Bio News – September, 2019

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

7/31　Lyndra Therapeutics、月 1 回服用の経口避妊薬の開発資金 1,300 万ドルをゲイツ財団から調達

7/31　癌診断の Exact Sciences が同業の Genomic Health を 28 億ドルで買収

8/1　Amgen、バイオシミラーに押されて 2Q 売上減少

8/2　Fujifilm、Biogen のデンマークの生物薬製造拠点取得完了

8/2　Salk Institute の有力なキメラ研究者がヒト細胞混合サルを作製

8/5　Rakuten Medical に楽天が更に 1 億ドル投資

8/6　第一三共、稀な関節腫瘍の治療薬 Turalio が FDA に承認された

8/6　加熱装置からの蒸気吸引(Vaping)と関連する重度肺疾患が米国ウィスコンシン州で発生

8/6　Sanofi のデングワクチン再投入をフィリピン政府が検討

フィリピンで今年これまでに 10 万人超が被って 450 人超が死んでいるデング流行を封じるべく、小児死亡との関連を受けて使用中止となった Sanofi の Dengvaxia ワクチンの再投入をフィリピン政府が検討中。

8/6　カメの胚、卵の中で動いて性別決定に影響 -研究

https://headlines.yahoo.co.jp/hl?a=20190806-00000027-jij_afp-sctch

8/6　新治療実用化へ意欲…理研退職の高橋政代氏

https://headlines.yahoo.co.jp/hl?a=20190806-00050034-yomidr-sctch

8/7　脳震盪を起こさなくてもフットボールは脳にダメージを与え得る - 米ロチェスター大学研究

8/7　NIH の研究者が、微生物叢疾患と女性の健康を専門とする会社、LUCA Biologics を開始(マサチューセッツ州ケンブリッジ)

8/7　Gilead、男性と性交する男性/元男性女性の HIV 予防 Descovy 用途を FDA が支持

8/7　GSK、エボラワクチンを非営利ワクチン推進団体 Sabin Vaccine Institute に譲る

8/7　Novartis の脊髄性筋萎縮症遺伝子治療 Zolgensma のデータ捏造を FDA が調査

Novartis が AveXis を買収して手に入れた 200 万ドルかかる遺伝子治療 Zolgensma (onasemnogene abeparvovec) の承認申請に使われた動物試験結果の捏造(manipulation)の懸念を米国 FDA が調査。

8/8　Allergan、AbbVie による 630 億ドルの買収による独占懸念解消のため 2 剤を手放す

8/8　Teva、CFO の Michael McClellan 氏が家庭の事情により退社

8/8　魚の眠りにヒトとの共通点　日米仏チームが発見

https://headlines.yahoo.co.jp/hl?a=20190808-00000532-san-sctch

8/9　京大 iPS 事業 新法人移管了承…文科省専門家会合

8/9　人工肝臓で脂肪肝の再現に成功、医療への応用に光 -米ピッツバーグ大

https://headlines.yahoo.co.jp/article?a=20190809-00010000-nknatiogeo-sctch

8/9　遺伝子操作ベイビーに「ノー」、WHO が声明

8/9　Apple の iPhone 等の携帯装置とアプリでアルツハイマー病認知症を識別しうる

Eli Lilly、Evidation Health、Apple 主催の実用性評価試験の途中解析の結果、iPhone や睡眠センサー等の肌身離さず持ち歩く通信/感知携帯装置とアプリを介して軽度認知機能障害（MCI）とアルツハイマー型認知症を識別しうることが示された。
この試験ではいずれも Apple の携帯装置・iPhone, Apple Watch, iPad, Beddit 睡眠モニターとアプリを組み合わせて被験者のデータが集められた。

8/9　健康/医療の人工知能（AI）研究所に英国が 2 億 5,000 万ポンドを投じる

8/9　Bayer、iPS 細胞から作る細胞薬の BlueRock（マサチューセッツ州ケンブリッジ）を前金 2 億 4,000 万ドルで買収

8/9　AI で急性腎障害の高精度予測を実現、見えてきたグーグルの医療分野における野望と課題

https://headlines.yahoo.co.jp/article?a=20190809-00010005-wired-sctch

8/9　簡単で効率良い遺伝子改変ラット作出技術開発　京大など

https://headlines.yahoo.co.jp/hl?a=20190809-00000587-san-sctch

8/10　米国裁判所が Amgen の特許を支持し、Sandoz の Enbrel バイオシミラー発売を不許可

Amgen の昨年米国売り上げ 48 億ドルの抗 TNF α 薬 Enbrel の特許 2 つを米国地裁が有効と判断し、Novartis 後発品事業 Sandoz のバイオシミラーErelzi（etanercept）の発売を許しなかった。Sandoz は上訴する予定。
Amgen は Enbrel バイオシミラーに関して韓国の Samsung Bioepis も訴えており、審理が継続中。

8/10　カリフォルニア大学の教授 30 人超が Elsevier に抗議して Cell Press への協力を拒否

8/14　性別産み分け、ウシでは9割成功　技術的にはヒトにも

8/14　エボラ出血熱、ついに「治療可能」に

8/14　GSK、Merck KGaA のラテンアメリカ事業長引き抜き～米国製薬トップに据える

女性 CEO が舵を取る製薬会社 GlaxoSmithKline（GSK）の米国製薬事業長に Merck KGaA のラテンアメリカ生物薬事業トップ女性 Maya Martinez-Davis 氏が就任。

8/15　黄色ブドウ球菌はタバコの煙で“進化”し、薬剤への耐性を強める -英研究

8/15　Zolgensma データ捏造で苦境の Novartis が米国製薬事業長を 9 月から替える

8/15　ゲイツ財団、医療情報会社への投資担当者 Andrew Trister 氏を Apple から引き抜き

8/16　猫アレルギーにさようなら？＝スイスのバイオベンチャー企業、ワクチン開発

8/16　インドの溶媒回収会社が米国の降圧薬発癌性物質汚染に寄与したかもしれない

米国向けに出荷されたバルサルタン（valsartan）等の降圧薬の発癌性ニトロソアミン不純物（NDMA や NDEA）汚染を招いた恐れがある製造体制の不備を指摘する警告を米国 FDA がインドの溶媒回収会社 Lantech Pharmaceuticals に通知。
Lantech の工場で作られた全製品に紛れ込んでいたかもしれないニトロソアミンが米国向け出荷品の汚染を招いた恐れがあると FDA は言っている。

8/20　遺伝子治療 Zolgensma のごまかしを受けて追われた AveXis 元最高科学責任者（CSO）が不正を否定

8/21　痛みを感じる仕組みに新説、皮膚に新たな感覚器官を発見 −カロリンスカ研究所他

8/22　Pfizer、5 億ドルを投じてノースカロライナ州に遺伝子治療製造工場を新築

8/22　Elanco、Bayer の動物医療事業を 76 億ドルで買収

8/22　タンパク質の誤配送を校正、細胞内のメカニズム発見 −京産大など

https://headlines.yahoo.co.jp/hl?a=20190822-00000000-kyt-sctch

8/22　再発の乳がん細胞に「弱点」 増殖促す分子をたたけ

https://headlines.yahoo.co.jp/hl?a=20190822-00000060-asahi-soci

8/22　着床前診断の審査見直しへ　申請 500 件超、病気も多様化

https://headlines.yahoo.co.jp/hl?a=20190822-00000159-kyodonews-soci

8/23　Merck & Co、オーストリアの Themis Bioscience の技術を頼りにワクチンを開発

8/24　テレビ広告に薬価を表示させるのを阻んだ判決を米国政府が受け入れず上訴

8/26　BMS による買収に関連して Celgene が手放す Otezla を Amgen が 134 億ドルで買収

8/26　加熱式タバコ（ベイピング）で初の死亡者 −イリノイ州

8/28　遺伝子治療薬「コラテジェン」（アンジェス −大阪府）で国内初の医療保険適用

8/29　iPS から作った角膜細胞を世界で初めて患者の目に移植 −大阪大

https://headlines.yahoo.co.jp/hl?a=20190829-00000042-mai-sctch

https://headlines.yahoo.co.jp/hl?a=20190829-00000586-san-sctch

https://headlines.yahoo.co.jp/hl?a=20190829-18441803-kantelev-sctch

https://headlines.yahoo.co.jp/hl?a=20190829-00000602-san-sctch

8/29　赤ワイン摂取で腸内細菌叢の多様性が増大 −King’s College London 研究

8/29　協和キリンのパーキンソン病薬を FDA が承認

企業関連ニュース/他のトップページに戻る

今月の研究関連ニュース/他

1. ノックアウトマウスが皮膚と眼の疾患の新しい遺伝子の案内役に

2. マウスの「野生化」は、動物モデルの結果をヒトの結果に変換させるのに役立つ

3. アレルギー反応を引き起こす免疫細胞のサブタイプ発見 −マウス実験
   細胞の標的化がヒトのアナフィラキシーの予防に役立つ可能性

4. 腫瘍上の細菌が膵臓癌患者の免疫応答と生存に影響
   長期生存と結び付く特定の微生物叢：糞便移植治療のポイントを発見

5. ビリルビンが、黄疸だけではなく、脳を保護する可能性 −マウス研究

6. 動物モデルにおいて、ストレスが食欲にどのように影響するか

7. 生物の様々な変異をゲノム編集するための新技術

8. 「肥満ワクチン」開発に光　マウスの腸内細菌減らしたら

9. 短時間睡眠とリンクする遺伝子発見 −マウス実験

1. ノックアウトマウスが皮膚と眼の疾患の新しい遺伝子の案内役に

アルビニズム（白化症）は、眼と皮膚の両方に影響を与える可能性のある稀な遺伝性疾患の中で最もよく知られている。アルビノ発症の条件に関連するいくつかの遺伝子が特定されてはいるが、多くは未だ謎のままである。
カリフォルニア大学デービス校（UC Davis）の研究者らが率いる研究チームは、遺伝子をターゲットにした「ノックアウト」マウスのスクリーニングで、これらの遺伝子変異を多数特定、その結果が *Scientific Reports* 誌で、8 月 1 日に発表された。
皮膚、眼、神経組織は全て同じ初期胚組織から発生するため、リンクされている。ファコマトーシスと呼ばれる、白化症とは別の稀な皮膚と眼の障害グループも、胚発生の初期段階で偶発的に発現することが分かっている。
研究チームは International Mouse Phenotyping Consortium (IMPC) によって作成された遺伝子ノックアウトマウスの一般公開データベースで、皮膚、毛、または色素異常のマウスを検索、その中から眼の欠陥を持っているマウスをクロスチェックした。その結果、皮膚と眼の両方に影響を与える 52 個の遺伝子リストを作成、その中で、これまで知られていなかった 35 個を特定することができた。
研究者らは、この研究が、遺伝性疾患を専門とする臨床医のリソースになることを願っている、言っている。

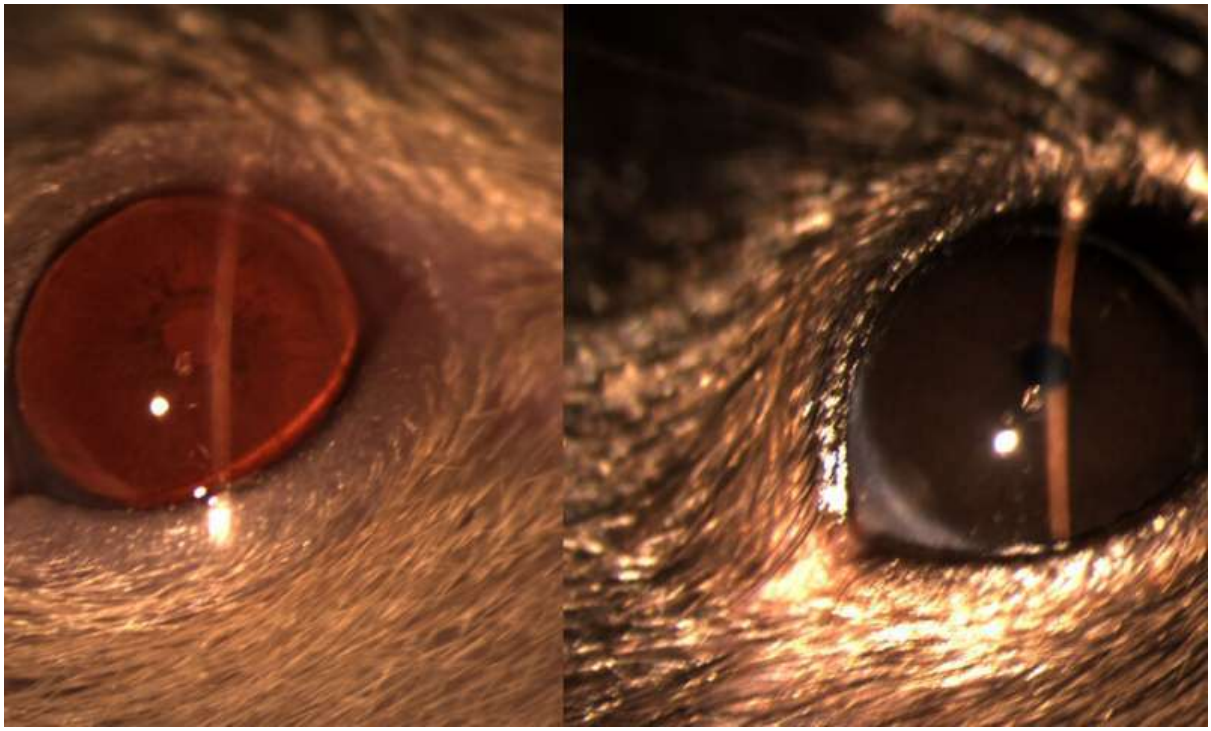
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-08-knockout-mice-genes-eye-skin.html

AUGUST 1, 2019

Knockout mice are guide to new genes for eye and skin disorders

by UC Davis



A team led by UC Davis researchers has used a public database of genetic knockout mice to identify dozens of genetic mutations linked to eye and skin disorders, including forms of albinism and phakomatoses. The newly discovered genes could help clinicians identify related human genes in patients with no known cause for their disorder. This image shows an eye from an albino mouse lacking pigment (left) and a normal mouse. Credit: Ala Moshiri, UC Davis

Albinism is the best-known of a group of rare genetic disorders that can affect both eyes and skin. Some genes have been identified that are linked to these conditions, but many remain mysterious. Now a team led by UC Davis researchers has identified dozens of these genetic mutations in a screen of gene-targeted "knockout" mice. The authors hope the work, published Aug. 1 in *Scientific Reports*, will be a resource for clinicians specializing in genetic disorders.

"This mouse data may be of interest to clinicians, especially for patients with no known genetic cause for their condition," said Ala Moshiri, associate professor of ophthalmology in the UC Davis School of Medicine and corresponding author on the paper.

Skin, eyes and nerve tissue are linked because they all develop from the same early embryonic tissue. Another group of rare eye and skin disorders distinct from albinism, called phakomatoses, are also caused by genetic alterations inherited from parents or that occur by accident early in embryo development.

Albino people and animals lack pigment in their hair, skin and eyes. The degree of pigment loss varies, depending probably on the genetic change responsible. Some albinos are entirely lacking in pigment; at the other end of the scale, some people with "blonde" coloration may have a mild form of albinism.

There are known genes linked to albinism in humans, but not all cases have a clear genetic cause.

Lab mouse a model for human genetics

Moshiri, Bret Moore, resident at the UC Davis Veterinary Medical Teaching Hospital and an international team of colleagues searched the public database of gene knockout mice created by the International Mouse Phenotyping Consortium (IMPC) for animals with skin, hair or pigmentation abnormalities. Then they cross-checked for those which also had eye defects. That produced a list of 52 genes affecting both skin and eye organ systems, 35 of which were previously unknown.

"I expect the majority of these genes will cause similar problems in humans," Moshiri said.

The IMPC is an international effort including the Mouse Biology Program at UC Davis. The IMPC collaborators create mice with targeted deletions of a single gene ("knockout" mice) and examine the effects. So far, the consortium has produced lines of knockout mice for about 6,000 genes, of which more than 5,000 have been characterized, or phenotyped, across 11 body systems.

Identifying mouse genes related to a specific disorder can help identify the equivalent genes in humans. Sequencing an entire human genome is relatively easy in 2019, but working out which genetic change is tied to a specific disease or disorder is much harder because humans are so genetically variable. Laboratory mice, on the other hand, are inbred on a consistent genetic background, making it much easier to link traits to a single genetic change. Armed with a list of candidate genes from mice, clinicians could home in on specific genes in human patients.

Explore further

300 blind mice uncover genetic causes of eye disease

More information: Genome-wide screening of mouse knockouts reveals novel genes required for normal integumentary and oculocutaneous structure and function, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-47286-2

Journal information: Scientific Reports

Provided by UC Davis

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2. マウスの「野生化」は、動物モデルの結果をヒトの結果に変換させるのに役立つ

国立衛生研究所の研究者らは、マウス研究をヒトの健康の進歩へとより良く変換できるような新しいマウスモデルを開発した。
研究者らが「野生化」と呼ぶマウスモデルは、野生マウスの微生物叢と病原体を持ち、実験用マウスの遺伝的特徴を維持。2件の前臨床研究において、実験用マウスがヒトの免疫応答を反映しなかったのに対して、この野生化マウスは反映することが分かった。
NHI の国立糖尿病・消火器・腎臓病研究所（NIDDK）の研究者らが率いるこの研究は、*Science* 誌オンライン版で公開されている。
研究者らは、免疫系研究のために最も一般的に使用されている実験用マウス系統の胚をメスの野生マウスに移植し、その後、そのメスが出産した野生化ベイビーを飼育した。研究者らはまた、野生化マウスの微生物叢が 5 世代にわたって安定していること、環境的チャレンジに対する回復力があること（抗生物質を 7 日間与えた場合、実験用マウスの腸内微生物叢は変化し、回復しなかったが、野生化マウスの微生物叢は完全に回復した）を発見した。
研究者らは、免疫反応を標的とするために使用される薬物が前臨床試験で実験用マウスの治療では成功したが、結果としてヒトでの治療効果が得られなかった 2 つの研究を使って、野生化マウスと実験用マウスを同じ薬で治療したところ、実験用マウスではなく野生化マウスが、臨床試験で見られた人間の反応を模倣した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190801142515.htm

'Wildling' mice could help translate results in animal models to results in humans

Researchers create mouse colony to address shortcomings of laboratory mice

Date:

August 1, 2019

Source:

NIH/National Institute of Diabetes and Digestive and Kidney Diseases

Summary:

Researchers developed a new mouse model that could improve the translation of research in mice into advances in human health. The mouse model, which the scientists called 'wildling,' acquired the microbes and pathogens of wild mice, while maintaining the laboratory mice's genetics that make them more useful for research.

Researchers at the National Institutes of Health developed a new mouse model that could improve the translation of research in mice into advances in human health. The mouse model, which the scientists called "wildling," acquired the microbes and pathogens of wild mice, while maintaining the laboratory mice's genetics that make them more useful for research. In two preclinical studies, wildlings mirrored human immune responses, where lab mice failed to do so. Led by scientists at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the study published online in *Science*.

"We wanted to create a mouse model that better resembles a mouse you'd find in the wild," said Barbara Rehermann, M.D., chief of the Immunology Section in NIDDK's Liver Diseases Branch and senior author on the study. "Our rationale was that the immune responses and microbiota of wild mice and humans are likely shaped in a similar way -- through contact with diverse microbes out in the real world."

Microbiota refers to the trillions of tiny microbes, such as bacteria, fungi, and viruses, that live in and on the bodies of people and animals and play a critical role in keeping immune systems healthy. Unlike squeaky clean lab mice raised in artificial settings, wild mice have developed symbiotic relationships with microbes they have encountered in the outside world -- just as people have done.

Rehermann and Stephan Rosshart, M.D., the study's lead author and NIDDK postdoctoral fellow, have long sought to improve animal models of complex diseases in humans. In 2017, they led research showing that transferring wild mice gut microbiota into lab mice helped the mice survive an otherwise lethal flu virus infection and fight colorectal cancer.

In the current study, they transplanted embryos of the most commonly used strain of laboratory mice for immune system research into female wild mice, who then gave birth to and raised wildlings. The researchers and their collaborators compared the microbiota of the wildlings, wild mice and lab mice. They found that the wildlings acquired the microbes and pathogens of wild mice and closely resembled wild mice in their bacterial microbes present at the gut, skin, and vagina, as well as in the number and kinds of fungi and viruses present.

"A healthy microbiome is important not only for the immune system, but also for digestion, metabolism, even the brain," said Rosshart, who recently completed his fellowship in NIDDK and will open a new lab in Germany. "The wildling model could help us better understand what causes diseases, and what can protect us from them, thus benefitting many areas of biomedical research."

The researchers also tested the stability and resilience of the wildlings' microbiota and found the microbiota was stable across five generations and resilient to environmental challenges. For example, when the mice were given antibiotics for seven days, the lab mice's gut microbiota changed and did not recover, while the wildlings' microbiota fully recovered. Further, when the mice were fed a 10-week high-fat diet, the microbiota of the lab mice changed significantly and never returned to baseline. The wildlings' microbiota changed only mildly and recovered shortly after the diet ended. The authors suggest that the stability and resilience of wildlings, if the model is used widely, could improve the validity and reproducibility of biomedical studies.

Finally, the researchers tested how well the wildlings could predict human immune responses. To do so, they drew from two studies where drugs used to target immune responses were successful in treating lab mice in preclinical trials but consequently failed to have therapeutic effects in humans. In the current study, the researchers treated wildlings and lab mice with the same drugs. The wildlings, but not the lab mice, mimicked the human responses seen in clinical trials.

"We always strive for effective ways to shorten the gap between early lab findings and health advances in people, and the wildling model has the potential to do just that," said NIDDK Director Griffin P. Rodgers, M.D. "By helping to predict immune responses of humans, the wildling model could lead to important discoveries to help treat and prevent disease, and ultimately, improve human health."

The research was supported by the intramural research programs of NIDDK, the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Allergy and Infectious Diseases (NIAID). Additional NIH support came from NIDDK through grant DK113136 and from NIAID through grant AI137157-01.

Story Source:

Materials provided by **NIH/National Institute of Diabetes and Digestive and Kidney Diseases**.
Note: Content may be edited for style and length.

Journal Reference:

1. Stephan P. Rosshart, Jasmin Herz, Brian G. Vassallo, Ashli Hunter, Morgan K. Wall, Jonathan H. Badger, John A. McCulloch, Dimitrios G. Anastasakis, Aishe A. Sarshad, Irina Leonardi, Nicholas Collins, Joshua A. Blatter, Seong-Ji Han, Samira Tamoutounour, Svetlana Potapova, Mark B. Foster St. Claire, Wuxing Yuan, Shurjo K. Sen, Matthew S. Dreier, Benedikt Hild, Markus Hafner, David Wang, Iliyan D. Iliev, Yasmine Belkaid, Giorgio Trinchieri, Barbara Rehermann. **Laboratory mice born to wild mice have natural microbiota and model human immune responses**. *Science*, 2019; 365 (6452): eaaw4361 DOI: 10.1126/science.aaw4361

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3. アレルギー反応を引き起こす免疫細胞のサブタイプ発見 –マウス実験
細胞の標的化がヒトのアナフィラキシーの予防に役立つ可能性

アレルギーは、アナフィラキシー、気道の収縮による極端な反応、突然の血圧低下を引き起こす場合、生命を充分に脅かす可能性がある。コネチカット州ニューヘイブンのイェール大学、コネチカット州ファーミントンのジャクソンラボ ゲノム医学研究所、および彼らの共同研究者らは、このアナフィラキシーやその他のアレルギー反応に関連する抗体の産生を促進する免疫細胞のサブタイプを特定した。この研究は、重度のアレルギー反応を防ぐための新しい治療法の潜在的ターゲットを明らかにするものだとして、*Science* 誌に掲載されている。

研究者らが発見したのは、DOCKS8 免疫不全症候群と呼ばれる稀な遺伝性免疫疾患を持つよう飼育された実験用マウスにおける、T 細胞のサブタイプ –T 濾胞性ヘルパー細胞 13 または Tfh13 細胞と呼ばれる– である。ヒトにおいては、DOCK8 欠乏症により、皮膚および呼吸器系のウイルス感染が再発し、重度のアレルギーや喘息を生じる。研究者らは、DOCK8 欠乏症マウスには、正常なマウスには見られないサイトカインと呼ばれる化学メッセンジャーのユニークな組み合わせを生み出す T 濾胞性ヘルパー細胞があることを発見した。

正常な免疫系をもつマウスを呼吸器系および食物アレルゲンで感作し、アナフィラキシーにつながる重度のアレルギー反応を誘発したところ、非アレルギー性マウスには Tfh13 細胞が欠けていたが、アレルギー性マウスには Tfh13 細胞と高親和性 IgE の両方があった。遺伝子操作により、マウスの Tfh13 細胞の発達を防ぐと、動物がアレルゲンに対してアナフィラキシーIgE を作らないことを発見した。

研究者らは、Tfh13 細胞を標的とすることが、アレルギー疾患の予防や治療に対する新しい戦略になるかもしれない、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190801142538.htm

Scientists discover immune cell subtype in mice that drives allergic reactions

Study suggests targeting cell may help prevent anaphylaxis in humans

Date:

August 1, 2019

Source:

NIH/National Institute of Allergy and Infectious Diseases

Summary:

Allergies can be life-threatening when they cause anaphylaxis, an extreme reaction with constriction of the airways and a sudden drop in blood pressure. Scientists have identified a subtype of immune cell that drives the production of antibodies associated with anaphylaxis and other allergic reactions. The research reveals a potential target for new therapies to prevent severe allergic reactions.

FULL STORY

Allergies can be life-threatening when they cause anaphylaxis, an extreme reaction with constriction of the airways and a sudden drop in blood pressure. Scientists have identified a subtype of immune cell that drives the production of antibodies associated with anaphylaxis and other allergic reactions. The research was funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, and reveals a potential target for new therapies to prevent severe allergic reactions. The findings are published online today in the journal *Science*.

Investigators at Yale University, New Haven, Connecticut, the Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, and their collaborators discovered a subtype of T cells -- called T follicular helper cell 13, or Tfh13 cells -- in laboratory mice bred to have a rare genetic immune disease called DOCK8 immunodeficiency syndrome. In humans, DOCK8 deficiency leads to recurrent viral infections of the skin and respiratory system and to severe allergies and asthma.

Allergies and anaphylaxis are linked to the production of high levels of high-affinity IgE antibodies, which bind strongly to allergens to spur allergic reactions. The investigators noted that mice with a DOCK8 deficiency had novel T follicular helper cells, not found in normal mice, that produced a unique combination of chemical messengers called cytokines.

They then took mice with normal immune systems and sensitized them with respiratory and food allergens to induce severe allergic reactions leading to anaphylaxis. While non-allergic mice lacked Tfh13 cells, allergic mice had both Tfh13 cells and high-affinity IgE. With genetic manipulation, the scientists prevented Tfh13 cell development in mice and found that the animals did not make anaphylactic IgE to allergens. To transfer this insight to humans, they then compared blood samples from people with peanut or respiratory allergies to those of non-allergic volunteers and found that individuals with allergies and the associated IgE had elevated levels of Tfh13 cells.

The study authors conclude that Tfh13 cells are responsible for directing antibody-producing B cells to create high-affinity IgE and that Tfh13 cells may be required for allergic disease, including anaphylaxis. They say targeting Tfh13 cells may represent a new strategy to prevent or treat allergic diseases. While such a strategy would likely not replace life-saving, emergency epinephrine when anaphylaxis occurs, therapies targeting Tfh13 cells might prevent the onset of anaphylaxis when an allergic person is exposed to an allergen.

Story Source:

Materials provided by **NIH/National Institute of Allergy and Infectious Diseases**. *Note: Content may be edited for style and length.*

Journal Reference:

1. U Gowthaman et al. **Identification of a T follicular helper cell subset that drives anaphylactic IgE**. *Science*, 2019 DOI: 10.1126/science.aaw6433

Cite This Page:

- MLA
- APA
- Chicago

NIH/National Institute of Allergy and Infectious Diseases. "Scientists discover immune cell subtype in mice that drives allergic reactions: Study suggests targeting cell may help prevent anaphylaxis in humans." ScienceDaily. ScienceDaily, 1 August 2019. <www.sciencedaily.com/releases/2019/08/190801142538.htm>.

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4. 腫瘍上の細菌が膵臓癌患者の免疫応答と生存に影響
長期生存と結び付く特定の微生物叢：糞便移植治療のポイントを発見

長期間に渡って生き延びる数少ない膵臓癌患者とどんな治療を施しても膵臓癌に打ち負ける多くの患者との主な相違点は、免疫応答を刺激あるいは抑制する腫瘍上の細菌の特徴である、とテキサス州立大学 MD アンダーソン癌センターの研究者ら主導のチームが *Cell* 誌に報告している。
彼らは、また、長期生存者からの糞便微生物叢移植（FMT）が、腫瘍上の細菌である微生物叢を変化させ、この疾患を患っているマウスモデルにおいて免疫反応を促し、腫瘍を窒息させることを示している。
Moon Shots Program ™ は、科学的発見の開発を患者の生命を救う臨床的進歩へと加速させようという共同の取り組みであるが、今回このプログラムによって膵臓癌の糞便移植の臨床試験の開発資金が提供された。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-08/uotm-bot080619.php

NEWS RELEASE 8-AUG-2019

Bacteria on tumors influences immune response and survival of patients with pancreatic cancer

Study finds specific microbiome tied to long-term survival; points to fecal transplant treatment

UNIVERSITY OF TEXAS M. D. ANDERSON CANCER CENTER

IMAGE: Florencia McAllister, M.D. **view more**

Credit: MD Anderson Cancer Center

HOUSTON -- A key difference between the few pancreatic cancer patients who survive long-term and the many whose disease overcomes all treatments is the bacterial signatures on their tumors that either stimulate or suppress immune response, a team led by researchers from The University of Texas MD Anderson Cancer Center reports in the journal *Cell*.

The researchers also showed that fecal microbiota transplants (FMT) from long-term survivors prompted immune response and stifled tumors in a mouse model of the disease by altering the bacteria on the tumor - its microbiome.

"Results of the FMT experiments represent a significant therapeutic opportunity to improve pancreatic cancer treatment by altering the tumor immune microenvironment," said senior author Florencia McAllister, M.D., assistant professor of Clinical Cancer Prevention at MD Anderson. "There is promise here but we have a lot of work ahead."

MD Anderson's Pancreatic Cancer Moon Shot™ has provided McAllister with funding to develop a clinical trial of fecal transplants for pancreatic cancer. The Moon Shots Program™ is a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patients' lives.

Most patients with pancreatic ductal adenocarcinoma - the most common form of pancreatic cancer - have late-stage disease when diagnosed. Just 9% survive to five years. Those with earlier stage cancer that can be surgically removed have a high recurrence rate and median survival of 24-30 months.

No genomic biomarkers have been identified that shed light on the reasons for long-term survival in that fraction of patients, McAllister said.

Long-term survivors have diverse tumor microbiome

While recent research has shown that the composition and diversity of microbes living in the digestive tract - the gut microbiome - can affect how cancer immunotherapy works, little research has focused on the bacteria in the tumor and how it might affect prognosis and survival, McAllister said. "We've known there are bacteria on pancreatic tumors, so we asked 'do these bacteria have a role in cancer?'"

To launch the first such study in pancreatic cancer, McAllister and colleagues analyzed the bacterial DNA in tumors of long-term survivors matched to short-term survivors from two independent cohorts at MD Anderson and Johns Hopkins Hospital. In the MD Anderson cohort, median survival was 10 years for the long-term survivors (22 patients) and 1.6 years for the short-term survivors (21 patients). In the validation cohort from Johns Hopkins, 15 patients had overall survival greater than 10 years, and 10 survived fewer than five years.

Using 16S rRNA gene sequencing, the team found the long-term survivors had much greater diversity of bacterial species than the short-term survivors. Stratifying the MD Anderson patients only by this diversity measure showed those with high diversity had median survival of 9.66 years and those with low diversity had median survival of 1.66 years.

The diversity results were independent of other factors, such as previous therapies, body mass index, and antibiotics use, making it a predictor of survival for surgical patients and indicating the potential importance of the tumor microbiome in cancer progression.

Researchers also found marked differences in the bacterial communities found in each survivor group. The long-term survivors showed a relative abundance of Pseudoxanthomonas, Saccharropolyspora and Streptomyces. The presence of all three taxa, as well as the species Bacillus Clausii, predicted better outcomes for patients in both MD Anderson and Johns Hopkins cohorts.

Specific microbiome boosts immune attack on tumors

Immunohistochemistry showed a greater density of T cells, including the CD8-positive cell-killing variety, in the tumors of long-term survivors in both the MD Anderson and Johns Hopkins cohorts, consistent with previous research that showed more active immune response in long-term survivors.

McAllister and colleagues found a strong correlation between immune cell infiltration and the microbiome diversity of the tumors. Additional analysis showed immune infiltration and activation of T cells was associated with the three enriched bacterial types discovered on long-term survivors' tumors.

With an apparent connection between the tumor microbiome and immune response, the team set out to find a way to change the tumor microbiome.

Using the gut microbiome to alter tumor microbiome

"You cannot modulate the tumor microbiome directly, but you can modulate the gut microbiome, and if there's cross-talk between the gut and the tumor microbiomes, you could change the tumor microbiome indirectly," McAllister said.

The team compared the bacteria in the gut, in the tumor and in adjacent tissue in three surgery patients. They found the gut microbiome represents about 25% of the tumor microbiome, but is absent from the normal, adjacent tissue, suggesting bacteria in the gut can colonize pancreatic tumors.

The researchers transplanted fecal microbiota from patients with advanced cancer into mice and found that the donor microbiome represented about 5% of the resultant tumor microbiome but that 70% of the overall tumor microbiome had been otherwise altered by the transplant.

"Now we know you can completely change the bacterial composition of the tumor microbiome by doing FMT," McAllister said.

Reversing immune suppression with fecal transplants

Next, they performed stool transplants into mice from patients who had advanced pancreatic cancer, patients who had survived more than five years and had no evidence of disease, and healthy controls.

Five weeks after tumor implementation, mice that had received FMT from patients with advanced disease had much larger tumors than those that received FMT from long-term survivors (70% smaller average size) or healthy controls (50% smaller average size).

Immune profiling showed the mice that received the FMT from long-term survivors had significantly higher numbers and greater activation of CD8-positive T cells compared to the other two groups. Those who received FMT from advanced-stage patients had increased regulatory T cells and myeloid-derived suppressor cells, both of which suppress immune response.

To evaluate whether the effect of FMT relies on the immune system, the team depleted T cells in a group of mice treated with the long-term survivor FMT, which completely blocked the anti-tumor effect of the transplant.

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Co-authors with McAllister are first authors Erick Riquelme, Ph.D., and Yu Zhang, Ph.D., both of Clinical Cancer Prevention. Other co-authors from that department are Maria Montiel, M.D., Michelle Zoltan, Pompeyo Quesada, Vidhi Chandra, Hanwen Xu, Ph.D., and Samir Hanash, M.D., Ph.D.; Liangliang Zhang, Ph.D., Wenli Dong, Lei Feng, Kim-Anh Do, Ph.D., and Christine Peterson, Ph.D., of Biostatistics; Robert Jenq, M.D., and Jennifer Wargo, M.D., of Genomic Medicine; Anthony San Lucas, Ph.D., and Paul Scheet, Ph.D., of Epidemiology; Jared Burks, Ph.D., of Leukemia; Ching-Wei D. Tzeng, M.D., Michael Kim, M.D., Matthew Katz, M.D., of Surgical Oncology; Anirban Maitra, M.B.B.S., of Sheikh Ahmed Pancreatic Cancer Research Center at MD Anderson; Ismet Sahin, Ph.D., of Texas Southern University; Deborah Nejman, Ph.D., and Ravid Straussman, M.D., Ph.D., of Weizmann Institute of Science, Rehovot, Israel; Cynthia Sears, M.D., and Laura Wood, M.D., of Johns Hopkins University School of Medicine; James Robert White, Ph.D., of Resphera Biosciences, Baltimore, MD, and Nadim Ajami, Ph.D., and Joseph Petrosino, Ph.D., of Baylor College of Medicine.

This research was funded by the American Gastroenterological Association Research Foundation, PanCAN/AACR Career Development Award, MD Anderson Philanthropic Funds, MD Anderson's Moon Shots Program, Emerson Collective Award, NCI K12 Paul Calabresi Clinical Scholarship Award, Stand Up To Cancer-Lustgarten Foundation grant, a grant from the National Cancer Institute of the National Institutes of Health R25E (CA056452) and MD Anderson's Cancer Center Support Grant from the NCI (CA016672).

McAllister, Riquelme and Zhang are filing a patent based on findings presented in this paper. Other declarations of interests are available in the paper.

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5. ビリルビンが、黄疸だけではなく、脳を保護する可能性 –マウス研究

ジョンズ ホプキンズ大学の研究者らは、マウス研究によって、ビリルビンが脳の保護にユニークな役割を果たしていることを発見した。胆汁色素であるビリルビンは、黄疸の人の皮膚を黄変させることで最も一般的に知られており、肝臓または血液の健康状態のマーカーとして臨床検査で測定される。
Cell Chemical Biology 誌で 7 月 25 日に公開された報告に記載されている新しい研究では、研究チームはビリルビンを生成しないように遺伝子操作された実験マウスのニューロンを使用した。また細胞が成長するにつれて細胞をさまざまな酸化ストレスに源に晒した。この結果を、正常なマウスの脳細胞と比較すると、遺伝子組み換えマウスのニューロンはこれらのストレッサーに対して、特にスーパーオキシドと呼ばれる有害な形の酸素の影響をはるかに受けやすいことを発見。
また、脳損傷についての研究においては、ビリルビンを欠いたマウスは、通常の 2～3 倍の影響があることを発見した。この発見は、脳やその他の場所でのビリルビンの役割の科学的理解を促進し、過度のスーパーオキシドレベルと参加ストレスが特徴的なハンチントン病やパーキンソン病などの神経変性疾患の新しい治療法に繋がる可能性がある、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/07/190716113022.htm

More than just jaundice: Mouse study shows bilirubin may protect the brain

Researchers have found bilirubin plays a unique role in protecting the brain

Date:

August 12, 2019

Source:

Johns Hopkins Medicine

Summary:

In studies in mice, researchers report they have found that bilirubin, a bile pigment most commonly known for yellowing the skin of people with jaundice, may play an unexpected role in protecting brain cells from damage from oxidative stress.

FULL STORY

In studies in mice, Johns Hopkins Medicine researchers report they have found that bilirubin, a bile pigment most commonly known for yellowing the skin of people with jaundice, may play an unexpected role in protecting brain cells from damage from oxidative stress.

Bilirubin is commonly measured in lab tests as a marker for liver or blood health, and high levels may indicate disease. However, whether it has a role in healthy people has remained unclear.

The Johns Hopkins Medicine team says its interest in the compound's function in the brain arose from testing which tissues in the mouse body produced bilirubin. Surprisingly, the researchers found "exceptional levels" of the stuff in mouse brains -- five to 10 times higher production than in rodents' livers.

"Bilirubin is normally considered a waste product, but this level of production takes a lot of metabolic energy, and it seemed bizarre for bilirubin to not have a function," says Bindu Paul, Ph.D., faculty research instructor at the Johns Hopkins University School of Medicine's Solomon H. Snyder Department of Neuroscience, and a member of the research team.

The new study, described in a report published July 25 in *Cell Chemical Biology*, set out to find the purpose for harboring so much bilirubin in the brain. The team noted that past studies proposed that bilirubin might be an important antioxidant. Since the brain is so metabolically active and vulnerable to oxidative damage, the research group considered the possibility that bilirubin might be particularly important to protecting the brain against oxidative stress.

For their experiments, the team used mouse neurons grown in the laboratory that were genetically engineered to not produce bilirubin. As the cells grew, the researchers exposed them to various sources of oxidative stress by introducing reactive molecules to their environment.

When compared with normal mouse brain cells, the researchers found that the genetically modified mouse neurons were far more vulnerable to these stressors -- particularly at the hand of a harmful form of oxygen called superoxide.

Chirag Vasavda, an M.D./Ph.D. student in Solomon Snyder's laboratory and first author on the study, notes that superoxide is an important chemical cell messenger linked to learning, memory and development in the brain.

However, excessive brain cell activity can lead to uncontrolled superoxide levels, which can trigger oxidative stress and initiate a series of harmful reactions that cause damage to the brain. "Our initial experiments hinted to us that bilirubin might play an important role in controlling the levels of superoxide in the brain," says Vasavda.

The research team suspected that bilirubin's ability to regulate superoxide originated in its chemical structure, which allows it to grab on to and neutralize the harmful molecule in a way that other antioxidants, such as glutathione and cysteine, cannot.

To test this, the researchers stimulated excessive brain cell activity in normal brains and brains engineered to lack bilirubin. They found that brains lacking the bilirubin-production gene accumulated excessive superoxide. Then they stimulated brain activity in normal mice and mice lacking bilirubin to test whether removing bilirubin worsens brain damage or cell death.

The researchers found that mice that lacked bilirubin had about two to three times more brain damage as their normal counterparts, suggesting that bilirubin protected normal brains against harmful superoxide reactions.

This discovery, the investigators say, advances scientific understanding of bilirubin's role in the brain and elsewhere and could lead to novel treatments for neurodegenerative diseases such as Huntington's and Parkinson's that are marked by excessive superoxide levels and oxidative stress.

Story Source:

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

Journal Reference:

1. Chirag Vasavda, Ruchita Kothari, Adarsha P. Malla, Robert Tokhunts, Anthony Lin, Ming Ji, Cristina Ricco, Risheng Xu, Harry G. Saavedra, Juan I. Sbodio, Adele M. Snowman, Lauren Albacarys, Lynda Hester, Thomas W. Sedlak, Bindu D. Paul, Solomon H. Snyder. **Bilirubin Links Heme Metabolism to Neuroprotection by Scavenging Superoxide**. *Cell Chemical Biology*, 2019; DOI: 10.1016/j.chembiol.2019.07.006

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- Chicago

Johns Hopkins Medicine. "More than just jaundice: Mouse study shows bilirubin may protect the brain: Researchers have found bilirubin plays a unique role in protecting the brain." ScienceDaily. ScienceDaily, 12 August 2019. <www.sciencedaily.com/releases/2019/08/190812094502.htm>.

6. 動物モデルにおいて、ストレスが食欲にどのように影響するか

ヒューストンのテキサス大学健康科学センター（UTHealth）の摂食障害の研究者らは、活性化されるとストレスレベルが高まり食欲減退を引き起こす神経回路を発見した。この知見は *Nature Communications* 誌に掲載されている。
国立精神衛生研究所によると、研究者らは、精神障害の中で最も高い死亡率を示す神経性食欲不振と呼ばれる重度の摂食障害の治療法を開発の助けとなる、と信じているという。
研究チームは、マウスの脳の 2 つの部分、脳の摂食関連ゾーンである視床下部、および脳の感情ゾーンである腹側外側中隔を接続する神経回路に注目した。研究者らが神経回路を活性化した時、不安レベルが増加し、食欲が減少した。逆に、神経回路を阻害すると、不安レベルが低下し、空腹感が増加した、としている。
彼らは、光遺伝学と呼ばれる研究手法を使用して、問題のニューロンのオンとオフを切り替えた。主執筆者であり、McGovern Medical School の Yuanzhong Xu 博士は、この発見を確認するには追加の前臨床試験が必要であると述べている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190816191450.htm

How stress can curb the desire to eat in an animal model

Date:

August 16, 2019

Source:

University of Texas Health Science Center at Houston

Summary:

Eating disorder researchers have discovered a neurocircuit in mice that, when activated, increased their stress levels while decreasing their desire to eat.

FULL STORY

Eating disorder researchers at The University of Texas Health Science Center at Houston (UTHealth) have discovered a neurocircuit in mice that, when

activated, increased their stress levels while decreasing their desire to eat. Findings appear in *Nature Communications*.

The scientists believe their research could aid efforts to develop treatments for a serious eating disorder called anorexia nervosa, which has the highest mortality rate of any mental disorder, according to the National Institute of Mental Health. People with anorexia nervosa avoid food, severely restrict food, or eat very small quantities of only certain foods. Even when they are dangerously underweight, they may see themselves as overweight.

"We have identified a part of the brain in a mouse model that controls the impact of emotions on eating," said Qingchun Tong, PhD, the study's senior author and an associate professor in the Center for Metabolic and Degenerative Disease at McGovern Medical School at UTHealth.

Because mice and humans have similar nervous systems, Tong, the Cullen Chair in Molecular Medicine at UTHealth, believes their findings could shed light on the part of the human brain that regulates hunger.

The investigators believe they are among the first to demonstrate the role of this neurocircuit in the regulation of both stress and hunger.

While previous research has established that stress can both reduce and increase a person's desire to eat, the neural mechanisms that act on the regulation of eating by stress-related responses largely remain a mystery.

Tong's team focused on a neurocircuit connecting two parts of the mouse brain: the paraventricular hypothalamus, an eating-related zone in the brain, and the ventral lateral septum, an emotional zone in the brain. The neurocircuit acts as an on/off switch.

When researchers activated the neurocircuit, there was an increase in anxiety levels and a decrease in appetite. Conversely, when the investigators inhibited the neurocircuit, anxiety levels dropped and hunger increased.

The scientists used a research technique called optogenetics to turn the neurons in question on and off.

Yuanzhong Xu, PhD, the study's lead author and an instructor at McGovern Medical School, said additional preclinical tests are needed to confirm their findings.

Coauthors from UTHealth include Yungang Lu, PhD; Ryan Cassidy; Leandra Mangieri, PhD; Canjun Zhu, PhD; Zhiying Jiang, PhD; Xugen Huang, PhD; and Nicholas Justice, PhD. Also contributing to the paper were Yong Xu, MD, PhD, and Benjamin Arenkiel, PhD, of Baylor College of Medicine.

Tong and Justice are on the faculty of The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences.

Story Source:

Materials provided by **University of Texas Health Science Center at Houston**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yuanzhong Xu, Yungang Lu, Ryan M. Cassidy, Leandra R. Mangieri, Canjun Zhu, Xugen Huang, Zhiying Jiang, Nicholas J. Justice, Yong Xu, Benjamin R. Arenkiel, Qingchun Tong. **Identification of a**

neurocircuit underlying regulation of feeding by stress-related emotional responses. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-11399-z

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University of Texas Health Science Center at Houston. "How stress can curb the desire to eat in an animal model." ScienceDaily. ScienceDaily, 16 August 2019. <www.sciencedaily.com/releases/2019/08/190816191450.htm>.

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7. 生物の様々な変異をゲノム編集するための新技術

マウスのゲノム編集をするための新しいツール（SATI と呼ばれる）が、Salk Institute の研究者らによって開発され、8 月 23 日に *Cell Reports* 誌で発表された。
研究チームはこれがハンチントン病や希少な早老化症候群である早老症など、広範囲に及ぶ遺伝子の突然変異によって引き起こされる多くの障害の治療に役立つ新遺伝子編集ツールの開発へと拡張できる、としている。
DNA を変更する技術（特に HITI と呼ばれる CRISPR-Cas9 ベースの遺伝子編集技術）は、細胞の通常の DNA 修復メカニズムを使用して、皮膚や腸内の細胞の分裂に最も効果的とされる。しかしながら、DNA の重要な領域をターゲットにすることができず、生体組織にはさまざまな種類の細胞が含まれている為そのような技術の作成は困難であった。
今回開発された SATI（細胞間線形化単一相同性アームドナー媒介イントロン-ターゲティング統合の略）と呼ばれる新しい遺伝子ノックイン法は、ゲノムの追加領域を標的化できるようにする以前の HITI メソッドの進歩型である。
タンパク質の非コード領域は DNA の大部分（～98%）を構成し、遺伝子のオンとオフを含む多くの細胞機能を制御するため、将来の遺伝子治療の貴重な標的になる可能性がある。今回の SATI 技術において、研究者らは遺伝子の機能に影響を及ぼさない、DNA のこれらの非コード領域を標的とし、広範囲の突然変異と細胞型の標的化を可能にする汎用ツールを作成した。また、概念実証として、既存のゲノム編集ツールを使用して修復することが困難な突然変異によって引き起こされる早老化のマウスモデルに焦点を当てた、としている。
又、この研究論文上には数名の日本人研究者の名前が見うけられる。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190823182700.htm

A novel technology for genome-editing a broad range of mutations in live organisms

Scientists develop a new gene-editing tool that could help treat many disorders caused by gene mutations

Date:

August 23, 2019

Source:

Salk Institute

Summary:

Researchers have developed a new tool -- dubbed SATI -- to edit the mouse genome, enabling the team to target a broad range of mutations and cell types. The new genome-editing technology could be expanded for use in a broad range of gene mutation conditions such as Huntington's disease and the rare premature aging syndrome, progeria.

FULL STORY

Gene editing concept (stock image).

Credit: © vchalup / Adobe Stock

The ability to edit genes in living organisms offers the opportunity to treat a plethora of inherited diseases. However, many types of gene-editing tools are unable to target critical areas of DNA, and creating such a technology has been difficult as living tissue contains diverse types of cells.

Now, Salk Institute researchers have developed a new tool -- dubbed SATI -- to edit the mouse genome, enabling the team to target a broad range of mutations and cell types. The new genome-editing technology, described in *Cell Research* on August 23, 2019, could be expanded for use in a broad range of gene mutation conditions such as Huntington's disease and the rare premature aging syndrome, progeria.

"This study has shown that SATI is a powerful tool for genome editing," says Juan Carlos Izpisua Belmonte, a professor in Salk's Gene Expression Laboratory and senior author of the paper. "It could prove instrumental in developing effective strategies for target-gene replacement of many different types of mutations, and opens the door for using genome-editing tools to possibly cure a broad range of genetic diseases."

Techniques that modify DNA -- notably the CRISPR-Cas9 system -- have generally been most effective in dividing cells, such as those in the skin or the gut, using the cells' normal DNA repair mechanisms. The Izpisua Belmonte lab previously showed that their CRISPR/Cas9-based gene-editing technology, called HITI (for homology-independent targeted integration), could target both dividing and non-dividing cells. Protein-coding regions function like recipes for making proteins, while areas called non-coding regions act as chefs deciding how much food to make. These non-coding regions make up the vast majority of DNA (~98%) and regulate many cellular functions including turning genes off and on, so could be a valuable target for future gene therapies.

"We sought to create a versatile tool to target these non-coding regions of the DNA, which would not affect the function of the gene, and enable the targeting of a broad range of mutations and cell types," says Mako Yamamoto, co-first author on the paper and a postdoctoral fellow in the Izpisua Belmonte lab. "As a proof-of-concept, we focused on a mouse model of premature aging caused by a mutation that is difficult to repair using existing genome-editing tools."

The new gene knock-in method, which the scientists call SATI (short for intercellular linearized Single homology Arm donor mediated intron-Targeting Integration) is an advancement of the previous HITI method to enable it to target additional areas of the genome. SATI works by inserting a normal copy of the problematic gene into the non-coding region of the DNA before the mutation site. This new gene then becomes integrated into the genome alongside the old gene via one of several DNA repair pathways, relieving the organism of the detrimental effects of the original, mutated gene, without risking damage associated with fully replacing it.

The scientists tested the SATI technology in living mice with progeria, which is caused by a mutation in the LMNA gene. Both humans and mice with progeria show signs of premature aging, cardiac dysfunction and dramatically shortened life span due to the accumulation of a protein called progerin. By using SATI, a normal copy of LMNA gene was inserted in the progeria mice. The researchers were able to observe diminished features of aging in several tissues including the skin and spleen, along with an extension of life span (45% increase compared to untreated progeria mice). A similar extension of life span, when translated to humans, would be more than a decade. Thus, the SATI system represents the first in vivo gene correction technology that can target non-coding regions of DNA in multiple tissue types.

Next, the team aims to improve the efficiency of SATI by increasing the number of cells that incorporate the new DNA.

"Specifically, we will investigate the details of the cellular systems involved in DNA repair to refine the SATI technology even further for better DNA correction," says Reyna Hernandez-Benitez, co-first author on the paper and a postdoctoral fellow in the Izpisua Belmonte lab.

Other authors included Keiichiro Suzuki, Rupa Devi Soligalla, Emi Aizawa, Fumiyuki Hatanaka, Masakazu Kurita, Pradeep Reddy, Alejandro Ocampo, Tomoaki Hishida, Masahiro Sakurai, Amy N. Nemeth, Concepcion Rodriguez Esteban of Salk; Zhe Li, Christopher Wei and Kun Zhang of the University of California San Diego; Estrella Nuñez Delicado of Universidad Catolica San Antonio de Murcia; Jun Wu of University of Texas Southwestern Medical Center; Josep M. Campistol of the Hospital Clinic of Barcelona in Spain; Pierre Magistretti of the King Abdullah University of Science and Technology in Saudi Arabia; Pedro Guillen of the Clinica CEMTRO in Spain; Jianhui Gong, Yilin Yuan and Ying Gu of the BGI-Shenzhen in China; Guang-Hui Liu of the Chinese Academy of Sciences; and Carlos López-Otín from the Universidad de Oviedo in Spain.

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Foundation, The Glenn Foundation, KAUST, The Moxie Foundation, the Fundación Dr. Pedro Guillen, the Asociación de Futbolistas Españoles, and Universidad Católica San Antonio de Murcia (UCAM).

Story Source:

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

Journal Reference:

1. Keiichiro Suzuki, Mako Yamamoto, Reyna Hernandez-Benitez, Zhe Li, Christopher Wei, Rupa Devi Soligalla, Emi Aizawa, Fumiyuki Hatanaka, Masakazu Kurita, Pradeep Reddy, Alejandro Ocampo, Tomoaki Hishida, Masahiro Sakurai, Amy N. Nemeth, Estrella Nuñez Delicado, Josep M. Campistol, Pierre Magistretti, Pedro Guillen, Concepcion Rodriguez Esteban, Jianhui Gong, Yilin Yuan, Ying Gu, Guang-Hui Liu, Carlos López-Otín, Jun Wu, Kun Zhang, Juan Carlos Izpisua Belmonte. **Precise in vivo genome editing via single homology arm donor mediated intron-targeting gene integration for genetic disease correction**. *Cell Research*, 2019; DOI: 10.1038/s41422-019-0213-0

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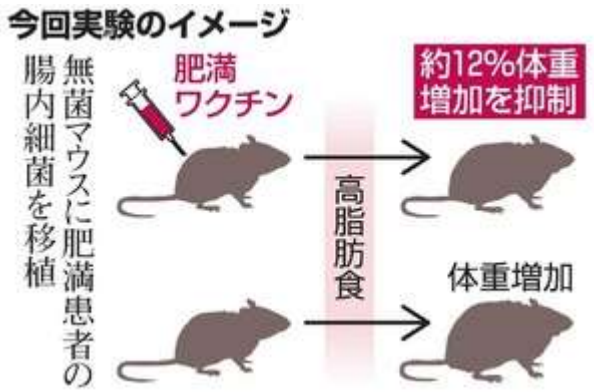
8.「肥満ワクチン」開発に光　マウスの腸内細菌減らしたら

https://digital.asahi.com/articles/ASM8Q633NM8QPLBJ007.html?rm=487

朝日新聞 DIGITAL

2019 年 8 月 23 日 22 時 13 分



ワクチンでマウスの体重増加を抑制

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大阪市立大や東京大などの研究チームが23日、肥満に関連する腸内細菌をワクチン注射で減らしたところ、高脂肪食を与えたマウスの体重増加を抑えられたと発表した。食べても太りにくい「肥満ワクチン」につながる可能性があるという。米消化器病学会誌に掲載された。

チームは、肥満や糖尿病との関連が報告されている腸内細菌（クロストリジウム・ラモーサム）に注目。腸の粘膜で免疫を活性化させるワクチンをつくった。

実験では、無菌マウスにヒトの肥満患者の腸内細菌を移植し、高カロリーのえさを与えた。ワクチンを注射したマウス9匹は、腸内細菌がふんとして排出されて減り、ワクチンを注射しないマウス7匹と比べて、体重増加が約12%抑制された。

腸内細菌が減少したマウスの体内では、小腸などで体内にブドウ糖を吸収するはたらきが活発化せず、肥満や糖尿病を抑える効果が期待できるという。

大阪市立大の植松智（さとし）教授（ゲノム免疫学）は「これまでと全く異なる新しいタイプのワクチンができた。特定の腸内細菌を減らすことで、将来的に食べても太りにくい肥満ワクチンにつながる可能性がある」と話している。

このワクチンは、腸や消化器などの粘膜で免疫の働きを高める仕組み。あらかじめ注射しておくと、体内の細胞が免疫の働きを記憶。病原体や、免疫反応を引き起こす物質（抗原）に反応して、抗体たんぱく質を活性化させることができる。この仕組みは特許化し、製薬会社と共同研究しているという。

チームはこの仕組みが、肺炎球菌の感染を抑制したり、コレラ毒素による下痢を抑制したりすることも確認した。

論文はサイト（https://doi.org/10.1053/j.gastro.2019.08.021）で読める。（田中誠士）

研究関連ニュース／他のトップページに戻る

9. 短時間睡眠とリンクする遺伝子発見

近年概日リズムの遺伝学についてはよく研究されているが、睡眠上役割を果たす他の遺伝子、特に我々の体に必要な睡眠の量を調節する遺伝子についてはあまり知られていない。今回、UCSF（カリフォルニア大学サンフランシスコ校）の研究者らは、平均よりも睡眠が大幅に少ない複数のメンバーを持つ家族を研究することにより、睡眠量に直接影響を与えると思われる新しい遺伝子を特定した。この調査結果は、8 月 28 日にジャーナル *Neuron* で報告されている。
今回、遺伝子連鎖研究と全エクソームシーケンスを使用して遺伝子 ADRB1 が同定された。その後、研究者らは、遺伝子の変異バージョンを持つマウスで多くの実験を行った。彼らは、これらのマウスが通常のマウスに比べて平均 55 分寝ていないことを発見。（この遺伝子を持つ人間は平均より 2 時間睡眠が短い。）さらなる分析は、この遺伝子が、呼吸や眼球運動、睡眠などの潜在意識活動に関与する脳幹の一部である背側橋において高レベルで発現していることを示し、この領域の正常な ADRB1 ニューロンが覚醒時だけでなく、レム（急速な眼球運動）睡眠中にも活発であることを発見（ただし、ノンレム睡眠中は静かであった）。また ADRB1 ニューロンを活性化するために光を使用すると、マウスはすぐに眠りから覚めた、ともしている。
研究者らは、睡眠は複雑なため、これから更に多くのステップが必要となるものの、この研究が最終的に睡眠と覚醒を制御する新しいタイプの薬を開発するためのアプリケーションを持つかもしれないと付け加えている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190828111247.htm

Gene linked to needing less sleep identified

Date:

August 28, 2019

Source:

Cell Press

Summary:

The genetics of circadian rhythms have been well studied in recent years, but much less is known about other types of genes that play a role in sleep. Now, by studying a family with several members who require significantly less sleep than average, a team of researchers has identified a new gene that they believe has a direct impact on how much someone sleeps.

FULL STORY

The genetics of circadian rhythms have been well studied in recent years, but much less is known about other types of genes that play a role in sleep, specifically those that regulate how much sleep our bodies require. Now, by studying a family with several members who require significantly less sleep than average, a team of researchers has identified a new gene that they believe has a direct impact on how much someone sleeps. They report their findings on August 28 in the journal *Neuron*.

"It's remarkable that we know so little about sleep, given that the average person spends a third of their lives doing it," says Louis Ptáček, a neurologist at the University of California, San Francisco (UCSF), and one of the paper's two senior authors. "This research is an exciting new frontier that allows us to dissect the complexity of circuits in the brain and the different types of neurons that contribute to sleep and wakefulness."

The family whose DNA led to the identification of this gene is one of several that Ptáček and UCSF geneticist Ying-Hui Fu, the paper's other senior author, are studying and includes several members who function normally on only six hours of sleep. The gene, ADRB1, was identified using genetic linkage studies and whole-exome sequencing, which revealed a novel and very rare variant.

The first step in deciphering the role of the gene variant involved studying its protein in the test tube. "We wanted to determine if these mutations caused any functional alterations compared with the wild type," Fu says. "We found that this gene codes for ß1-adrenergic receptor, and that the mutant version of the protein is much less stable, altering the receptor's function. This suggested it was likely to have functional consequences in the brain."

The researchers then conducted a number of experiments in mice carrying a mutated version of the gene. They found that these mice slept on average 55 minutes less than regular mice. (Humans with the gene sleep two hours less than average.) Further analysis showed that the gene was expressed at high levels in the dorsal pons, a part of the brain stem involved in subconscious activities such as respiration and eye movement as well as sleep.

Additionally, they discovered that normal ADRB1 neurons in this region were more active not only during wakefulness, but also during REM (rapid eye movement) sleep. However, they were quiet during non-REM sleep. Furthermore, they found that the mutant neurons were more active than normal neurons, likely contributing to the short sleep behavior.

"Another way we confirmed the role of the protein was using optogenetics," Fu explains. "When we used light to activate the ADRB1 neurons, the mice immediately woke up from sleep."

Ptáček acknowledges some limitations of using mice to study sleep. One of these is that mice exhibit different sleep patterns than humans, including, for example, sleeping in a fragmented pattern, rather than in a single continuous period. "But it's challenging to study sleep in humans, too, because sleep is a behavior as well as a function of biology," he says. "We drink coffee and stay up late and do other things that go against our natural biological tendencies."

The investigators plan to study the function of the ADRB1 protein in other parts of the brain. They also are looking at other families for additional genes that are likely to be important. "Sleep is complicated," Ptáček notes. "We don't think there's one gene or one region of the brain that's telling our bodies to sleep or wake. This is only one of many parts."

Fu adds that the work may eventually have applications for developing new types of drugs to control sleep and wakefulness. "Sleep is one of the most important things we do," she says. "Not getting enough sleep is linked to an increase in the incidence of many conditions, including cancer, autoimmune disorders, cardiovascular disease, and Alzheimer's."

Story Source:

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

Journal Reference:

1. Guangsen Shi, Lijuan Xing, David Wu, Bula J. Bhattacharyya, Christopher R. Jones, Thomas McMahon, S.Y. Christin Chong, Jason A. Chen, Giovanni Coppola, Daniel Geschwind, Andrew Krystal, Louis J. Ptáček, Ying-Hui Fu. **A Rare Mutation of β1-Adrenergic Receptor Affects Sleep/Wake Behaviors**. *Neuron*, 2019; DOI: 10.1016/j.neuron.2019.07.026

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