Bio News – January, 2024

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

11/30　Lilly、バイオテック養成所 Gateway Labs をカリフォルニア州サンディエゴに来年前半に開設予定

バイオテックを住まわせて支援する創薬起業養成所 Gateway Labs を Eli Lilly が米国西海岸カリフォルニア州サンディエゴに来年 2024 年前半に開設する。
Gateway Labs の入居企業は最新の研究設備を使うことができ、Lilly の科学者、研究者、経営陣とやり取りしたり Lilly が持つ実務や科学の知恵に浴することができる。
Gateway Labs は西海岸のサンフランシスコと東海岸のボストンにすでに開設されているが、それら 2 つの湾岸拠点に現時点で 15 社が入居しており、20 を超える治療や治療技術が開発されている。入居企業の 2019 年以降の調達資金は 10 億ドル。

Lilly Announces Plans to Open its First-ever Gateway Labs Site in San Diego | Eli Lilly and Company

11/30　ウィントンキンモグラを 87 年ぶりに確認 -南ア

砂の中を「泳ぐ」ウィントンキンモグラがこのほど、南アフリカで 87 年ぶりに確認された。調査担当者が 28 日、明らかにした。

ウィントンキンモグラ。EWT 提供（2023 年 11 月 28 日提供）。AFPBB News

絶滅危機にある野生動物と生息環境保護に取り組む南アの団体 EWT のエスター・マシュー（Esther Matthew）氏は、「探偵小説のような調査」の結果、砂丘でウィントンキンモグラが生息している痕跡を見つけたと説明した。

12/1　原因不明の難病サルコイドーシス、免疫細胞が腫れ物に 京大など解明

原因不明の難病「サルコイドーシス」の患者では、特定の代謝機能が強まった免疫細胞が集まって肉芽腫という腫れ物をつくっていると、京都大と東京大、関西医大、兵庫医大の研究チームが突き止めた。その機能をじゃまする化学物質を加えると、マウス実験では肉芽腫がなくなった。チームは製薬会社と連携し、新薬の開発を進める。

12/1　大麻グミ、43 店舗に販売停止命令　クッキーからも有害成分　厚労省

「大麻グミ」に含まれる大麻の有害成分に似た合成化合物「HHCH（ヘキサヒドロカンナビヘキソール）」で健康被害が出ている問題で、武見敬三厚生労働相は 1 日の閣議後記者会見で、立ち入り検査の結果、全国 43 の店舗や事業所で同成分を含む製品が確認され、販売停止命令を出したことを明らかにした。

12/1　ADC 技術の ImmunoGen（本社：マサチューセッツ州ウォルサム）を AbbVie が 101 億ドルで買収

AbbVie to Buy Cancer Biotech ImmunoGen for More Than $10 Billion - WSJ

12/2　「HHCH」きょうから所持・使用・販売が禁止　年明けには包括規制も　厚労省

いわゆる“大麻グミ”から検出された大麻由来の成分に似た合成化合物「HHCH」について、今日から所持や使用、販売が禁止される。
“大麻グミ”を食べた人が救急搬送されるなど体調不良を訴える人が相次いでいることを受け、厚労省は大麻由来の成分に似た合成化合物「HHCH」を先月、「指定薬物」に指定した。
今日から所持や使用、販売が禁止され、違反した場合は 3 年以下の懲役、または 300 万円以下の罰金が科される。
さらに、「HHCH」を規制しても、類似した新たな薬物が出回ることが予想されるため、厚労省は年明けにも類似した構造の物質を「指定薬物」として包括的に規制していく考えだ。

12/5　Roche が Carmot を買収して肥満薬を手中に

Roche joins race for obesity drugs with $2.7 billion Carmot deal | Reuters

12/5　iPS 細胞からヒト受精卵に似た構造を再現　−京大が論文発表

iPS 細胞などから、ヒトの受精卵（胚〈はい〉）に似た構造を作り、体ができる初期段階を再現することに京都大 iPS 細胞研究所などのグループが成功し、5 日英科学誌「ネイチャー」（https://www.nature.com/articles/s41586-023-06871-2）に発表した。ヒトの発生や不妊の仕組み解明につながると期待される一方、急速に進む技術をどう位置づけるか世界中で議論されている。
精子と卵子が受精してできた胚が子宮に着床し胎児に育っていくが、初期に胚が成長する仕組みはよくわかっていない。動物とヒトには違いがあり、ヒト胚でないとわからないことが多い。しかし、人間に育つ本物のヒト胚の研究は倫理的に制限されている。着床後の胚を観察することもむずかしい。
そこで、ヒトの発生の仕組みを理解する研究手法として、iPS 細胞や受精卵から作る胚性幹（ES）細胞といった多能性幹細胞を使い、胚そっくりな構造「胚モデル」を作る研究が進められてきた。これらの細胞は大量に作製でき、研究の制限はない。
胎児が育つには、体を作る細胞、栄養や成長するための信号を送る「原始内胚葉」になる細胞、母親と胎児をつなぐ胎盤になる細胞の 3 種類の細胞が必要だ。
グループは普通の iPS 細胞よりも発生の初期段階の細胞に近い「ナイーブ型多能性幹細胞」を 2014 年に作製した。この細胞と、グループが開発した方法で原始内胚葉に分化させた細胞を、いっしょに培養すると着床前の胚モデルができた。

12/5　人の「非統合胚モデル」作製　着床後相当まで再現 −京大

人の多能性幹細胞を実験容器内で培養して生み出した胚モデル（疑似的な胚）を、半透過性の膜で仕切った胎盤の前段階の細胞と相互作用させることで、母体の子宮内膜に着床した後に相当する成長過程まで再現できたと、京都大 iPS 細胞研究所などの研究チームが 5 日発表した。
この「非統合胚モデル」は、胎児に近づく可能性に歯止めをかけつつ、さまざまな組織や臓器ができ始める仕組みを解明し、移植用臓器を生み出す技術を向上させるのに役立つと期待される。論文は英

科学誌「ネイチャー」電子版に掲載された。
多能性幹細胞とは、受精卵が成長した胚の一部を採取して作る胚性幹細胞（ES 細胞）や、皮膚などの細胞に遺伝子群を導入して作る人工多能性幹細胞（iPS 細胞）。
近年、胚モデルへの培養技術が進歩し、着床後に相当する段階まで成長させられるようになった。本物の胚を成長させ続けるのは倫理面で問題があるため、代替手段とされる。それでも胎児に近づくにつれ、懸念が強まっている。
このため同研究所の高島康弘准教授らは、着床期の胚モデルのうち、将来胎児になる細胞と栄養分になる卵黄嚢（らんおうのう）を、胎盤になる細胞から分離して培養する技術を開発。それぞれの細胞から放出されるたんぱく質が半透過性の膜を通って相互作用できるようにし、体の前後軸が形成され、血管の細胞などができ始める様子を観察した。

12/5　100 歳を超える淡水魚を 2 種確認、なぜか「老化しない」驚きの巨大魚の仲間、最新研究

10 月 20 日付で学術誌「Scientific Reports」に発表された最新の研究で、北米の広い範囲に生息するスモールマウス・バッファローフィッシュ（Ictiobus bubalus）とブラック・バッファローフィッシュ（Ictiobus niger）が、100 年以上生きることが確認された。
栗色から青系までさまざまな色を持つこの魚は、ほんの数年前まで、20 代半ばまでしか生きられないと考えられていた。しかし、2019 年の研究で、体重 35 キログラム近くになることもあるビッグマウス・バッファローフィッシュ（Ictiobus cyprinellus）が 112 歳まで生きる可能性があると判明した。さらに、2023 年 1 月には、カナダのサスカチュワン州で 127 歳のビッグマウス・バッファローフィッシュが見つかった。約 1 万 2,000 種におよぶ真骨類の淡水魚としては、知られている限り、最も長生きする種だ。

12/6　日本国内初“黒トリュフ”の人工発生に成功

12/6　1.3 億年前、雄の蚊も吸血か　琥珀から発見 -レバノン

中東レバノンの約 1 億 3,000 万年前（白亜紀前期）の地層から発見された半透明の琥珀（こはく）の中に、雄の蚊（カ）が入っていたと、中国科学院南京地質古生物研究所とフランス国立自然史博物館の研究チームが 6 日までに発表した。琥珀から見つかった蚊では最古となる。論文は米科学誌「カレント・バイオロジー」に掲載された。

12/6　第 43 回島津賞に京大医学研究科の岩田想教授

島津科学技術振興財団は 6 日、2023 年度の第 43 回島津賞に京都大学大学院医学研究科の岩田想教授を選定したと発表した。同賞は科学技術、主として科学計測に係る領域で基礎的研究および応用・実用化研究において著しい成果をあげた功労者を表彰する。
受賞の対象になった岩田教授の業績は「膜タンパク質の 3 次元から 4 次元構造解析方法の開発」。

12/6　イヌの謎の呼吸器疾患が全米で拡大、おそらく新たな病気

12/6　Sanofi が量子物理学と人工知能による創薬の Aqemia（本社：パリ）と組んで低分子薬を開発

Sanofi deepens drug discovery pact with Aqemia using genAI | FirstWord Pharma

AQEMIA Announces a Major Multi-year Collaboration of $140 Million With Sanofi | Business Wire

12/7　Sanofi が 2030 年までに年間売り上げ 10 億ドルを超えうる製品を発表

Sanofi Sees Annual Sales From New Pharma Assets Above $10.8 Billion by 2030 | Morningstar

12/8　老化で精子の遺伝子制御が変化、子の神経発達障害リスクに -東北大

父親の加齢が精子の遺伝子の働きに影響し、子の神経発達障害のリスクになることがマウスの実験で分かったと、東北大学の研究グループが発表した。既に、DNA や DNA を巻き取るタンパク質への物質の結合による影響について示していたが、遺伝子の働きを調整する「マイクロ RNA」も変化していることを、新たに明らかにした。
メスは出生時に持つ卵母細胞が卵子となり、1 個ずつ排卵されていくのに対し、オスの精子は精巣で次々作られる。卵子の老化は広く知られてきたが、精子の側について、後天的に遺伝子の働き方が変わる「エピジェネティック」な変化に焦点を当てる成果となった。

12/9　Pfizer の骨髄腫薬 Elrexfio を欧州も承認

Pfizer Elrexfio gets European Commission approval for Multiple Myeloma (medicaldialogues.in)

12/10　合成メラニンを米大学が開発　強力な日焼け止めや保湿材、皮膚の損傷治療に期待

ノースウェスタン大学の科学者は、10 年近くにわたる研究の末、新しいタイプの非常に効果的な日焼け止めの促進剤や保湿剤として使用できる合成メラニンを開発した。人間や動物の天然メラニンは、皮膚や目、毛髪に色素沈着をもたらす。この物質は日光に反応して色素が増加し、日焼けによる損傷から細胞を守る働きがある。合成メラニンは人間の皮膚にある天然のメラニンを模倣しており、日焼けや化学熱傷による皮膚の損傷を治すために局所的に塗布することもできる。効果は皮膚そのものと体内全体の両方に現れる。この研究成果は最近、英科学誌ネイチャーに掲載された。
この技術は、傷ついた皮膚から発生するフリーラジカルを除去することで機能する。フリーラジカルの活動を抑制せずに放置すると、細胞に損傷を与え、最終的には皮膚の老化や皮膚がんを引き起こす可能性がある。合成メラニンは人間の天然メラニンに比べ、1 グラム当たりに消去できるフリーラジカルの量が多い。研究チームは、フリーラジカル除去能力の高いメラニン構造に改良を加えた。合成メラニンは肌に塗ると表面にとどまり、下の層には吸収されない。合成メラニンは皮膚を安定させ、治癒の行程を設定するが、これは表層と全身の両方に見られる。

12/12　Sanofi が Maze（本社：カリフォルニア州南サンフランシスコ）からポンペ病薬を手に入れる取り引きを米国の反対で断念

Sanofi terminates deal on drug license after US FTC objects | Reuters

12/13　アルツハイマー病新薬レカネマブの薬価、年 298 万円　中医協承認

アルツハイマー病の治療薬「レカネマブ」（商品名レケンビ）について、厚生労働相の諮問機関に当たる「中央社会保険医療協議会」（中医協）は 13 日、薬の公定価格（薬価）を 500 ミリグラム 11 万 4,443 円、1 人当たり 1 年間の治療で約 298 万円とすることを承認した。公的医療保険が適用される。
レカネマブは、製薬大手「エーザイ」と米製薬会社「バイオジェン」が開発した。病気の原因と考えられている脳内の異常物質に直接働きかけて取り除く初めての薬。根治薬ではないが、病気の進行を遅らせる効果が期待される。9 月に厚労相が製造販売を了承していた。中医協の承認を受け、エーザイは今月 20 日にレカネマブの販売を始めると発表した。

12/13　iPS で子宮頸がん治療　免疫細胞投与、来夏にも治験　−順天堂大など

順天堂大などは 13 日、人工多能性幹細胞（iPS 細胞）から作製した免疫細胞で子宮頸（けい）がんを縮小させることに成功したと発表した。ゲノム編集技術によって拒絶反応を起こしにくくしており、来年夏にも治験を始める方針という。研究成果は、米学術雑誌「Cell Reports Medicine」のオンライン版に掲載された。

12/14　Pfizer の Seagen（本社：ワシントン州ボセル市）買収が成立

12/14 『Nature』誌今年の 10 人にチャット GPT、日本からは阪大の林教授

英科学誌ネイチャーは、科学に重要な役割を果たした「今年の 10 人」に、対話型 AI（人工知能）の ChatGPT（チャット GPT）や大阪大の林克彦教授らを選んだと発表した。人以外が選ばれたのは初。一方で、AI が盗用に使われる危険性や、間違いやバイアスがかかるといった問題も指摘されている。いずれにせよチャット GPT のような生成 AI の革命は始まり、後戻りはできないとした。
「驚くべき科学的成果で、いすから転げ落ちた」というコメントとともに紹介されたのが大阪大の林さん。遺伝的に 2 匹のオスの両親をもつ赤ちゃんマウスを誕生させた論文で世界を驚かせた。

Making mice with two dads: this biologist rewrote the rules on sexual reproduction (nature.com)

12/15 CARsgen（本社：テキサス州ベルエア市）の 3 つの CAR-T の臨床試験を FDA が差し止め

ノースキャロライナ州ダラムの製造拠点の査察での懸念を受けて CARsgen Therapeutics のキメラ抗原受容体 T 細胞（CAR-T）3 つ・CT053（zevor-cel）、CT041、CT071 の臨床試験を FDA が差し止め。

FDA puts 3 CARsgen CAR-Ts on hold after inspecting facility (fiercebiotech.com)

12/16 米国国立衛生研究所（NIH）、生物医学ポスドクの最低初任給を現在の$56,484 から $70,000 に引き上げることを推奨

NIH の諮問グループは、現在の経済状況を鑑みてもこの給与の増加が米国の生物医学的競争力を保護するために重要である、としている。

12/18 市販薬、20 歳未満に乱用対策　多量購入禁止へ制度見直し

医薬品販売制度に関する厚生労働省の検討会は 18 日、依存性がある成分を含む一般用医薬品（市販薬）を 20 歳未満が多量購入することを禁じる制度見直し案を大筋了承した。若年層を中心に薬の過剰摂取（オーバードーズ）が広がっているのを受けた乱用対策。同省は来年、厚生科学審議会部会で議論し、医薬品医療機器法改正を目指す。

12/19 iPS 視細胞、移植後 2 年の「安全」確認…異常なく生着も機能改善は限定的

目で光を感じる細胞を iPS 細胞（人工多能性幹細胞）から作り、難病「網膜色素変性症」の患者 2 人に移植した世界初の臨床研究について、手術を行った神戸市立神戸アイセンター病院などのチームは、2 年間の経過観察で安全性を確認できたと発表した。今後は治療効果の向上が課題となる。論文が国際科学誌に掲載された。

12/20 Novo Nordisk Foundation が呼吸器感染症ワクチン開発事業を立ち上げる

結核やインフルエンザなどの始末に負えない呼吸器感染症幾つかへの新しい、又は、より良いワクチンを作る事業を Novo Nordisk Foundation が最大 2 億 6,000 万ドルを投じて立ち上げる。
Novo Nordisk Foundation Initiative for Vaccines and Immunity (NIVI) と銘打つその事業は 2 期にわたる。来年から 2027 年までの第 1 期では職員を募り、国際的な提携を確立し，肝要な研究を開始。
2028 年以降の第 2 期にはデンマークのコペンハーゲンに 150～200 人の従業員がすっかり揃う予定。

Major new vaccines initiative aims to fight deadly airborne infections (prnewswire.com)

12/21 大麻の類似成分含む 38 製品、製造・販売を全国一律禁止　厚労省

12/21 大塚製薬が Ionis（本社：カリフォルニア州カールズバッド市）の遺伝性血管浮腫薬 donidalorsen の欧州販売権利を取得

Ionis announces European licensing agreement with Otsuka for donidalorsen in hereditary angioedema (prnewswire.com)

12/22　イヌの尿から iPS 細胞作製　手法確立、研究進展に期待　−大阪公立大など

大阪公立大などは 22 日、イヌの尿から採取した細胞から人工多能性幹細胞（iPS 細胞）の安定的な作製に成功したと発表した。イヌの iPS 細胞の研究は、ヒトやマウスと比べて遅れていたが、再生医療や遺伝子疾患の研究、治療薬開発などへの応用が期待される。論文は同日、米科学誌ステムセル・リポーツ電子版に掲載された。

12/22　Eli Lly、冬眠の仕組みから薬の標的を同定する Fauna Bio（本社：カリフォルニア州エミリービル市）と組んで肥満薬を探す

Lilly, Fauna Bio Ink Potential $494M Deal to Find Obesity Drug Targets | BioSpace

12/22　Sanofi の ADC・tusamitamab ravtansine が Ph3 失敗で開発が全て中止に

Sanofi's pipeline aspirations take a hit with ADC failure | FirstWord Pharma

12/23　統合失調症薬を擁する Karuna（本社：マサチューセッツ州ボストン）を Bristol Myers Squibb が 140 億ドルで買収

Bristol Myers to buy schizophrenia drugmaker Karuna Therapeutics for $14 bln | Reuters

12/25　血管裂ける「大動脈解離」女性の発生率、過小評価されていた −熊本大

大動脈の内側の壁が裂け、死につながることも多い「急性大動脈解離」は、男性がなりやすい病気とされてきたが、実は男女差はないことを熊本大などのチームが明らかにした。女性は病院到着前に亡くなるケースが多いため、これまで過小評価されてきた可能性があるという。

12/26　食道がんの再発防げ　禁酒・節酒で「前がん状態」が改善 −京大など

食道がんで内視鏡手術を受けた患者が、禁酒・節酒を続けることで、食道の粘膜表層の異状が減り、再発を抑えられることが、京都大や岡山大などの研究チームによる調査でわかった。がんになる前段階の「前がん状態」が改善したという。

12/26　iPS 治験が米でも開始へ　パーキンソン病対象、日本から細胞を空輸

住友ファーマ（大阪市）は 26 日、米国でカリフォルニア大サンディエゴ校が、iPS 細胞を使ったパーキンソン病の治療をめざす臨床試験（治験）を始めると発表した。京都大 iPS 細胞研究財団から提供される iPS 細胞を使う。財団によると、海外の治験でこの iPS 細胞が使われるのは初めて。

12/26　国立医薬品食品衛生研の部長、論文データを捏造

国立医薬品食品衛生研究所は 26 日、研究所の食品衛生管理部長（当時）による 2021 年 9 月発表の論文にデータの捏造（ねつぞう）、改ざんが認められたと発表した。部長に論文取り下げを勧告しており、今後処分を検討するという。昨年 12 月、職員から告発があり、調査委員会が調べていた。

12/26　新たに 6 成分を指定薬物に　大麻グミ問題　販売・所持を禁止　厚労省

「大麻グミ」などによる健康被害が相次いだ問題で、厚生労働省は 27 日、大麻に似た有害な 6 成分を新たに指定薬物に追加した。来年 1 月 6 日からこれらの成分を含む製品の販売や所持、使用が禁止される。

指定薬物に追加されたのは、大麻に似た有害成分「ヘキサヒドロカンナビフォロール（HHCP）」など 6 種類。厚労省は 21 日、HHCP などを含むグミやクッキーなど 38 製品を危険ドラッグとして製造や販売を禁止していた。
厚労省は 11 月、大麻に似た別の有害成分「ヘキサヒドロカンナビヘキソール（HHCH）」を指定薬物としたが、これに代わり HHCP が流通していた。今回の指定では、HHCP のほか、HHCH や HHCP に類似し、まだ流通が確認されていない成分も規制対象とした。

12/26　飲むと“満腹感”得られる電子カプセル　胃の中で振動し食事量 40%削減、米 MIT など開発

A vibrating ingestible bioelectronic stimulator modulates gastric stretch receptors for illusory satiety | Science Advances

12/27　ノンアルコール飲料はやはりお酒の量を減らす、実力示す世界初の研究結果、米国でも人気に

ノンアル飲料の提供で飲酒量を減らせることを世界で初めて示したとする論文が 10 月 2 日付で医学誌「BMC Medicine」に発表されるなど、健康に役立つ可能性が明らかになりつつある。

12/27　AstraZeneca が中国の CAR-T 開発会社 Gracell を約 12 億で買収

AstraZeneca to buy China's Gracell Biotechnologies in $1.2 billion deal | Reuters

12/27　Amgen、肺癌薬 Lumakras の本承認を FDA から得られず

Amgen's request for full approval of Lumakras denied by FDA (fiercepharma.com)

12/29　マクロファージに癌細胞を食べさせる抗体の選択権利をアステラス製薬が Elpiscience Biopharma（本社：中国上海）から取得

Elpiscience Biopharma, Astellas Pharma Collaborate For Novel Bi-specific Macrophage Engagers | Nasdaq

12/30　米国での新年のお祝いの後は緊急避妊薬が 10%ほど余計に売れる

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. マウスモデルで脳卒中後に失われた脳機能の回復に成功

2. 妊娠高血圧症候群は予防できるか？ -マウス実験

3. 神経の活性化によりインスリン産生細胞を再生
   -マウス糖尿病の治療に成功-

4. 特定の遺伝的変異が肥満の予防に役立つ可能性 -マウス実験

5. 遺伝的要因にも関わらずアルツハイマー病を回避した患者からの手がかり:マウス実験による新展開

6. 妊娠時の悪阻の原因解明とマウス実験から見えた治療の可能性

7. マウスは進化の過程で遺伝子治療薬として働く RNA を獲得していた

8. ゼブラフィッシュの発生の初期段階を詳細に記述した遺伝子アトラス
   ゼブラフィッシュは、脊椎動物の胚発生の進行を研究するための強力なモデル

1. マウスモデルで脳卒中後に失われた脳機能の回復に成功

日付：2023 年 11 月 30 日
ソース：ルンド大学
概要：

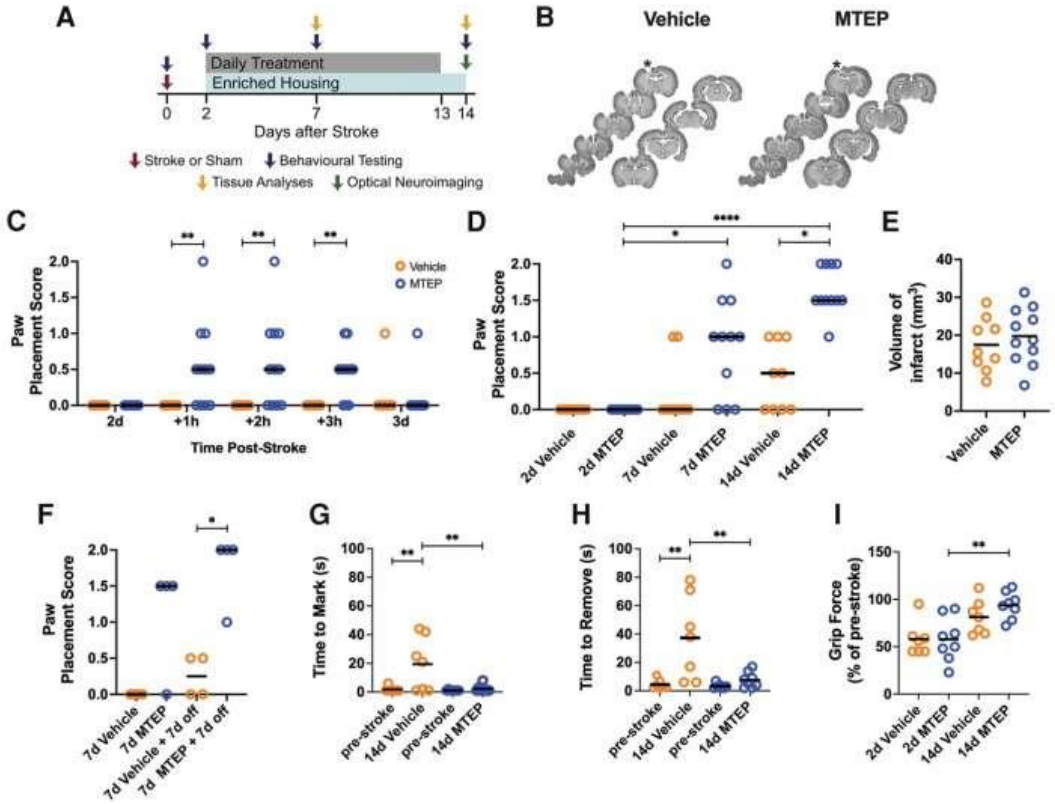
ルンド大学の研究者らは、マウスモデルにおいて、小さな分子を使用して、脳卒中後に喪失した脳機能を回復させることに成功した。
最近『Brain』誌に発表されたこの研究は、スエーデンのルンド大学の研究チームがローマ・ラ・サペインザ大学およびセントルイスのワシントン大学と主導した国際研究で、脳の神経細胞ネットワークにおけるコミュニケーションを調節する受容体である代謝型グルタミン酸受容体（mGluR5）を阻害する物質を投与したマウスとラットで有望な結果が示された。
脳梗塞では、脳への血流不足が損傷を引き起こし、大部分の神経細胞ネットワークに影響を与える神経細胞の損失に急速につながり、これにより、麻痺、感覚運動障害、視覚および言語の困難だけでなく、痛みやうつ病も発生する可能性がある。現在、脳卒中後の機能を改善または回復させる承認された薬は、急性期（脳卒中の発生後 4.5 時間以内）の凝固溶解治療以外には存在していない。
今回、mGluR5 を阻害する一群の物質を用いたマウスおよびラットへの治療において、約 60%の脳卒中患者が経験する感覚運動機能の喪失が改善される有望な結果が示された。
研究者らは、この成果が将来的に脳卒中回復療法となる可能性があり、臨床的な治療につながることを期待している。

研究関連ニュース/他のトップページに戻る

＜英文＞Researchers restore lost brain function after stroke in mouse models (medicalxpress.com)

Researchers restore lost brain function after stroke in mouse models

by Lund University



Inhibition of mGluR5 improves lost sensorimotor function after photothrombotic stroke in rats. (A) The study design. (B) Serial coronal NeuN stained sections of representative brains from Vehicle- (left) and MTEP- (right) treated rats subjected to photothrombotic (PT)-stroke. Cortical infarct is indicated by an asterisk. (C) Paw placement score at 2 days after PT-stroke and 1, 2 and 3 h and 3 days after the first injection (Vehicle, n = 9; MTEP, n = 11) [Kruskal–Wallis test with a post hoc Dunn's multiple comparison (MC) test; **P < 0.01; bar denotes median]. (D) Paw placement at 2, 7 and 14 days after PT-stroke (Kruskal–Wallis test with a post hoc Dunn's MC test; *P < 0.01, **P < 0.01, ***P < 0.001; bar denotes median). (E) Mean volume of infarct (mm^3) assessed 14 days after stroke in Vehicle- (n = 9) or MTEP- (5 mg/kg, i.p., n = 11) treated rats (unpaired two-tailed t-test; bar denotes mean). (F) Paw placement in MTEP-treated animals 7 days and after an additional 7 days without (off) treatment compared to Vehicle (Kruskal–Wallis test with a post hoc Dunn's MC test; *P < 0.05; bar denotes median). (G and H) Adhesive removal test. (G) Mean time (s) to mark and (H) mean time (s) to remove an adhesive on the left forepaw of Vehicle- (n = 7) or MTEP- (n = 8) treated rats; one-way ANOVA with a post hoc Sidak's MC test; *P < 0.05, **P < 0.01; bar denotes mean. (I) Grip test. Mean grip force of right paw in % of pre-stroke force levels (Vehicle, n = 7; MTEP, n = 8); one-way ANOVA with a post hoc Sidak's MC test; **P < 0.01; bar denotes mean. d = days.

Researchers have succeeded in restoring lost brain function in mouse models of stroke using small molecules that in the future could potentially be developed into a stroke recovery therapy. "Communication between nerve cells in large parts of the brain changes after a stroke and we show that it can be partially restored with the treatment," says Tadeusz Wieloch, senior professor of neurobiology at Lund University in Sweden.

"Concomitantly, the rodents regain lost somatosensory functions, something that around 60 percent of all stroke patients experience today. The most remarkable result is that the treatment began several days after a stroke," Wieloch continues.

In an ischemic stroke, lack of blood flow to the brain causes damage, which rapidly leads to nerve cell loss that affects large parts of the vast network of nerve cells in the brain. This may lead to loss of function such as paralysis, sensorimotor impairment and vision and speech difficulties, but also to pain and depression.

There are currently no approved drugs that improve or restore the functions after a stroke, apart from clot-dissolving treatment in the acute phase (within 4.5 hours of the stroke). Some spontaneous improvements occur, but many stroke patients suffer chronic loss of function. For example, about 60 percent of stroke sufferers experience lost somatosensory functions such as touch and position sense.

An international study published recently in the journal *Brain* and led by a research team from Lund University in collaboration with the University of Rome La Sapeinza and Washington University at St. Louis shows promising results in mice and rats that were treated with a class of substances that inhibit the metabotropic glutamate receptor (mGluR5), a receptor that regulates communication in the brain's nerve cell network.

"Rodents treated with the GluR5 inhibitor regained their somatosensori functions," says Tadeusz Wieloch, who led the study.

Two days after the stroke, i.e. when the damage had developed and function impairment was most prominent, the researchers started treating the rodents that exhibited the greatest impaired function.

"A temporary treatment effect was seen after just 30 minutes, but treatment for several weeks is needed to achieve a permanent recovery effect. Some function improvement was observed even when the treatment started 10 days after a stroke," says Tadeusz Wieloch.

Importantly, sensorimotor functions improved, even though the extent of the brain damage was not diminished. This, explains Tadeusz Wieloch, is due to the intricate network of nerve cells in the brain, known as the connectome, i.e. how various areas of the brain are connected and communicate with each to form the basis for various brain functions.

"Impaired function after a stroke is due to cell loss, but also because of reduced activity in large parts of the connectome in the undamaged brain. The receptor mGluR5 is apparently an important factor in the reduced activity in the connectome, which is prevented by the inhibitor which therefore restores the lost brain function," says Tadeusz Wieloch.

The results also showed that sensorimotor function was further improved if treatment with the mGluR5 inhibitor is combined with somatosensory training by housing several rodents in cages enriched with toys, chains, grids, and plastic tubes.

The researchers hope that in the future their results could lead to a clinical treatment that could be initiated a few days after an ischemic stroke.

"Combined with rehabilitation training, it could eventually be a new promising treatment. However, more studies are needed. The study was conducted on mice and rats, and of course, needs to be repeated in humans. This should be possible since several mGluR5 inhibitors have been studied in humans for the treatment of neurological diseases other than stroke, and shown to be tolerated by humans," says Tadeusz Wieloch.

More information: Jakob Hakon et al, Inhibiting metabotropic glutamate receptor 5 after stroke restores brain function and connectivity, *Brain* (2023). DOI: 10.1093/brain/awad293

Journal information: Brain

Provided by Lund University

2. 妊娠高血圧症候群は予防できるか？ –マウス実験

日付：2023 年 12 月 1 日
ソース：メディカル・カレッジ・オブ・ウィスコンシン
概要：

妊娠高血圧症候群は早期の警告サインがなく、妊娠の約 10%で発生する。通常の血圧が正常であるにもかかわらず、妊婦患者は突然高血圧となり、腎臓のろ過力が低下するため尿中の蛋白質が増加、妊娠高血圧症候群による持続的な高血圧は、母親と胎児に臓器損傷や生命を脅かす合併症を引き起こす可能性がある。現在、この病態の根本的な原因には治療法がない。
妊娠高血圧症候群の原因についての新しい理論の一つに焦点を当てた MCW（メディカル・カレッジ・オブ・ウィスコンシン）の研究者らは、胎盤の特定の細胞層である合胞葉胎盤（STB）に注目した。この細胞層は母体と発育中の胎児の間のバリアの重要な部分である。今回、研究者らは、この部位での細胞ストレスが妊娠高血圧症候群を引き起こす可能性があることを示した。
研究者らは G タンパク質共役受容体（GPCR）シグナルを特定の細胞タイプ内で正確に操作できるように設計された新しいマウスモデルを開発。これにより、マウスの胎盤の STB 層で妊娠高血圧症候群に関連するシグナル伝達経路を活性化することが可能になった。研究チームは、妊娠の早い段階または中間段階で特定のシグナル経路を非常に短時間活性化させた場合でも、マウスの妊娠中に重大な影響が生じることを示した。これらのマウスは、高血圧、腎損傷、その他の解剖学的および細胞の変化を含む、妊娠高血圧症候群の典型的な徴候すべてを発症させた。一部のマウスでは、妊娠高血圧症候群を引き起こす信号にさらされた後、細胞内でエネルギーを生成するミトコンドリアへのストレスを軽減する薬の効果を検証した。この薬は妊娠高血圧症候群の兆候および症状の発症に対して重要な保護を提供した。
研究者らは、将来的には妊娠高血圧症候群の予防が可能になるかもしれない、として 2023 年 12 月の『Science Advances』誌にこの研究成果を発表している。

研究関連ニュース/他のトップページに戻る

＜英文＞Can preeclampsia be prevented? | ScienceDaily

Can preeclampsia be prevented?

Date:

December 1, 2023

Source:

Medical College of Wisconsin

Summary:

Preeclampsia is a mysterious condition that occurs in about one of 10 pregnancies without any early warning signs. After 20 weeks or more of normal blood pressure during the pregnancy, patients with preeclampsia will begin to experience elevated blood pressure and may also have increased levels of protein in their urine due to hypertension reducing the filtering power of the kidneys. Prolonged hypertension due to preeclampsia can lead to organ damage and life-threatening complications for mothers and fetuses.

FULL STORY

Preeclampsia is a mysterious condition that occurs in about one of 10 pregnancies without any early warning signs. After 20 weeks or more of normal blood pressure during the pregnancy, patients with preeclampsia will begin to experience elevated blood pressure and may also have increased levels of protein in their urine due to hypertension reducing the filtering power of the kidneys. Prolonged hypertension due to preeclampsia can lead to organ damage and life-threatening complications for mothers and fetuses.

There is no cure for the underlying causes of preeclampsia, so physicians focus on managing and monitoring patients' blood pressure to allow for as close to a full-term gestation as possible. With severe disease, pre-term deliveries are necessary.

"For some patients who can make it to full term, a preeclampsia diagnosis is scary at first but ultimately a bump in the road," says Jennifer McIntosh, DO, MS, associate professor of obstetrics and gynecology at the Medical College of Wisconsin (MCW). "For those who get it earlier on, it can be terrifying and life-changing, potentially including a long hospital stay before delivery and significant supportive care for the infant in the NICU afterwards."

More research is needed into what causes preeclampsia to guide the development of potential new ways to diagnose, treat and prevent this common yet cryptic condition.

"The worldwide incidence of preeclampsia is rising, so research grows more important by the day," Dr. McIntosh says. "Preeclampsia has existed for as long as women have been giving birth, and yet the only cure for it is delivering the baby. I believe we can be innovative and do better for our patients."

MCW scientists published results on a study of one of the emerging theories for what causes preeclampsia in *Science Advances* in December 2023. The experiments focus on a particular layer of cells of the placenta called the syncytiotrophoblast (STB), which is a key part of the barrier between the mother and developing fetus. This blockade helps keep a mother's fully formed immune system from reacting to the fetus and potentially responding as if the fetus was a foreign threat such as a viral or bacterial invader. The barrier also works in reverse to keep the fetus's growing immune system from reacting to its mother's cells and tissues. The study's

authors investigated the hypothesis that an abnormal amount of cellular and molecular stresses to the STB can damage the placenta and lead to preeclampsia.

"There is considerable evidence that these stresses accumulate, however, how and why it happens continues to be an open question," says Justin Grobe, PhD, MCW professor of physiology and biomedical engineering and the co-corresponding author on the *Science Advances* manuscript with Dr. McIntosh. "We felt it was important to continue to validate the STB stress findings before advancing work on our hypothesis that elevated hormones of pregnancy contribute to the accumulation of stress by overstimulating the STB."

The research team began by studying placentas donated for research purposes through the MCW Maternal Research Placenta & Cord Blood Bank. By comparing "normal" placentas with placentas from pregnancies where patients suffered from preeclampsia, investigators demonstrated that preeclampsia was associated with higher levels of cellular stresses in the STB layer on the placenta. Additionally, the researchers found a hyperactive level of activity of the G?q protein known to play a role in transmitting signals related to the levels of several hormones present in excessive amounts during preeclampsia.

"The donated human placenta samples were critical to identifying potential mechanisms of STB stress," says Megan Opichka, PhD '23, research and development scientist at BioSpyder Technologies and first author on the publication. "Because these samples are collected upon delivery, we then needed to develop an animal model to determine if these sources of stress may actually be causative."

Based on the findings of hyperactive signaling through G-protein-coupled receptors (GPCRs) in samples from patients with preeclampsia, the scientists developed a new mouse model genetically engineered to enable the precise manipulation of GPCR signals within specific cell types. This allowed the researchers to activate the signaling pathways associated with preeclampsia within the STB layer of the mouse's placenta. The team demonstrated that even a very brief activation of the identified signaling cascades during the early or middle portions of gestation led to significant consequences during the mouse pregnancy. These mice developed all the signature signs of preeclampsia, including high blood pressure, kidney damage and other anatomical and cellular changes. In some mice exposed to the preeclampsia inducing signals, the scientists tested the effects of a medicine that reduces stress on the mitochondria that generate energy within each cell. The drug provided substantial protection against developing the signs and symptoms of preeclampsia.

"With our unique model, we can study the effects of contributing factors to preeclampsia throughout pregnancy," Dr. Grobe says. "We can test specific signaling cascades in specific cells and tissues at specific times to observe their effects. We have only scratched the surface on what we can learn."

"This will absolutely be a springboard for future research," Dr. McIntosh adds. "Because the drug we tested, MitoQ, is generally known to be safe, we're working on plans for a clinical pilot study to test appropriate dosage and efficacy in advance of pursuing larger clinical studies of preeclampsia in the future."

So, can preeclampsia be prevented? While today the answer is no, MCW scientists now are one step closer with these experimental results. And they are continuing to work as a team to achieve this goal through additional studies.

"What drives my research is my frustration about the lack of understanding of what causes preeclampsia," says Dr. McIntosh. "We need to continue linking the bench and the bedside together so that we can understand the causes and use them to bring a cure to the bedside."

Story Source:

Materials provided by **Medical College of Wisconsin**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Megan A. Opichka, M. Christine Livergood, Kirthikaa Balapattabi, McKenzie L. Ritter, Daniel T. Brozoski, Kelsey K. Wackman, Ko-Ting Lu, Kaleigh N. Kozak, Clive Wells, Agnes B. Fogo, Katherine N. Gibson-Corley, Anne E. Kwitek, Curt D. Sigmund, Jennifer J. McIntosh, Justin L. Grobe. **Mitochondrial-targeted antioxidant attenuates preeclampsia-like phenotypes induced by syncytiotrophoblast-specific Gαq signaling**. *Science Advances*, 2023; 9 (48)
DOI: 10.1126/sciadv.adg8118

3. 神経の活性化によりインスリン産生細胞を再生 -マウス糖尿病の治療に成功-

日付：2023 年 12 月 4 日
ソース：東北大学
概要： https://www.tohoku.ac.jp/japanese/2023/11/press20231110-01-insulin.html

多くの糖尿病は、血糖値を下げるホルモン（インスリン）を産生する唯一の細胞である膵臓のβ細胞（注 1）が減少することで血糖値が上昇し発症します。このβ細胞を体内で増やす治療法が世界中で求められていますが、現在のところ開発されていません。
東北大学大学院医学系研究科糖尿病代謝内科学分野および東北大学病院糖尿病代謝科の今井淳太准教授、川名洋平助教、片桐秀樹教授らのグループは、マウスにおいて、脳と膵臓をつなぐ自律神経の一種である迷走神経（注 2）（膵臓迷走神経）を刺激することで、体の中でβ細胞を増やすことが可能であることを世界で初めて発見しました。本研究ではオプトジェネティクスという手法を用い、光によって膵臓迷走神経を刺激する方法（注 3）を開発しました。さらに、インスリンが減って糖尿病を発症しているマウスの膵臓迷走神経をこの方法を用いて刺激することで、β細胞を再生し、マウス糖尿病を治療することにも成功しました。この成果により、膵臓迷走神経刺激によってβ細胞を増やすという糖尿病の根本的な予防・治療法の開発につながることが大いに期待されます。また、β細胞の数や働きを調節する仕組みや糖尿病発症のメカニズムの解明も進むものと考えられます。
本研究成果は、2023 年 11 月 9 日午後 4 時（ロンドン時間、日本時間 11 月 10 日午前 1 時）『Nature Biomedical Engineering』誌に掲載されました。

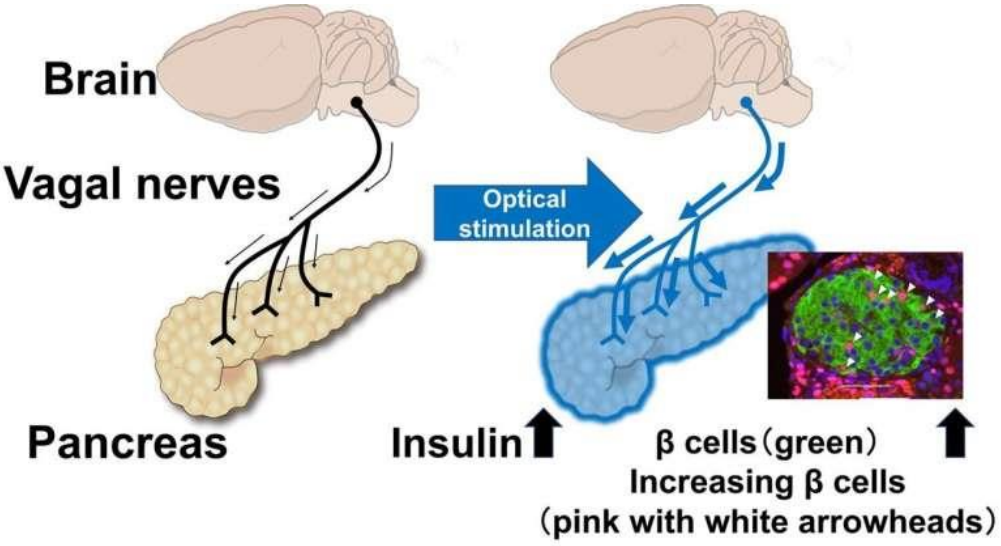
研究関連ニュース/他のトップページに戻る

＜英文＞Research reveals that stimulating nerves connected to the pancreas can regenerate insulin-producing cells (medicalxpress.com)

DECEMBER 4, 2023

Research reveals that stimulating nerves connected to the pancreas can regenerate insulin-producing cells

by Tohoku University



Stimulating the vagus nerve connected to the pancreas in mice by blue light increases blood insulin and β-cell numbers. The picture represents a clusters of beta cells (green) in islets of Langerhans in the pancreas. The nuclei of increasing β-cells are shown in pink with white arrowheads. Credit: Junta Imai et al

Insulin is a hormone that decreases blood glucose levels. The only cells that produce insulin are pancreatic beta cells (β-cells), and a decrease in these cells is a major cause of diabetes. Although therapies aimed at increasing pancreatic β-cells are eagerly awaited, a strategy that can increase β-cells has, thus far, not been developed.

In a promising advancement, a research group from the Tohoku University Graduate School of Medicine has revealed that stimulating autonomic vagal nerves connected to the pancreas can improve the function and also increase the number of pancreatic β-cells in mice.

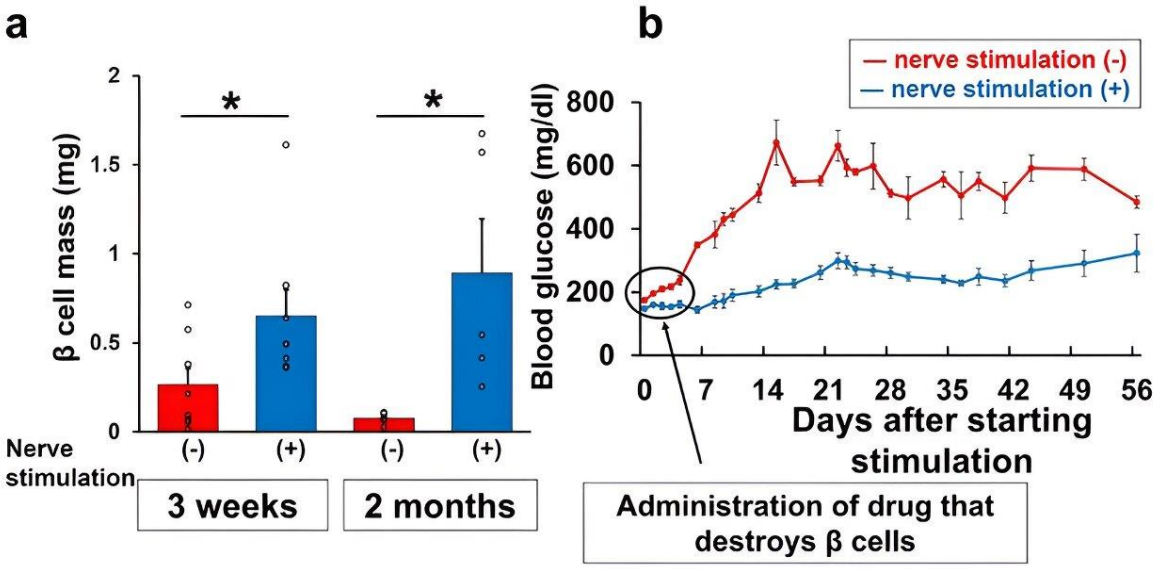
The group, which was led by Associate Professor Junta Imai, Assistant Professor Yohei Kawana, and Professor Hideki Katagiri, published their findings in the journal *Nature Biomedical Engineering* on November 9, 2023.

"Using optogenetics, we first developed a means to stimulate individually the vagus nerve leading to the pancreas in mice," says Imai. "This novel method led to a marked elevation in the amount of insulin in the blood when sugar was administered, indicating improved β-cell function."

Additional stimulation of this nerve over two weeks more than doubled the original number of β-cells. Stimulating the pancreatic vagal nerves activated β-cells in terms of both quality and quantity.

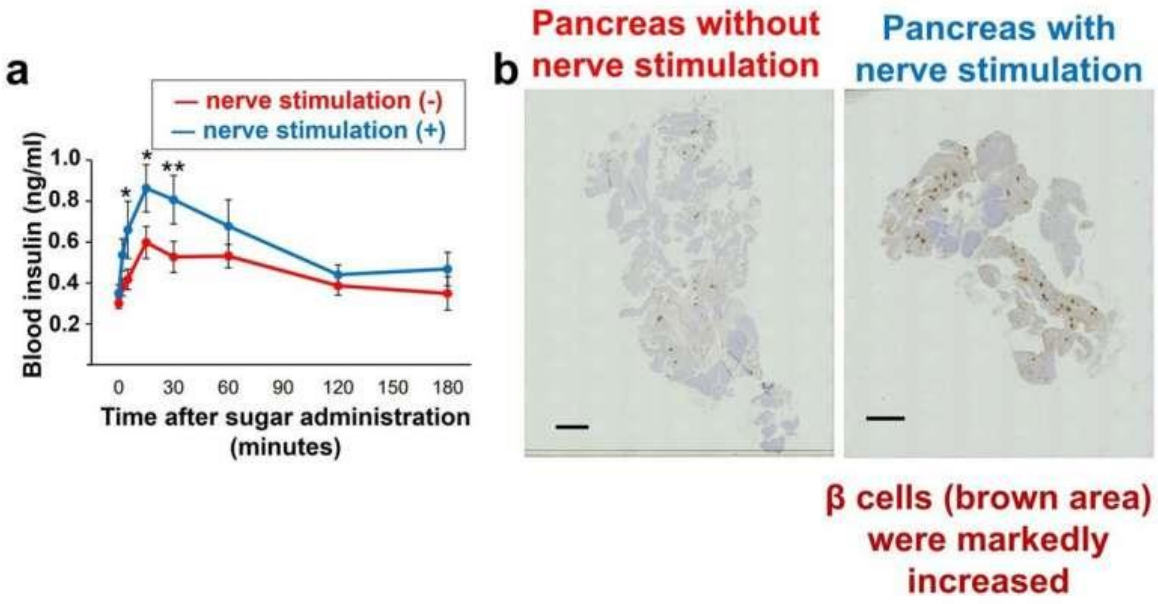
When Imai and his colleagues applied this method to a mouse model of insulin-deficient diabetes, the regeneration of pancreatic β-cells ameliorated diabetes in these mice. This represents the first successful treatment of diabetes in mice by stimulating the vagal nerves connected to the pancreas.

"We hope our achievements lead to the development of new strategies and preventive methods for diabetes," adds Imai. "We also expect it to advance our understanding of the mechanisms that regulate the function and number of pancreatic β-cells, as well as the causes of diabetes."



Stimulating the pancreatic vagal nerve connected to the pancreas restored depleted β-cells in diabetic mice (a) and improved blood glucose levels. Credit: Junta Imai et al

The research in the project was supported by the Japan Science and Technology Agency (JST), [Moonshot R&D] as well as by the Japan Agency for Medical Research and Development (AMED-PRIME).



Stimulating the pancreatic vagus nerve connected to the pancreas increased blood insulin after sugar was administered (a) and β-cell numbers (b). The brown area indicated the pancreatic β-cells clustered in the islets of Langerhans. Credit: Junta Imai et al

More information: Yohei Kawana et al, Optogenetic stimulation of vagal nerves for enhanced glucose-stimulated insulin secretion and β cell proliferation, *Nature Biomedical Engineering* (2023). DOI: 10.1038/s41551-023-01113-2

Journal information: Nature Biomedical Engineering

Provided by Tohoku University

4. 特定の遺伝的変異が肥満の予防に役立つ可能性 –マウス実験

日付：2023 年 12 月 7 日
ソース：ワイル・コーネル医科大学
概要：

『Molecular Metabolism』誌のオンライン版に掲載されたこの研究は、ヒトの遺伝的変異が個人の体重増加の感受性にどのように影響するかについて新たな洞察を提供している。Weill Cornell Medicine の研究者らは、ボディーマス指数（BMI）に関連するグルコース依存性インスリン分泌性ポリペプチド（GIP）受容体にヒトの遺伝的変異を有するマウスを開発した。研究者らは、このマウスがより一般的な別の受容体変異体を持つマウスよりも糖の処理がうまく、痩せた状態を維持できることを発見した。すなわち、この遺伝子変異が細胞内で異なる振る舞いをし、それがより効率的な新陳代謝に寄与する可能性があり、この変異が新しい肥満治療戦略の可能性を指摘している、としている。
米国疾病管理予防センターによると、この発見は、米国の 1 億人以上の成人が罹患している肥満を治療する新たな戦略を示す可能性がある、としている。

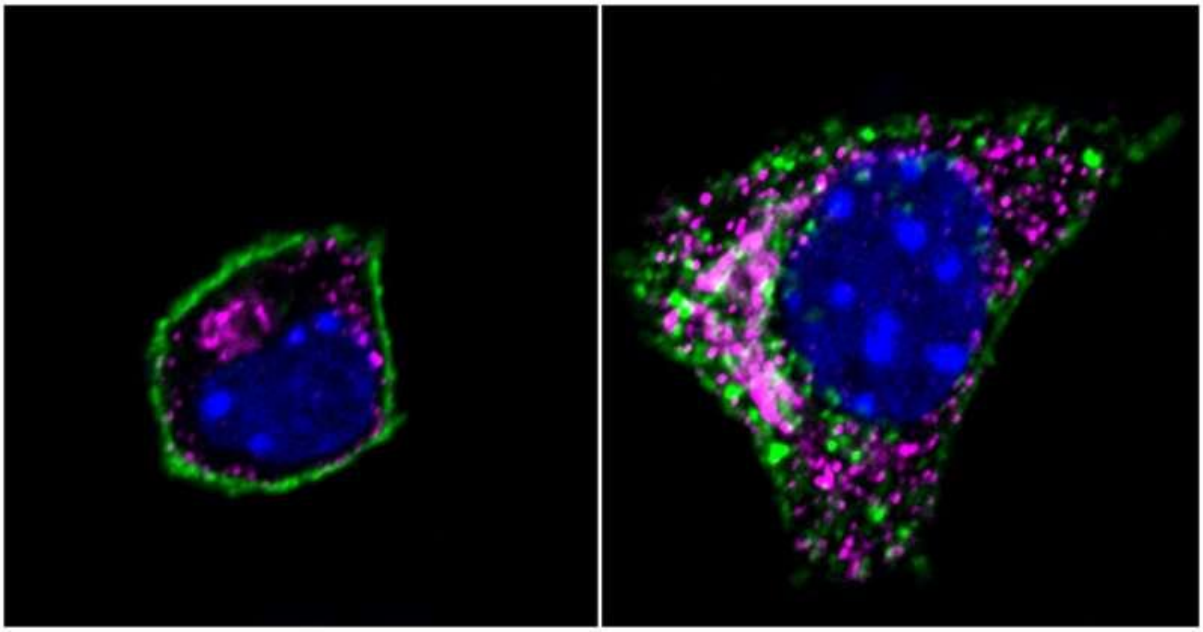
研究関連ニュース/他のトップページに戻る

＜英文＞Specific genetic variant may help prevent obesity (medicalxpress.com)

DECEMBER 7, 2023

Specific genetic variant may help prevent obesity

by Weill Cornell Medical College



The images of insulin-producing beta cells show GIP receptors Q354 variant (green), the Golgi Network (magenta) and the nucleus (blue). Left: GIP receptors are localized at the plasma membrane surrounding the cell. Right: After the receptor binds the GIP hormone, it moves inside the cell to the Golgi Network. Credit: *Molecular Metabolism*

A preclinical study by Weill Cornell Medicine investigators shows that a specific human genetic variant of a receptor that stimulates insulin release may help individuals resist obesity. The researchers discovered that this variant behaves differently in the cell, possibly contributing to more efficient metabolism.

The study, posted online in *Molecular Metabolism*, provides new insight into how human genetic variations affect an individual's susceptibility to weight gain. The researchers developed mice with a human genetic variant in the glucose-dependent insulinotropic polypeptide (GIP) receptor associated with leaner body mass index (BMI).

They found that the mice were better at processing sugar and staying leaner than mice with a different, more common receptor variant. The discovery may point to new potential strategies to treat obesity, which affects more than 100 million adults in the United States, according to the Centers for Disease Control and Prevention.

"Our work demonstrates how basic science research can yield important insights about complex biology," said the study's senior author Dr. Timothy McGraw, a professor of biochemistry in cardiothoracic surgery and in biochemistry at Weill Cornell Medicine. "These GIP receptors and their behavior at the cellular level profoundly impact metabolism and weight regulation."

GENETIC VARIANTS OF THE GIP RECEPTOR

Genetic variants are differences in DNA sequence that occur naturally between individuals in a given population. Genome-wide association studies, which use statistics to carefully link genetic variants to particular traits, show about 20 percent

of people of European descent have one copy of the GIP receptor with the Q354 gene variant, and about 5 percent have two copies of the variant. The GIP receptor interacts with a hormone released in response to glucose levels after a meal.

"Studies suggest that people with at least one copy of this GIP receptor variant have altered metabolism that reduces their risk of developing obesity," said the study's lead author, Dr. Lucie Yammine, a post-doctoral associate in biochemistry at Weill Cornell Medicine.

To understand how this gene variant may decrease the risk of obesity, the team used CRISPR-Cas9 technology to genetically engineer mice with the variant in the gene encoding the GIP receptor, similar to the human version. They found that female mice with the variant were leaner on a typical mouse diet than female litter mates without it.

Male mice with the gene variant were about the same weight as litter mates without it while consuming a regular diet, but the gene variant protected them from weight gain when fed a high-fat diet, which caused obesity in litter mates.

"We found that a change in one amino acid in the GIP receptor gene affected the whole body in terms of weight," Dr. Yammine said. Mice with the variant were more sensitive to the GIP hormone that triggers insulin release, which controls blood sugar levels and helps the body convert food into energy.

HOW THE VARIANT MAY PROVIDE AN ADVANTAGE AGAINST OBESITY

The researchers compared what happened to mouse cells with and without the variant when exposed to glucose or the GIP hormone. Pancreatic cells from mice with the genetic variant produced more insulin in response to both glucose and the GIP hormone, which may explain why they are better at processing glucose.

"What's interesting about these receptors is their location in the cell has a big impact on how they signal and their activity," Dr. McGraw said. He explained that when the GIP hormone binds to the receptor, the receptor moves from the cell surface to inside the cell. When the GIP hormone eventually falls off the receptor, the receptor returns to the cell surface.

The team found that the GIP receptor variant stays inside the cell compartment four times longer than the typical receptor. Dr. McGraw suggested that this may allow the receptor to send more messages to the machinery inside cells, which helps process sugar more efficiently.

Still, more research is needed to confirm the effects of this variant on the receptor's behavior. The researchers also want to learn if there are differences in the receptor's behavior in other cell types, like brain cells, which play a crucial role in regulating hunger.

Recently, the Food and Drug Administration has approved several weight loss drugs that mimic natural hormones in the body and interact with receptors like GIP, including semaglutide (Wegovy) and tirzepatide (Zepbound). This has increased the interest in studying new ways to target the GIP receptor for obesity.

"Our work suggests that the movement of the receptor from the cell surface to the interior is an important factor in controlling metabolism. Therefore, drugs regulating the GIP receptor behavior and location could provide an important new avenue to combat obesity," said Dr. Yammine.

In the meantime, Dr. McGraw noted that it is essential to understand how people with different genetic variants in the GIP receptor respond to currently available weight loss medications. "A better appreciation of how different variants of receptors impact metabolism might allow for a precision medicine approach—matching a specific drug to a genetic variant—for weight loss," he said.

More information: Lucie Yammine et al, Spatiotemporal regulation of GIPR signaling impacts glucose homeostasis as revealed in studies of a common GIPR variant, *Molecular Metabolism* (2023). DOI: 10.1016/j.molmet.2023.101831

Journal information: Molecular Metabolism

Provided by Weill Cornell Medical College

5. 遺伝的要因にも関わらずアルツハイマー病を回避した患者からの手がかり：マウス実験による新展開

日付：2023 年 12 月 11 日
ソース：ワシントン大学医学部
概要：

一人の女性が強い遺伝的傾向にもかかわらずアルツハイマー病を回避したことが、病気の阻止の鍵となる可能性があるとして、セントルイスにあるワシントン大学の研究者らは、彼女の特異な遺伝的変異に焦点を当てた。その結果、研究者らは、アルツハイマー病の初期の無症状段階と認知機能の低下が始まる遅期段階との関連を切断する手がかりを見つけた。特に、Christchurch 変異と呼ばれる APOE 遺伝子の変異が、アミロイドベータと呼ばれるタンパク質が脳に蓄積する初期段階と、別のタンパク質であるタウが蓄積し認知機能の低下が始まる遅期段階との関連を断ち切る可能性が示唆されている。
そこで、研究者らは遺伝子的に変異を持つマウスを作成：すなわち、アミロイドを過剰に生成する傾向があるマウスに、Christchurch 変異を持つヒトの APOE 遺伝子を組み込む遺伝子組み換えマウスを作成した後、ヒトの微量のタウをマウスの脳に注入した。
通常、既にアミロイドで満たされた脳にタウを導入すると、タウが注入部位で凝集し、その後他の部位に広がる病理的なプロセスが始まる。しかし、Christchurch 変異を持つマウスでは異なり、前述の女性と同様に、これらのマウスは広範なアミロイドプラークにもかかわらず、軽微なタウ病理を発展させたのみであった。
研究者らは、その鍵となる要因が脳のごみ処理細胞であるミクログリアの活動レベルであることを発見。ミクログリアは通常、アミロイドプラークの周りに集まる。Christchurch 変異を持つマウスでは、アミロイドプラークを取り囲むミクログリアが活性化され、タウ凝集体を摂取・分解する能力を向上させていた。
この研究は、アルツハイマー病の予防に新しいアプローチを提案している。

研究関連ニュース/他のトップページに戻る

＜英文＞Clues to preventing Alzheimer's come from patient who, despite genetics, evaded disease | ScienceDaily

Clues to preventing Alzheimer's come from patient who, despite genetics, evaded disease

Breaking link between early, late stages of disease may prevent dementia

Date:

December 11, 2023

Source:

Washington University School of Medicine

Summary:

A woman who never developed Alzheimer's despite a strong genetic predisposition may hold the key to stopping the disease in its tracks. Studying the woman's unique complement of genetic mutations, researchers have found clues that could help cut the link between the early, asymptomatic stage and the late stage, when cognitive decline sets in.

FULL STORY

Alzheimer's disease has plagued one large Colombian family for generations, striking down half of its members in the prime of life. But one member of that family evaded what had seemed would be fate: Despite inheriting the genetic defect that caused her relatives to develop dementia in their 40s, she stayed cognitively healthy into her 70s.

Researchers at Washington University School of Medicine in St. Louis now think they know why.

A previous study had reported that, unlike her relatives, the woman carried two copies of a rare variant of the *APOE* gene known as the Christchurch mutation.

In this study, researchers used genetically modified mice to show that the Christchurch mutation severs the link between the early phase of Alzheimer's disease, when a protein called amyloid beta builds up in the brain, and the late phase, when another protein called tau accumulates and cognitive decline sets in. So the woman stayed mentally sharp for decades, even as her brain filled with massive amounts of amyloid.

The findings, published Dec. 11 in the journal *Cell*, suggest a new approach to preventing Alzheimer's dementia.

"Any protective factor is very interesting, because it gives us new clues to how the disease works," said senior author David M. Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor of Neurology.

"As people get older, many begin to develop some amyloid accumulation in their brains. Initially, they remain cognitively normal. However, after many years the amyloid deposition begins to lead to the accumulation of the tau protein. When this happens, cognitive impairment soon ensues. If we can find a way to mimic the effects of the *APOE* Christchurch mutation, we may be able to stop people who already are on the path to Alzheimer's dementia from continuing down that path."

Alzheimer's develops over the course of about 30 years. The first two decades or so are silent; amyloid slowly accumulates in the brain without causing ill effects.

When amyloid levels reach a tipping point, however, they kick off phase two, which involves multiple interrelated destructive processes: A protein called tau forms tangles that spread through the brain; brain metabolism slows down, and the brain begins to shrink; and people start to experience memory and thinking problems.

The disease follows the same pattern in people with genetic and nongenetic forms of Alzheimer's.

The Colombian families carry a mutation in a gene called *presenilin-1* that causes their brains to develop far too much amyloid buildup beginning in their 20s.

People who carry the mutation accumulate amyloid so quickly that they reach the tipping point and start showing signs of cognitive decline in middle age.

One rare exception is a woman who had more amyloid in her brain in her 70s than her relatives did in their 40s, but only very minimal signs of brain injury and cognitive impairment.

"One of the biggest unanswered questions in the Alzheimer's field is why amyloid accumulation leads to tau pathology," Holtzman said.

"This woman was very, very unusual in that she had amyloid pathology but not much tau pathology and only very mild cognitive symptoms that came on late. This suggested to us that she might hold clues to this link between amyloid and tau."

A 2019 study had revealed that, along with a mutation in *presenilin-1*, the woman also carried the Christchurch mutation in both copies of her *APOE* gene, another gene associated with Alzheimer's disease.

But with only one person in the world known to have this particular combination of genetic mutations, there were not enough data to prove that the Christchurch mutation was responsible for her remarkable resistance to Alzheimer's and not simply a coincidental finding.

To solve this puzzle, Holtzman and first author Yun Chen, a graduate student, turned to genetically modified mice.

They took mice genetically predisposed to overproduce amyloid and modified them to carry the human *APOE* gene with the Christchurch mutation.

Then, they injected a tiny bit of human tau into the mouse brains.

Normally, introducing tau into brains already brimming with amyloid seeds a pathological process in which tau collects into aggregates at the site of injection, followed by the spread of such aggregates to other parts of the brain.

Not so in the mice with the Christchurch mutation. Much like the Colombian woman, the mice developed minor tau pathology despite extensive amyloid plaques.

The researchers discovered that the key difference was the activity levels of microglia, the brain's waste-disposal cells.

Microglia tend to cluster around amyloid plaques. In mice with the *APOE* Christchurch mutation, the microglia surrounding amyloid plaques were revved up and hyperefficient at consuming and disposing of tau aggregates.

"These microglia are taking up the tau and degrading it before tau pathology can spread effectively to the next cell," Holtzman said. "That blocked much of the downstream process; without tau pathology, you don't get neurodegeneration, atrophy and cognitive problems. If we can mimic the effect that the mutation is having, we may be able to render amyloid accumulation harmless, or at least much less harmful, and protect people from developing cognitive impairments."

Story Source:

Materials provided by **Washington University School of Medicine**. Original written by Tamara Bhandari. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yun Chen, Sihui Song, Samira Parhizkar, Jennifer Lord, Yiyang Zhu, Michael R. Strickland, Chanung Wang, Jiyu Park, G. Travis Tabor, Hong Jiang, Kevin Li, Albert A. Davis, Carla M. Yuede, Marco Colonna, Jason D. Ulrich, David M. Holtzman. **APOE3ch alters microglial response and suppresses Aβ-induced tau seeding and spread**. *Cell*, 2023; DOI: 10.1016/j.cell.2023.11.029

6. 妊娠時の悪阻の原因解明とマウス実験から見えた治療の可能性

日付：2023 年 12 月 13 日
ソース：ケンブリッジ大学
概要：

妊婦の多ければ 10 人中 7 人に吐き気や嘔吐が生じ、妊婦 100 人中 1～3 人ほどは特に重度の悪心嘔吐を被り、妊娠悪阻（つわり）として知られるそれら重度の悪心嘔吐は悪くすると胎児の命にも関わる。
今日『Nature』誌に掲載されたケンブリッジ大学による新しい研究は、多くの女性が妊娠中に吐き気や嘔吐を経験する理由を明らかにした。原因は、胎児が産生する GDF15 と呼ばれるホルモンであり、母親の症状は胎児が生成するホルモンの量と妊娠前に母親がこのホルモンに曝露された量の組み合わせに依存する、としている。血中の GDF15 が多い妊婦ほど嘔吐や妊娠悪阻をより被っており、妊婦の血中の GDF15 の殆どは胎児（胎盤の胎児の領分）由来であった。
また、妊娠していないときの GDF15 が少ない女性ほど妊娠悪阻を生じ易く、逆に GDF15 が多いことと関連する病気である β サラセミアの女性には妊娠時の悪心嘔吐が殆ど認められなかった。
この発見から、母親を妊娠前に GDF15 に曝露することで妊娠悪阻を予防できる可能性が示唆されている。妊娠前に GDF15 により慣れていると妊娠中に GDF15 が上昇してもどうやらより平気でいられることはマウス実験でも示されている。

研究関連ニュース/他のトップページに戻る

＜英文＞Cause of pregnancy sickness -- and potential treatment | ScienceDaily

Cause of pregnancy sickness -- and potential treatment

Date:

December 13, 2023

Source:

University of Cambridge

Summary:

A new study has shown why many women experience nausea and vomiting during pregnancy -- and why some women, including the Duchess of Cambridge, become so sick they need to be admitted to hospital. The culprit is a hormone produced by the fetus -- a protein known as GDF15. But how sick the mother feels depends on a

combination of how much of the hormone is produced by the fetus and how much exposure the mother had to this hormone before becoming pregnant.

FULL STORY

A Cambridge-led study has shown why many women experience nausea and vomiting during pregnancy -- and why some women, including the Duchess of Cambridge, become so sick they need to be admitted to hospital.

The culprit is a hormone produced by the fetus -- a protein known as GDF15. But how sick the mother feels depends on a combination of how much of the hormone is produced by the fetus and how much exposure the mother had to this hormone before becoming pregnant.

The discovery, published today in *Nature*, points to a potential way to prevent pregnancy sickness by exposing mothers to GDF15 ahead of pregnancy to build up their resilience.

As many as seven in ten pregnancies are affected by nausea and vomiting. In some women -- thought to be between one and three in 100 pregnancies -- it can be severe, even threatening the life of the fetus and the mother and requiring intravenous fluid replacement to prevent dangerous levels of dehydration. So-called hyperemesis gravidarum is the commonest cause of admission to hospital of women in the first three months of pregnancy.

Although some therapies exist to treat pregnancy sickness and are at least partially effective, widespread ignorance of the disorder compounded by fear of using medication in pregnancy mean that many women with this condition are inadequately treated.

Until recently, the cause of pregnancy sickness was entirely unknown. Recently, some evidence, from biochemical and genetic studies has suggested that it might relate to the production by the placenta of the hormone GDF15, which acts on the mother's brain to cause her to feel nauseous and vomit.

Now, an international study, involving scientists at the University of Cambridge and researchers in Scotland, the USA and Sri Lanka, has made a major advance in understanding the role of GDF15 in pregnancy sickness, including hyperemesis gravidarum.

The team studied data from women recruited to a number of studies, including at the Rosie Maternity Hospital, part of Cambridge University Hospitals NHS Foundation Trust and Peterborough City Hospital, North West Anglia NHS Foundation Trust. They used a combination of approaches including human genetics, new ways of measuring hormones in pregnant women's blood, and studies in cells and mice.

The researchers showed that the degree of nausea and vomiting that a woman experiences in pregnancy is directly related to both the amount of GDF15 made by

the fetal part of placenta and sent into her bloodstream, and how sensitive she is to the nauseating effect of this hormone.

GDF15 is made at low levels in all tissues outside of pregnancy. How sensitive the mother is to the hormone during pregnancy is influenced by how much of it she was exposed to prior to pregnancy -- women with normally low levels of GDF15 in blood have a higher risk of developing severe nausea and vomiting in pregnancy.

The team found that a rare genetic variant that puts women at a much greater risk of hyperemesis gravidarum was associated with lower levels of the hormone in the blood and tissues outside of pregnancy. Similarly, women with the inherited blood disorder beta thalassemia, which causes them to have naturally very high levels of GDF15 prior to pregnancy, experience little or no nausea or vomiting.

Professor Sir Stephen O'Rahilly, Co-Director of the Wellcome-Medical Research Council Institute of Metabolic Science at the University of Cambridge, who led the collaboration, said: "Most women who become pregnant will experience nausea and sickness at some point, and while this is not pleasant, for some women it can be much worse -- they'll become so sick they require treatment and even hospitalisation.

"We now know why: the baby growing in the womb is producing a hormone at levels the mother is not used to. The more sensitive she is to this hormone, the sicker she will become. Knowing this gives us a clue as to how we might prevent this from happening. It also makes us more confident that preventing GDF15 from accessing its highly specific receptor in the mother's brain will ultimately form the basis for an effective and safe way of treating this disorder."

Mice exposed to acute, high levels of GDF15 showed signs of loss of appetite, suggesting that they were experiencing nausea, but mice treated with a long-acting form of GDF15 did not show similar behaviour when exposed to acute levels of the hormone. The researchers believe that building up woman's tolerance to the hormone prior to pregnancy could hold the key to preventing sickness.

Co-author Dr Marlena Fejzo from the Department of Population and Public Health Sciences at the University of Southern California whose team had previously identified the genetic association between GDF15 and hyperemesis gravidarum, has first-hand experience with the condition. "When I was pregnant, I became so ill that I could barely move without being sick. When I tried to find out why, I realized how little was known about my condition, despite pregnancy nausea being very common.

"Hopefully, now that we understand the cause of hyperemesis gravidarum, we're a step closer to developing effective treatments to stop other mothers going through what I and many other women have experienced."

The work involved collaboration between scientists at the University of Cambridge, University of Southern California, University of Edinburgh, University of Glasgow and Kelaniya University, Colombo, Sri Lanka. The principal UK funders of the study were the Medical Research Council and Wellcome, with support from the National Institute for Health and Care Research Cambridge Biomedical Research Centre.

Story Source:

Journal Reference:

1. M. Fejzo, N. Rocha, I. Cimino, S. M. Lockhart, C. J. Petry, R. G. Kay, K. Burling, P. Barker, A. L. George, N. Yasara, A. Premawardhena, S. Gong, E. Cook, D. Rimmington, K. Rainbow, D. J. Withers, V. Cortessis, P. M. Mullin, K. W. MacGibbon, E. Jin, A. Kam, A. Campbell, O. Polasek, G. Tzoneva, F. M. Gribble, G. S. H. Yeo, B. Y. H. Lam, V. Saudek, I. A. Hughes, K. K. Ong, J. R. B. Perry, A. Sutton Cole, M. Baumgarten, P. Welsh, N. Sattar, G. C. S. Smith, D. S. Charnock-Jones, A. P. Coll, C. L. Meek, S. Mettananda, C. Hayward, N. Mancuso, S. O'Rahilly. **GDF15 linked to maternal risk of nausea and vomiting during pregnancy**. *Nature*, 2023; DOI: 10.1038/s41586-023-06921-9

7. マウスは進化の過程で遺伝子治療薬として働く RNA を獲得していた

日付：2023 年 12 月 13 日
ソース：北海道大学
概要：https://www.hokudai.ac.jp/news/2023/12/rnarna-1.html

北海道大学大学院薬学研究院の中川真一教授と摂南大学の芳本　玲講師らの研究グループは、発見以来 40 年以上、機能が不明だったマウスの RNA（4.5SH RNA）の、新たな役割を発見しました。
マウスのゲノム DNA には正常な mRNA を作る上で不具合となり得る配列が多数存在しています。それらが mRNA に取り込まれると致死性の遺伝病の原因となりますが、4.5SH RNA にはそれらを一括して無毒化する、解毒剤のような働きがありました。つまり、マウスは進化の過程で、いわば天然の遺伝子治療薬を獲得していたことになります。更に、4.5SH RNA は二つのモジュールから構成されていることも分かりました。一つは異常な配列を見つけるためのセンサーの役割を、もう一つは異常な配列が mRNA に取り込まれないようにするためのツールを連れてくる役割を果たしています。この発見は、このセンサー部分を変更することにより、特定の遺伝子変異のみを認識する新しい遺伝子治療薬を開発できる可能性を示唆しています。これが実現すれば、遺伝病を引き起こす変異を長期的に無毒化する新しい遺伝子治療の道が開かれるかもしれません。
なお、本研究成果は、2023 年 12 月 14 日（木）公開の『Molecular Cell』誌に掲載されました。

研究関連ニュース/他のトップページに戻る

＜英文＞Mice possess natural gene therapy system | EurekAlert!

NEWS RELEASE 13-DEC-2023

Mice possess natural gene therapy system

Peer-Reviewed Publication

HOKKAIDO UNIVERSITY

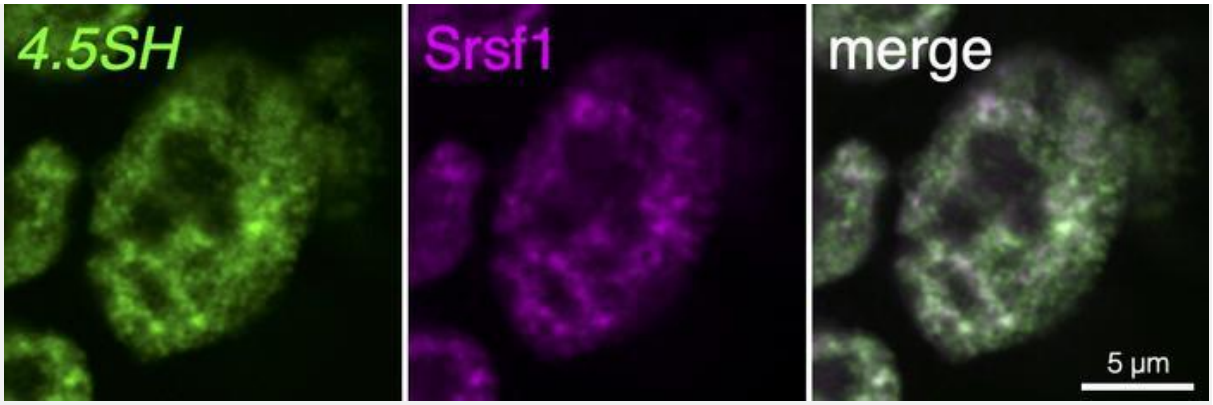


IMAGE:

4.5SH RNA (GREEN) IS LOCATED IN THE NUCLEAR SPECKLES (SRSF1, MAGENTA)—STRUCTURES IN THE CELL NUCLEUS ASSOCIATED WITH GENE EXPRESSION—IN EMBRYONIC STEM CELLS, WHERE IT PLAYS AN ESSENTIAL ROLE IN RNA PROCESSING. (REI YOSHIMOTO, ET AL. *MOLECULAR CELL*. DECEMBER 13, 2023)

view more

CREDIT: REI YOSHIMOTO, ET AL. MOLECULAR CELL. DECEMBER 13, 2023

A previously mysterious small RNA molecule in mice is found to play a crucial role in gene expression, and may be the first identified member of a new class of regulatory RNAs.

RNA (ribonucleic acid) is best known as the messenger RNA (mRNA) that carries a copy of a gene's information out from the cell nucleus to where it can be decoded to make protein molecules. But RNA also performs other key functions, including the regulation of gene activity by a variety of small non-coding RNAs—those whose genetic sequence is not used to generate proteins.

One such non-coding RNA is the small RNA called 4.5SH, found only in small rodents including mice and rats. It is produced from multiple copies of its gene, leading to the accumulation of up to 10,000 copies of the RNA molecule per cell.

A team of researchers led by Professor Shinichi Nakagawa at Hokkaido University has discovered a new role for 4.5 SH RNA—circumventing mutations in mouse DNA during the maturation of mRNA. Their findings were published in the journal *Molecular Cell*.

"4.5SH RNA was discovered in the 1970s, yet despite its abundance and presence in many types of tissues, its function had remained a mystery for over 40 years," says Nakagawa.

To understand its role, the researchers created mutations in mouse embryos that abolished 4.5SH production, discovering that this caused early death at the embryo stage.

“It was known that the mouse genome has many lethal mutations in genes that code essential proteins,” explains Nakagawa. “4.5 SH RNA has the ability to detoxify these mutations in bulk—essentially, it is a natural gene therapy to protect against mutations.”

Analysis of the structure of 4.5SH RNA showed that it is composed of two modules. One serves as a sensor to find abnormal sequences, and the other brings in a tool that prevents the incorporation of the abnormal sequences into mRNA by a process called alternative splicing.

“To our knowledge, this is the first example of a naturally produced RNA that can regulate alternative splicing in a definitive on/off manner,” says Nakagawa. “Our research also suggests that a substantial portion of such non-coding RNAs may be involved in controlling alternative splicing.”

The researchers were also able to use 4.5SH to design a programmable molecular system that could manipulate splicing in cells in selected ways. This might become a new and useful tool for genetic engineering.

“Our discovery suggests the possibility of developing new gene therapy drugs that recognize only specific genetic mutations by modifying the sensor module of 4.5 SH RNA, so we may be able to prevent toxic regions associated with disease from being expressed,” Nakagawa explains.

JOURNAL

Molecular Cell

DOI

10.1016/j.molcel.2023.11.019

METHOD OF RESEARCH

Experimental study

SUBJECT OF RESEARCH

Animals

ARTICLE TITLE

4.5SH RNA counteracts deleterious exonization of SINE B1 in mice

ARTICLE PUBLICATION DATE

13-Dec-2023

COI STATEMENT

Patent applications (JP21663/2022-076674 and PCT/JP2023/015828) have been submitted by Rei Yoshimoto and Shinichi Nakagawa based on the results of this study.

8. ゼブラフィッシュの発生の初期段階を詳細に記述した遺伝子アトラス

ゼブラフィッシュは、脊椎動物の胚発生の進行を研究するための強力なモデル

日付：2023 年 12 月 18 日
ソース：ワシントン大学医学部
概要：

NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development（NICHD）の研究者らは、ゼブラフィッシュの発達のアトラスを発表した。このアトラスは、発生の初めの 5 日間におけるほぼすべての細胞タイプ内で活性化される遺伝子発現プログラムを詳細に記述している。この期間中、受精卵は単一の細胞から異なる細胞タイプへと成熟する。ゼブラフィッシュは、人間の発達と疾患に関する洞察を提供する強力なモデルであり、研究者らは、このアトラスが、人間の疾患に関連する細胞の開発プログラムの予測に役立つ、としている。
この成果は『Developmental Cell』誌に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞Genetic atlas detailing early stages of zebrafish development | ScienceDaily

Genetic atlas detailing early stages of zebrafish development

Zebrafish are a powerful model for studying embryonic progression in vertebrates

Date:

December 18, 2023

Source:

NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development

Summary:

Researchers have published an atlas of zebrafish development, detailing the gene expression programs that are activated within nearly every cell type during the first five days of development, a period in which embryos mature from a single cell into distinct cell types.

FULL STORY

Researchers at the National Institutes of Health have published an atlas of zebrafish development, detailing the gene expression programs that are activated within nearly every cell type during the first five days of development, a period in which embryos mature from a single cell into distinct cell types. These diverse cells become tissues and organs that form juvenile fish capable of swimming and looking for food. The findings are published in *Developmental Cell*.

"Perhaps surprisingly, tiny zebrafish provide us with significant insight into human development and disease. Many of the gene expression programs that direct embryonic growth are similar across fish, people, and other animals," said Christopher McBain, Ph.D., scientific director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which conducted the work.

"Since zebrafish are visibly transparent, fertilize eggs externally, and are easy to study genetically, they represent a unique and effective way to model human disease."

The process of embryonic development is orchestrated by instructions in DNA that direct different programs of gene expression within individual cells, which give different cell types their unique functional characteristics.

To create the atlas, the study team used a method called single-cell RNA sequencing to identify gene expression programs over the course of five days, with samples taken every two to 12 hours.

The resulting atlas follows nearly 490,000 cells continuously over 120 hours after fertilization, with an average of 8,621 transcripts and 1,745 genes detected per cell.

The study team then sorted these data among known cell types and cell states during development.

To highlight the atlas' utility, the team focused on the development of understudied cells, including intestinal cells called BEST4+ cells, which are linked to gastrointestinal diseases and cancer in people.

Little is known about how these cells develop because they are absent in other common model organisms, such as mice.

By using the atlas, the team computationally predicted the full developmental program of BEST4+ cells, including signals that initiate the cells' development and transcription factors that carry out the process.

These findings can be evaluated in model organisms or clinical samples to better understand the role of BEST4+ cells in human disease.

"Our atlas on early zebrafish development is an extremely thorough resource that describes the expression program of hundreds of cell types across 62 developmental stages," said senior author Jeffrey A. Farrell, Ph.D., an Earl Stadtman Investigator and head of NICHD's Unit on Cell Specification and Differentiation.

"From this atlas, we made discoveries about understudied cells, including intestinal cells involved in human diseases, smooth muscle that surrounds the intestine, and cells that surround blood vessels. There are many more advances waiting to be uncovered, and we look forward to seeing what the research community can do with our open-source atlas."

The atlas is publicly accessible to the broader research community at https://daniocell.nichd.nih.gov. In addition to browsing the data online through the website, data may also be downloaded in additional formats for reanalysis. A timelapse of early zebrafish development is available for viewing, as well as microscopy images related to the study. To learn more about the NIH Zebrafish Facility, visit the NIH Virtual Tour.

Story Source:

Materials provided by **NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Abhinav Sur, Yiqun Wang, Paulina Capar, Gennady Margolin, Morgan Kathleen Prochaska, Jeffrey A. Farrell. **Single-cell analysis of shared signatures and transcriptional diversity during zebrafish development**. *Developmental Cell*, 2023; 58 (24): 3028 DOI: 10.1016/j.devcel.2023.11.001