BIO NEWS

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In-Vivo Science International Inc.

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目次

2018 年 10 月のニュース

＝研究編（詳細については各番号をクリックして下さい)＝

2018 年 10 月のニュース

＝企業関連ニュース他＝

・Novo Nordisk、中国とデンマークの研究開発（R&D）400 職に続き、米国のおよそ 250 職を削減（9/29)

・Lilly、Ph1 準備段階の経口 GLP-1 糖尿病薬を前金 5,000 万ドルで中外製薬から取得（9/29)

・Pfizer の COO・Albert Bourla 氏が来年 1 月 1 日に CEO に就任、現在の会長兼 CEO・Ian Read 氏は会長職に専念（10/1)

・本庶佑氏にノーベル医学・生理学賞　がん免疫治療薬を開発（10/1)

・「ネイチャー誌、サイエンス誌の 9 割は嘘」 ノーベル賞の本庶氏説く、常識を疑う大切さを（10/1)

・本庶氏　賞金は「京大に寄付」（10/2)

・本庶氏ノーベル賞　-オプジーボ開発の小野薬品「巡り合わせに感謝」「ともに歩んだ 20 数年間」（10/2)

・血液癌を治療する臍帯血細胞製品の Ph3 を進めている Gamida Cell が IPO を計画（10/3)

・飲む水の量の底上げで尿路感染症（UTI）再発を予防しうる（10/3)

・Boston、GSK の 5 つの開発プログラム取得　～Novartis からと併せて合計 8 つ（10/4)

・ニコチン含量が多くて色々な味が選べる Juul が電子タバコの中で最も売れている（10/4)

・乳がんの徴候、AI が診断へ -米 Google 系列の英 DeepMind Technologies と東京慈恵医大付属病院（10/4）

・アスピリンが健康な高齢者の癌死亡率を増加させるという予想外の結果　-オーストラリア Monash 大学　ASPREE 試験い（10/5)

・エーザイの食欲抑制剤 lorcaserin で太り過ぎ/肥満患者の糖尿病発現リスクが低下（10/5)

・欧州のバイオテクノロジー業界への投資は今年 80 億ドルを超えそう（10/8)

欧州のバイオテクノロジー業界への投資は今年これまでの 9 か月間に去年通年の総額 68 億 5,000 万ドル（$6.85 billion）に迫る 63 億 4,800 万ドル（$6.348 billion）を既に記録し、今年通年では 80 億ドルを超える見通し。Galapagos、Argenx、ProQR Therapeutics などが良好な試験結果に支えられてそれぞれ 3 億 4,610 万ドル（$346.1 million）、3 億 60 万ドル（$300.6 million）、1 億 410 万ドル（$104.1 million）を調達している。

・＜世界気温＞早ければ 2020 年にも 1.5 度上昇　-IPCC (気候変動に関する政府間パネル) 特別報告書（10/8)

・バイオテック業界屈指の遺伝子治療開発品品揃えを誇る Orchard Therapeutics（本社：ロンドン）が 1 億 7,300 万ドルの IPO 調達を計画（10/9)
・GSK が手を引いた抗癌剤を開発する Rgenix がその開発資金 4,000 万ドル調達（10/10)
・Allergan の脂肪細胞を冷やして減らす CoolSculpting による顎下美容を FDA が承認（10/11)
・大塚製薬、Proteus Digital Health と組んでセンサー入り治療薬を更に手広く開発（10/12)
・オス 2 匹からマウス誕生…精子の遺伝情報で -中国科学院など（10/12)
・<オプジーボ>ノーベル賞効果で関心高まるも…効果は限定的（10/13)
・Shire、ジョージア州コビントンの血漿分画工場が開設（10/14)
やがて Shire が買う Baxalta として製薬事業を独立させる前の Baxter International が 2012 年に明らかにしたジョージア州コビントンに 10 億ドルかけて血漿分画工場を作る計画だが、会社が変わっても生き延び、武田薬品が買う Shire を主として 10 月 11 日（木）に開設された。
・EU 離脱後が不明瞭な英国への投資は控えると、AstraZeneca 会長（10/16)
・Eagle Genomics が Microsoft と組んで微生物叢データ人工知能解析を提供（10/16)
・米国ケンブリッジ拠点の HiFiBiO が抗癌免疫抗体の H-Immune を取得（10/16)
・処方薬のテレビ CM にその値段を記させることを米国政府が計画（10/17)
・大塚傘下の大鵬薬品の投資事業 Taiho Ventures が手持ちを 3 億ドルに大幅増額（10/17)
・Pfizer が世界の従業員 90,200 人の 2%ほどを削減する（10/19)
・Sosei が 3,500 万ポンド（4,520 万ドル）をつぎ込んだ MiNA Therapeutics の買収権を行使せず（10/20)
・Celgene、Merck KGaA 出身の Alise Reicin 氏を臨床開発リーダーに任命（10/23)
・国内初、天然記念物アマミトゲネズミの繁殖成功（10/23)
・多剤耐性結核、新薬の臨床試験で 80%が治癒 画期的成果 -ベラルーシ（10/23)
・武田薬品、フランスの腸内微生物標的薬開発会社 Enterome のクローン病薬を共同開発して米国で共同販売、米国以外は武田担当（10/24)
・Pfizer が廃止を決めた神経事業の化合物の開発を引き継ぐ新会社 Cerevel Therapeutics が発足（10/24)
・CRISPR 遺伝子編集を売る Synthego が 1 億 1,000 万ドル調達（10/24)

・Deerfield、ノースカロライナ大学チャペルヒル校の創薬研究に 6,500 万ドルを投資 (10/24)
・病や睡眠障害を招く「体内時計の乱れ」実態調査 -厚労省 (10/27)
・武田薬品、Shire 買収の欧州許可を得る為に胃腸薬 SHP647 を手放すことを提案 (10/30)

目次に戻る

1. 2018 ノーベル医学生理学賞

2018 年 10 月 1 日

本庶さん、がん治療「第４の道」導く　衝撃の新薬に結実

朝日新聞 DIGITAL

受賞の知らせを受け、会見で喜びを語る京大の本庶佑特別教授＝2018年10月1日午後7時31分、京都市左京区、佐藤慈子撮影

スウェーデンのカロリンスカ医科大は１日、ノーベル医学生理学賞を京都大の本庶（ほんじょ）佑（たすく）特別教授（７６）と米テキサス大ＭＤアンダーソンがんセンターのジェームズ・アリソン教授（７０）に贈ると発表した。２人は、免疫をがんの治療に生かす手がかりを見つけた。新しいタイプの治療薬の開発につながり、がん治療に革命をもたらした。

【動画】「感謝いたしております」 本庶佑・京都大特別教授が会見

本庶さんの成果は、「オプジーボ」などの免疫チェックポイント阻害剤と呼ばれる薬に結びついた。

体内では通常、免疫が働いてがん細胞を異物とみなして排除する。しかし、免疫細胞には自身の働きを抑えるブレーキ役の分子があるため、がん細胞はこれを使って攻撃を避け、がんは進行してしまう。

２人はそれぞれブレーキ役の分子の役割を発見し、この働きを抑えてがんへの攻撃を続けさせる新しい治療を提案した。

がん治療は従来、外科手術、放射線、抗がん剤が中心だったが、「免疫でがんを治す」という第４の道をひらいた。

１日の会見で本庶さんは、「回復して『あなたのおかげだ』と（患者から）言われると、自分の研究が意味があったとうれしく思う。これからも多くの患者を救えるよう研究を続けたい」などと話した。

本庶さんのグループが見つけたブレーキは「ＰＤ―１」という分子。京都大医学部教授だった１９９２年、マウスの細胞を使った実験で新しい分子として発表した。さらに、ＰＤ―１をつくれないマウスの体内ではがんの増殖が抑えられることを確認。この分子の働きを妨げる抗体をマウスに注射し、がんを治療する効果があることを２００２年に報告した。

ＰＤ―１の働きを抑える薬は、本庶さんと特許を共同出願した小野薬品工業と、米製薬大手ブリストル・マイヤーズスクイブが開発。末期のがん患者でも進行をほぼ抑え、生存できること

があり、世界中に衝撃を与えた。薬は「オプジーボ」と名付けられて１４年、世界に先駆けて日本で皮膚がんの悪性黒色腫（メラノーマ）の治療薬として承認された。肺がんや胃がんなどでも効果が確認され、現在は６０カ国以上で承認されている。

ジェームズ・アリソン教授は９０年代半ば、ＰＤ―１とは別の病原体を攻撃する免疫細胞の表面にある「ＣＴＬＡ―４」という分子が、免疫のブレーキ役を果たしていることを解明。この分子の働きを妨げることで免疫を活性化し、がん細胞を攻撃できると発案。マウスの実験で証明した。

ＣＴＬＡ―４については、「ヤーボイ」というメラノーマの治療薬として６０カ国以上で承認されている。

日本のノーベル賞受賞は、１６年の医学生理学賞の大隅良典・東京工業大栄誉教授に続き２６人目。医学生理学賞は８７年の利根川進・米マサチューセッツ工科大教授、１２年の山中伸弥・京都大教授、１５年の大村智・北里大特別栄誉教授、１６年の大隅氏に続いて５人目。授賞式は１２月１０日にストックホルムである。賞金の９００万スウェーデンクローナ（約１億１５００万円）は受賞者で分ける。
https://headlines.yahoo.co.jp/hl?a=20181001-00000103-asahi-soci

英文記事：
https://www.sciencedaily.com/releases/2018/10/181001093316.htm

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2018 Nobel Prize in Physiology or Medicine

Cancer therapy: Inhibiting the brakes on the immune system

Date:

October 1, 2018

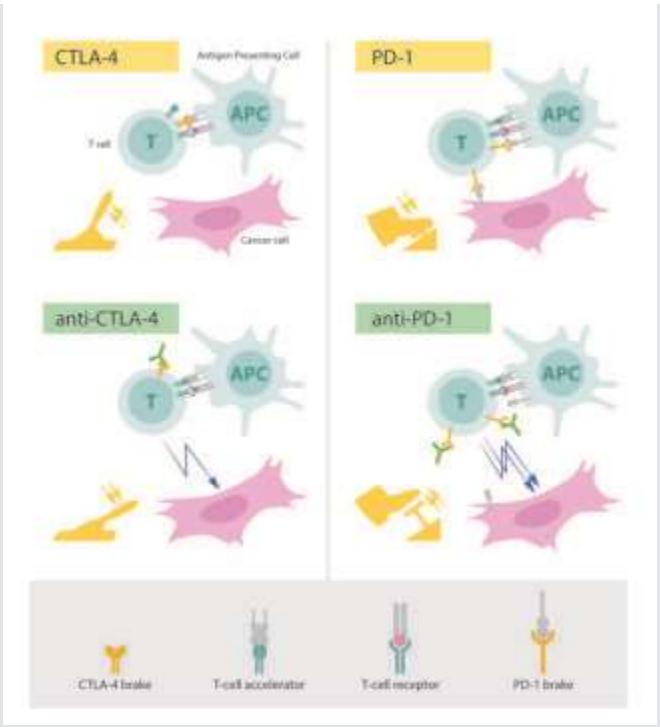
Source:

Nobel Foundation

Summary:

The 2018 Nobel Prize in Physiology or Medicine is being awarded jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.

FULL STORY



Upper left: Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as 'non-self'. A protein functioning as a T-cell accelerator is also required for T cell activation. CTLA-4 functions as a brake on T cells that inhibits the function of the accelerator. Lower left: Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells. Upper right: PD-1 is another T-cell brake that inhibits T-cell activation. Lower right: Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.

Credit: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén

The Nobel Assembly at Karolinska Institutet has today decided to award the 2018 Nobel Prize in Physiology or Medicine jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.

Cancer kills millions of people every year and is one of humanity's greatest health challenges. By stimulating the inherent ability of our immune system to attack tumor cells this year's Nobel Laureates have established an entirely new principle for cancer therapy.

James P. Allison studied a known protein that functions as a brake on the immune system. He realized the potential of releasing the brake and thereby unleashing our immune cells to attack tumors. He then developed this concept into a brand new approach for treating patients.

In parallel, Tasuku Honjo discovered a protein on immune cells and, after careful exploration of its function, eventually revealed that it also operates as a brake, but with a different mechanism of action. Therapies based on his discovery proved to be strikingly effective in the fight against cancer.

Allison and Honjo showed how different strategies for inhibiting the brakes on the immune system can be used in the treatment of cancer. The seminal discoveries by the two Laureates constitute a landmark in our fight against cancer.

Can our immune defense be engaged for cancer treatment?

Cancer comprises many different diseases, all characterized by uncontrolled proliferation of abnormal cells with capacity for spread to healthy organs and tissues. A number of therapeutic approaches are available for cancer treatment, including surgery, radiation, and other strategies, some of which have been awarded previous Nobel Prizes. These include methods for hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukemia (Thomas 1990). However, advanced cancer remains immensely difficult to treat, and novel therapeutic strategies are desperately needed.

In the late 19th century and beginning of the 20th century the concept emerged that activation of the immune system might be a strategy for attacking tumor cells. Attempts were made to infect patients with bacteria to activate the defense. These efforts only had modest effects, but a variant of this strategy is used today in the treatment of bladder cancer. It was realized that more knowledge was needed. Many scientists engaged in intense basic research and uncovered

fundamental mechanisms regulating immunity and also showed how the immune system can recognize cancer cells. Despite remarkable scientific progress, attempts to develop generalizable new strategies against cancer proved difficult.

Accelerators and brakes in our immune system

The fundamental property of our immune system is the ability to discriminate "self" from "non-self" so that invading bacteria, viruses and other dangers can be attacked and eliminated. T cells, a type of white blood cell, are key players in this defense. T cells were shown to have receptors that bind to structures recognized as non-self and such interactions trigger the immune system to engage in defense. But additional proteins acting as T-cell accelerators are also required to trigger a full-blown immune response (see Figure). Many scientists contributed to this important basic research and identified other proteins that function as brakes on the T cells, inhibiting immune activation. This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues.

A new principle for immune therapy

During the 1990s, in his laboratory at the University of California, Berkeley, James P. Allison studied the T-cell protein CTLA-4. He was one of several scientists who had made the observation that CTLA-4 functions as a brake on T cells. Other research teams exploited the mechanism as a target in the treatment of autoimmune disease. Allison, however, had an entirely different idea. He had already developed an antibody that could bind to CTLA-4 and block its function (see Figure). He now set out to investigate if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. Allison and co-workers performed a first experiment at the end of 1994, and in their excitement it was immediately repeated over the Christmas break. The results were spectacular. Mice with cancer had been cured by treatment with the antibodies that inhibit the brake and unlock antitumor T-cell activity. Despite little interest from the pharmaceutical industry, Allison continued his intense efforts to develop the strategy into a therapy for humans. Promising results soon emerged from several groups, and in 2010 an important clinical study showed striking effects in patients with advanced melanoma, a type of skin cancer. In several patients signs of remaining cancer disappeared. Such remarkable results had never been seen before in this patient group.

Discovery of PD-1 and its importance for cancer therapy

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. Determined to unravel its role, he meticulously explored its function in a series of elegant experiments performed over many years in his laboratory at Kyoto University. The results showed that PD-1, similar to CTLA-4, functions as a T-cell brake, but operates by a different mechanism (see Figure). In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo and other groups. This paved the way for utilizing PD-1 as a target in the treatment of patients. Clinical development ensued, and in 2012 a key study demonstrated clear efficacy in the treatment of patients with different types of cancer. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

Immune checkpoint therapy for cancer today and in the future

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as "immune checkpoint therapy," has fundamentally changed the outcome for certain groups of patients with advanced cancer. Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with the aim of improving therapies and reducing side effects.

Of the two treatment strategies, checkpoint therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer, renal cancer, lymphoma and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma. Thus, Allison and Honjo have inspired efforts to combine different strategies to release the brakes on the immune system with the aim of eliminating tumor cells even more efficiently. A large number of checkpoint therapy trials are currently underway against most types of cancer, and new checkpoint proteins are being tested as targets.

For more than 100 years scientists attempted to engage the immune system in the fight against cancer. Until the seminal discoveries by the two laureates, progress into clinical development was

modest. Checkpoint therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how cancer can be managed.

Key publications

Ishida, Y., Agata, Y., Shibahara, K., & Honjo, T. (1992). Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.*, *11* (11), 3887-3895.

Leach, D. R., Krummel, M. F., & Allison, J. P. (1996). Enhancement of antitumor immunity by CTLA-4 blockade. *Science*, *271* (5256), 1734-1736.

Kwon, E. D., Hurwitz, A. A., Foster, B. A., Madias, C., Feldhaus, A. L., Greenberg, N. M., Burg, M.B. & Allison, J.P. (1997). Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. *Proc Natl Acad Sci USA*, *94* (15), 8099-8103.

Nishimura, H., Nose, M., Hiai, H., Minato, N., & Honjo, T. (1999). Development of Lupus-like Autoimmune Diseases by Disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*, *11*, 141-151.

Freeman, G.J., Long, A.J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L.J., Malenkovich, N., Okazaki, T., Byrne, M.C., Horton, H.F., Fouser, L., Carter, L., Ling, V., Bowman, M.R., Carreno, B.M., Collins, M., Wood, C.R. & Honjo, T. (2000). Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*, *192* (7), 1027-1034.

Hodi, F.S., Mihm, M.C., Soiffer, R.J., Haluska, F.G., Butler, M., Seiden, M.V., Davis, T., Henry-Spires, R., MacRae, S., Willman, A., Padera, R., Jaklitsch, M.T., Shankar, S., Chen, T.C., Korman, A., Allison, J.P. & Dranoff, G. (2003). Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci USA*, *100* (8), 4712-4717.

Iwai, Y., Terawaki, S., & Honjo, T. (2005). PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol*, *17* (2), 133-144.

James P. Allison was born 1948 in Alice, Texas, USA. He received his PhD in 1973 at the University of Texas, Austin. From 1974-1977 he was a postdoctoral fellow at the Scripps Clinic and Research Foundation, La Jolla, California. From 1977-1984 he was a faculty member at University of Texas System Cancer Center, Smithville, Texas; from 1985-2004 at University of California,

Berkeley and from 2004-2012 at Memorial Sloan-Kettering Cancer Center, New York. From 1997-2012 he was an Investigator at the Howard Hughes Medical Institute. Since 2012 he has been Professor at University of Texas MD Anderson Cancer Center, Houston, Texas and is affiliated with the Parker Institute for Cancer Immunotherapy.

Tasuku Honjo was born in 1942 in Kyoto, Japan. In 1966 he became an MD, and from 1971-1974 he was a research fellow in USA at Carnegie Institution of Washington, Baltimore and at the National Institutes of Health, Bethesda, Maryland. He received his PhD in 1975 at Kyoto University. From 1974-1979 he was a faculty member at Tokyo University and from 1979-1984 at Osaka University. Since 1984 he has been Professor at Kyoto University. He was a Faculty Dean from 1996-2000 and from 2002-2004 at Kyoto University.

Story Source:

Materials provided by **Nobel Foundation**. *Note: Content may be edited for style and length.*

目次に戻る

2. 細胞の老化を遅らせる方法

2018 年 10 月 2 日

人は年を重ねるにつれて、損傷した細胞を蓄積する。細胞が一定レベルの損傷を受けると、細胞老化という老化過程を経る。細胞は又、免疫系にそれらの損傷した細胞をクリアするように指示する炎症因子を放出し、損傷した細胞を除去することもできるが、年を取るにつれて効果的に除去することができなくなり、蓄積が重なり、炎症を引き起こし、組織を分解する酵素が放出される。
今回ミネソタ大学医学部を始めとする研究者らは、Fisetin（フィセチン）と呼ばれる天然物質が体内のこれらの損傷細胞のレベルを低下させることを発見し、この知見を *EBioMedicine* 誌に発表した。フィセチンは多くの果物や野菜に含まれており、彼らは、このフィセチンを老齢マウスに対して処置し、マウスの健康と寿命が改善した、としている。

英文記事：
https://www.eurekalert.org/pub_releases/2018-10/uomm-uom100218.php

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PUBLIC RELEASE: 2-OCT-2018

University of Minnesota Medical School researchers have discovered how to slow aging

Natural product found to reduce the level of damaged cells in the body, caused by aging

University of Minnesota Medical School

MINNEAPOLIS, MN- October 2, 2018- Previous research published earlier this year in *Nature Medicine* involving University of Minnesota Medical School faculty Paul D. Robbins and Laura J. Niedernhofer and Mayo Clinic investigators James L. Kirkland and Tamara Tchkonia, showed it was possible to reduce the burden of damaged cells, termed senescent cells, and extend lifespan and improve health, even when treatment was initiated late in life. They now have shown that treatment of aged mice with the natural product Fisetin, found in many fruits and vegetables, also has significant positive effects on health and lifespan.

As people age, they accumulate damaged cells. When the cells get to a certain level of damage they go through an aging process of their own, called cellular senescence. The cells also release inflammatory factors that tell the immune system to clear those damaged cells. A younger person's immune system is healthy and is able to clear the damaged cells. But as people age, they aren't cleared as effectively. Thus they begin to accumulate, cause low level inflammation and release enzymes that can degrade the tissue.

Robbins and fellow researchers found a natural product, called Fisetin, reduces the level of these damaged cells in the body. They found this by treating mice towards the end of life with this compound and see improvement in health and lifespan. The paper, "Fisetin is a senotherapeutic that extends health and lifespan," was recently published in *EBioMedicine*.

"These results suggest that we can extend the period of health, termed healthspan, even towards the end of life," said Robbins. "But there are still many questions to address, including the right dosage, for example."

One question they can now answer, however, is why haven't they done this before? There were always key limitations when it came to figuring out how a drug will act on different tissues, different cells in an aging body. Researchers didn't have a way to identify if a treatment was actually attacking the particular cells that are senescent, until now.

Under the guidance of Edgar Arriaga, a professor in the Department of Chemistry in the College of Science and Engineering at the University of Minnesota, the team used mass cytometry, or CyTOF,

technology and applied it for the first time in aging research, which is unique to the University of Minnesota.

"In addition to showing that the drug works, this is the first demonstration that shows the effects of the drug on specific subsets of these damaged cells within a given tissue." Robbins said.

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Dr. Niedernhofer is the director and Dr. Robbins co-director of the Medical Discovery Team on Aging and the new Institute on the Biology of Aging and Metabolism (iBAM) at the University of Minnesota Medical School which are focusing on basic and translational research to identify novel and effective approaches to improve the health of the aging population.

About the University of Minnesota Medical School:

The University of Minnesota Medical School is at the forefront of learning and discovery, transforming medical care and educating the next generation of physicians. Our graduates and faculty produce high-impact biomedical research and advance the practice of medicine. Visit med.umn.edu to learn how the University of Minnesota is innovating all aspects of medicine.

目次に戻る

3. 早産研究のため、遺伝子改変マウスにヒト遺伝子注入

2018 年 10 月 2 日

シンシナティー小児病院医療センターの研究者らが、*PLoS Biology* 誌に発表した研究によると、ヒトの妊娠が他の動物と比較してユニークである早産研究の為にトランスジェニックの実験用マウスに必要十分なヒト DNA を注入することに成功した、としている。
その結果、胎盤内でコルチコトロフィン放出ホルモン（CRH）と呼ばれるストレスホルモンの発現を制御するものが発見された。CRH 発現レベルは、ヒトの出生時期と関連しているが、残念なことに、妊娠マウスや他の非霊長類は、胎盤で CRH を自然に発現しないため、研究者らは実験用マウスがホルモンを発現するのに必要な遺伝子機構を組み込む方法を理解しなければならなかった。
ヒト DNA がマウスの胎盤で発現され実行された後、研究者らは CRISPR/Cas9 と呼ばれる遺伝子編集技術を用いて THE1B として知られるレトロウィルスの DNA 領域を選択的に編集した。そして、トランスジェニックマウスにおいて THE1B の制限された欠損が CRH 発現を抑制し、出生時期を正常化することを発見した、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/10/181002102928.htm

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Making mice a tiny bit more human to study preterm birth

Research enhances ability to study biology of persistent public health problem

Date:

October 2, 2018

Source:

Cincinnati Children's Hospital Medical Center

Summary:

Preterm birth remains a global epidemic linked to a lifetime of potential health complications. It also is difficult to study in living creatures -- especially the uniquely precise biology of preterm birth in humans. Researchers report successfully inserting just enough human DNA into transgenic laboratory mice that it allowed the team to study a unique part of human pregnancy compared to other animals.

FULL STORY

A scientist at the Cincinnati Children's Perinatal Institute performs DNA tests as researchers study the genetics and biology of preterm birth, a global health epidemic that can lead to a lifetime of medical problems. Institute researchers report in PLoS Biology finding new clues about what controls the timing of birth and how these may lead to new answers for this persistent public health challenge.

Credit: Cincinnati Children's

Preterm birth remains a global epidemic linked to a lifetime of potential health complications. It also is difficult to study in living creatures -- especially the uniquely precise biology of preterm birth in humans.

Researchers report in *PLoS Biology* successfully inserting just enough human DNA into transgenic laboratory mice that it allowed the team to study a unique part of human pregnancy compared to other animals.

As a result, the scientists at the Cincinnati Children's Perinatal Institute and Department of Pediatrics at the University Of Cincinnati College Of Medicine discovered what controls expression of a stress hormone called corticotrophin-releasing hormone (CRH) in the placenta. The placenta supports the fetus and provides communication with the mother.

CRH expression levels are linked to birth timing in humans and indicate whether a pregnancy will be preterm, post-term, or the normal term of 37-42 weeks. Unfortunately, pregnant mice and other non-primate species don't naturally express CRH in the placenta. The scientists had to figure out how to get the animals to incorporate the genetic machinery needed to express the hormone.

This is important because researchers still don't know what CRH does in the placenta during pregnancy. Having transgenic mice with the necessary human DNA to express CRH in the placenta should help them find out, according to Louis Muglia, MD, senior investigator on the study, Co-Director of the Perinatal Institute and Director of Human Genetics at Cincinnati Children's.

"The challenge with studying human pregnancy is the typical biomedical approach requires a relevant animal for research," Muglia said. "It's been done for cancer and many other diseases. The problem is pregnancy in humans is different enough that it's not been possible to effectively translate the findings from the animal studies to humans."

Transgenic mouse models that mimic key aspects of human pregnancy also should help researchers uncover more information about how epigenetics affect birth timing. This could help answer long-standing questions about whether environmental exposures, like social stress or poor nutrition, influence the expression of genes important to birthing healthy, full-term babies.

Nature Finds a Way

To get pregnant laboratory mice to express CRH, Muglia's team decided to test evolutionary genetics and biology. They experimented with something called a retroviral long terminal repeat (LTR) known as THE1B.

Retroviral LTRs are identical sequences of DNA that continually repeat themselves and allow viruses to insert their genetic material into the genome of a host species. In the case of THE1B, it jumped into the genome of anthropoid primates (humankind's closest evolutionary relatives) 50 million years ago.

The research team developed a hypothesis that THE1B's invasion of the anthropoid primate genome may have initiated CRH expression in the placenta during pregnancy.

They tested this by microinjecting into transgenic mice 180 kilobytes of human DNA containing the THE1B LTR and CRH. Muglia said researchers didn't know if it would work, but in a vivid display of genetic adaptability the mice integrated and activated the DNA in the placenta.

"We were fortunate that the mice already had the machinery waiting and ready to activate and incorporate the human DNA and CRH in their placenta during pregnancy," he said.

Glimpse of Pregnancy Control

After the human DNA was up and running in the mouse placentas, the researchers selectively edited DNA regions of THE1B with a precise gene-editing technique called CRISPR/Cas9. They found that the restricted deletion of THE1B silenced CRH expression and normalized birth timing in the transgenic mice.

Their data also uncovered an interaction between THE1B and a transcription factor called DLX3, which is expressed in the placenta. Transcription factors in essence are genes that tell other genes what to do. During pregnancy, DLX3 is critical to normal development of the placenta.

Collectively the study's findings suggest that retroviral insertion of THE1B into the anthropoid genome initiated CRH expression in the placenta by working with DLX3. ThThe data also suggest

that intentionally manipulating placental CRH levels can alter the timing of birth. The authors stress the current study is still early and its findings are a small part of a large and complex puzzle that requires more research.

In their ongoing studies of CRH, THE1B and DLX3, the scientists will use this new information to explore how these biological pieces fit into the complex puzzle of what controls the timing of human pregnancies.

First author of the study is Caitlin Dunn-Fletcher, a student in the Medical Scientist Training Program (MD/PhD) at the UC College of Medicine and member of the Muglia laboratory team in the division of Human Genetics at Cincinnati Children's.

Funding support for the research came in part from the March of Dimes Prematurity Research Center Ohio Collaborative and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD091527, R21HD090196).

Story Source:

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

Journal Reference:

1. Caitlin E. Dunn-Fletcher, Lisa M. Muglia, Mihaela Pavlicev, Gernot Wolf, Ming-An Sun, Yueh-Chiang Hu, Elizabeth Huffman, Shivani Tumukuntala, Katri Thiele, Amrita Mukherjee, Sandra Zoubovsky, Xuzhe Zhang, Kayleigh A. Swaggart, Katherine Y. Bezold Lamm, Helen Jones, Todd S. Macfarlan, Louis J. Muglia. **Anthropoid primate–specific retroviral element THE1B controls expression of CRH in placenta and alters gestation length**. *PLOS Biology*, 2018; 16 (9): e2006337 DOI: 10.1371/journal.pbio.2006337

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- MLA
- APA
- Chicago

Cincinnati Children's Hospital Medical Center. "Making mice a tiny bit more human to study preterm birth: Research enhances ability to study biology of persistent public health problem." ScienceDaily. ScienceDaily, 2 October 2018. <www.sciencedaily.com/releases/2018/10/181002102928.htm>.

目次に戻る

４．脳の睡眠スイッチを同定 -マウス実験

2018 年 10 月 8 日

約 20 年前、Beth Israel Deaconess Medical Center (BIDMC) の研究者らは、一連の神経細胞を発見し、これが脳のスイッチを切って脳を眠らせるのではないかとしていた。今日 *Nature Communications* 誌で発表された新しい研究で、同上の研究者らは、視床下部の腹側視索前核（VLPO）と呼ばれるこれらの細胞が実際に正常な睡眠に不可欠であることをマウスで実証している。
研究者チームは、遺伝子操作されたマウスにおいて、いくつかの異なるツールを用いて人工的に VLPO ニューロンを活性化した。ある実験では、レーザー光線を用いてニューロン細胞を活性化させ、別の実験では、VLPO ニューロンを選択的に活性化する化学物質を用いた。どちらの場合にもこれらの細胞を活性化すると深く睡眠を促進した、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/10/181008083502.htm

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Out like a light: Researchers ID brain's 'sleep switch'

Sleep promoting neurons also tied to regulating body temperature

Date:

October 8, 2018

Source:

Beth Israel Deaconess Medical Center

Summary:

Scientists demonstrate in mice that that specific brain cells -- located in a region of the hypothalamus called the ventrolateral preoptic nucleus (VLPO) -- are in fact essential to normal sleep.

FULL STORY

Two decades ago, Clifford B. Saper, MD/PhD, Chairman of the Department of Neurology at Beth Israel Deaconess Medical Center (BIDMC), and colleagues discovered a set of nerve cells they thought might be the switch that turns the brain off, allowing it to sleep. In a new study published in *Nature Communications* today, Saper and colleagues demonstrate in mice that that these cells -- located in a region of the hypothalamus called the ventrolateral preoptic nucleus (VLPO) -- are in fact essential to normal sleep.

"Our paper is the first test of what happens when you activate the VLPO neurons," said Saper, who is also James Jackson Putnam Professor of Neurology and Neuroscience at Harvard Medical School. "The findings support our original observation that the VLPO cells are essential to normal sleep."

Working with genetically engineered mice, Saper's team artificially activated the VLPO neurons using several different tools. In one set of experiments, the scientists activated the neuron cells using a laser light beam to make them fire, a process called optogentics. In another test, the team used a chemical to selectively activate the VLPO neurons. In both cases, activating these cells profoundly drove sleep.

The results confirmed Saper and colleagues' earlier findings that these neurons are active during sleep and that damage to them causes insomnia -- as seen in Saper's subsequent work with laboratory animals and, in 2014, in older people who have lost cells of the VLPO as part of the natural aging process.

Based on that previous body of work, it came as a surprise when another team of researchers reported just the opposite. In a 2017 publication, experiments stimulating the VLPO neurons woke laboratory animals up. In their current paper, Saper's team cleared up the seeming contradiction.

"We found that when the VLPO cells are stimulated one to four times per second, they fire each time they are stimulated, resulting in sleep," Saper said. "But if you stimulate them faster than that,

they begin to fail to fire and eventually stop firing altogether. We learned our colleagues in the other lab were stimulating the cells 10 times per second, which was actually shutting them off."

Additionally, Saper's team also found that activating the VLPO cells caused a fall in body temperature. Scientists already knew that warm temperatures activate VLPO cells, and that body temperature dips slightly during sleep, when the VLPO neurons are firing.

"We thought that this is why people need to curl up under a warm blanket to get to sleep," Saper added.

However, with continued activation, body temperature in the mice fell by as much as five or six degrees Celsius. Saper's team proposed that excessive firing of these same neurons may be responsible for the prolonged sleep and decline in body temperature in animals that hibernate. In follow up, Saper's team is already looking at the relationship between sleep and body temperature in ongoing studies.

Story Source:

Materials provided by **Beth Israel Deaconess Medical Center**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Daniel Kroeger, Gianna Absi, Celia Gagliardi, Sathyajit S. Bandaru, Joseph C. Madara, Loris L. Ferrari, Elda Arrigoni, Heike Münzberg, Thomas E. Scammell, Clifford B. Saper, Ramalingam Vetrivelan. **Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-06590-7

Cite This Page:

- MLA

- APA
- Chicago

Beth Israel Deaconess Medical Center. "Out like a light: Researchers ID brain's 'sleep switch': Sleep promoting neurons also tied to regulating body temperature." ScienceDaily. ScienceDaily, 8 October 2018. <www.sciencedaily.com/releases/2018/10/181008083502.htm>.

目次に戻る

5. ゲノム編集を使って遺伝病が治癒 -マウス実験

2018 年 10 月 8 日

スイスでは全ての新生児がフェニルケトン尿症という遺伝病についてスクリーニングされる。赤ん坊にフェニルケトン尿症が認められた場合、フェニルアラニンが体内に蓄積しないよう特別な食事が必要とされる。というのも過剰のフェニルアラニンは精神および運動発達を遅れさせ、未治療のまま放置すると、精神障害に苦しむ可能性も出てくるからだ。
この代謝障害の原因は酵素フェニルアラニンヒドロキシラーゼ（Pah）の青写真を提供する遺伝子の突然変異であるとされている。Pah は肝臓の細胞によって産生され、フェニルアラニンを代謝するが、この疾患は「常染色体劣性」と呼ばれ、母親から 1 つの突然変異遺伝子と父親から 1 つの変異遺伝子を継承することによって発症し、これまで治療法は存在しなかった。
ETH Zurich（スイス連邦工科大学チューリッヒ校）の研究チームは、肝臓細胞の両方の変異遺伝子を矯正して病気を治癒する方法をとって、既にマウスでは治癒に成功した、として *Nature Medicine* 誌に発表した。

英文と記事：
https://www.eurekalert.org/pub_releases/2018-10/ez-gdh100518.php

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PUBLIC RELEASE:8-OCT-2018

Genetic disease healed using genome editing

ETH Zurich

IMAGE: Based on the Crispr-Cas method, researchers developed a tool for the targeted correction of defective genes. view more

Credit: colourbox

Parents of newborns may be familiar with the metabolic disorder phenylketonuria: in Switzerland, all newborn babies are screened for this genetic disease. If a baby is found to have phenylketonuria, it needs a special diet so that the amino acid phenylalanine does not accumulate in the body. Excess phenylalanine delays mental and motor development. If left untreated, the children may suffer massive mental disability.

The cause of this metabolic disorder is a mutation in a gene that provides the blueprint for the enzyme phenylalanine hydroxylase (Pah). This enzyme, which is produced by the cells of the liver, metabolizes phenylalanine. The disorder is referred to as "autosomal recessive": the child develops the disease if it inherits one mutated gene from the mother and one from the father. There has been no cure for this disorder to date.

Enhancement of the CRISPR/Cas9 system

A team of researchers led by ETH professor Gerald Schwank has now taken advantage of a method to correct both mutated genes in the liver cells and thus heal the disease. They have succeeded, at least in mice.

With the help of a CRISPR/Cas9 system extended by one enzyme, the researchers changed the sequence of the DNA building blocks for the corresponding gene in adult mice. The liver cells were subsequently able to produce functioning Pah enzymes, and the mice were healed.

Let's look at the details: The CRISPR/Cas9 system enhanced by the enzyme cytidine deaminase binds to the locus on the gene that needs to be corrected and locally opens both DNA strands. The deaminase converts the disease-causing DNA base pair C-G into T-A, which is the base pair that occurs at that spot in healthy individuals. This corrects the error in the DNA sequence of the Pah enzyme.

In traditional CRISPR/Cas editing, inducing a DNA double-stranded break is the central element of genome editing. The double strand is cut at a defined point, and the cell attempts to repair the cut using various mechanisms. If a matching DNA sequence is added to the cell from outside, it enables a specialized repair mechanism to precisely modify the specific genetic sequence.

The problem here is that most human cells primarily use other DNA repair mechanisms that produce additional undesired mutations.

More sparing genome editing

The researchers realized that the new genome editing tool is much more efficient than the traditional CRISPR/Cas9 method: up to 60 percent of all copies of the gene with errors in the mouse liver were corrected. This resulted in the concentration of phenylalanine falling to normal levels, and the animals no longer showing any signs of the disorder after being treated with the genome editing tool.

To transfer the genetic code for the new editing tool to the liver cells, the researchers implanted the required genes into adeno-associated viruses and injected them into the blood of the mice. The virus then infected the liver cells, thereby introducing the genes for the editing tool into the liver cell.

Healing other metabolic diseases

"This approach has great potential for application in humans", says Gerald Schwank. However, this study is only a first proof of concept. Clinical studies in other animal models would have to follow in order to test the efficacy and safety of the new genome editing tool for application in humans.

Previous methods of genome editing have only limited success at correcting target mutations directly in animals. The correction rate in the liver of adult mice has previously been only a few percent, explains Schwank. "Here we've achieved several fold higher editing rates - nobody has managed that so far."

Schwank considers the risks to be low. After applying the editing tool in the mouse model the researchers looked for non-target mutations, that is, on sites where there shouldn't be mutations. But they didn't find any. Schwank would like to examine this more closely in a follow-up study. «The human liver consists of several billion cells. In none of them we want to induce any mutations that could cause cancer», emphasizes Schwank. Testing is also needed to find out whether the adeno-associated virus used by the researchers as a vehicle for applying the editing tool gene causes any adverse effects.

Focus on further metabolic disorders

"The use of a base editor was the key to our success", explains Schwank's doctoral candidate and primary author of the study, Lukas Villiger. They were developed at the Massachusetts Institute of Technology (MIT) and presented just two years ago in a scientific journal. Before that, the ETH researchers had been working with traditional CRISPR/Cas approaches. In 2016, Schwank and Villiger starting using the techniques developed by the US researchers. "Even with the new base editors, the path still didn't follow a straight line - we had to tinker around quite a bit", says Villiger. The biggest surprise was that this system is so much more effective than the traditional CRISPR/Cas toolbox.

Schwank is now looking for funding to conduct trails on other animal models such as pigs. "The liver of the mouse differs in size and structure from that of humans or pigs, so we definitely have to expand the scope of our trials to other organisms to make progress."

Phenylketonuria is not the only genetic metabolic disorder that affects the liver. For example, urea cycle disorders prevent the body from removing ammonia (as a by-product from foods containing nitrogen) from the blood and metabolizing it to urea. This results primarily in central nervous dysfunctions. The only currently available option to cure this disease is liver transplantation. Therefore, Schwank would like to test the newly developed genome editing tool for use in such diseases as well.

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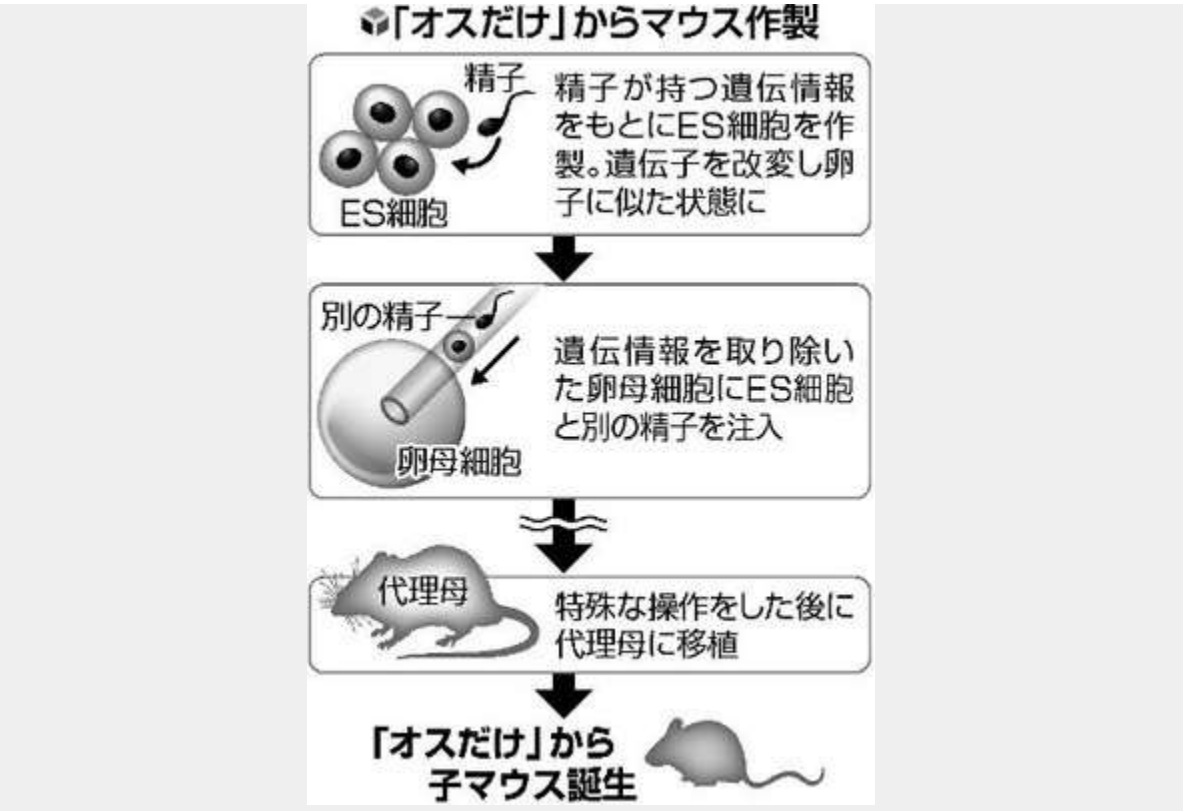
目次に戻る

6. オス２匹からマウス誕生 –精子の遺伝情報で

2018年10月12日



（写真：読売新聞）

【ワシントン＝三井誠】２匹のオスの精子が持つ遺伝情報をもとに子マウスを初めて誕生させたと、中国科学院などの研究チームが１１日に発表した。精子をもとに作ったＥＳ細胞（胚性幹細胞）を改変して卵子に似せ、別の精子と合わせるなどして受精卵のような状態にしたという。すぐに人間に応用することは難しいが、生命倫理面で議論を呼びそうだ。論文が米科学誌「セル・ステムセル」に掲載される。

マウスや人間などの哺乳類は卵子と精子で遺伝情報の働き方が異なり、どちらか一方の遺伝情報では通常、発育が進まない。２００４年に東京農業大の河野友宏教授らが卵子だけを使って子マウスを誕生させたと発表したが、精子だけの例はなかった。

中国の研究チームは精子が持つ遺伝情報をもとにＥＳ細胞を作製。遺伝子を効率良く改変できる「ゲノム編集技術」を使って、卵子に似せるために７個の遺伝子を働かないよう操作した。

https://headlines.yahoo.co.jp/hl?a=20181012-00050000-yom-sci

英文記事：

https://www.sciencedaily.com/releases/2018/10/181011143115.htm

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Mouse pups with same-sex parents born in China using stem cells and gene editing

Date:

October 11, 2018

Source:

Cell Press

Summary:

Researchers were able to produce healthy mice with two mothers that went on to have normal offspring of their own. Mice from two dads were also born but only survived for a couple of days. The work looks at what makes it so challenging for animals of the same sex to produce offspring and suggests that some of these barriers can be overcome using stem cells and targeted gene editing.

FULL STORY

This image shows a healthy adult bimaternal mouse (born to two mothers) with offspring of her own.

Credit: Leyun Wang

Researchers at the Chinese Academy of Sciences were able to produce healthy mice with two mothers that went on to have normal offspring of their own. Mice from two dads were also born but only survived for a couple of days. The work, presented October 11 in the journal *Cell Stem Cell*, looks at what makes it so challenging for animals of the same sex to produce offspring and suggests that some of these barriers can be overcome using stem cells and targeted gene editing.

"We were interested in the question of why mammals can only undergo sexual reproduction. We have made several findings in the past by combining reproduction and regeneration, so we tried to

find out whether more normal mice with two female parents, or even mice with two male parents, could be produced using haploid embryonic stem cells with gene deletions," says co-senior author Qi Zhou.

While some reptiles, amphibians, and fish can reproduce with one parent of the same sex, it's challenging for mammals to do the same even with the help of fertilization technology. In mammals, because certain maternal or paternal genes are shut off during germline development by a mechanism called genomic imprinting, offspring that don't receive genetic material from both a mother and a father might experience developmental abnormalities or might not be viable. By deleting these imprinted genes from immature eggs, researchers have produced bimaternal mice -- mice with two mothers -- in the past. "However, the generated mice still showed defective features, and the method itself is very impractical and hard to use," says Zhou.

To produce their healthy bimaternal mice, Zhou, co-senior author Baoyang Hu, co-senior author Wei Li, and their colleagues used haploid embryonic stem cells (ESCs), which contain half the normal number of chromosomes and DNA from only one parent and which the researchers believe were the key to their success. The researchers created the mice with two mothers by deleting three imprinting regions of the genome from haploid ESCs containing a female parent's DNA and injected them into eggs from another female mouse. They produced 29 live mice from 210 embryos. The mice were normal, lived to adulthood, and had babies of their own.

One advantage of using haploid ESCs is that even before the problematic genes are knocked out, they contain less of the imprinting programming that ultimately causes maternal- or paternal-specific genes to be expressed. "We found in this study that haploid ESCs were more similar to primordial germ cells, the precursors of eggs and sperm. The genomic imprinting that's found in gametes was 'erased,'" says Hu.

Twelve live, full-term mice with two genetic fathers were produced using a similar but more complicated procedure. Haploid ESCs containing only a male parent's DNA were modified to delete seven key imprinted regions. The edited haploid ESCs were then injected -- along with sperm from another male mouse -- into an egg cell that had its nucleus, and therefore its female genetic material, removed. This created an embryo containing only genomic DNA from the two male parents. These embryos were transferred along with placental material to surrogate mothers, who carried them to term.

These pups survived 48 hours after birth, but the researchers are planning to improve the process so that the bipaternal mice live to adulthood. Similar results were achieved in 2011 but using a method that relied on a female intermediary produced from the first father's stem cells to mate with the second father. That method sidestepped the problem of genomic imprinting but presents ethical and practical hurdles if this technology were to ever be considered for humans.

Li notes that there are still obstacles to using these methods in other mammals, including the need to identify problematic imprinted genes that are unique to each species and concerns for the offspring that don't survive or that experience severe abnormalities. They do hope, however, to explore these techniques in other research animals in the future.

"This research shows us what's possible," he says. "We saw that the defects in bimaternal mice can be eliminated and that bipaternal reproduction barriers in mammals can also be crossed through imprinting modification. We also revealed some of the most important imprinted regions that hinder the development of mice with same sex parents, which are also interesting for studying genomic imprinting and animal cloning."

Story Source:

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

Journal Reference:

1. Zhi-Kun Li, Le-Yun Wang, Li-Bin Wang, Gui-Hai Feng, Xue-Wei Yuan, Chao Liu, Kai Xu, Yu-Huan Li, Hai-Feng Wan, Ying Zhang, Yu-Fei Li, Xin Li, Wei Li, Qi Zhou, Bao-Yang Hu. **Generation of Bimaternal and Bipaternal Mice from Hypomethylated Haploid ESCs with Imprinting Region Deletions**. *Cell Stem Cell*, 2018; DOI: 10.1016/j.stem.2018.09.004

目次に戻る

7. 血液を凝固させるたんぱく質を標的とする新たな免疫療法 -マウス実験

2018 年 10 月 15 日

通常、血液のたんぱく質フィブリンが脳に入ることはないが、いくつかの神経障害では血液中の大きな分子が脳に入るのを防ぐ血液の脳関門が異常に透過性になり、フィブリンが脳に溢れて炎症を引き起こす。このプロセスは、多発性硬化症、アルツハイマー病など複数の障害において神経細胞を死亡させる原因となっている可能性がある。しかし、フィブリンを標的とする方法は、負傷後の過剰な出血を防ぐ血液凝固という有益な役割も損ねてしまう為、科学者らにずっと避けられていた。
今回、グラッドストーン研究所のチームは、このたんぱく質の凝固機能を損なうことなく、脳の神経変性に寄与するフィブリンの炎症性および酸化活性をブロックする抗体を開発し、その成果を *Nature Immunology* 誌の 10 月 15 日号オンライン版で発表した。
これによると、アルツハイマー病のマウスモデルでは、脳内にアミロイドたんぱく質の蓄積を既に発症している動物をこの抗体で治療、プラセボ処置マウスと比較して、処置マウスは脳の炎症が少なく、ニューロンが少なくなった、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/10/181015132957.htm

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New immunotherapy targeting blood-clotting protein

Researchers have stopped the detrimental effects of blood-brain barrier leaks to protect against multiple sclerosis and Alzheimer's disease

Date:

October 15, 2018

Source:

Gladstone Institutes

Summary:

A team has developed an antibody that blocks the inflammatory and oxidative activity of fibrin, which contributes to neurodegeneration in the brain, without compromising the protein's clotting function.

FULL STORY

Normally, the blood protein fibrin does not enter the brain. But in several neurological disorders, the blood-brain barrier -- which keeps large molecules in the blood from entering the brain -- becomes abnormally permeable, allowing fibrin to leak into the brain and trigger inflammation. Emerging evidence points to a leaky blood-brain barrier as an early event in brain diseases that causes neurodegeneration. In fact, this process may lead to the death of nerve cells in multiple sclerosis, Alzheimer's disease, and other disorders.

Until now, however, treatments to inhibit the blood from harming the brain were not available. Although studies in patients with multiple sclerosis or Alzheimer's disease (and in related animal models) indicate that fibrin may play a role in promoting these disorders, most researchers have shied away from targeting fibrin to treat neurological diseases because of concerns that targeting the protein would impair its beneficial role in blood clotting, which prevents excessive bleeding after injuries.

Scientists from the Gladstone Institutes may have overcome this challenge with a new immunotherapy. A team led by Senior Investigator Katerina Akassoglou, PhD, developed an

antibody that blocks the inflammatory and oxidative activity of fibrin, which contributes to neurodegeneration in the brain, without compromising the protein's clotting function.

To come up with a very precise and highly effective antibody, the researchers focused on targeting only a small region of the fibrin protein that is involved in activating the immune system in the brain. This way, they avoided interfering with the part of the protein responsible for clotting.

"We have developed a monoclonal antibody to target a major culprit in the blood that damages the brain," said Akassoglou, who is also a professor in the Department of Neurology at UC San Francisco. "Fibrin-targeting immunotherapy could protect the brain from the toxic effects of blood leakage and may also have beneficial effects in other organs affected by inflammatory conditions with vascular damage."

For their new study, published online on October 15 in the journal *Nature Immunology*, Akassoglou and her colleagues used models of neurodegeneration simulating two major brain diseases that are associated with blood-brain barrier leakage, chronic inflammation, and vascular abnormalities: multiple sclerosis and Alzheimer's disease.

The therapeutic fibrin antibody entered the brain, accumulated at fibrin-rich areas, and protected against neuroinflammation and neurodegeneration in both disease models. Molecular analysis showed that the treatment also reduced activation of biochemical pathways that contribute to inflammation and oxidative stress, a potential source of molecules that can poison cells, including neurons.

"We discovered that fibrin also contributes to brain disease through oxidative stress -- an unanticipated result," explained first author Jae Kyu Ryu, PhD, a staff research scientist on Akassoglou's team. "Treatment with the antibody put a damper on this fibrin-driven oxidative mechanism, which may contribute to many different neurodegenerative diseases."

In the mouse model of Alzheimer's disease, animals were treated with the antibody after they had already developed accumulations of amyloid proteins in the brain, a hallmark of the disease. Compared to placebo-treated mice, the treated mice had less brain inflammation and lost fewer neurons.

Similarly, treatment with the antibody reduced activation of inflammatory cells and their accumulation at sites of inflammation in the mouse model of multiple sclerosis. In addition, it reduced the loss of nerve axons, which often degenerate in patients with multiple sclerosis.

"Our study supports that vascular damage leading to immune-driven neurodegeneration may be a common thread between diseases of different etiologies with blood-brain barrier leaks," said Akassoglou. "Targeting fibrin with immunotherapy is a new approach that could be used to test the therapeutic benefits of suppressing this pathogenic mechanism in multiple disease contexts."

Using this approach, Akassoglou and her team could be in a position to achieve neuroprotection in diverse disorders without shutting down protective immune responses or blood clotting.

The next step will be to make a version of the antibody that can be used in human patients. Given that the treatment targets an immune response and a blood clotting factor, Akassoglou cautions, however, that tests monitoring the immune system and blood clotting will be important during clinical evaluation.

Story Source:

Materials provided by **Gladstone Institutes**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Jae Kyu Ryu, Victoria A. Rafalski, Anke Meyer-Franke, Ryan A. Adams, Suresh B. Poda, Pamela E. Rios Coronado, Lars Østergaard Pedersen, Veena Menon, Kim M. Baeten, Shoana L. Sikorski, Catherine Bedard, Kristina Hanspers, Sophia Bardehle, Andrew S. Mendiola, Dimitrios Davalos, Michael R. Machado, Justin P. Chan, Ioanna Plastira, Mark A. Petersen, Samuel J. Pfaff, Kenny K. Ang, Kenneth K. Hallenbeck, Catriona Syme, Hiroyuki Hakozaki, Mark H. Ellisman, Raymond A. Swanson, Scott S. Zamvil, Michelle R. Arkin, Stevin H. Zorn, Alexander R. Pico, Lennart Mucke, Stephen B. Freedman, Jeffrey B. Stavenhagen, Robert B. Nelson, Katerina Akassoglou. **Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration**. *Nature Immunology*, 2018; DOI: 10.1038/s41590-018-0232-x

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Gladstone Institutes. "New immunotherapy targeting blood-clotting protein: Researchers have stopped the detrimental effects of blood-brain barrier leaks to protect against multiple sclerosis and Alzheimer's disease." ScienceDaily. ScienceDaily, 15 October 2018. <www.sciencedaily.com/releases/2018/10/181015132957.htm>.

目次に戻る

8. 父親のニコチン使用が子や孫の代に認知障害を引き起こす可能性

2018 年 10 月 16 日

フロリダ州立大学タラハシー校の研究者らによるオープンアクセスジャーナル *PLOS Biology* で 10 月 16 日に発表されたマウス研究によると、父親のニコチンへの曝露は子供や孫の代に認知障害を引き起こす可能性があり、この直接曝露ではないものによって引き起こされる効果は、父親の精子におけるエピジェネティックな変化による可能性がある、としている。
ちなみに、母親のニコチンへの曝露については、複数世代の子孫における注意欠陥障害 (ADHD) を含む重大な危険因子として既に認識されている。
このことが父親についても言えるのかどうか調べるべく、今回、研究者らは、雄のマウスの飲料水中に低用量のニコチンを曝露し、その後ニコチンに全く曝されていなかった雌のマウスと、これらの雄マウスを繁殖させた。父親は行動的に正常であったが、子孫は雄雌マウス共に多動性や注意力欠如、認知的柔軟性を示した。又、この世代の雌マウスから生まれた雄マウスも依然として認知的柔軟性を示した。
元のニコチンに暴露された雄の精子の分析から、脳の発達および学習に重要なドーパミン D2 遺伝子を含む複数の遺伝子のプロモーター領域が、エピジェネティックに修飾されていることを示しており、これらの改変が子孫における認知障害に寄与した可能性が高い、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/10/181016142422.htm

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Father's nicotine use can cause cognitive problems in children and grandchildren

Mouse study implicates epigenetic changes in paternal sperm DNA

Date:

October 16, 2018

Source:

PLOS

Summary:

A father's exposure to nicotine may cause cognitive deficits in his children and even grandchildren, according to a new study. The effect, which was not caused by direct secondhand exposure, may be due to epigenetic changes in key genes in the father's sperm.

FULL STORY

A father's exposure to nicotine may cause cognitive deficits in his children and even grandchildren, according to a study in mice publishing on October 16 in the open-access journal *PLOS Biology* by Pradeep Bhide of Florida State University in Tallahassee and colleagues. The effect, which was not caused by direct secondhand exposure, may be due to epigenetic changes in key genes in the father's sperm.

Exposure of mothers to nicotine and other components of cigarette smoke is recognized as a significant risk factor for behavioral disorders, including attention deficit hyperactivity disorder, (or ADHD) in multiple generations of descendants. Whether the same applies to fathers has been less clear, in part because in human studies it has been difficult to separate genetic factors (such as a genetic predisposition to ADHD) from environmental factors, such as direct exposure to cigarette smoke.

To overcome this difficulty, Deirdre McCarthy, Pradeep Bhide and colleagues exposed male mice to low-dose nicotine in their drinking water during the stage of life in which the mice produce sperm. They then bred these mice with females that had never been exposed to nicotine. While the fathers were behaviorally normal, both sexes of offspring displayed hyperactivity, attention deficit, and cognitive inflexibility. When female (but not male) mice from this generation were bred with

nicotine-naïve mates, male offspring displayed fewer, but still significant, deficits in cognitive flexibility. Analysis of spermatozoa from the original nicotine-exposed males indicated that promoter regions of multiple genes had been epigenetically modified, including the dopamine D2 gene, critical for brain development and learning, suggesting that these modifications likely contributed to the cognitive deficits in the descendants.

Nicotine and cigarette smoke have been previously shown to cause widespread epigenetic changes, Bhide said. "The fact that men smoke more than women makes the effects in males especially important from a public health perspective. Our findings underscore the need for more research on the effects of smoking by the father, rather than just the mother, on the health of their children."

Story Source:

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

Journal Reference:

1. Deirdre M. McCarthy, Thomas J. Morgan, Sarah E. Lowe, Matthew J. Williamson, Thomas J. Spencer, Joseph Biederman, Pradeep G. Bhide. **Nicotine exposure of male mice produces behavioral impairment in multiple generations of descendants**. *PLOS Biology*, 2018; 16 (10): e2006497 DOI: 10.1371/journal.pbio.2006497

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PLOS. "Father's nicotine use can cause cognitive problems in children and grandchildren: Mouse study implicates epigenetic changes in paternal sperm DNA." ScienceDaily. ScienceDaily, 16 October 2018. <www.sciencedaily.com/releases/2018/10/181016142422.htm>.

目次に戻る

9. 新 脳内アルコールターゲット

2018 年 10 月 22 日

脳内にアルコールが入ると、腹側被蓋領域（VTA）－「快楽センター」として知られている － と呼ばれる特別な領域にニューロンが誘発され、気持ちの良い感覚を生成する神経伝達物質であるドーパミンが放出され、もっとアルコールを摂取する価値があるぞ、というメッセージが脳に送られる。科学者らは、長年にわたり、アルコールが VTA 中のニューロンにドーパミンを放出させる分子経路の最初のステップを探し求めてきたが、今回イリノイ大学シカゴ校エピジェネティックスのアルコール研究センターの研究者らが、KCNK13 というカリウムチャンネルについて発見し、*Neuropharmacology* 誌に発表した。
これによると、アルコールが VTA のドーパミン放出ニューロンの膜内にある KCNK13 を遮断すると、ニューロンがその活性を高め、より多くのドーパミンを放出する、としている。彼らは、遺伝的手法を用いて、マウスの VTA における KCNK13 を約 15%減少させたところ、これらのマウスは正常なマウスと比較して 20~30%多くのアルコールを摂取した。又、別の実験では、より少ない KCNK13 を発現したマウスから採取した VTA 領域におけるニューロンの応答を調べた。これらのニューロンがアルコールに暴露された時、正常なマウスからの VTA ニューロンよりもアルコールに対する応答が 50%低かった。
研究者らは、KCNK13 チャンネルの量の変動が、特定の人々の過敏な飲酒の素因に関与している可能性がある、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/10/181022150948.htm

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New target of alcohol in the brain

Date:

October 22, 2018

Source:

University of Illinois at Chicago

Summary:

When alcohol enters the brain, it causes neurons in a specialized region called the ventral tegmental area, or VTA -- also known as the "pleasure center" -- to release dopamine, a neurotransmitter that produces those feel-good sensations, and tells the brain that whatever it just experienced is worth getting more of.

FULL STORY

When alcohol enters the brain, it causes neurons in a specialized region called the ventral tegmental area, or VTA -- also known as the "pleasure center" -- to release dopamine, a neurotransmitter that produces those feel-good sensations, and tells the brain that whatever it just experienced is worth getting more of.

Scientists have long sought the first step in the molecular pathway by which alcohol causes neurons in the VTA to release dopamine.

Now, researchers in the Center for Alcohol Research in Epigenetics at the University of Illinois at Chicago report in the journal *Neuropharmacology*, that alcohol blocks a potassium channel called KCNK13 that sits within the membrane of dopamine-releasing neurons in the VTA. When the potassium channel gets blocked, the neurons increase their activity and release more dopamine.

"The KCNK13 channel is absolutely required for alcohol to stimulate the release of dopamine by these neurons," said Mark Brodie, professor of physiology and biophysics in the UIC College of Medicine and lead author of the study. "Without the channel, alcohol can't stimulate the release of dopamine, and so drinking is likely less rewarding. We think that the KCNK13 channel presents an

extremely exciting new target for drugs that could potentially help people with alcohol use disorder to stop drinking."

Other drugs on the market to treat alcohol use disorder cause feelings of nausea with drinking, or interfere with the action of alcohol in other parts of the brain.

"Currently available drugs reduce the impact of alcohol on the brain that is akin to turning down the volume on a stereo," he said. "A drug that would target KCNK13 would be different in that it would be like an on/off switch. If it's turned off, alcohol just wouldn't trigger increased dopamine release."

Brodie explained that without the channel, the VTA would still be able to release dopamine in response to other pleasurable indulgences, like chocolate cake.

"This channel seems to be specific to alcohol effects in the VTA, so targeting it with a drug would dampen the effects of alcohol only," he said.

Brodie and his colleagues used genetic techniques to reduce KCNK13 in the VTA of mice by about 15 percent compared with normal mice. When allowed to binge on alcohol, these mice drank 20 percent to 30 percent more than normal mice.

"We believe that mice with less KCNK13 in the VTA drank more alcohol in order to achieve the same 'reward' from alcohol as normal mice, presumably because alcohol was triggering the release of less dopamine in their brains," Brodie said.

In another experiment, the researchers examined the response of neurons in the VTA region taken from the mice that expressed less KCNK13. When these neurons were exposed to alcohol, they were 50 percent less responsive to alcohol than VTA neurons from normal mice.

Brodie speculates that variations in the amount of the KCNK13 channel could be involved in predisposing certain people to binge drinking.

"If someone has naturally lower levels of this channel, then in order to produce the pleasurable effects of alcohol, that person would have to drink much more, and may be at higher risk for binge drinking disorder," he said.

Brodie and his colleagues will continue to investigate the role of KCNK13 and examine how selective manipulation of the channel in other brain areas and cell types might alter alcohol-related behaviors.

"We are the first to show that KCNK13 is a primary, direct target of alcohol and that this channel is important for regulating alcohol consumption. KCNK13 represents a novel target for the development of alcohol use disorder drugs, of which we have relatively few today," Brodie said.

Story Source:

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

Journal Reference:

1. Chang You, Antonia Savarese, Bertha J. Vandegrift, Donghong He, Subhash C. Pandey, Amy W. Lasek, Mark S. Brodie. **Ethanol acts on KCNK13 potassium channels in the ventral tegmental area to increase firing rate and modulate binge–like drinking**. *Neuropharmacology*, 2019; 144: 29 DOI: 10.1016/j.neuropharm.2018.10.008

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University of Illinois at Chicago. "New target of alcohol in the brain." ScienceDaily. ScienceDaily, 22 October 2018. <www.sciencedaily.com/releases/2018/10/181022150948.htm>.

目次に戻る

10. 肥満マウス 天然蛋白質で脂肪の３分の１を失う

2018 年 10 月 29 日

ジョージタウン大学医療センター主導による研究によって、癌研究者もびっくりしたという成果が *Scientific Reports* 誌に掲載された。
研究者らが癌において可能性があるとしてその役割を調査していた蛋白質が実は代謝の強力な調節因子であることが判明した。肥満マウスの実験室株でこの蛋白質を強制的に発現させると、脂肪量の顕著な減少が示されたのだ。この蛋白質 FGFBP3 (略 BP3) は、線維芽細胞増殖因子 (FGF) 結合蛋白質 (BP) ファミリーに属し、天然蛋白質であり人工的な薬物ではない。FGF は、虫からヒトに至るまでの生物に見出され、細胞増殖の調節、創傷治癒および傷害に対する応答など広範な生物学的過程に関与する。今回 18 日にわたる８回の BP3 治療が肥満マウスの脂肪を３分の１に減らすのに充分であることが分かった、としている。
このエキサイティングな研究結果を踏まえて、BP3 蛋白質がメタボリックシンドロームの為のヒト療法として、これから更なる研究が必要だ、ともしている。

英文記事：
https://medicalxpress.com/news/2018-10-obese-mice-fat-natural-protein.html

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Obese mice lose a third of their fat using a natural protein

October 29, 2018, Georgetown University Medical Center

To the great surprise of cancer researchers, a protein they investigated for its possible role in cancer turned out to be a powerful regulator of metabolism. The Georgetown University-led study found that forced expression of this protein in a laboratory strain of obese mice showed a remarkable reduction of their fat mass despite a genetic predisposition to eat all the time.

The study, published in *Scientific Reports*, suggests that the protein FGFBP3 (BP3 for short) might offer novel therapy to reverse disorders associated with metabolic syndrome, such as type 2 diabetes and fatty liver disease.

Because BP3 is a natural protein and not an artificial drug, clinical trials of recombinant human BP3 could begin after a final round of preclinical studies, investigators say.

"We found that eight BP3 treatments over 18 days was enough to reduce the fat in obese mice by over a third," says the study's senior investigator, Anton Wellstein, MD, Ph.D., a professor of oncology and pharmacology at Georgetown Lombardi Comprehensive Cancer Center.

The treatments also reduced a number of obesity-related disorders in the mice, such as hyperglycemia—excess blood sugar that is often linked to diabetes—and eliminated the fat in their once fatty livers. Clinical as well as microscopic examination of the mice showed no side effects, researchers say.

Obesity, which affects more than 650 million people worldwide, is the major driver for metabolic syndromes, which includes disorders such as insulin resistance, glucose intolerance, hypertension and elevated lipids in the blood.

BP3 belongs to the family of fibroblast growth factor (FGF) binding proteins (BP). FGFs are found in organisms ranging from worms to humans and are involved in a wide range of biological processes, such as regulating cell growth, wound healing and response to injury. Some FGFs act like hormones.

BP1, 2, and 3 are "chaperone" proteins that latch on to FGF proteins and enhance their activities in the body. Wellstein has long researched the BP1 gene because its production is elevated in a range of cancers, suggesting that growth of some cancers is linked to the excess delivery of FGFs. Only recently has Wellstein turned his attention, and that of his lab and colleagues, to BP3 to understand its role.

The researchers found that this chaperone binds to three FGF proteins (19, 21, and 23) that are involved in the control of metabolism. FGF19 and FGF 21 signaling regulates the storage and use of carbohydrates (sugars) and lipids (fats). FGF23 controls phosphate metabolism.

"We found that BP3 exerts a striking contribution to metabolic control," Wellstein says. "When you have more BP3 chaperone available, FGF19 and FGF21 effect is increased through the increase of their signaling. That makes BP3 a strong driver of carbohydrate and lipid metabolism. It's like having a lot more taxis available in New York City to pick up all the people who need a ride."

"With metabolism revved up, sugar in the blood, and fat processed in the liver are used for energy and is not stored," Wellstein says. "And warehouses of fat are tapped as well. For example, the job of FGF21 is to control break down of fat, whether it is stored or just eaten."

While the study results are exciting, additional research is required before BP3 protein can be investigated as a human therapy for metabolic syndromes, he says.

Explore further: **Some cancer therapies may provide a new way to treat high blood pressure**

More information: Elena Tassi et al. Fibroblast Growth Factor Binding Protein 3 (FGFBP3) impacts carbohydrate and lipid metabolism, *Scientific Reports* (2018). **DOI: 10.1038/s41598-018-34238-5**

Journal reference: Scientific Reports

Provided by: Georgetown University Medical Center