研究成果のインパクト・今後の展開

今回の研究成果は、転写因子 JunB がエフェクター型の制御性 T 細胞の機能を調節し、肺と大腸の炎症の抑制に重要な役割を果たすことを明らかにしました（図3）。このような役割はこれまでに報告されている制御性 T 細胞の分化および機能制御に関わる転写因子では見られていないユニークなものです。小泉博士は「制御性 T 細胞の JunB の活性を高めることは、自己免疫疾患やアレルギー疾患の新たな治療法となると期待されます。逆に、制御性 T 細胞の JunB の活性を抑えることで肺がんや大腸がんに対する免疫を特異的に促進

し、他の組織への副作用の少ない新たながん免疫療法の開発につながる可能性もあります」と、述べています。



JunB は制御性 T 細胞において特定の免疫抑制機能分子の発現を制御する。

用語説明

※1 転写因子
特定の遺伝子群の発現を制御する因子。様々な細胞機能に関わる。

※2 制御性 T 細胞
成熟した T 細胞（リンパ球）の一種で、ヒトの遺伝性免疫疾患の原因とされる転写因子 Foxp3 の発現を特徴とする。免疫抑制機能を持ち、免疫の恒常性の維持に必須な役割を果たす。

※3 自己免疫疾患
自己の身体を構成する物質に対しておこる免疫反応により発生する疾患。関節リウマチ、多発性硬化症、炎症性腸疾患、全身性エリテマトーデスなどがある。それらの多くは特定疾患に指定される難病で、国内では年々増えている（難病情報センター特定疾患医療受給者証所持者数 http://www.nanbyou.or.jp/entry/1356）。

※4 がん免疫療法
免疫システムを利用してがんを治す治療法。

※5 免疫チェックポイント分子
過剰な免疫応答を抑制する機能を持つ分子。免疫チェックポイントを阻害することで効果的ながん免疫を誘導することができる。

※6 ナイーブ型の制御性 T 細胞
リンパ系の組織に存在する、抗原と反応したことがない制御性 T 細胞。

※7 エフェクター型の制御性 T 細胞
ナイーブ型制御性 T 細胞が抗原と反応することで活性化した制御性 T 細胞。様々な臓器に蓄積し、強い免疫抑制機能を持つ。

※8 ヘルパーT 細胞
成熟した T 細胞（リンパ球）の一種。免疫反応を指揮する役割を果たす。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181217081807.htm

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Protein police keep the immune system in check

Date:

December 17, 2018

Source:

Okinawa Institute of Science and Technology (OIST) Graduate University

Summary:

Researchers learn how a key transcription factor helps regulate the immune system and could be critical to understanding autoimmune disease and cancer immunosuppression.

FULL STORY

Our immune systems defend our bodies against dangerous invaders and help clean up when damage is done. But if our bold protectors are left unsupervised, they sometimes do their jobs too well and end up harming healthy tissues. Researchers at the Okinawa Institute of Science and Technology Graduate University (OIST) have now described how a specific transcription factor, which modulates gene expression, plays a critical role in keeping the immune system in line in mice.

The key transcription factor, known as JunB, helps control the activity of cells whose job it is to suppress immune activity. These cells are called effector regulatory T cells, or eTreg cells for short. The researchers found that JunB helps switch eTreg cells into their "active state" and promotes their immunosuppressive functions. Their results, published on December 17, 2018, in *Nature Communications*, could give important insight into the development of autoimmune disease and cancer immunosuppression.

"We found that JunB regulates select functions of eTreg cells, specifically in the lung and colon," said Dr. Shin-ichi Koizumi, co-first author of the study and a postdoctoral scholar in the Immune Signal Unit, led by Prof. Hiroki Ishikawa. "If we can manipulate JunB expression, we may be able to regulate tissue-specific immune responses. This could lead to the development of new therapies for cancer and autoimmune disease."

Koizumi led the study with his co-author Dr. Daiki Sasaki, another postdoctoral scholar in the unit. The researchers studied mutant mice to learn what would happen if eTreg cells lacked JunB. Without this key layer of regulation, mice appear to develop severe inflammation in their lungs and colons. This suggests that JunB helps prevent autoimmunity in a specific subset of organs, and without its watchful surveillance, the immune system will attack those tissues.

"Interestingly, in contrast to other Treg mutants, inflammation is restricted to these particular organs," said Prof. Ishikawa. "In the future, JunB expressed by eTregs may itself may be a therapeutic target for colon and lung cancers."

Tissue Specificity Key for Future Clinical Applications

In a previous study, the researchers reported that JunB helps control the differentiation of T helper cells, another subset of cells that regulate the immune system. They depleted JunB expression in mice for that experiment, as well, and noticed that eTreg cells levels dropped significantly in the colon. They hypothesized that JunB is not only important to T helper cells, but to eTreg cells, too.

Effector Treg cells begin as central Treg cells, or cTreg cells, until they are exposed to antigens -- proteins that label foreign substances in the body so the immune system can find them. cTreg cells then differentiate into eTreg cells, and in turn, significantly boost their JunB expression. The researchers found that, without JunB, eTreg cells are unable to accumulate in the colon and thus their numbers fall drastically.

In the lung and spleen, eTreg levels remained normal but the cells' function was compromised. Those tissues exhibited severe inflammation and autoimmunity because JunB wasn't present to rein in the host immune response.

Looking forward, the researchers want to learn exactly how JunB interacts with other transcription factors to keep the immune system at bay. With better understanding of the mechanism as a whole, scientists may someday be able to modulate immune responses in specific tissues. At present, treatments often affect immune responses across the entire body and lead to unfortunate side effects. Doctors need a more targeted approach.

"We want to completely elucidate the transcription program in eTreg cells," said Koizumi. "If we can induce a new transcription program in eTreg cells, we could potentially manipulate immune responses in various tissues and treat a range of cancers and autoimmune-related diseases."

Story Source:

Materials provided by **Okinawa Institute of Science and Technology (OIST) Graduate University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Shin-ichi Koizumi, Daiki Sasaki, Tsung-Han Hsieh, Naoyuki Taira, Nana Arakaki, Shinichi Yamasaki, Ke Wang, Shukla Sarkar, Hiroki Shirahata, Mio Miyagi, Hiroki Ishikawa. **JunB regulates homeostasis and suppressive functions of effector regulatory T cells**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-07735-4

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- APA
- Chicago

Okinawa Institute of Science and Technology (OIST) Graduate University. "Protein police keep the immune system in check." ScienceDaily. ScienceDaily, 17 December 2018. <www.sciencedaily.com/releases/2018/12/181217081807.htm>.

目次に戻る

8. マリファナが十代の脳を傷つける可能性 -遺伝的に気弱なマウスを使った研究

2018 年 12 月 17 日

ジョンズホプキンズ大学医学部の研究者らは、深刻なヒト様の精神疾患に関連する遺伝子を持つ青年マウスの研究において、マリファナがどのようにして脳に障害を与えるか、可能な説明を明らかにした、としている。
研究者らは、2019 年の *Biological Psychiatry* 誌の印刷版で発表される報告の中で、精神分裂症、双極性障害に関連する稀な遺伝子変異を有する思春期のマウスの特定の脳細胞において、マリファナへの曝露はその炎症度を高める、としている。又、非ステロイド性抗炎症薬 NS398 を使用して、マリファナによる脳損傷を防ぐことができた、としている。
マウスで見られた炎症は、おそらくマリファナを喫煙する多くのヒトの中でも活性化されているが、どうしてそしてどうやって一部のマウスと一部のヒトのみ遺伝的に炎症反応や脳の損傷を増やす傾向があるのか、その理由を説明するのにこの結果が役立つだろう。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181217101747.htm

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How marijuana may damage teenage brains in study using genetically vulnerable mice

Date:

December 17, 2018

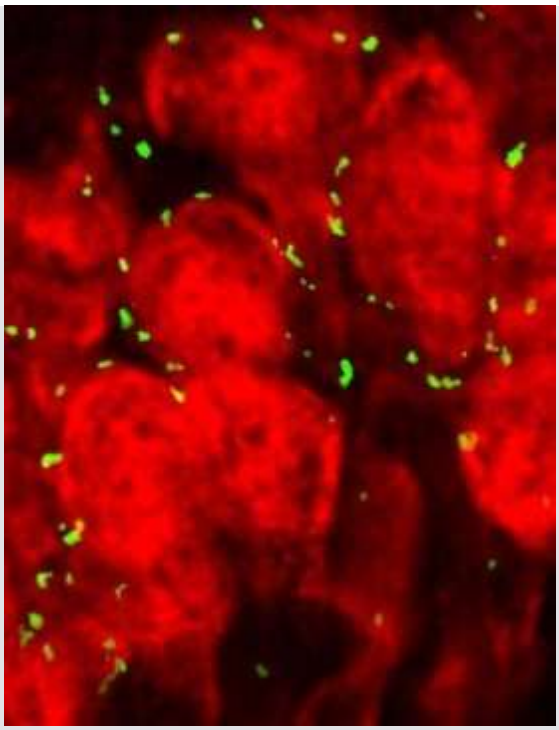
Source:

Johns Hopkins Medicine

Summary:

In a study of adolescent mice with a version of a gene linked to serious human mental illnesses, researchers say they have uncovered a possible explanation for how marijuana may damage the brains of some human teens.

FULL STORY



Control: Neurons (red) in the brain's hippocampus. Inhibitory signals (green) that suppress the neurons from firing are located in the synapses--the junctions where the neurons connect and communicate with each other.

Credit: Pletnikov lab

In a study of adolescent mice with a version of a gene linked to serious human mental illnesses, Johns Hopkins Medicine researchers say they have

uncovered a possible explanation for how marijuana may damage the brains of some human teens.

In a report that will be published in a 2019 print issue of the journal *Biological Psychiatry*, the researchers say they showed that pot exposure increases inflammation in a specific type of brain cell in adolescent mice that carries a rare genetic mutation linked to schizophrenia, bipolar disorder and other major psychiatric disorders. In a proof-of-concept experiment, the investigators then used a nonsteroidal anti-inflammatory drug, NS398, to suppress the pot-induced inflammation in the brain. The researchers report they were able to prevent marijuana's brain damage in mice that appear genetically susceptible to the harmful effects.

"The inflammation we saw in our mice is probably activated in many people who smoke marijuana, but our results may help explain why and how some mice¾and some people¾are genetically predisposed to experience an enhanced inflammatory response and brain damage," says Mikhail "Misha" Pletnikov, M.D., Ph.D, professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine.

"Now that marijuana is moving toward widespread legalization and recreational use, it's important to learn more about why it's not harmless to everyone," says Atsushi Kamiya, M.D., Ph.D., a co-senior author on this study and associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "There's still a lot that we don't know about how pot specifically affects the brain."

Although far more research must be done to determine if their findings apply to humans, Pletnikov says, it's already clear that heavy cannabis use is linked to long-lasting cognitive problems, but only in a percentage of those who used pot during adolescence. The challenge for scientists has been to identify the risk factors that may increase adverse effects of cannabis. Having that information, Pletnikov says, could lead to efficient preventive strategies. Building on the knowledge that only a select population of teen pot smokers have later cognitive problems, the researchers chose to experiment with a mouse model for psychiatric illnesses that carries a mutation in the DISC1 gene originally found in a Scottish family with many members diagnosed with schizophrenia, bipolar disorder and major depression.

The researchers used mice that make the faulty DISC1 protein in their brains. When the mice were about 30 days old, the rodent equivalent of teenagers, the researchers injected them with 8 milligrams per kilogram D9-tetrahydrocannabinol (THC) -- the active chemical in marijuana

responsible for feeling high -- every day for three weeks, somewhat mimicking the exposure from daily smoking during adolescence.

Then the researchers stopped the THC exposure for three weeks before testing the mice for behavioral and cognitive deficits.

"Essentially, we let them have their fun as teenagers and then let enough time elapse to their young adulthood, or in human terms the time when people reach their late 20s, are living an adult life and may begin to notice cognitive problems," says Pletnikov.

Mice like to explore previously unvisited places or new objects, but examine familiar places or objects much less, suggesting mice have recognition memory. For this reason, researchers often use the Y maze test or the novel object recognition test to evaluate recognition memory in mice. In the Y maze test, a maze shaped like a letter "Y," mice were initially exposed to two open arms and one blocked arm. Later, when the previously blocked arm became accessible, control mice spent more time in the previously blocked arm compared with the previously visited arms. In the novel object recognition test, mice were initially presented with two identical objects; later, one of the objects was replaced with a new one. Control mice spent much more time exploring the new object compared with the familiar one. In both tests, control mice showed good recognition memory. In contrast, male DISC1 mice exposed to THC showed deficient recognition memory as they explored the previously blocked arm of the Y maze and the new object as much as they examined the familiar arms and objects.

The researchers say this indicates poorer recognition memory in the DISC1 mice exposed to marijuana. The effects of THC on recognition memory in the female DISC1 mice were less profound than in male DISC1 mice, so the researchers chose to focus on the male mice for remaining experiments.

"In people, women appear to have more persistent cognitive effects from smoking marijuana in their teens than do men, and this is a difference we can't explain at this time," says Pletnikov.

To find out what particular brain cells might be more responsible for mediating damage from THC, the researchers then genetically engineered their mice so that the mutant DISC1 was turned on only in neurons that send electrical responses and encode memory, or only in astrocytes, the "helper" brain cells that provide support and protection to the neurons.

They then exposed both groups of mice to THC in their adolescence as before (three weeks straight, then off for three weeks) and again performed the same tests for recognition memory.

They found that only when the mutant DISC1 was turned on in astrocytes did the mice have cognitive problems.

Then, to see what the faulty DISC1 did in these astrocytes to worsen the pot-induced cognitive problems, the researchers looked at which genes became more or less active in the brain of the mice with mutant DISC1 after exposure to THC compared with the DISC1 mice without THC exposure or control mice exposed to THC. They identified 56 genes related to inflammation that were specifically turned on in the brain of mutant DISC1 mice exposed to THC.

To see if tamping down brain inflammation could prevent the memory problems in the DISC1 mutant mice exposed to THC, the researchers used an anti-inflammatory medication.

Adolescent mutant DISC1 mice were given the anti-inflammatory medication NS398 30 minutes before their daily injections with THC. When the mice were older and tested, they didn't have memory problems in the cognitive tests, Pletnikov says.

"If our results turn out to be applicable to people, they suggest we could develop safer anti-inflammatory treatments to prevent long-term consequences of marijuana use," says Pletnikov. Kamiya adds that being able to identify those who are susceptible and preventing them from partaking in marijuana use is another option for protecting teens' memory.

As for future work, Pletnikov's and Kamiya's laboratories are collaborating to expand these studies with other animal models to determine how various genetic vulnerabilities may play a role in marijuana's effects on the developing brain.

Story Source:

Materials provided by **Johns Hopkins Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yan Jouroukhin, Xiaolei Zhu, Alexey V. Shevelkin, Yuto Hasegawa, Bagrat Abazyan, Atsushi Saito, Jonathan Pevsner, Atsushi Kamiya, Mikhail V. Pletnikov. **Adolescent Δ9-Tetrahydrocannabinol Exposure and Astrocyte-Specific Genetic Vulnerability Converge on Nuclear Factor-κB–**

Cyclooxygenase-2 Signaling to Impair Memory in Adulthood. *Biological Psychiatry*, 2018; DOI: 10.1016/j.biopsych.2018.07.024

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- Chicago

Johns Hopkins Medicine. "How marijuana may damage teenage brains in study using genetically vulnerable mice." ScienceDaily. ScienceDaily, 17 December 2018. <www.sciencedaily.com/releases/2018/12/181217101747.htm>.

目次に戻る

9. 胎児組織研究ガイド：論争、危険性、他の選択肢

2018 年 12 月 17 日

ウィスコンシン大学医学公衆衛生学部の移植の Will Burlingham 教授のところで作製しているマウスは、平凡な普通のげっ歯類ではない。それらのマウスは、新生児が心臓手術を受けた時に残った組織由来のヒト様免疫系を移植された、一部動物、そして一部ヒト、である。そして NHI が、これらのマウスに興味を持っているという。何故ならば、中絶からの胎児組織を埋め込んだマウスは、政治的にも議論の余地がある研究ツールであるから。
しかしこれらのマウスは、胎児組織で作られたマウスほど科学的に有用ではなく、寿命が短く、ヒト様の免疫系も完全ではない。また、Burllingham のマウスは、４月に発表されたばかりで、まだ実験段階にあり、また他の選択肢にも同じことが言える。
しかし NHI の興味が示す様に、政府機関は胎児組織に代わるものを見つける努力を急いでおり、トランプ政権は胎児組織の代替品の研究に 2,000 万ドルの資金を投入する予定だと発表した。

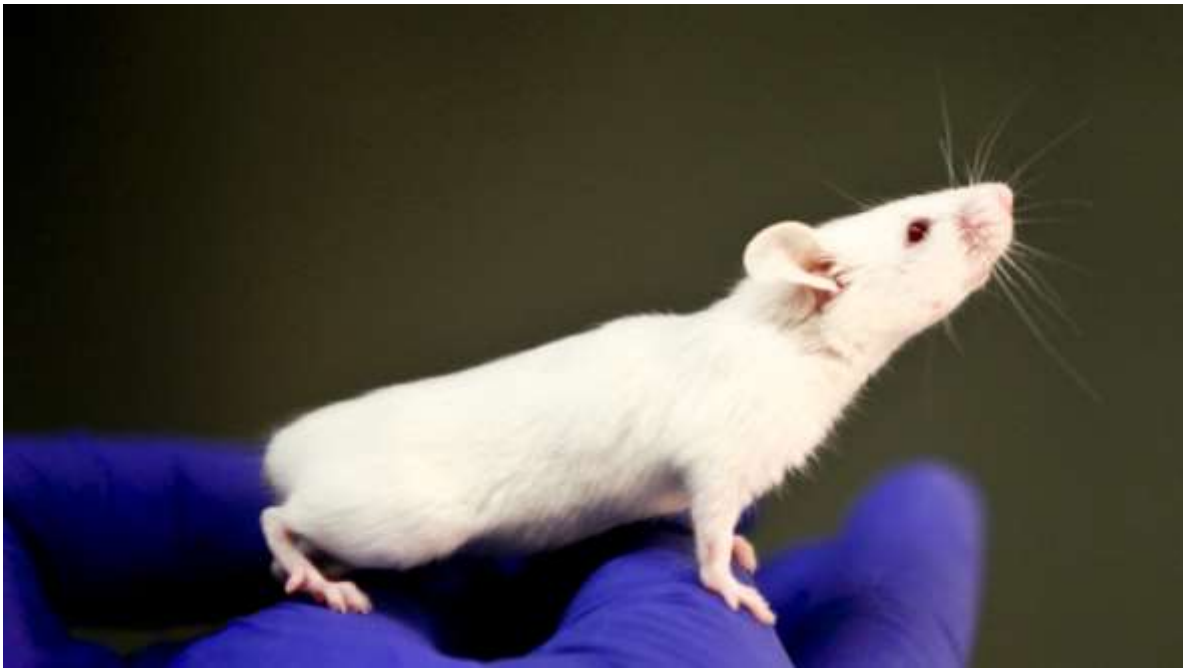
英文記事：
https://www.statnews.com/2018/12/17/there-arent-any-good-alternatives-to-fetal-tissue-research-scientists-warn/?utm_source=STAT+Newsletters&utm_campaign=e787d17def-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-e787d17def-150065641

POLITICS

A guide to fetal tissue research: the controversy, the stakes, and the hunt for alternatives

By IKE SWETLITZ @ikeswetlitz

DECEMBER 17, 2018



A humanized "BLT" mouse is created by introducing human bone marrow, liver, and thymus tissues into animals without an immune system of their own. UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE

WASHINGTON — Two weeks ago, Will Burlingham, a professor of transplantation at the University of Wisconsin School of Medicine and Public Health, got a surprise call from the National Institutes of Health: Would he like a little extra money to create more laboratory mice?

"It's like Santa came early," Burlingham told STAT. "We've been advised that we need to gear up and hire people."

These aren't just run-of-the-mill rodents. Burlingham's mice are part-animal, part-person, implanted with a human-like immune system derived from tissue leftover when newborns undergo heart surgery. And the NIH is taking an interest in these mice because scientists might, in some cases, be able to use them instead of a more politically controversial research tool — mice implanted with fetal tissue that comes from abortions.

But mice made with similar techniques simply aren't as useful, scientifically, as their counterparts created with fetal tissue. They tend to die more quickly, and the human-like immune systems the scientists want to study are less complete.

Burlingham's mice in particular are still highly experimental, too — he and his colleagues haven't yet run tests to compare how the mice compare to their cousins made using fetal tissue. Their research was only just published, in April.

The same is true for other alternatives to fetal tissue: There are no alternatives that can, today, serve all the same purposes as the controversial technology.

Related:
Freeze on fetal tissue procurement may impede work at NIH cancer lab, agency says

"The consensus is that there are certain things about fetal tissue that make [it] unique," said Paul Knoepfler, a professor at the University of California, Davis, School of Medicine. "Certain experiments can really only be done on actual fetal tissue."

But as the NIH's call to Burlingham shows, the agency is upping its efforts to find alternatives to fetal tissue, though a top agency official told STAT that some research projects might always require fetal tissue. The Trump administration

announced last week that it intends to devote as much as $20 million to research into alternatives to fetal tissue, the latest step in an ongoing Trump administration audit of the way federally funded research uses fetal tissue. (It declined to comment on conversations with Burlingham.)

At an NIH meeting Thursday, Director Francis Collins said that research into alternatives is "scientifically, highly justified," but also defended the value of fetal tissue research, saying, "There is strong evidence that scientific benefits can come from fetal tissue research, which can be done with an ethical framework."

As part of the Trump administration audit, NIH in September froze the acquisition of new fetal tissue purchases. That has already upset research at an HIV lab in Montana and may soon hamper work in groups studying cancer and eye disease. Spokespeople for the Department of Health and Human Services, and the NIH, said that the audit was not intended to interrupt current research (but that has been the result) and that the NIH is working to get the labs the tissue they need.

The research is controversial because fetal tissue comes from abortions. For years, Republicans have argued that the organizations that collect this tissue and sell it to researchers are profiting off the enterprise, which is against federal law and which the organizations themselves dispute.

Related:
NIH to spend up to $20 million on search for alternatives to fetal tissue for research

In some ways, alternatives have distinct advantages, scientists said. Some are easier or cheaper to manufacture. They are less politically controversial — in some states, it is illegal to do any research on fetal tissue, and using other kinds of tissue can make it easier for scientists to collaborate. Researchers have been working on developing tools that do not depend on fetal tissue for decades.

Below, STAT looks at several looming questions for the future of fetal tissue research — why it matters, what alternatives are out there, and which research areas will be hit hardest by the Trump administration's changes.

Why do scientists use fetal tissue?

Some scientists use the tissue as an ingredient to build human-like models to test drugs and study diseases. Others do research on the tissue itself to learn more about the fetus. The work applies to a wide variety of diseases, from cancer to HIV to Zika to eye disorders.

"There's a wide variety of human diseases that either are traceable to developmental problems, or we can learn more about them using fetal tissue," Knoepfler said.

It's difficult to quantify the number of scientists who are using fetal tissue in their research. Multiple scientists told STAT that their colleagues who use fetal tissue in their research would be loathe to discuss it because of the political controversy. And the oft-cited number of $103 million — the NIH's estimate of how much research it funds that has anything to do with fetal tissue this year — isn't a great estimate, since it includes money spent parts of the research project that don't use fetal tissue.

Trending Now:
What will 2019 bring for science and medicine? We asked the experts

Can an alternative deliver the same kind of science?

The feasibility of alternatives depends on what exactly the researchers are trying to do. Finding an alternative to mice created with fetal tissue is probably going to be easier than finding an alternative to using fetal tissue to study fetal tissue, said Carrie Wolinetz, associate director for science policy and acting chief of staff at the NIH.

"If you are studying human fetal development, or diseases specific to fetal development — Zika is a very good example of that — there might not be ultimately an alternative that would really substitute," Wolinetz said. If a woman is infected with ZIka virus while she is pregnant, the fetus can develop microcephaly, a disease that shrinks their brains.

She added, "Again, science is amazing and it goes in all sorts of directions, so you never say never, but this is an example where it's sort of harder conceptually to imagine an alternative."

What kinds of alternatives are out there?

In an announcement last week, the NIH put forward three general categories of alternatives — stem cells, organoids, and different kinds of humanized mice — while also keeping the door open for other scientific ideas.

Those are broad categories, and exactly how well each would work as an alternative — or how feasible the technology is — varies. Stem cells are a more fundamental technology than the other two in that list — more like a building block for future alternatives to fetal tissue. They could be used to create tissue samples that would remove the need to use actual tissue from a fetus.

Many scientists are already using other humanized mice and organoids to test drugs and study diseases. Some scientists gave brain organoids cancer; and others manufactured mini-hearts that can beat like the real ones.

Humanized mice

Burlingham isn't the only researcher who's found a way to create mice with a human-like immune system without using fetal tissue.

Scientists start by genetically engineering a mouse that does not have an immune system. Then they grow something that resembles a human immune system inside of that mouse — this time using stem cells or other tissue, rather than fetal tissue. All those mice will allow the scientists to study how certain disease affect the human immune system, like HIV, without experimenting on humans.

Related:
We've created human-pig chimeras — but we haven't weighed the ethics

But mice created with fetal tissue tend to live longer, and their immune systems are more complete, which make them better, in certain cases, for studying the long-term effects of a drug or the progression of a disease.

It's also difficult to actually make those mice, said Jerome Zack, a professor in the David Geffen School of Medicine at the University of California, Los Angeles, who recently founded a company based on technology that comes from humanized mice. Scientists need to do individual surgeries on the mice to insert the human immune system. And they need special facilities to house the animals.

Organoids

Another alternative the NIH put forth are "organoids," which are little blobs of cells that resemble human organs. In order to make them, scientists take stem cells, or similar cells, and grow them in a dish so that they all develop into cells of the same organ. That means that the cellular blob mimics some of the organ's properties.

Organoids, however, are also imperfect for researchers who are using fetal tissue. They aren't miniature versions of the organ — a stomach organoid wouldn't digest food, for example. They don't have the same network of veins and arteries to deliver blood. And they don't have the same physical structure as the real organs.

Related:

That all makes it hard to study a disease that affects the entire organ, Knoepfler said. There might be ways around the differences, such as building in blood vessels, he said, but "that's still sort of in its infancy."

Take microcephaly, he suggested. Using actual organs is pivotal to understanding the condition.

"The actual fetal brain is going to have features that are just not going to be present in an organoid," Knoepfler said. "Like, in an organoid study, you might have predominantly the front part of the brain, but microcephaly affects the whole brain."

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目次に戻る

10. 食事療法がマウスの自己免疫に及ぼす影響

2018 年 12 月 20 日

食事の変化は、ループス（狼瘡）など自己免疫疾患の人にとって、有益か？Yale 大学が率いる研究チームは、狼瘡のマウスモデルを使用して、食生活の変化が感受性マウスの自己免疫疾患の発症予防に役立つことを明らかにした。この研究は *Cell Host & Microbe* 誌に掲載されている。
彼らは、最初に、マウスの腸の中で、病気につながる免疫反応を引き起こす細菌、Lactobacillus reuteri を同定した。具体的には、狼瘡を起こしやすいマウスでは、この細菌は樹状細胞として知られる免疫細胞、ならびに疾患の進行を悪化させる免疫系経路を刺激した。これに対する食事療法の潜在的な影響を調査するために、マウスに「レジスタントスターチ」-人間の高繊維食を模した食事療法- を与えた。レジスタントスターチは小腸では吸収されず、大腸で発酵し、善玉菌を濃縮し、短鎖脂肪酸の分泌を引き起こす。これは、次に、そうでなければ自己免疫疾患につながるであろう腸外での Lactobacillus reuteri 細菌の増殖と移動の両方を抑制する。
調査結果がどのように人間に変換されるのかを見分けるためにもっと多くの研究が必要だが、この研究は食事、腸内細菌、そして自己免疫との間の重要な関連を述べている。

英文記事：
https://www.sciencedaily.com/releases/2018/12/181220111821.htm

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Impact of diet intervention on autoimmunity in mice

Date:

December 20, 2018

Source:

Yale University

Summary:

Could a change in diet be beneficial to people with autoimmune diseases such as lupus? Researchers have revealed how a dietary intervention can help prevent the development of this autoimmune disease in susceptible mice.

FULL STORY

Could a change in diet be beneficial to people with autoimmune diseases such as lupus? A Yale-led team of researchers have revealed how a dietary intervention can help prevent the development of this autoimmune disease in susceptible mice. The study was published in *Cell Host & Microbe*.

For the study, led by Yale immunobiologist Martin Kriegel, the research team used mouse models of lupus. They first identified a single bacterium, *Lactobacillus reuteri*, in the gut of the mice that triggered an immune response leading to the disease. Specifically, in lupus-prone mice, L. reuteri stimulated immune cells known as dendritic cells, as well as immune system pathways that exacerbated disease development.

To investigate the potential impact of diet on this process, first author Daniel Zegarra-Ruiz fed the mice "resistant starch" -- a diet that mimics a high-fiber diet in humans. The resistant starch is not absorbed in the small intestine but ferments in the large intestine, enriching good bacteria and causing the secretion of short-chain fatty acids. This, in turn, suppresses both the growth and movement of L. reuteri bacteria outside the gut that would otherwise lead to autoimmune disease.

While more research is needed to discern how the findings translate to humans, the study details an important link between diet, gut bacteria, and autoimmunity. "We dissected, molecularly, how diets can work on the gut microbiome," said Kriegel. "We identified a pathway that is driving autoimmune disease and mitigated by the diet."

The study also found an imbalance of gut microbes in a subset of lupus patients that was similar to what they observed in lupus-prone mice not given the starch diet. In this subset of lupus patients, the high-fiber diet could potentially be beneficial to prevent or ameliorate the condition, in

addition to other diseases that activate the same immune pathway, Kriegel noted. "It may have implications beyond lupus."

Story Source:

Materials provided by **Yale University**. Original written by Ziba Kashef. *Note: Content may be edited for style and length.*

Journal Reference:

1. Daniel F. Zegarra-Ruiz, Asmaa El Beidaq, Alonso J. Iñiguez, Martina Lubrano Di Ricco, Silvio Manfredo Vieira, William E. Ruff, Derek Mubiru, Rebecca L. Fine, John Sterpka, Teri M. Greiling, Carina Dehner, Martin A. Kriegel. **A Diet-Sensitive Commensal Lactobacillus Strain Mediates TLR7-Dependent Systemic Autoimmunity**. *Cell Host & Microbe*, 2018; DOI: 10.1016/j.chom.2018.11.009

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