Bio News – April, 2021

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

3/2　妊婦のワクチン治験を開始　Pfizer、米など 9 カ国で

3/2　AstraZeneca も（Merck に続いて）COVID-19 ワクチンで高値の Moderna 株式現金化～12 億ドル獲得

3/2　医薬品流通の McKesson が米国で J&J の COVID-19 ワクチン出荷開始

3/2　世界のコロナ新規感染者、再び増加 WHO 事務局長が「ワクチン頼み」を警告

3/3　“飲兵衛”はドーパミン受容体が増える 酒量増の仕組み解明

酒量が日々増えてしまうのは、脳内で幸福感ややる気を高める神経伝達物質「ドーパミン」の受容体が増えるためであることをハエの実験で解明したと、東北大学などの研究グループが発表した。ヒトのアルコール依存症も同じと考えられ、将来的に対策につながるか注目される。

3/3　Novavax の COVID-19 ワクチンは米国で 5 月に認可される可能性～武田が日本試験開始

3/4　新型コロナに感染しやすく…「悪さする抗体」発見　阪大

大阪大学の研究グループは、新型コロナウイルスに対する免疫反応で体内にできる「抗体」の中に、ウイルスに感染しやすくなる働きを持つ抗体があることを発見した。抗体は通常、病気の原因となるウイルスを排除する働きを持つが、いわば「悪さをする抗体」だという。

3/4　インドネシアの「ワクチン開発」に…大阪大学が”技術提供”

インドネシアの新型コロナウイルスワクチンの開発に向け、大阪大学が技術提供する。4 日、オンラインで学術協定を結んだのは、大阪大学微生物病研究所とインドネシアのバンドン工科大学。協定では 5 年間、バンドン工科大学へ技術を提供し、インドネシアの国産新型コロナワクチンの開発に向け、協力する事が決まった。

3/6　大型類人猿に初めてコロナワクチンを接種、米動物園

サンディエゴ動物園に暮らす 4 頭のオランウータンと 5 頭のボノボが、動物用医薬品企業が開発したワクチンの試験投与を 2 度受けた。

3/8　インスリン用注射器で 7 回接種可能に　京都の病院が発表

医療従事者への優先接種が始まっている Pfizer 製ワクチンは、使用方法を記した添付文書で、1 瓶で 6 回分接種できるとされる。だが、一般的な注射器では内部に薬剤が残り、特殊な注射器が普及するまでは 5 回しか接種できない。国は 2 月、全国の自治体に 1 瓶 5 回分で準備するよう通知していた。

3/9　テナガザルが謎の出産　おりに 1 頭だけ飼育なのに「なぜ」　長崎

3/9　1 瓶から 7 回接種の注射器、国内で生産へ　テルモが開発

医療機器大手のテルモは、Pfizer 製のワクチン 1 瓶から 7 回接種できる注射器を開発。3 月末から生産を始める。

3/9　難病「肺高血圧症」重症化の仕組み解明　新治療法に期待

心臓から肺に血液を送る肺動脈が狭くなる難病「肺高血圧症」が悪化する仕組みを、国立循環器病研究センターのグループが解明した。

3/9　HAM 発症に影響与える遺伝子確認　京大チーム、早期発見に前進

九州に患者が多い厚生労働省指定難病「HTLV1 関連脊髄症（HAM）」の発症に影響を与える遺伝子を複数発見したと、京都大ゲノム医学センターの松田文彦センター長らの研究チームが 8 日発表。この遺伝子によって作られるタンパク質のアミノ酸配列が、HAM の発症する確率を変化させることも特定。今後、早期の発見と治療につながる可能性がある。論文は、国立科学アカデミーが発行する機関誌のオンライン版に 2 日掲載された。

3/9　マウントサイナイ医科大学がマンハッタンのビルの一角にバイオ研究拠点を築く

3/10　武田薬品が T 細胞活性化剤 COBRA を開発する Maverick（カリフォルニア州ブリスベン）を約束より 1 年早く、最大 5 億 2,500 万ドルで買収

3/10　Cue Health の処方不要の COVID-19 検査の店頭販売を FDA が取り急ぎ許可

3/10　COVID-19 ワクチンのアレルギー反応 2%、アナフィラキシーは非常に稀で 0.025%

去年 12 月中旬から今年 2 月中旬の約 2 か月間に米国ボストンの Mass General Brigham（MGB）病院の職員 64,900 人が Pfizer/BioNTech か Moderna の新型コロナウイルス感染症（COVID-19）予防 mRNA ワクチン 1 回目接種を済ませ、接種後すぐのアレルギー反応の発生率は 2.1%（1365/64,900 人）、アナフィラキシーが判明したのは 16 人（0.025%）であった。

3/10　「潰瘍性大腸炎」 患者 9 割に特定の「抗体」 京大発見

3/12　ワクチン接種停止相次ぐ　AstraZeneca 製、血栓発症例受け　欧州

オーストリアで女性が死亡するなど接種後に血栓ができる例が複数報告されていることを受けた動き。11 日にはイタリアやデンマークなども「予防的措置」として一部または全ての接種停止に踏み切った。欧州連合（EU）欧州医薬品庁（EMA）は 11 日、接種と血栓の関連に否定的な見解を 2 日連続で発表。「接種は継続できる」と訴えたが、アストラ製ワクチンへの懸念を払拭できなければ、欧州の接種計画に大きな狂いが生じる恐れもある。
同社は日本では 2 月に承認を申請。今月中の供給開始を目指している。

3/12　AstraZeneca 製ワクチン、使用中止する理由なし WHO

3/13　イタリア、15 日から過半数の州で都市封鎖 変異株が急拡大

3/13　日米豪印首脳、ワクチン供給連携で一致　中国念頭に協力強化

日本、米国、オーストラリア、インドの 4 カ国（通称クアッド）は 12 日夜、初の首脳会合をオンライン形式で開いた。東・南シナ海での海洋秩序への挑戦に対して海洋安全保障を含む協力を促進し、インド太平洋地域での新型コロナウイルスワクチンの生産と供給で連携する共同声明をまとめた。
インドで製造するワクチンを増産し、調達と輸送網の整備に向けて協力。4 カ国が協力してインド太平洋地域での「安全で手頃な価格で有効なワクチン」の供給拡大を図る方針で、中国製ワクチン供給で発展途上国への影響力を強める中国の「ワクチン外交」に対抗。

3/15　遺伝子治療で、辛い慢性痛が治る日が来るかも　マウス実験 -UC San Diego

カリフォルニア大学サンディエゴ校の研究チームが慢性痛の有望な治療法の研究成果について「Science Translational Medicine」誌で発表。「SCN9A」という痛みに関連する遺伝子につて、ゲノム編集技術 CRISPR/Cas-9 と、ジンクフィンガータンパク質を利用した昔からある手法の、一般的な 2 つの遺伝子操作技術を用いて、マウスに遺伝子編集を行なったところ、痛みに対する耐性が高くなり、全般的に痛みの緩和が長く続いた（人間における数週間から数ヶ月に相当すると想定）。

3/16　仏独伊など AstraZeneca 製の接種見合わせ　EU医薬品庁、緊急会合へ

AstraZeneca 製の新型コロナウイルスワクチンをめぐって15日、ドイツ、フランス、イタリア、スペインが相次いで接種を一時中断すると発表した。接種後に血栓ができる症例が、欧州で複数報告されたための措置。欧州連合（EU）で薬事審査を担う欧州医薬品庁（EMA）は18日、対応をめぐって緊急会合を開く。

3/16　変異ウイルス検査 4 倍に　全体の 40%に拡大

感染力が強いとされる、変異した新型コロナウイルスの広がりを調査するため、政府は、陽性者の検体に対する遺伝子解析を、現在の 4 倍に拡大する方向で検討していることがわかった。 国内での変異ウイルスの確認は、現在、陽性者全体のおよそ 10%の検体を遺伝子解析して変異ウイルスかどうかを判定している。

3/16　国産ワクチン年内供給困難に　塩野義、大規模治験難しく

塩野義が開発を進める新型コロナウイルス予防ワクチンは現在、治験の第1、2段階にあたる第1／2相試験を国内で実施している。同時に、最終段階の治験となる、偽薬を用いた、世界の流行地域の数万人を対象にした治験に向けて準備を進めており、その予算は数百億円規模を見込む。ところが、世界では米 Pfizer 製や英 AstraZeneca 製など実用化したワクチンの接種が広まっていることから、未承認のワクチンの治験参加者の確保が難しくなり、年内に大規模な治験を実施できる国が少なくなっている。

3/16　COVID-19 やその他の診断製品を売る GenMark を Roche が 18 億ドルで買収

https://www.evaluate.com/vantage/articles/news/deals/roche-buys-genmark-covid-19-tests-and-more

3/16　AstraZeneca が COVID-19 ワクチンの血栓の心配は不要であることを示す情報発表

AstraZeneca の新型コロナウイルス感染症（COVID-19）ワクチン AZD1222（ChAdOx1 nCoV-19）の使用を欧州の幾つかの国が血栓の懸念で止めていることを背景にして同社がその心配はないことを示す同ワクチン接種およそ 1,700 万人の情報を示した。

3/17　抗うつ薬がコロナ治療に効果　九州大など、細胞への侵入阻害確認

九州大大学院などの研究グループは 17 日、既存の抗うつ薬「クロミプラミン」（商品名アナフラニール）に、新型コロナウイルスが細胞内に侵入するのを妨げ、侵入後もウイルスの増殖を抑制する効果があることを突き止めたと発表した。動物実験に続いて患者らの臨床試験を進める。

3/18　ヒトの iPS 細胞から胚盤胞　世界初、新たな生命つくる可能性も

ヒトの iPS 細胞や ES 細胞から、受精卵が胎児になる初期段階である「胚盤胞（はいばんほう）」を世界で初めてつくったと、米国とオーストラリアのチームがそれぞれ発表した。将来的に、細胞から生命

を新たにつくる技術につながる可能性があり、倫理的な課題も残る。18 日付の英科学誌ネイチャーに掲載された。

3/18　乳幼児の RS ウイルス急増　熊本、去年の 7.5 倍

3/19　AstraZeneca 製ワクチン「安全」と欧州当局 仏独など使用再開へ

3/20　昼寝の多さは自己責任ではなく遺伝？ 昼寝と生活習慣病に関わる遺伝子を発見 –ハーバード大学

3/23　潰瘍性大腸炎などの薬、胎児に影響の可能性　マウス実験で

潰瘍（かいよう）性大腸炎などに使われる薬「チオプリン」が、胎児の遺伝子の型によっては、悪影響を及ぼす可能性があることを、滋賀医科大と東北大の研究グループが動物実験で見つけた。今後、ヒトでの影響がないか調べていく。

3/24　血液や尿でコロナ陽性判定　PCR より感染リスク減期待 –熊本大

3/24　白血病、遺伝子操作した免疫細胞で治療　信州大が治験へ

3/25　Pfizer が COVID-19 以外の mRNA ワクチンの独自開発に取り組む

ドイツの BioNTech との提携で備えた技術を使って Pfizer は新型コロナウイルス感染症（COVID-19）以外の病気の数々への mRNA ワクチンの独自開発を始める。

3/25　AstraZeneca の COVID-19 ワクチンの米国 Ph3 試験主解析での有効性 76%

AstraZeneca の新型コロナウイルス感染症（COVID-19）ワクチン AZD1222 の米国第 3 相試験（D8110C00001）の効果は 2 月 17 日時点までの途中解析では 79%、その発表の 3 日後の 25 日に公表された主解析での効果は途中解析を若干下回る 76%。

3/25　GSK が Moncef Slaoui 氏をセクシャルハラスメントで解雇

トランプ大統領の時の米国政府の新型コロナウイルス感染（COVID-19）への取り組み Operation Warp Speed の舵取りの一人として知られる Moncef Slaoui 氏を GlaxoSmithKline（GSK）が不正行為により解雇。

3/25　コロナ研究に iPS 細胞を活用へ　患者の血液から作製した iPS 細胞　京大が無償で研究機関に提供

3/26　変異株が増えていることにより米国が Lilly の COVID-19 抗体 bamlanivimab 提供中止

3/26　Novartis が 14 か月前に開設したばかりの遺伝子治療 Zolgensma 製造工場（コロラド州ロングモント）を閉鎖

3/27　空気中の新型コロナウイルスを検出するセンサーを Thermo Fisher Scientific（マサチューセッツ州ウォルサム）が発売

3/27　AstraZeneca の COVID-19 ワクチン AZD1222 の点鼻を調べる試験が Oxford 大学により始められている

3/28　Amazon 製 COVID-19 テストキット（社内用）を FDA が承認

https://www.statnews.com/2021/03/26/amazon-on-the-move-in-health-care-is-granted-authorization-for-its-own-covid-19-test/

3/29　米 NY 州、娯楽用大麻合法化へ 知事と議員が合意

3/30　ワクチン 2 回で「感染 90%防ぐ」 米疾病対策センター

3/30　新生児の血液で難病を早期発見　神戸大の研究グループが新生児スクリーニング検査を始める

3/30　Wave Life Sciences（マサチューセッツ州ケンブリッジ）が武田薬品との提携対象のハンチントン病薬 2 つの開発中止

成功すれば武田薬品の持ち物になる筈のハンチントン病薬 2 つ・WVE-120101 と WVE-120102 が Ph1b/2a 試験で思うような成績を残せず Wave Life Sciences が開発を中止。

3/30　ワクチン年内生産、25 億回分に拡大　Pfizer/BioNTech

ドイツのバイオ医薬品企業ビオンテックは 30 日、米製薬大手ファイザーと共同開発した新型コロナウイルスワクチンについて、今年の生産目標を従来の 20 億回分から 25 億回分に引き上げたと明らかにした。

3/30　米感染者、再び増加傾向　バイデン大統領は規制維持呼び掛け―新型コロナ

https://www.jiji.com/jc/article?k=20210330000699&g=int

3/31　WHO 新型コロナ起源の報告書公表 武漢研究所からの流出可能性は極めて低い

WHOの国際調査チームは30日、報告書を公表し、ウイルスは自然界から中間的な動物を媒介してヒトへと拡がった可能性が「非常に高い」と指摘した一方、武漢にあるウイルス研究所から流出した可能性は「極めて低い」とした。

3/31　日米など 14 か国、コロナ起源調査に懸念 WHO 報告書受け共同声明

https://www.afpbb.com/articles/-/3339686

3/31　独、アストラ製ワクチン接種は 60 歳以上に限定へ　当局が提言

カナダ保健当局も29日、アストラゼネカ製ワクチンの55歳未満への接種を中断すると発表.

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. 高脂肪食が心臓病タンパク質を過剰に活性化する可能性 -マウス実験

2. お腹の脂肪には一日おきの絶食は効かない
   マウス研究によると、どこの脂肪かによってダイエット効果が異なる

3. ウイルス感染後の肺疾患発症に関与する免疫細胞 -マウス研究
   調査結果が、喘息、COPD、重度 COVID-19 がどのように引き起こされるかの説明に繋がる可能性

4. マウスとヒトの病原体に対する耐性の相違

5. 妊娠中の一般的な化学物質への曝露が乳癌に対する保護を低下させる可能性 -マウス実験
   UMass Amhurst の研究は、プロピルパラベンが内分泌攪乱物質であると示唆

6. BMI1、アルツハイマー病から守る有望な遺伝子

7. 2 型糖尿病の夜明け現象に関連する概日時計遺伝子 Rev-erb -マウス実験

8. ジャンプに必要な遺伝子
   ジャンプできない珍しいタイプのウサギを使った実験で同定

9. 最新の遺伝子編集技術 -プライム編集

1. 高脂肪食が心臓病タンパク質を過剰に活性化する可能性 –マウス実験

日付:2021 年 3 月 2 日
ソース:レディング大学
概要:

「Biochemical and Biophysical Research Communications」誌に掲載されている論文で、英レディング大学の研究者らは、マウスに高脂肪食を与えることが心臓細胞の酸化ストレスレベルに対して及ぼす影響について調査報告している。
研究者らは、心臓の酸化ストレスの増加に関連すると考えられている重要なタンパク質 Nox2 に焦点を当てた。この研究では、高脂肪食を与えられたマウスは 2 倍の量の Nox2 活性を持っていることが分かった。研究者らは、また、Nox2 が心臓のストレスの原因に関与しているかどうかを確認するために、Nox2 を「ノックアウト」してタンパク質が細胞レベルで活性化するのを防ぐよう特別に飼育されたマウスと結果を比較した。「ノックアウト」マウスにも同様に高脂肪食を与えたところ、同レベルの酸化ストレスの上昇はほとんどまたはまったく見られなかった。
この実験で高脂肪食を与えられたマウスは、カロリー消費量の 45%を脂肪から、20%をタンパク質から、35%を炭水化物から摂取した。そして、心臓病に繋がるとされる心臓肥大のために心臓細胞が最大 1.8 倍大きくなった、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＞High fat diets may over-activate destructive heart disease protein -- ScienceDaily

HIGH FAT DIETS MAY OVER-ACTIVATE DESTRUCTIVE HEART DISEASE PROTEIN

Date:

March 2, 2021

Source:

University of Reading

Summary:

Consumption of a high fat diet may be activating a response in the heart that is causing destructive growth and lead to greater risk of heart attacks, according to new research.

FULL STORY

Consumption of a high fat diet may be activating a response in the heart that is causing destructive growth and lead to greater risk of heart attacks, according to new research.

In a paper published in *Biochemical and Biophysical Research Communications*, researchers looked at the effect of feeding mice a high fat diet on oxidative stress levels on heart cells. The team from the University of Reading found that cells from the mice had twice the amount of oxidative stress, and led to heart cells being up to 1.8 times bigger due to cardiac hypertrophy which is associated with heart disease.

Named first author Dr Sunbal Naureen Bhatti, from the University of Reading said:

"Our research shows one way in which a high fat diet can cause damage to the muscle cells that make up our hearts. It appears that a switch happens at a cellular level when the mice were fed on a high fat regime which causes a normally harmless protein, Nox2, to become overactive. The precise nature of how the Nox2 protein goes onto cause oxidative damage and set off destructive hypertrophy is still being researched.

"We are really just scratching the surface of how the protein Nox2 responds to diets, but our research clearly demonstrates that high fat diets has the potential to cause significant damage to the heart."

The researchers focused on a key protein Nox2 which believed to be associated with increasing oxidative stress in the heart. The study found that the mice fed a high fat diet had twice the amount of Nox2 activity, which also led to a similar amount of reactive oxygen species (ROS), a free radical that is associated with pathological damage of the body.

To check whether Nox2 was involved in causing the cardiac stress, the team compared the results with mice bred specifically to 'knock out' Nox2, stopping the protein from activating at a cellular level. The 'knock out' mice were also fed a high fat diet, but showed little or none of the same raised levels of oxidative stress.

In addition, the team used three experimental treatments which are known to reduce Nox2-related ROS production, and found that all three showed some promise in reducing the effect of ROS in damaging the mice hearts.

The mice that were fed high fat diets received 45% of their calorie consumption from fat, 20% from protein and 35% carbohydrate.

Story Source:

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

Journal Reference:

1. Sunbal N. Bhatti, Jian-Mei Li. **Nox2 dependent redox-regulation of Akt and ERK1/2 to promote left ventricular hypertrophy in dietary obesity of mice**. *Biochemical and Biophysical Research Communications*, 2020; 528 (3): 506
DOI: 10.1016/j.bbrc.2020.05.162

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2. お腹の脂肪には一日おきの絶食は効かない
マウス研究によると、どこの脂肪かによってダイエット効果が異なる

日付：2021 年 3 月 3 日
ソース：シドニー大学
概要：

シドニー大学の研究者らは、最先端の機器を使用して、ヒトの「突き出たお腹」に蓄積する胃の周りの脂肪が、時間の経過と共に適応して減量に対してより抵抗力のある「保存モード」に入ることを発見した。調査結果は、「Cell Reports」誌で本日公開される。
研究者らは、マウス研究で、断続的絶食中に脂肪組織の舞台裏で何が起こるかをマッピングし、脂肪沈着の種類と身体の場所に応じて、劇的な変化のカスケードを引き起こすことを示した。
この論文の上級著者である Larance 博士は、マウスの生理機能がヒトに類似していること、代謝がはるかに速いこと、などからヒトの治験よりも迅速に変化を観察でき、ヒトでサンプリングするのが難しい組織を調べることができるため、マウスモデルの使用がヒトの研究に先立って有用である、と言っている。そしてこの研究が、将来的には、このお腹の脂肪の抵抗性が発生するメカニズムとどんなタイプの食事療法がこの脂肪に取り組むのに適しているのか、明らかにする可能性がある、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＞Belly fat resistant to every-other-day fasting: Studies in mice show fat location matters for intermittent fasting -- ScienceDaily

BELLY FAT RESISTANT TO EVERY-OTHER-DAY FASTING

Studies in mice show fat location matters for intermittent fasting

Date:

March 3, 2021

Source:

University of Sydney

Summary:

Scientists have mapped out what happens to fat deposits during intermittent fasting (every second day), with an unexpected discovery that some types of fat are more resistant to weight loss.

FULL STORY

In a mouse study, Australian researchers have mapped out what happens behind the scenes in fat tissue during intermittent fasting, showing that it triggers a cascade of dramatic changes, depending on the type of fat deposits and where they are located around the body.

Using state-of-the-art instruments, University of Sydney researchers discovered that fat around the stomach, which can accumulate into a 'protruding tummy' in humans, was found to go into 'preservation mode', adapting over time and becoming more resistant to weight loss.

The findings are published today in *Cell Reports*.

A research team led by Dr Mark Larance examined fat tissue types from different locations to understand their role during every-other-day fasting, where no food was consumed on alternate days.

The fat types where changes were found included visceral "belly" fat, which is fat tissue surrounding our organs including the stomach, and subcutaneous fat, which lies just under the skin and is associated with better metabolic health.

"While most people would think that all fat tissue is the same, in fact, the location makes a big difference," said senior author Dr Larance from the Charles Perkins Centre and School of Life and Environmental Sciences at the University of Sydney.

"Our data show both visceral and subcutaneous fat undergo dramatic changes during intermittent fasting," said Dr Larance, who is also a Cancer Institute of NSW Future Research Fellow.

Why visceral fat can be resistant to weight loss

During fasting, fat tissue provides energy to the rest of the body by releasing fatty acid molecules.

However, the researchers found visceral fat became resistant to this release of fatty acids during fasting.

There were also signs that visceral and subcutaneous fat increased their ability to store energy as fat, likely to rapidly rebuild the fat store before the next fasting period.

Dr Larance said it was possible that a history of repeated fasting periods triggered a preservation signalling pathway in visceral fat.

"This suggests the visceral fat can adapt to repeated fasting bouts and protect its energy store," he said.

"This type of adaptation may be the reason why visceral fat can be resistant to weight loss after long periods of dieting."

Dr Larance said using a mouse model was a useful analogue ahead of studies in humans.

"Mouse physiology is similar to humans, but their metabolism is much faster, allowing us to observe changes more rapidly than in human trials, and examine tissues difficult to sample in humans," he said.

Future research in mice and humans could uncover the mechanisms by which this resistance occurs and also which types of diet and other interventions may be best at tackling belly fat.

Mapping out the inner workings of fat deposits

The research team examined more than 8500 proteins located in fat deposits, creating a catalogue of changes that occurred during intermittent fasting, using a technique called proteomics.

Proteomics -- the study of all proteins -- a relatively new area of study that takes its name from genomics (the study of all genes), monitors how proteins react under certain conditions, which in this case is intermittent fasting.

The results provide a rich source of data that helps to paint a more complete picture of the inner workings of fat tissue.

It was via proteomics that the research team were alerted of major cellular changes caused by intermittent fasting and, after further analysis, highlighted the visceral fat's preservation mechanism in action.

The study was conducted using the instruments of the Sydney Mass Spectrometry in the Charles Perkins Centre, part of the University of Sydney's Core Research Facilities.

Dr Larance says it should be noted that findings from the intermittent study may not apply to different diet regimes such as the 5:2 diet (fasting 2 days out of 7) or calorie restriction, which is common in people wanting to lose weight.

The results lay the foundation for future studies, which will dissect the molecules responsible for why visceral fat is resistant to energy release during fasting, and help determine what diet plans would be most beneficial for metabolic health.

"This sort of research has been enabled by these new instruments that allow us to 'look beyond the streetlight' -- it's hypothesis generating; we knew we would find something but we didn't know what," Dr Larance explained.

"Now that we've shown 'belly fat' in mice is resistant to this diet, the big question will be to answer why, and how do we best tackle it?"

Story Source:

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

Journal Reference:

1. Dylan J. Harney, Michelle Cielesh, Renee Chu, Kristen C. Cooke, David E. James, Jacqueline Stöckli, Mark Larance. **Proteomics analysis of adipose depots after intermittent fasting reveals visceral fat preservation mechanisms**. *Cell Reports*, 2021; 34 (9): 108804 DOI: 10.1016/j.celrep.2021.108804

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3. ウイルス感染後の肺疾患発症に関与する免疫細胞 –マウス研究

調査結果が、喘息、COPD、重度 COVID-19 がどのように引き起こされるかの説明に繋がる可能性

日付：2021 年 3 月 9 日
ソース：セントルイス ワシントン大学医学部
概要：

セントルイス ワシントン大学医学部の科学者らは、呼吸器ウイルスに感染後引き起こされることがある慢性肺疾患の発症に免疫細胞の一種を関与させており、この免疫細胞（樹状細胞と呼ばれる保護細胞の一種）の活性化が、喘息や慢性閉塞性肺疾患（COPD）などの進行性肺疾患を引き起こす一連のイベントを開始する初期スイッチとして機能することを示唆している。
慢性肺疾患を発症しやすくする呼吸器ウイルスに感染したマウスを研究することによって、研究者らは、これらの樹状細胞が気道内層細胞に炎症シグナルを増加させる方法で気道内層と通信することを示した。炎症により、気道内層細胞が通常の境界を超えて成長し、粘液を過剰産生して炎症を引き起こす細胞に変わり、咳や呼吸困難を引き起こす。
「The Journal of Immunology」誌に掲載されたこの研究は、慢性肺疾患の潜在的な予防または治療戦略への扉を開くものであり、インフルエンザや COVID-19 などのウイルス感染症で入院した患者の臨床サンプル中のこれらの樹状細胞のレベルを迅速に測定することによって、医師が呼吸不全や死亡のリスクが高い患者を特定するのに役立つ、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＞Immune cell implicated in development of lung disease following viral infection | EurekAlert! Science News

NEWS RELEASE 9-MAR-2021

IMMUNE CELL IMPLICATED IN DEVELOPMENT OF LUNG DISEASE FOLLOWING VIRAL INFECTION

Findings could help explain how asthma, COPD, severe COVID-19 are triggered

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Research News

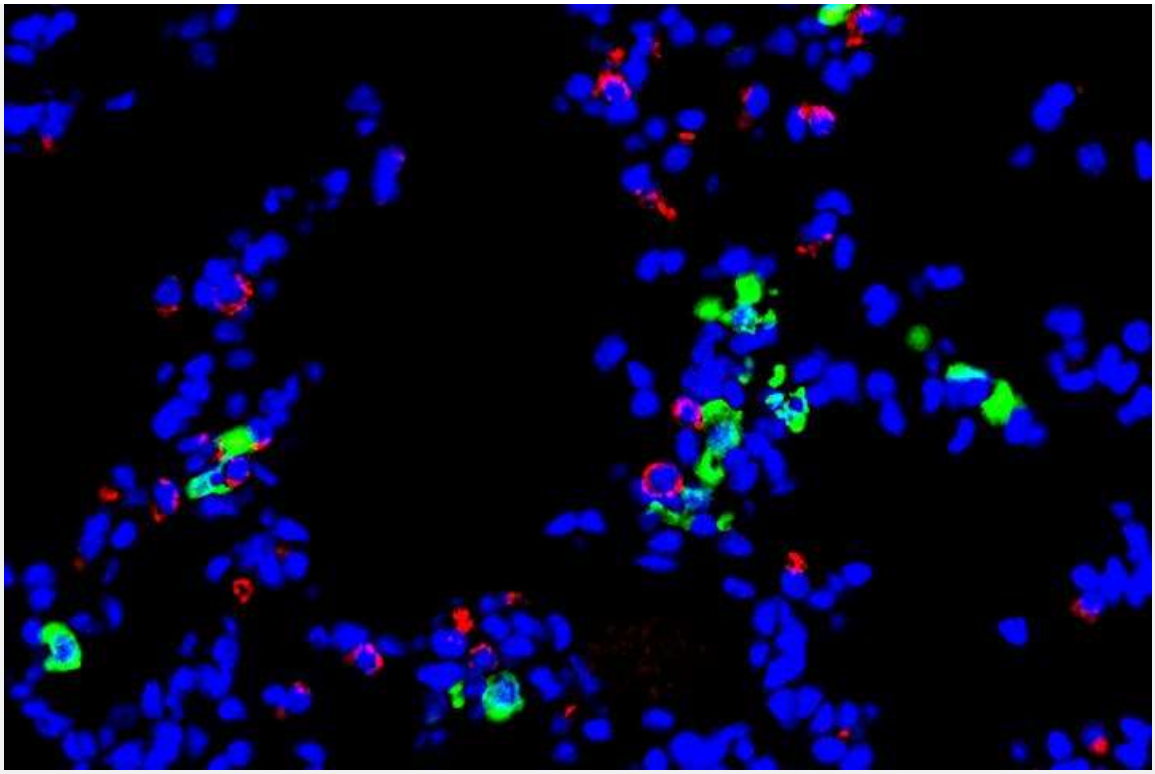

IMAGE: A NEW STUDY FROM WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS IMPLICATES A TYPE OF IMMUNE CELL -- CALLED A DENDRITIC CELL -- IN THE DEVELOPMENT OF CHRONIC LUNG... **view more**

CREDIT: HOLTZMAN LAB

Scientists at Washington University School of Medicine in St. Louis have implicated a type of immune cell in the development of chronic lung disease that sometimes is triggered following a respiratory viral infection. The evidence suggests that activation of this immune cell -- a type of guardian cell called a dendritic cell -- serves as an early switch that, when activated, sets in motion a chain of events that drives progressive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD).

The new study, published in The *Journal of Immunology*, opens the door to potential preventive or therapeutic strategies for chronic lung disease. More immediately, measuring the levels of these dendritic cells in clinical samples from patients hospitalized with a viral infection, such as influenza or COVID-19, could help doctors identify which patients are at high risk of respiratory failure and death.

Studying mice with a respiratory viral infection that makes the animals prone to developing chronic lung disease, the researchers showed that these dendritic cells communicate with the lining of the airway in ways that cause the airway-lining cells to ramp up their growth and inflammatory signals. The inflammation causes airway-lining cells to grow beyond their normal

boundaries and turn into cells that overproduce mucus and cause inflammation, which in turn causes cough and difficulty breathing.

"We're trying to understand how a viral infection that seems to be cleared by the body can nevertheless trigger chronic, progressive lung disease," said senior author Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine. "Not everyone experiences this progression. We believe there's some switch that gets flipped, triggering the bad response. We're identifying that switch and ways to control it. This work tells us that this type of dendritic cell is sitting right at that switch point."

Holtzman's past work had implicated the lining of the airway -- where the viral infection takes hold -- as the likely trigger for this process.

"But this study suggests that the cascade starts even further upstream," said Holtzman, also director of the Division of Pulmonary and Critical Care Medicine. "Dendritic cells are telling the cells lining the airway what to do. There's more work to be done, but this data tells us that the dendritic cells play an important role in getting the airway-lining cells onto the wrong path."

Holtzman calls this dendritic cell a type of sentinel because its job is to detect an invading virus and trigger the body's initial immune response against the infection. The problem comes when the cell doesn't shut down properly after the threat has passed.

"Many people never develop chronic lung disease after a viral infection," Holtzman said. "But others have a genetic susceptibility to this type of disease. People who are susceptible to virus-triggered disease include patients with asthma, COPD, and viral infections such as COVID-19. It's really critical to look for ways to fix this disease response and prevent the problems that might occur after the virus has gone."

In the meantime, Holtzman said, high levels of these dendritic cells and their products in the lungs of hospitalized patients could serve as a warning to doctors that such patients are likely to develop severe disease and should be provided with respiratory interventions and other supportive therapies that are precisely tailored to their disease process.

"Similarly, if this process is not underway, the patient might be more likely to avoid these types of long-term problems," Holtzman said. "We're pursuing this line of research to help improve prediction of severe lung disease after infection and to provide companion therapies that could prevent this switch from being flipped or flip it back to reverse the disease."

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This work was supported by the National Institute of Allergy and Infectious Diseases (NIAID), grant number R01 AI130591 and the National Heart, Lung, and Blood Institute (NHLBI), grant

number R35 HL145242, both of the National Institutes of Health (NIH); the Cystic Fibrosis Foundation; and the Hardy Trust and Schaeffer Funds.

Wang X, Wu K, Keeler SP, Mao D, Agapov EV, Zhang Y, Holtzman MJ. TLR3-activated monocyte-derived dendritic cells trigger progression from acute viral infection to chronic disease in the lung. The *Journal of Immunology*. Jan. 29, 2021.

Washington University School of Medicine's 1,500 faculty physicians also are the medical staff of Barnes-Jewish and St. Louis Children's hospitals. The School of Medicine is a leader in medical research, teaching and patient care, ranking among the top 10 medical schools in the nation by U.S. News & World Report. Through its affiliations with Barnes-Jewish and St. Louis Children's hospitals, the School of Medicine is linked to BJC HealthCare.

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4. マウスとヒトの病原体に対する耐性の相違

日付：2021 年 3 月 15 日
ソース：ハーバード大学
概要：

数兆の共生微生物が身体の粘膜および表皮表面に生息しており、この微生物叢が宿主のさまざまな病原体に対する耐性と感受性に影響を与えることが確実視されている。ただし、病原体の感染に対する宿主の耐性は、すべての生物で等しく発達しているわけではない。例えば、マウスの腸内細菌叢は、ヒトの腸内細菌叢よりも、細菌サルモネラ・チフィムリウムなどの特定の病原体による感染からより効果的に保護することが知られている。
実際に、ハーバード大学の研究チームは、Wyss のマイクロ流体 Organs-on-Chip（Organ Chip）テクノロジーを利用して、マウスの腸のさまざまな解剖学的セクションと、In-Vitro での複雑な生きている微生物叢との共生をモデル化した。研究者らは、操作されたマウスの結腸のチップの上皮表面に対する S.typhimurium（サルモネラ菌）の破壊的影響を要約し、マウスとヒトの微生物叢の比較分析で、共生細菌 Enterococcus faecium（エンテロコッカス フエシウム菌）が S.typhimurium（サルモネラ菌）感染に対する宿主耐性に寄与することを確認した。このプロジェクトは、DARPA が支援する Wyss Institute の「Technologies for Host Resilience」（THoR）プロジェクトの下で開始された。このプロジェクトの目標は、特定の動物種とヒトで観察された違いを研究することにより、感染に対する耐性への重要な貢献を明らかにすることである。また、これらの動物を使用して微生物叢と宿主応答の研究を前進させ、これにより得られた結果をヒトの結腸のチップと直接比較することができれば、将来的には、ヒトに最も関連性のあるホスト応答の機能を特定することに焦点を当てることができる、としている。
この研究は、「Frontiers in Cellular and Infection Microbiology」誌に掲載されている。

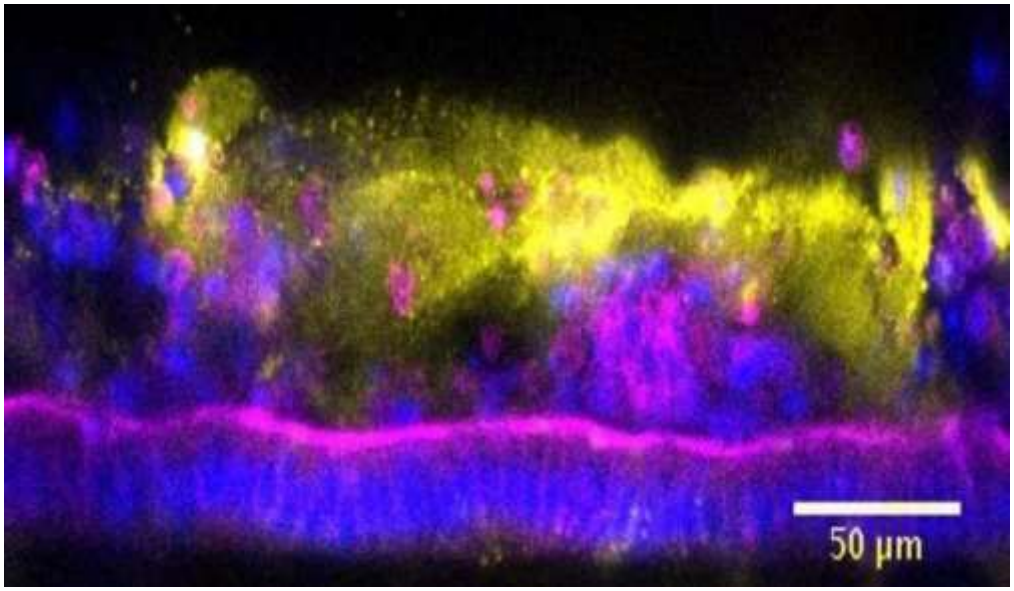
研究関連ニュース/他のトップページに戻る

＜英文＞Of mice and men and their different tolerance to pathogens (medicalxpress.com)

MARCH 15, 2021

OF MICE AND MEN AND THEIR DIFFERENT TOLERANCE TO PATHOGENS

by Harvard University



This cross section of a mouse Colon Chip shows the actin cytoskeleton of epithelial cells in magenta, the overlying mucus in yellow, and the cells' nuclei in blue. The team used this chip in a comparative analysis of mouse and human microbiomes to test their different abilities to induce tolerance to the pathogen Salmonella typhimurium. Credit: Wyss Institute at Harvard University

Trillions of commensal microbes live on the mucosal and epidermal surfaces of the body and it is firmly established that this microbiome affects its host's tolerance and sensitivity of the host to a variety of pathogens. However, host tolerance to infection with pathogens is not equally developed in all organisms. For example, it is known that the gut microbiome of mice protects more effectively against infection with certain pathogens, such as the bacterium Salmonella typhimurium, than the human gut microbiome.

This raises the interesting possibility that analyzing differences between host-microbiome interactions in humans and other species, such as mice, and pinpointing individual types of bacterial that either protect or sensitize against certain pathogens, could lead to entirely new types of therapeutic approaches. However, while the intestinal microbiome composition and its effect on host immune responses have been well investigated in mice, it is not possible to study how the microbiome interacts directly with the epithelial cells lining the intestine under highly defined conditions, and thereby uncover specific bacterial strains that can induce host-tolerance to infectious pathogens.

Now, a collaborative team led by Wyss Founding Director Donald Ingber, M.D., Ph.D. at Harvard's Wyss Institute for Biologically Inspired Engineering and Dennis Kasper, M.D. at Harvard Medical School (HMS) has harnessed the Wyss's microfluidic Organs-on-Chip (Organ Chip) technology to model the different anatomical sections of the mouse intestine and their symbiosis with a complex living microbiome in vitro. The researchers recapitulated the destructive effects of S. typhimurium on the intestinal epithelial surface in an engineered mouse Colon Chip, and in a comparative analysis of mouse and human microbiomes were able to confirm the commensal bacterium Enterococcus faecium contributes to host

tolerance to S. typhimurium infection. The study is published in *Frontiers in Cellular and Infection Microbiology*.

The project was started under a DARPA-supported "Technologies for Host Resilience" (THoR) Project at the Wyss Institute, whose goal it was to uncover key contributions to tolerance to infection by studying differences observed in certain animal species and humans. Using a human Colon Chip, Ingber's group had shown in a previous study how metabolites produced by microbes derived from mouse and human feces have different potential to impact susceptibility to infection with an enterohemorrhagic E. coli pathogen.

"Biomedical research strongly depends on animal models such as mice, which undoubtedly have tremendous benefits, but do not provide an opportunity to study normal and pathological processes within a particular organ, such as the intestine, close-up and in real-time. This important proof-of-concept study with Dennis Kasper's group highlights that our engineered mouse Intestine Chip platform offers exactly this capability and provides the possibility to study host-microbiome interactions with microbiomes from different species under highly controllable conditions in vitro," said Ingber. "Given the deep level of characterization of mouse immunology, this capability could greatly help advance the work of researchers who currently use these animals to do research on microbiome and host responses. It enables them to compare their results they obtain directly with human Intestine Chips in the future so that the focus can be on identifying features of host response that are most relevant for humans." Ingber also is the Judah Folkman Professor of Vascular Biology at HMS and Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences.

Engineering a mouse Intestine-on-Chip platform

In their new study, the team focused on the mouse intestinal tract. "It has traditionally been extremely difficult to model host-microbiome interactions outside any organism as many bacteria are strictly anaerobic and die in normal atmospheric oxygen conditions. Organ Chip technology can recreate these conditions, and it is much easier to obtain primary intestinal and immune cells from mice than having to rely on human biopsies," said first-author Francesca Gazzaniga, Ph.D., a Postdoctoral Fellow who works between Ingber's and Kasper's groups and spear-headed the project.

Gazzaniga and her colleagues isolated intestinal crypts from different regions of the mouse intestinal tract, including the duodenum, jejunum, ileum, and colon, took their cells through an intermediate "organoid" step in culture in which small tissue fragments form and grow, which they then seeded into one of two parallel microfluidically perfused channels of the Wyss' Organ Chips to create region-specific Intestine Chips. The second independently perfused channel mimics the blood vasculature, and is separated from the first by a porous membrane that allows the exchange of nutrients, metabolites, and secreted molecules that intestinal epithelial cells use to communicate with vascular and immune cells.

Homing in on the pathogen

The team then honed in on S. typhimurium as a pathogen. First, they introduced the pathogen into the epithelial lumen of the engineered mouse Colon Chip and recapitulated the key features associated with the break-down of intestinal tissue integrity known from mouse studies, including the disruption of normally tight adhesions between neighboring epithelial cells, decreased production of mucus, a spike in secretion of a key inflammatory chemokine (the mouse homolog of human IL-8), and changes in epithelial gene expression. In parallel, they showed that the mouse Colon Chip supported the growth and viability of complex bacterial consortia normally present in mouse and human gut microbiomes.

Putting these capabilities together, the researchers compared the effects of specific mouse and human microbial consortia that had previously been maintained stably in the intestines of 'gnotobiotic' mice that were housed in germ-free conditions by the Kasper team. By collecting complex microbiomes from the stool of those mice, and then inoculating them into the Colon Chips, the researchers observed chip-to-chip variability in consortium composition, which enabled them to relate microbe composition to functional effects on the host epithelium. "Using 16s sequencing gave us a good sense of the microbial compositions of the two consortia, and high numbers of one individual species, Enterococcus faecium, generated by only one of them in the Colon Chip, allowed the intestinal tissue to better tolerate the infection," said Gazzaniga. "This nicely confirmed past findings and validated our approach as a new discovery platform that we can now use to investigate the mechanisms that underlie these effects as well as the contribution of vital immune cell contributions to host-tolerance, as well as infectious processes involving other pathogens."

"The mouse intestine on a chip technology provides a unique approach to understand the relationship between the gut microbiota, host immunity, and a microbial pathogen. This important interrelationship is challenging to study in the living animal because there are so many uncontrollable factors. The beauty of this system is that essentially all parameters you wish to study are controllable and can easily be monitored. This system is a very useful step forward," said Kasper, who is the William Ellery Channing Professor of Medicine and Professor of Immunology at HMS.

The researchers believe that their comparative in vitro approach could uncover specific cross-talk between pathogens and commensal bacteria with intestinal epithelial and immune cells, and that identified tolerance-enhancing bacteria could be used in future therapies, which may circumvent the problem increasing antimicrobial resistance of pathogenic bacterial strains.

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5. 妊娠中の一般的な化学物質への曝露が乳癌に対する保護を低下させる可能性 –マウス実験

UMass Amhurst の研究は、プロピルパラベンが内分泌攪乱物質であると示唆

日付：2011 年 3 月 18 日
ソース：マサチューセッツ大学アムハースト校
概要：

マサチューセッツ大学アムハースト校の研究によると、低用量のプロピルパラベン（食品、医薬品、化粧品に含まれる化学防腐剤）は、妊娠時の乳房の変化を様変わりさせ、妊娠ホルモンが通常伝達する乳癌に対する保護を弱める可能性がある。「Endocrinology」誌で 3 月 16 日に発表された調査結果は、プロピルパラベンがホルモンの作用を妨げる内分泌攪乱化学物質である、と示唆している。
研究チームは、妊娠と授乳の脆弱な時期にプロピルパラベンにさらされると、乳腺の再編成が悪影響を受けるかどうかをテストした。彼らは、妊娠中および授乳中に雌マウスを環境用量のプロピルパラベンに曝露してから 5 週間後に母親の乳腺を調べた。すると、プロピルパラベンを曝露されていない妊娠中のマウスと比較して、曝露されたマウスは妊娠に典型的ではない乳腺の変化を示した、と報告している。これらのマウスは細胞増殖率が増加しており、これが乳癌の危険因子である可能性があるとしている。それらはまた、より密度の低い上皮構造、より少ない免疫細胞タイプ、およびより薄い乳管周囲コラーゲン、乳腺の結合組織を有していた。
研究者らは、妊娠中や授乳中の女性はプロピルパラベンや他のパラベンを含む製品の使用を避けるように啓蒙していくべきだと付け加えている。

研究関連ニュース/他のトップページに戻る

＜英文＞Exposure to common chemical during pregnancy may reduce protection against breast cancer | EurekAlert! Science News

NEWS RELEASE 16-MAR-2021

EXPOSURE TO COMMON CHEMICAL DURING PREGNANCY MAY REDUCE PROTECTION AGAINST BREAST CANCER

UMass Amherst research suggests propylparaben is an endocrine disruptor

UNIVERSITY OF MASSACHUSETTS AMHERST

Research News

IMAGE: SENIOR AUTHOR LAURA VANDENBERG IS AN ASSOCIATE PROFESSOR IN THE UMASS AMHERST SCHOOL OF PUBLIC HEALTH AND HEALTH SCIENCES. **view more**

CREDIT: UMASS AMHERST

Low doses of propylparaben - a chemical preservative found in food, drugs and cosmetics - can alter pregnancy-related changes in the breast in ways that may lessen the protection against breast cancer that pregnancy hormones normally convey, according to University of Massachusetts Amherst research.

The findings, published March 16 in the journal *Endocrinology*, suggest that propylparaben is an endocrine-disrupting chemical that interferes with the actions of hormones, says environmental health scientist Laura Vandenberg, the study's senior author. Endocrine disruptors can affect organs sensitive to hormones, including the mammary gland in the breast that produces milk.

"We found that propylparaben disrupts the mammary gland of mice at exposure levels that have previously been considered safe based on results from industry-sponsored studies. We also saw effects of propylparaben after doses many times lower, which are more reflective of human intake," Vandenberg says. "Although our study did not evaluate breast cancer risk, these changes in the mammary tissue are involved in mitigating cancer risk in women."

Hormones produced during pregnancy not only allow breast tissue to produce milk for the infant, but also are partly responsible for a reduced risk of breast cancer in women who give birth at a younger age.

The researchers, including co-lead author Joshua Mogus, a Ph.D. student in Vandenberg's lab, tested whether propylparaben exposure during the vulnerable period of pregnancy and breastfeeding adversely alters the reorganization of the mammary gland. They examined the mothers' mammary glands five weeks after they exposed the female mice to environmentally doses of propylparaben during pregnancy and breastfeeding.

Compared with pregnant mice that had not received propylparaben, the exposed mice had mammary gland changes not typical of pregnancy, the researchers report. These mice had increased rates of cell proliferation, which Vandenberg says is a possible risk factor for breast cancer. They also had less-dense epithelial structures, fewer immune cell types and thinner periductal collagen, the connective tissue in the mammary gland.

"Some of these changes may be consistent with a loss of the protective effects that are typically associated with pregnancy," says Mogus, who was chosen to present the research, deemed "particularly newsworthy" by the Endocrine Society, at the international group's virtual annual meeting, ENDO 2021, beginning March 20.

Mogus says future studies should address whether pregnant females exposed to propylparaben are actually more susceptible to breast cancer. "Because pregnant women are exposed to propylparaben in many personal care products and foods, it is possible that they are at risk," Mogus says, adding that pregnant and breastfeeding women should try to avoid using products containing propylparaben and other parabens.

"This chemical is so widely used, it may be impossible to avoid entirely," Mogus adds. "It is critical that relevant public health agencies address endocrine-disrupting chemicals as a matter of policy."

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This research received funding from the University of Massachusetts Commonwealth Honors College Grant, the Endocrine Society's Summer Research Fellowship and the National Institutes of Health.

Other study co-authors are Charlotte LaPlante, Ruby Bansal, Klara Matouskova, Shannon Silva, Elizabeth Daniele, Mary Hagen and Karen Dunphy, all of UMass Amherst; Benjamin Schneider and Sallie Schneider of Baystate Medical Center in Springfield, Mass.; and D. Joseph Jerry of UMass Amherst's Department of Veterinary and Animal Sciences and Pioneer Valley Life Sciences Institute in Springfield.

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6. BMI1、アルツハイマー病から守る有望な遺伝子

日付：2021 年 3 月 23 日
ソース：モントリオール大学
概要：

モントリオール大学の研究チームは、「Cell Reports」誌と「Scientific Reports」誌に掲載された以前の論文で、BMI1 遺伝子の発現がアルツハイマー病の人々の脳で特異的に減少すること、また、培養したヒトニューロンまたはマウスにおける BMI1 の不活性化が、アルツハイマー病に関連する全ての病理学的マーカーを再現するのに充分であることを示していた。
今回アルツハイマー病を理解するためのもう 1 つのステップが行われ、脳の老化を阻害することで知られるこの BMI1 遺伝子の新しい機能が発見され、「Nature Communications」誌に掲載されている。
研究者らは、ニューロンの DNA が G4 構造と呼ばれる特定の方法で無秩序になるのを防ぐために BMI1 が必要であることを立証することができた。この無秩序の現象は、アルツハイマー病の人の脳で発生するが、健康な高齢者では発生しない。したがって、BMI1 は、とりわけ、ニューロンの機能を妨害する G4 の過剰な形成を防ぐことにより、アルツハイマー病から保護する、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＞BMI1, a promising gene to protect against Alzheimer's disease -- ScienceDaily

BMI1, A PROMISING GENE TO PROTECT AGAINST ALZHEIMER'S DISEASE

Date:

March 23, 2021

Source:

University of Montreal

Summary:

A molecular biologist discovers a new function for BMI1, which is known to counteract brain aging.

FULL STORY

Another step towards understanding Alzheimer's disease has been taken at the Maisonneuve-Rosemont Hospital Research Centre. Molecular biologist Gilbert Bernier, and professor of neurosciences at Université de Montréal, has discovered a new function for the BMI1 gene, which is known to inhibit brain aging. The results of his work have just been published in *Nature Communications.*

In his laboratory, Bernier was able to establish that BMI1 was required to prevent the DNA of neurons from disorganizing in a particular way called G4 structures. This phenomenon occurs in the brains of people with Alzheimer's disease, but not in healthy elderly people. Thus, BMI1 would protect against Alzheimer's by preventing, among other things, the excessive formation of G4s that disrupt the functioning of neurons.

"This discovery adds to our knowledge of the fundamental mechanisms leading to Alzheimer's," said Bernier. "There is still no cure for this disease, which now affects nearly one million Canadians. Any advance in the field brings hope to all these people and their families."

In previous articles published in the journals Cell Reports and Scientific Reports, Bernier demonstrated that the expression of the BMI1 gene is specifically reduced in the brains of people with Alzheimer's disease. He also showed that inactivation of BMI1 in cultured human neurons or in mice was sufficient to recapitulate all the pathological markers associated with Alzheimer's disease.

Story Source:

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

Journal Reference:

1. Roy Hanna, Anthony Flamier, Andrea Barabino, Gilbert Bernier. **G-quadruplexes originating from evolutionary conserved L1 elements interfere with neuronal gene expression in Alzheimer's disease**. *Nature Communications*, 2021; 12 (1) DOI: 10.1038/s41467-021-22129-9

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7. 2 型糖尿病の夜明け現象に関連する概日時計遺伝子 Rev-erb -マウス実験

日付:2021 年 3 月 25 日
ソース:ベイラー医科大学
概要:

ベイラー医科大学、中国の山東大学、およびその他の研究機関の共同研究者らは、2 型糖尿病の多くの患者に見られる朝だけの異常な血糖値の上昇である夜明け現象(dawn phenomenon)の理由を発見した。
彼らは、脳内に Rev-erb と呼ばれる概日時計遺伝子を欠くマウスが夜明け現象と同様の特徴を示すことを発見し、「Nature」誌に報告している。
研究者らは、2 型糖尿病患者を、夜明け現象のあるグループとないグループで比較して、Rev-erb 遺伝子の発現がこれら 2 つのグループで異なる時間的パターンに従っていることを発見した。そこで、最初に GABA ニューロンの Rev-erb 遺伝子をノックアウトすることによってマウスモデルを開発。彼らがこのアプローチを選択した理由は、遺伝子の発現が主に GABA ニューロンで構成される視交叉上核と呼ばれる特定の脳領域で高度に濃縮されているからである。そして、研究者らは、これらのマウスについて血糖値が高かったのは夕方だけであることを発見(マウスは夜行性で、夕方に活動的になる)。また、Rev-erb ノックアウトマウスで夕方に観察された異常に高いグルコースレベルが、インスリンによる肝臓のグルコース産生の不充分な抑制に起因することを発見。彼らのデータは、摂食行動や基礎的な肝臓のグルコース産生とは無関係に、肝臓のインスリン感受性リズムを調節する上での神経 Rev-erb の重要な役割を示している、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＞Circadian clock gene Rev-erb linked to dawn phenomenon in type 2 diabetes -- ScienceDaily

CIRCADIAN CLOCK GENE REV-ERB LINKED TO DAWN PHENOMENON IN TYPE 2 DIABETES

Date:

March 25, 2021

Source:

Baylor College of Medicine

Summary:

Researchers found that mice lacking the circadian clock gene called Rev-erb in the brain show characteristics similar to those of human dawn phenomenon in type 2 diabetes.

FULL STORY

Researchers at Baylor College of Medicine, Shandong University in China and other institutions may have found an explanation for dawn phenomenon, an abnormal increase of blood sugar only in the morning, observed in many patients with type 2 diabetes. They report in the journal *Nature* that mice lacking the circadian clock gene called Rev-erb in the brain show characteristics similar to those of dawn phenomenon.

The researchers then looked at Rev-erb gene expression in patients with type 2 diabetes comparing a group with dawn phenomenon to a group without it and found that the gene's expression followed a different temporal pattern between these two groups. The findings support the idea that an altered daily rhythm of expression of the Rev-erb gene may underlie dawn phenomenon. Future investigations may lead to therapies.

"We began this study to investigate what was the function of Rev-erb in the brain," said co-corresponding author Dr. Zheng Sun, associate professor of medicine-endocrinology, diabetes and metabolism at Baylor. "We are interested in this gene because it is a 'druggable' component of the circadian clock with potential applications in the clinic. Rev-erb is expressed only during the day but not at night. When we started, we did not know where this was going to lead us."

The researchers first developed a mouse model by knocking out the Rev-erb gene in GABA neurons. They chose this approach because the gene's expression is highly enriched in a particular brain area called the suprachiasmatic nucleus that is mainly composed of GABA neurons.

An unexpected finding

"We observed something very interesting in these mice," Sun said. "They were glucose intolerant -- that is they had high glucose levels -- only in the evening. Mice are nocturnal, meaning that they become active in the evening as people do in the morning."

When the body awakes and takes in food, insulin is secreted from the pancreas to signal the body to lower blood sugar. Insulin is more effective in doing this job upon waking than at other times of the day. This high insulin sensitivity is probably because the body is anticipating feeding behaviors upon waking up. In mice, high insulin sensitivity occurs in the evening, while in people it occurs in the morning.

Sun and his colleagues found that the abnormal higher glucose levels observed in the evening in Rev-erb knockout mice resulted from an insufficient suppression of liver glucose production by insulin. Their data demonstrate an essential role of neural Rev-erb in regulating the hepatic insulin sensitivity rhythm independent of eating behaviors or basal hepatic glucose production.

Next, the researchers looked to understand how defects in Rev-erb gene expression in the brain can result in changes in the ability of the liver to respond to insulin. They discovered that the suprachiasmatic nucleus GABA neurons in Rev-erb knockout mice had a higher firing activity

than those neurons of normal mice when the animals woke up, and that this neuronal hyperactivity was sufficient and necessary to cause glucose intolerance in the evening. In normal mice, these GABA neurons drop their firing activity in the evening, lowering sugar blood levels. Interestingly, by re-expressing Rev-erb back in the knockout mice, the researchers found that Rev-erb expression is only needed during the day, but not needed at night, which is in line with the highly oscillatory expression pattern of endogenous Rev-erb in normal condition.

Connecting with dawn phenomenon

Mice having higher glucose levels in the evening reminded Sun and his colleagues of dawn phenomenon observed in people with type 2 diabetes. "Given the similarities of the phenomenon in mice and people, we thought that maybe this gene that we are studying could be linked to the biology of dawn phenomena in diabetic patients," said Sun, a member of Baylor's Dan L Duncan Comprehensive Cancer Center and the Huffington Center on Aging.

In collaboration with Qilu Hospital of Shandong University in China, the researchers followed 27 type2 diabetes patients with continuous glucose monitoring. They found that, although the patients had diabetes with similar severity in terms of their basal glucose levels, obesity and other parameters, about half of the patients had dawn phenomenon while the other half did not.

"We collected the patients' blood at different times of the day and determined the expression of the Rev-erb gene in white blood cells, which has been reported to correlate well with the central clock in the brain," Sun said. "Interestingly, we found that the gene's expression followed a temporal pattern that was different between those with dawn phenomenon and those without," Sun said. "We propose that the altered temporal pattern of expression of this gene may explain dawn phenomena in people. It is possible that, in the future, a drug might be used to regulate this gene to treat the condition."

Story Source:

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

Journal Reference:

1. Guolian Ding, Xin Li, Xinguo Hou, Wenjun Zhou, Yingyun Gong, Fuqiang Liu, Yanlin He, Jia Song, Jing Wang, Paul Basil, Wenbo Li, Sichong Qian, Pradip Saha, Jinbang Wang, Chen Cui, Tingting Yang, Kexin Zou, Younghun Han, Christopher I. Amos, Yong Xu, Li Chen, Zheng Sun. **REV-ERB in GABAergic neurons controls diurnal hepatic insulin sensitivity**. *Nature*, 2021; DOI: 10.1038/s41586-021-03358-w

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8. ジャンプに必要な遺伝子

ジャンプできない珍しいタイプのウサギを使った実験で同定

日付：2021 年 3 月 25 日
ソース：PLOS –ポルト大学、ウプサラ大学
概要：

ウサギ、ノウサギ、カンガルー、一部のげっ歯類はすべてジャンプして移動するが、この種の動きは分子的および遺伝的レベルでの理解がなされていない。
3 月 25 日に「PLOS Genetics」誌に掲載された新しい論文で、研究者らは、sauteur d'Alfort と呼ばれる珍しい種類の飼いならされたウサギを使用してジャンプ関連遺伝子を同定した、と報告している。
研究者らは、ホッピングする代わりに後ろ足を持ち上げて前足で歩くという奇妙な歩行をする Sauteur d'Alfort ウサギを別の品種と繁殖させ、子孫のゲノムとジャンプ能力を比較することにより、この原因を特定した。彼らは、RAR 関連のオーファン受容体 B（RORB）遺伝子に特定の変異があることを確認。通常、RORB タンパク質はウサギの神経系の多くの領域に見られるが、変異により RORB を生成する脊髄のニューロン数が急激に減少することが、sauteur d'Alfort の奇妙な散歩の原因であり、機能的な RORB 遺伝子が、ウサギや他のホッピング動物が特徴的なジャンプ歩行を行うために必要であることを示している、としている。調査結果は、マウスでの以前の研究に基づいており、RORB 遺伝子を欠くマウスはアヒルのような歩き方をした。
研究者らは、この作業が背骨を持つ動物が動くさまざまな方法の理解を深めるものだ、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＞Gene required for jumping identified in rabbits: Experiments with a rare type of rabbit that can't jump pinpointed the necessary gene -- ScienceDaily

GENE REQUIRED FOR JUMPING IDENTIFIED IN RABBITS

Experiments with a rare type of rabbit that can't jump pinpointed the necessary gene

Date:

March 25, 2021

Source:

PLOS

Summary:

Rabbits and other hopping animals require a functional RORB gene to move around by jumping, according to a new study.

FULL STORY

Rabbits and other hopping animals require a functional RORB gene to move around by jumping, according to a new study by Miguel Carneiro of the Universidade do Porto and Leif Andersson of Uppsala University published March 25th in *PLOS Genetics*.

Rabbits, hares, kangaroos and some rodent species all travel by jumping, but this type of movement is not well understood on a molecular and genetic level. In the new paper, researchers investigated jumping-related genes using an unusual breed of domesticated rabbit called the sauteur d'Alfort. Instead of hopping, it has a strange gait where it lifts its back legs and walks on its front paws. By breeding sauteur d'Alfort rabbits with another breed and comparing the offspring's genomes and jumping abilities, the researchers identified the cause of this developmental defect. They identified a specific mutation in the RAR related orphan receptor B (RORB) gene. Typically, the RORB protein is found in many regions of the rabbit nervous system, but the mutation leads to a sharp decrease in the number of neurons in the spinal cord that produce RORB. This change is responsible for the sauteur d'Alfort's weird walk.

The new study demonstrates that a functional RORB gene is necessary for rabbits and likely other hopping animals to perform their characteristic jumping gait. The findings build on previous studies in mice, showing that animals that lack the RORB gene had a duck-like walk. Additionally, this work advances our understanding of the different ways that animals with backbones move.

"This study provides a rare example of an abnormal gait behavior mapped to a single base change and the first description of a gene required for saltatorial locomotion," the authors conclude. "It further demonstrates the importance of the RORB protein for the normal wiring of the spinal cord, consistent with previous studies in mouse."

Story Source:

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

Journal Reference:

1. Miguel Carneiro, Jennifer Vieillard, Pedro Andrade, Samuel Boucher, Sandra Afonso, José A. Blanco-Aguiar, Nuno Santos, João Branco, Pedro J. Esteves, Nuno Ferrand, Klas Kullander, Leif Andersson. **A loss-of-function mutation in RORB disrupts saltatorial locomotion in rabbits**. *PLOS Genetics*, 2021; 17 (3): e1009429 DOI: 10.1371/journal.pgen.1009429

9. 最新の遺伝子編集技術 –プライム編集

日付:2021 年 3 月 30 日
ソース:オーガスタ大学ジョージア医科大学
概要:

ジョージア医科大学の科学者らは、プライム編集と従来の CRISPR の両方で、マウスの平滑筋細胞の分化に関与する遺伝子をうまくシャットダウンした、と「Genome Biology」誌に報告している。これは、マウスモデルでのプライム編集使用で 2 番目に発表された研究である。
遺伝子編集ツール CRISPR はく評価されているが、実際にはゲノムにとって過酷なツールでもある。CRISPR は、DNA 二重らせんを切断するハサミであり、「編集」と呼ばれるものは、実際には細胞による迅速な修復の試みである。修復の試みではエラーが誘引され、作業サイトだけでなくゲノム全体でランダムに意図しない編集を行う可能性がある。この予測不可能な変更を、一種の「ゲノム破壊行為」とさえ呼ぶ批評家もいる。これに対して、プライム編集では DNA の二重らせんの一本鎖のみが切り取られる。
今回の実験においても、実際に、CRISPR を使用した場合、意図した編集が行われたサイトの近くと別の場所で意図しない遺伝子の塩基の挿入(insertions)または削除(deletions)の略である「インデル(indels)」の証拠が発見された。インデルは、ゲノム編集者が避けようとしている意図しない変更であり、ある病気を別の病気に置き換える可能性がある。しかし、プライム編集では、この実験において、本質的にインデルは見られなかった、としている。
彼らは、プライム編集は最新の遺伝子編集技術であり、疾患モデルをより正確に作成して遺伝問題を修正するための「遺伝子ツールボックス」の拡張に寄与するものだ、と言っている。

研究関連ニュース/他のトップページに戻る

＜英文＞Prime editing enables precise gene editing without collateral damage | EurekAlert! Science News

NEWS RELEASE 30-MAR-2021

PRIME EDITING ENABLES PRECISE GENE EDITING WITHOUT COLLATERAL DAMAGE

MEDICAL COLLEGE OF GEORGIA AT AUGUSTA UNIVERSITY

Research News

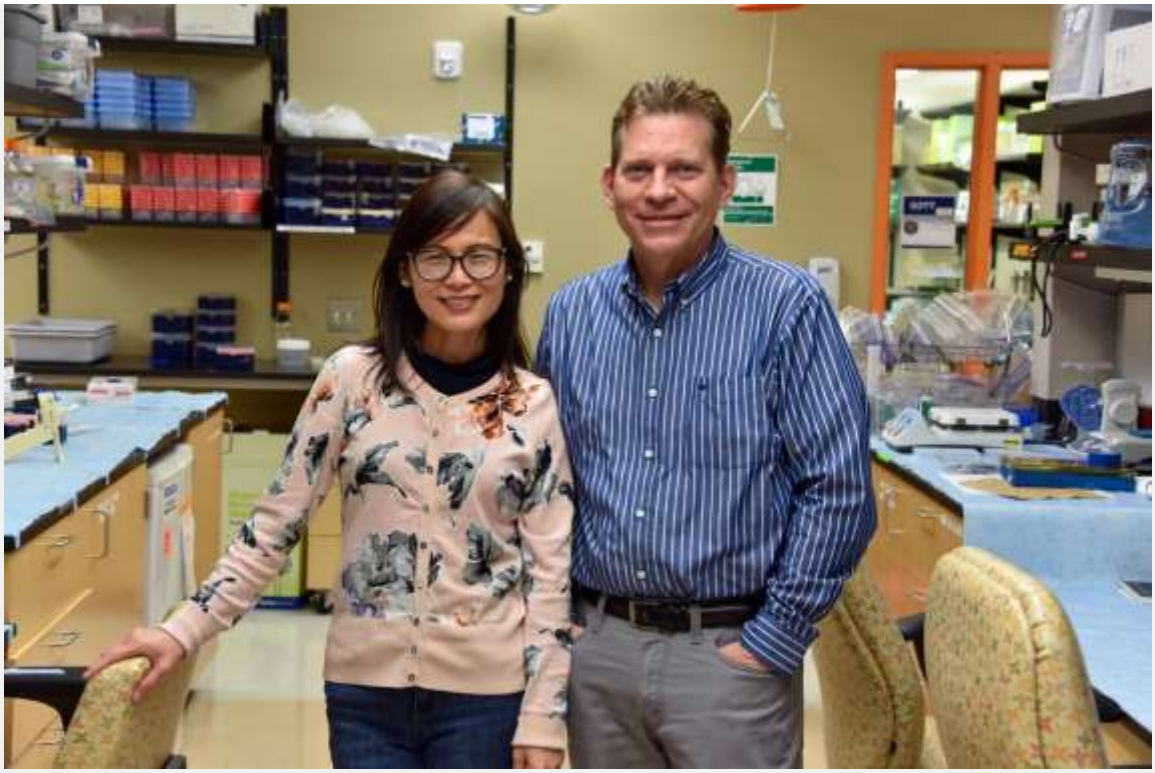

IMAGE: DRS. XIAOCHUN LONG AND JOSEPH MIANO. **view more**

CREDIT: KIM RATLIFF, AUGUSTA UNIVERSITY

The latest gene editing technology, prime editing, expands the "genetic toolbox" for more precisely creating disease models and correcting genetic problems, scientists say.

In only the second published study of prime editing's use in a mouse model, Medical College of Georgia scientists report prime editing and traditional CRISPR both successfully shut down a gene involved in the differentiation of smooth muscle cells, which help give strength and movement to organs and blood vessels.

However, prime editing snips only a single strand of the double-stranded DNA. CRISPR makes double-strand cuts, which can be lethal to cells, and produces unintended edits at both the work site as well as randomly across the genome, says Dr. Joseph Miano, genome editor, molecular biologist and J. Harold Harrison, MD, Distinguished University Chair in Vascular Biology at the MCG Vascular Biology Center.

"It's actually less complicated and more precise than traditional CRISPR," Miano says of prime editing, which literally has fewer components than the game-changing gene-editing tool CRISPR.

Miano was among the first wave of scientists to use CRISPR to alter the mouse genome in 2013. Two scientists were awarded the 2020 Nobel Prize in Chemistry for the now 9-year-old CRISPR, which enabled rapid development of animal models, as well as the potential to cure genetic diseases like sickle cell, and potentially reduce the destruction caused by diseases like cancer, in which environmental and genetic factors are both at play.

Prime editing is the latest gene-editing technology, and the MCG scientists report in the journal Genome Biology that they were able to use it to remove expression of a gene in smooth muscle tissue, illustrating prime editing's ability to create cell-specific knockout mice without extensive breeding efforts that may not result in an exact model, says Dr. Xiaochun Long, molecular biologist in the Vascular Biology Center. Miano and Long are corresponding authors of the new study.

Long, Miano and their colleagues did a comparative study using traditional CRISPR and prime editing in the gene Tspan2, or tetraspan-2, a protein found on the surface of cells. Long had earlier found Tspan2 was the most prominent protein in smooth muscle cell differentiation and was likely mutated in cardiovascular disease. She also had identified the regulatory region of this gene in cultured cells. However, it was unclear whether this regulatory region was important in mice.

They used CRISPR to create a subtle change in a snippet of DNA within the promoter region of Tspan2, in this case a three-base change, their standard approach to inactivating control regions of genes. DNA has four base pairs -- adenine, cytosine, guanine and thymine -- which pair up in endless different combinations to make us, and which gene-editing tools alter.

CRISPR created a double-strand break in the DNA and following the three-base change, the Tspan2 gene was no longer turned on in the aorta and bladder of mice.

They then used prime editing to make a single-strand break, or nick, and a single-base change -- like most of the gene mutations that occur in our body -- and found this subtle change also turned the Tspan2 gene off in the aorta and bladder, but without the collateral damage of CRISPR.

"We were trying to model what could happen with a single nucleotide change," says Miano. "We asked the question if we incorporate a single-base substitution, if we just make one base change, what happens to Tspan2 expression? The answer is it did the same thing as the traditional CRISPR editing: It killed the gene's expression."

But there were also important differences. Using CRISPR, they found evidence of significant "indels," short for insertions or deletions of bases in genes, which were unintended, both near the site where the intended edit was made and elsewhere.

The published paper includes a chart with numerous black bars illustrating where multiple nucleotides, the building blocks of DNA and RNA, are gone after using CRISPR. Indels are those unintended changes that genome editors strive to avoid because they can create deficits in gene expression and possible disease. With off-targeting, you could end up substituting one disease for another, Miano says.

But with prime editing, they saw essentially no indels either at the Tspan2 promoter region or elsewhere.

A Manhattan plot illustrated the off-targeting across all chromosomes using both techniques, with the CRISPR skyline stacking up like a real city while the prime editing skyline is comparatively flat.

"Prime editing is a less intrusive cut of the DNA. It's very clean," Miano says. "This is what we want: No detectable indels, no collateral damage. The bottom line is that unintended consequences are much less and it's actually less complicated to use."

Traditional CRISPR has three components, the molecular scissors, Cas9, the guide RNA that takes those scissors to the precise location on DNA and a repair template to fix the problem. Traditional CRISPR cuts both strands of the DNA, which also can happen in nature, can be catastrophic to the cell and must be quickly mended.

Prime editing has two arms, with a modified Cas9, called a Cas9 nickase, that will only make a single-strand cut. The scissors form a complex called the "prime editor" with a reverse transcriptase, an enzyme that can use an RNA template to produce a piece of DNA to replace the problematic piece in the case of a disease-causing mutation. PegRNA, or prime editing guide RNA, provides that RNA template, gets the prime editor where it needs to work and helps stabilize the DNA strands, which are used to being part of a couple.

During the repair of the nicked strand of targeted DNA, the prime editor "copies" a portion of the pegRNA containing the programmed edit, in this case a single-base substitution, so that the repaired strand will now carry the single base edit. In the case of creating a disease model, that enables scientists to "bias" the repair so the desired mutation is created, Miano says.

Dr. David Liu, chemical biologist, Richard Merkin Professor and director of the Merkin Institute of Transformative Technologies in Healthcare at Harvard University and the Massachusetts Institute of Technology, and his colleagues developed the first major gene editing technology to follow CRISPR. They reported on base editing technology in 2016, which uses "base editors" Liu described as "pencils, capable of directly rewriting one DNA letter into another by actually rearranging the atoms of one DNA base to instead become a different base." Liu and his postdoctoral fellow Dr. Andrew Anzalone, first reported on prime editing in the journal *Nature* in October 2019. Liu is a coauthor on the newly published study in *Genome Biology* on prime editing in mice.

Liu's original work on prime editing was done in culture, and others have shown its efficacy in plants. This is more proof of principle, Miano says.

The MCG scientists hope more of their colleagues will start using prime editing in their favorite genes to build experience and hasten movement toward its use in humans.

Their long-term goals including using safe, specific gene editing to correct genetic abnormalities during human development that are known to result in devastating malformations and disease like heart defects that require multiple major surgeries to correct.

Allison Yang, senior research assistant in the Miano lab, is preparing to use prime editing to do an in utero correction of the rare and lethal megacystis-microcolon-intestinal hypoperistalsis syndrome, which affects muscles of the bladder and intestines so you have difficulty moving food through the GI tract and emptying the bladder. In early work with CRISPR on vascular smooth muscle cells, Miano and colleagues inadvertently created a near-perfect mouse model of this human disease that can kill babies.

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Collaborators on the new study include scientists from Albany Medical College, St. Jude Children's Research Hospital, Cornell University, Synthego, and Harvard University. The research was supported by the National Institutes of Health.

Changes in just one DNA building block, or nucleotide, called single nucleotide polymorphisms, or SNPs, are the most common type of genetic variation in people, according to MedlinePlus, and each person has millions in their genome. A tiny proportion of SNPs, like the one that causes sickle cell disease, occur in parts of the DNA that produce proteins, which determine cell function. However, the vast majority of SNPs, such as the artificial one generated with prime editing here, occur in the human genome where no protein-coding genes are found. This noncoding portion of the genome, the so called 'dark matter,' comprises 99% of our entire DNA blueprint of life. Noncoding parts of the genome include regulatory elements like the one controlling Tspan2 expression.

Read the full study.

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