Bio News – April, 2024

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

3/1　Gilead、Trodelvy（トロデルビィ；sacituzumab govitecan）の非小細胞肺癌（NSCLC）相手の臨床試験費用として生命科学投資会社 Abingworth が最大 2 億 1,000 万ドル（$210 million）を提供

Gilead nets up to $210M from Abingworth to fund Trodelvy lung cancer trials | FirstWord Pharma

3/1　がん放射線治療の元素、国産化へ協定　原子力機構・がん研究センター

がん治療薬として期待される放射性元素を国内製造することを目指し、日本原子力研究開発機構と国立がん研究センターが 29 日、研究協定を結んだ。機構の高速実験炉「常陽」（茨城県）で 2026 年度中に試験製造を始めることを目指すという。
共同開発する元素は「アクチニウム 225」。がん細胞を攻撃する効果が高いとして各国で治験が進む一方、半減期が約 10 日で、世界で年間約 3 千人分しか供給がないという。

3/2　全世界で 10 億人以上が「肥満」、過去 30 年間で急増

1990 年から 2022 年の間に、肥満の割合が著しく上昇した一方で、低体重の割り合いはほとんどの国で減少したことが最新の研究で明らかになった。研究者たちは、低体重の問題に取り組みながらも肥満の割合を下げるために、より栄養価の高い食品を摂取することが重要だと考えている。
2 月 29 日に Lancet に掲載された研究によると、世界の成人女性の肥満の割合は 1990～2022 年の間に 2 倍以上に増え、成人男性では 3 倍に増えたことがわかった。子どもでは 1990 年と比べて 2022 年は 4 倍も高かった。

3/2　はしか、欧州急増し世界的に流行　ワクチン接種減影響か、日本でも

世界各地ではしかの感染が拡大している。世界保健機関（WHO）によると、2023 年は前年比 8 割増の 30 万人以上の感染が報告され、特に欧州での増加が目立つ。背景に新型コロナウイルス流行時、はしかのワクチン接種率が下がったことがある。日本でも 2 月以降複数の感染例が出ており、今後拡大が懸念されるとして、厚生労働省はワクチン接種を呼びかけている。

3/2　厚生労働省の睡眠ガイド 「成人は 6 時間以上」

「成人の睡眠時間は 6 時間以上が目安」――。厚生労働省が 2 月に公表した、健康づくりのための新たな睡眠ガイドで、そんな基準が示された。

3/3　2020 年の世界の新生児の出産時低体重（2500g 未満）の割合は 7 人に 1 人の 14.7%

2020 年の世界の新生児の 7 人に 1 人（14.7%）が出産時低体重（LBW；2500 g 未満）であり、20 年前の 2020 年のその割合 16.6%に比べて差し引きで 1.9%低くて済んでいた。
2030 年の LBW 率を 10.5%にすることが Global Nutrition Targe の目標の 1 つになっている。Global Nutrition Target は世界保健機関（WHO）が UNICEF や欧州委員会（EC）と協力して進めている。

National, regional, and global estimates of low birthweight in 2020, with trends from 2000: a systematic analysis - The Lancet

3/3　乗り物酔いを引き起こす神経を同定

スペインのバルセロナ自治大学と米国のワシントン大学のチームの新たな研究で乗り物酔いに与するマウスの VN 領域神経が同定された。その神経狙いの薬なら眠気を引き起こすことなく乗り物酔いを治療できそうだとしている。

The Culprits Behind Motion Sickness | TS Digest | The Scientist (the-scientist.com)

3/4　塩野義のコロナ薬ゾコーバ承認へ　厚労省部会が了承　有効性を確認

3/4　世界初の手術成功、男児が京大病院を退院　肺と肝臓の一部を同時移植

3/5　新型コロナ治療 塩野義の「ゾコーバ」国産で初めての正式承認

3/6　欧州各国で「オウム病」急増　5 人死亡、多数が入院　WHO

3/6　ソニーとネイチャーが女性研究者賞創設　数学・工学…賞金 3 千万円超

ソニーグループと英科学誌ネイチャーは 6 日、テクノロジー分野で活躍する優れた女性研究者を表彰する国際賞「ソニー・ウィメン・イン・テクノロジー・アワード・ウィズ・ネイチャー」を創設すると発表した。男性の半分以下とされるテック分野の女性研究者を支援する狙い。研究資金各 25 万ドル（約 3,750 万円）を贈る 3 人を来年初頭に発表する。

3/7　冬野菜は凍結耐性を高めるために細胞壁の多糖を増やす 埼玉大など発見

ホウレンソウなどの冬野菜は気温低下を感知し、凍結耐性を高めるために細胞壁の多糖を増やすことを、埼玉大学大学院理工学研究科の高橋大輔助教（植物生理学）らが突き止めた。この働きは多くの植物で認められており、凍結耐性を改変することで農作物の収量増加や品質の向上につながる可能性がある。

3/7　中年太りの仕組み解明　加齢で脳細胞縮み、飽食シグナル届きにくく 「腹八分目」で改善

加齢に伴い痩せにくくなる「中年太り」は、脳の神経細胞の一部が縮むことで肥満を防ぐシグナルが脳に届きにくくなるために起こることを名古屋大の研究グループが突き止め、7 日発表した。ラットによる実験では、食事を減らせば退縮が改善する傾向もみられたという。成果をまとめた論文が米科学誌オンライン版に掲載された。

3/8　はしかの世界的流行　欧州で 60 倍　国内も感染相次ぐ　国が注意喚起

3/8　iPS 心筋球移植　1 年で心不全に顕著な効果　来年にも実用化　慶大発ベンチャー

人工多能性幹細胞（iPS 細胞）から作った心臓の筋肉（心筋）の細胞を球状に加工した「心筋球」を、重い心不全患者の心臓に移植する世界初の治験で、移植後1年間の経過観察により長期間の顕著な症状改善効果が確認されたことが 8 日、分かった。実施した慶応大発の医療ベンチャー、ハートシード（東京都新宿区）は「来年にも実用化したい」としている。

3/9　「女性の腹囲は 90 センチ→77 センチ」 メタボ基準を新たに提案 -新潟大など

3/8　住友ファーマ（本社：マサチューセッツ州ケンブリッジ）が米国子会社の従業員をさらに 400 人ほどを削減

Sumitomo Pharma lays off 400 US staffers as sales slide (fiercepharma.com)

3/8　エーザイのアルツハイマー病薬 Leqembi の米国での普及が予想より遅れている

3/9　Lilly のアルツハイマー病薬 donanemab の米国承認審査がさらに長引く

3/10　卵子凍結費の助成、東京都が申請者全員に支給へ　当初想定の 9 倍超

3/11　政府肝いりの復興拠点　国内トップ級の給与でも研究者集まるか未知数

住民の帰還が進まない東京電力福島第 1 原発事故の被災地で、政府は産業基盤を構築する国家プロジェクト「福島イノベーション・コースト構想」を進めている。その司令塔役を担い、世界に冠たる「創造的復興の中核拠点」と掲げられた「福島国際研究教育機構」（F－REI、エフレイ）が 2023 年 4 月、福島県浪江町で産声を上げた。
エフレイは、福島の「F」と「Research（研究）」「Education（教育）」「Innovation（革新）」の頭文字から取った略称。国が新たに設立した特別法人で、岸田文雄首相が初代理事長として前金沢大学長の山崎氏を任命した。
研究分野は①ロボット②農林水産業③エネルギー④放射線科学・創薬医療、放射線の産業利用⑤原子力災害に関するデータや知見の集積・発信――の五つ。

3/12　承認薬の秘めた効果を見つける事業に米国政府が 3 年間に 5 千万ドル程を出す

手の施しようがない病気への承認薬の秘めた効果を人工知能（AI）を頼りに見つける非営利事業 Every Cure に米国政府が 5 千万ドル弱（4,830 万ドル、$48.3 million）を出す。
世間の健康に貢献する技術革新に取り組む研究開発支援する Advanced Research Projects Agency for Health (ARPA-H) からの出資。

Every Cure to Receive $48.3M from ARPA-H to Develop AI-Driven Platform to Revolutionize Future of Drug Development and Repurposing (prnewswire.com)

3/13　iPS 心筋シート、拡張型心筋症患者に移植へ　大阪大が国内初の治験開始

健常者の人工多能性幹細胞（iPS 細胞）から作った心臓の筋肉（心筋）細胞を拡張型心筋症の患者に移植する国内初となる治験を、大阪大の研究チームが始めたことが 12 日、関係者への取材で分かった。今後、4 人の患者に実施する予定。

3/13　芳香や悪臭主成分、簡単に特定　新装置開発　岩手大・島津製作所

岩手大と島津製作所（京都市）は 13 日、芳香や悪臭を放つ混合物の主成分を効率良く特定できるほか、さまざまな成分を自在に組み合わせることができる「アロマデザイナー」を共同開発したと発表した。既存の「ガスクロマトグラフ質量分析計（GC―MS）」を改良した装置で、同社が特注品として販売を始めており、1 年半から 2 年後に製品化する方針。

3/13　Lilly の人気の肥満薬 Zepbound を Amazon が配達

Eli Lilly の人気肥満薬 Zepbound（tirzepatide、チルゼパチド）やその他の薬を Amazon が 24 時間年中無休（24/7）で米国の患者に配達する。
この 1 月に Lilly は患者と医師の間を取り持ってそれら患者に Lilly の処方薬を直接届ける遠隔医療 LillyDirect を開始。その LillyDirect を介しての処方薬一揃いを Amazon の薬局事業 Amazon Pharmacy が患者の自宅に直接運べるようになる。

Lilly Makes Weight-Loss Drug Zepbound Available Through Amazon Pharmacy | BioSpace

3/14　新型コロナの流行で世界の平均寿命が「1.6 年短く」当初の予想上回る

新型コロナウイルスが世界的に大流行した最初の 2 年間で、世界人口の平均寿命が 1.6 年短くなったことが、英医学誌ランセットの研究から明らかになった。

3/14　たばこの煙が生理機能に悪影響を与える仕組み、岡山大が解明

岡山大学の上原孝教授と森本睦大学院生らは、理化学研究所、長崎大学、九州大学、東京大学との共同研究で、たばこの煙や排ガスに含まれる化学物質「メチルビニルケトン（MVK）」が生理機能に悪影響を与える仕組みを解明した。細胞内の恒常性維持に重要なたんぱく質に結合し、糖の取り込みに重要なインスリンなどの作用を抑制する。慢性暴露による糖尿病などの疾患発症のメカニズム解明や予防・治療法開発が期待される。

3/14　Madrigal の脂肪肝薬 Rezdiffra（レズディフラ）を FDA が脂肪肝薬としては初めて承認

Rezdiffra の 1 年間分の定価は 47,400 ドルで、同剤の年間売上は 50 億ドルを超えうるとアナリストは予想している。

US FDA approves first drug for fatty liver disease NASH | Reuters

3/15　家族性アルツハイマーの治験開始　レカネマブと新薬併用　新潟大など

新潟大と東京大の研究チームは 15 日までに、家族性アルツハイマー病の原因となる遺伝子を持つ人を対象に、治療薬「レカネマブ」と開発中の新薬を併せて投与し、効果と安全性を調べる国際臨床試験（治験）を開始したと発表した。昨年正式承認されたレカネマブともう 1 種類を併用する世界初の試みで、新たな治療法の開発につながることが期待されるという。

3/15　はしか感染拡大　ワクチン接種率低下に警鐘

はしかの世界的な流行に伴って、国内でも海外からの帰国者らの感染報告が相次ぎ、感染の広がりが懸念されている。だが、予防するための MR ワクチンの接種率は、過去 10 年で最低レベルだという。

3/15　コロナ助言機関、３月末で廃止

厚生労働省は、新型コロナウイルスの感染状況を分析してきた助言機関を 3 月末で廃止する。医療・公衆衛生分野などの専門家 15 人で構成し、開催回数は計 124 回に上った。昨年 5 月に新型コロナが感染症法上の 5 類となり、医療逼迫（ひっぱく）につながる感染拡大も起きていないことから、通常体制に移行する。最後に武見厚労相との懇談会を 3 月下旬に開く予定。

3/16　食い荒らしたサツマイモから異臭と苦み…「イモゾウムシ」鹿児島県本土で 16 年ぶり発見

鹿児島市喜入生見町で、サツマイモを食い荒らすイモゾウムシが発見された。鹿児島県・奄美大島以南で生息しており、県本土で見つかるのは 2008 年に指宿市で確認されて以来、16 年ぶり。食害に遭ったイモを食べても人体への影響はないという。

3/16　Lilly の肥満薬 Zepbound の米国での新規処方数が Novo の Wegovy を抜いた

Lilly weight-loss drug Zepbound new US prescriptions surpass Wegovy for first time | Reuters

3/17　「脳腫瘍」の状態を「少量の血液」から判別が可能に、東北大学の研究

3/18　昨年協和キリンが買収した英国ベースの Orchard の異染性白質ジストロフィー遺伝子治療 Lenmeldy を米国承認

US approves first gene therapy for children with rare genetic disease | Reuters

3/19　Pfizer のコロナ薬パキロビッドよりも強力なメインプロテアーゼ阻害剤ができた

An orally bioavailable SARS-CoV-2 main protease inhibitor exhibits improved affinity and reduced sensitivity to mutations | Science Translational Medicine

3/19　J&J と提携する Contineum（昨年 Pipeline Therapeutics から社名変更）が最大 1 億 5,000 万ドルの IPO 調達を計画

J&J-partnered Contineum jumps in IPO queue | FirstWord Pharma

3/20　23 年は観測史上最も暑い年、今年はさらに暑くなる可能性高い WMO

世界気象機関（WMO）は 19 日、2023 年が観測史上最も暑い年になったとの報告書を公表し、今年はさらに暑くなる可能性が高いと警告した。

3/20　マダニ媒介の感染症 SFTS 人から人への感染を国内で初確認

マダニを通じて感染する重症熱性血小板減少症候群（SFTS）が人から人へ感染したケースを国内で初めて確認した、と国立感染症研究所が 19 日発表した。
発表によると、人から感染したのは 20 代の男性医師。2023 年 4 月に SFTS と診断された 90 代男性の診療を担当し、この患者が死亡後にカテーテルを外すなどの処置をした。男性医師は、90 代男性と初めて接触してから 11 日後に 38 度の発熱や頭痛などの症状が出て、PCR 検査で SFTS と確定診断された。

3/20　武田薬品の Iclusig と化学療法による Ph+ 急性リンパ性白血病初治療を FDA が承認

武田薬品工業は、フィラデルフィア染色体陽性急性リンパ芽球性白血病と新たに診断された成人患者に対する療法である、化学療法併用でのポナチニブ（アイクルシグ）に関して、米食品医薬品局（FDA）から迅速承認を受けた。FDAが 19 日に発表した。

3/21　カワイルカの新種と判明、ペルーで発見の頭骨化石 世界最大種

ペルーのアマゾン（Amazon）熱帯雨林を流れるナポ（Napo）川近くで 2018 年に見つかった頭骨の化石が、新種のカワイルカのものであることが分かった。首都リマの国立自然史博物館（National Natural History）で 20 日、発表された。

3/21　DNA 切断の修復過程解明　発がん抑制など期待　東大

2 本の鎖による二重のらせん構造で遺伝子を構成している DNA は、紫外線や放射線、体内の活性酸素などにより頻繁に切断されるが、東京大の研究チームは「RAD51」と呼ばれるたんぱく質が、切断された二本鎖を修復する仕組みを解明したと発表した。修復がうまくいかないとがん化する恐れがあり、成果は発がんを抑制する治療法などの開発につながると期待される。論文は 21 日、英科学誌ネイチャーに掲載された。

3/21　協和キリンの異染性白質ジストロフィー遺伝子治療 Lenmeldy の定価 425 万ドル

18 日に米国 FDA に承認された協和キリンの子会社 Orchard Therapeutics の投与一回きりの異染性白質ジストロフィー（MLD）遺伝子治療 Lenmeldy（atidarsagene autotemcel、arsa-cel）の定価は 425 万ドル（6 億 4 千万円ほど）。

3/21　シャープと静岡大、プラズマクラスターイオンによるイネの初期生育促進効果を確認

シャープは、同社のプラズマクラスターイオン(PCI)技術が、植物の初期生育促進に寄与していることを初めて確認した。静岡大学農学部の一家崇志(いっか たかし)准教授および山下寛人助教との共同研究による。2016 年にはレタスでの育成効果を実証していたが、今回イネを使って植物の生育促進のメカニズムを初めて確認した。この成果を背景に、今後国内の植物工場への PCI 技術採用を働きかけていく。

3/22　ブタ腎臓、生存患者に初移植　執刀医「将来は透析なくなる」 米

ボストンのマサチューセッツ総合病院は 21 日、遺伝子を改変したブタの腎臓を末期腎不全の男性患者に移植することに成功したと発表した。
これまで脳死者に移植した例はあるが、生きた患者は世界で初めてだという。
執刀した同病院の河合達郎医師は時事通信の取材に「臓器移植が容易になり、将来的に人工透析（という治療法）の必要がなくなる可能性がある」と意義を語った。
移植されたブタの腎臓は、米バイオ企業イージェネシスが提供。拒絶反応を起こす遺伝子が取り除かれ、感染症を引き起こす恐れのある特定のウイルスを不活性化させるなど、移植に際したリスクを抑制している。

3/22　小林製薬、サプリで健康被害

小林製薬（大阪市）が販売した機能性表示食品のサプリメントを摂取した複数の人から腎疾患などの健康被害が報告された問題では、同社が1ヶ月以上にわたり調査を進めたが、被害の原因は特定できなかった。ただ、商品の一部からは「未知の成分」が検出されており、同社は商品の回収と並行し調査を継続する。

3/22　小林製薬がサプリ約 30 万個を自主回収 「紅麹コレステヘルプ」など 3 商品　男女 13 人が腎臓疾患を発症

小林製薬は腎臓疾患を引き起こす可能性があるとして、紅麹を使ったサプリメント商品を自主回収すると発表した。
小林製薬によりますと、悪玉コレステロールを下げるというサプリメント商品「紅麹コレステヘルプ」を摂取した 40 代から 70 代の男女 13 人が腎臓疾患を発症し、うち 6 人が入院した。

3/23　欧州でも健康被害報告、小林製薬同様「紅こうじ」由来サプリで

小林製薬（大阪市）が販売した「紅こうじ」成分配合のサプリメントを摂取した人から、腎疾患などの健康被害が相次いで報告された問題をめぐり、同様の成分を含むサプリメントの健康被害は 2014 年ごろに欧州でも確認されていた。
食品安全委員会によると、紅こうじ由来の成分には LDL コレステロール値を下げる効果が期待される一方、一部の紅こうじは腎臓の働きに影響を与える「シトリニン」というカビ毒を発生させる可能性が

3/23　エーザイ/Biogen のアルツハイマー病薬 Leqembi 欧州承認申請の専門家検討会やり直し

Lecanemab deliberations at the CHMP regarding the Marketing Authorisation Application in the EU have been rescheduled due to procedural reasons (prnewswire.com)

3/25　日本人がん患者の遺伝子変異の全体像判明 国立がん研が初の 5 万人ゲノム異常解析

国立がん研究センター研究所は欧米人などと異なる日本人のがん遺伝子変異の全体像が明らかになったと 2 月 29 日に発表した。
「がん遺伝子パネル検査」で得られた約 5 万人の患者のデータを活用し、遺伝子の変異を解析。がん

治療薬の標的となる変異があった割合は平均で約 15%だったという。遺伝子変異などを明らかにして治療効果が高いと見込める薬を選んで治療する「がんゲノム医療」に貴重なデータを与える成果で、国立がん研は今後も解析を続けて治療成績の向上につなげたいとしている。

3/26　小林製薬「紅麹原料」健康被害で新たに 1 人の死亡者、計 2 人に　小林製薬も発表

3/26　HIV 感染 7 年ぶり増、検査数 10 万件超に　厚労省委員会「積極的に検査を」

厚生労働省のエイズ動向委員会は 26 日、令和 5 年に新たにエイズウイルス（HIV）感染が判明した人は、前年比 37 人増の 669 人（速報値）で、7 年ぶりに増加に転じたと発表した。
検査件数は、同3万 3,033 件増の 10 万 6137 件。新型コロナウイルス流行以降、検査控えで流行前の半分程度まで件数が減少していたが、4 年ぶりに 10 万件を超えた。 新規エイズ患者数は、同 36 人増の 291 人（同）。HIV感染者とエイズ患者計 960 人で男性が全体の 9 割を超えている。感染経路別では同性間の性的接触が 633 人、異性間の性的接触が 133 人などだった。

3/27　免疫不全患者の COVID-19 を予防する Invivyd の抗体薬を米国 FDA が取り急ぎ認可

Invivyd Announces FDA Authorization for Emergency Use of (globenewswire.com)

3/28　台湾当局、日本に「紅麹」製品リストを要求

3/28　ウーバー、全国で処方薬を配達へ　薬局チェーンなど 4 社と提携

料理宅配サービスのウーバーイーツジャパンが、全国で処方薬の配達サービスを始めることが 28 日、分かった。医療機関にオンライン診療などのシステムを提供する企業と薬局チェーンの計 4 社と連携し、ウーバーイーツの配達員が薬を病院や薬局などから患者宅に届ける。医療機関の準備が整い次第、順次サービスを始める。

3/28　自閉スペクトラム症の新モデルマウスを作製 理研など

自閉スペクトラム症（ASD）の新たなモデルマウスを作製し、このマウスの実験で ASD 特有の行動変化の一部を薬剤投与で改善できることを確かめたと、理化学研究所（理研）や順天堂大学、東京大学の共同研究グループが 26 日、発表した。増加傾向にある ASD の理解や治療法の開発につながる成果と期待される。

3/28　「カニの殻」が「半導体」へ　-東北大学などの研究

生成 AI の進化発展もあって半導体の需要が高まっている。東北大学などの研究グループは、カニやエビ、昆虫などの殻や骨のキチンから作られるキトサンという物質を半導体などの材料として活用できる可能性を見いだした。
東北大学などの研究グループは、ベニズワイガニの殻から得られたキチンを脱アセチル化して作られるキトサンのナノファイバーを原料に電極を付けたシートにしてデバイス化し、電流を流したところ、半導体の n 型特性を示すことを発見し、米国物理学協会の学術誌で発表した。

3/28　サルの脳に「足し算、引き算細胞」発見　言語を持たない霊長類でも計算できる可能性

東北大大学院医学系チームは 28 日までに、サルを用いた実験で、脳に足し算、引き算を実行する際に強く反応する細胞があることを世界で初めて発見した。計算に特化した細胞が脳にあるわけではなく、手の運動を制御する細胞を再利用（リサイクル）することで計算を可能にしていることを示唆するものだという。今後は、脳機能から見た数学の学習法などへの応用が期待される。

3/29　iPS 細胞でコロナ変異株の性質特定、重症化予測が可能に　京大が手法開発

人工多能性幹細胞（iPS 細胞）から作った肺や気道の細胞に新型コロナウイルスを感染させて変異株の病原性を調べる手法を開発したと、京都大iPS細胞研究所の研究グループが 29 日、発表した。インフルエンザなどほかの呼吸器感染症に応用できるといい、グループは「重症化予測に役立てたい」としている。

3/29　小林製薬の紅麹サプリ問題　厚労省がコールセンターと連携室設置

3/29　世界で 1 日 10 億食が無駄に 国連

国連環境計画（UNEP）は 27 日、世界の食品廃棄物の統計「廃棄食品指標報告（Food Waste Index Report）」の最新版で、2022 年には世界全体で毎日 10 億食が廃棄されていたと発表した。8 億人近い人々が飢餓に苦しむ中で、1 兆ドル（約 150 兆円）以上に相当する食品が家庭や企業から廃棄されたという。

3/29　16 都府県、PFAS 指針値超　河川や地下水、111 地点

環境省は 29 日、泡消火剤などに含まれ、有害性が指摘されている有機フッ素化合物（PFAS）の一種、「PFOS」「PFOA」が全国 16 都府県の河川や地下水など 111 地点で国の暫定指針値（合算で 1 リットル当たり 50 ナノグラム）を超えていたと発表。

3/29　小林製薬の紅麹サプリからプベルル酸検出

サプリメント服用を巡って健康被害が起きた原因物質の可能性として、製造元の小林製薬（大阪市）の調査で、「プベルル酸」が浮上した。
厚生労働省によると、プベルル酸は青カビが作り出す物質で、抗生物質としての特徴がある。米国立衛生研究所（NIH）のデータベースなどでは、ヒヤシンスに病気をもたらす原因菌などから見つかった天然化合物としている。

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. アルツハイマー病マウスにおいて、40Hz の感覚ガンマリズム刺激がアミロイドの除去に寄与

2. 遺伝子コードの変化が、ヒトの先祖がなぜ尾を失ったかを説明する可能性 -マウス実験

3. AI 分析によると、妊娠中の喫煙は新生児の行動障害のリスクを高める可能性がある -マウス実験

4. マウスモデルで見つかったアルツハイマー病の最も早いバイオマーカーが新しい標的を指摘する可能性

5. 母親の肥満が肝癌を促進する可能性 -マウス実験

6. 質の低い睡眠と片頭痛発作との関連性 -マウス実験

7. 安全で高度に効果的な癌免疫療法へ向けた DNA オリガミベースのワクチン -マウス実験
   広範囲に適用可能なワクチンプラットフォームにより、アジュバント分子と様々な抗原のナノメートル単位の精密な間隔による抗腫瘍反応が向上

8. 老化した免疫系を活性化させ、ワクチンへの反応を改善するためのマウス研究

1. アルツハイマー病マウスにおいて、40Hz の感覚ガンマリズム刺激がアミロイドの除去に寄与

日付：2024 年 2 月 28 日
ソース：MIT ピコワー研究所
概要：

MIT を始めとする研究施設での研究により、40Hz の脳のガンマリズム周波数での光と音の刺激が、アルツハイマー病（AD）の進行を減少させ、ヒトや実験用マウスにおいて症状を治療できる可能性が高まっているとの結果が示されている。
MIT ピコワー研究所の研究者らは、彼らの新しい研究で、これらの効果に寄与する可能性のある重要なメカニズムを明らかにしている。それは、アルツハイマー病の病理学的特徴であるアミロイドタンパク質を、脳の血管に平行な、最近発見された、「配管」ネットワークである脳のグリンファティックシステムを介して除去することである。
この研究では、マウスモデルを使用し、感覚的なガンマ刺激が 40 Hz の電力との同期を増加させると、特定のタイプのニューロンがペプチドを放出することが示されている。研究結果は、これらの短いタンパク質信号が脳のグリンファティックシステムを介してアミロイド除去を促進する特定のプロセスを駆動することを示唆している、として『Nature』誌に発表している。

研究関連ニュース/他のトップページに戻る

＜英文＞How 40Hz sensory gamma rhythm stimulation clears amyloid in Alzheimer's mice | ScienceDaily

How 40Hz sensory gamma rhythm stimulation clears amyloid in Alzheimer's mice

Date:

February 28, 2024

Source:

Picower Institute at MIT

Summary:

Stimulating a key brain rhythm with light and sound increases peptide release from interneurons, driving clearance of Alzheimer's protein via the brain's glymphatic system, new study suggests.

FULL STORY

Studies at MIT and elsewhere are producing mounting evidence that light flickering and sound clicking at the gamma brain rhythm frequency of 40 Hz can reduce Alzheimer's disease (AD) progression and treat symptoms in human volunteers as well as lab mice. In a new study in *Nature* using a mouse model of the disease, researchers at The Picower Institute for Learning and Memory of MIT reveal a key mechanism that may contribute to these beneficial effects: clearance of amyloid proteins, a hallmark of AD pathology, via the brain's glymphatic system, a recently discovered "plumbing" network parallel to the brain's blood vessels.

"Ever since we published our first results in 2016, people have asked me how does it work? Why 40 Hz? Why not some other frequency?" said study senior author Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute and MIT's Aging Brain Initiative. "These are indeed very important questions we have worked very hard in the lab to address."

The new paper describes a series of experiments, led by Mitch Murdock when he was a Brain and Cognitive Sciences doctoral student at MIT, showing that when sensory gamma stimulation increases 40 Hz power and synchrony in the brains of mice, that prompts a particular type of neuron to release peptides. The study results further suggest that those short protein signals then drive specific processes that promote increased amyloid clearance via the glymphatic system.

"We do not yet have a linear map of the exact sequence of events that occurs," said Murdock, who was jointly supervised by Tsai and co-author and collaborator Ed Boyden, Y. Eva Tan Professor of Neurotechnology at MIT, a member of the McGovern Institute for Brain Research and an affiliate member of The Picower Institute. "But the findings in our experiments support this clearance pathway through the major glymphatic routes."

From Gamma to Glymphatics

Because prior research has shown that the glymphatic system is a key conduit for brain waste clearance and may be regulated by brain rhythms, Tsai and Murdock's team hypothesized that it might help explain the lab's prior observations that gamma sensory stimulation reduces amyloid levels in Alzheimer's model mice.

Working with "5XFAD" mice, which genentically model Alzheimer's, Murdock and co-authors first replicated the lab's prior results that 40 Hz sensory stimulation increases 40 Hz neuronal activity in the brain and reduces amyloid levels. Then they set out to measure whether there was any correlated change in the fluids that flow through the glymphatic system to carry away wastes. Indeed, they measured increases in cerebrospinal fluid in the brain tissue of mice treated with sensory gamma stimulation compared to untreated controls. They also measured an increase in the

rate of interstitial fluid leaving the brain. Moreover, in the gamma-treated mice he measured increased diameter of the lymphatic vessels that drain away the fluids and measured increased accumulation of amyloid in cervical lymph nodes, which is the drainage site for that flow.

To investigate how this increased fluid flow might be happening, the team focused on the aquaporin 4 (AQP4) water channel of astrocyte cells, which enables the cells to facilitate glymphatic fluid exchange. When they blocked APQ4 function with a chemical, that prevented sensory gamma stimulation from reducing amyloid levels and prevented it from improving mouse learning and memory. And when, as an added test they used a genetic technique for disrupting AQP4, that also interfered with gamma-driven amyloid clearance.

In addition to the fluid exchange promoted by APQ4 activity in astrocytes, another mechanism by which gamma waves promote glymphatic flow is by increasing the pulsation of neighboring blood vessels. Several measurements showed stronger arterial pulsatility in mice subjected to sensory gamma stimulation compared to untreated controls.

One of the best new techniques for tracking how a condition, such as sensory gamma stimulation, affects different cell types is to sequence their RNA to track changes in how they express their genes. Using this method, Tsai and Murdock's team saw that gamma sensory stimulation indeed promoted changes consistent with increased astrocyte AQP4 activity.

Prompted by peptides

The RNA sequencing data also revealed that upon gamma sensory stimulation a subset of neurons, called "interneurons," experienced a notable uptick in the production of several peptides. This was not surprising in the sense that peptide release is known to be dependent on brain rhythm frequencies, but it was still notable because one peptide in particular, VIP, is associated with Alzheimer's-fighting benefits and helps to regulate vascular cells, blood flow and glymphatic clearance.

Seizing on this intriguing result, the team ran tests that revealed increased VIP in the brains of gamma-treated mice. The researchers also used a sensor of peptide release and observed that sensory gamma stimulation resulted in an increase in peptide release from VIP-expressing interneurons.

But did this gamma-stimulated peptide release mediate the glymphatic clearance of amyloid? To find out, the team ran another experiment: they chemically shut down the VIP neurons. When they did so, and then exposed mice to sensory gamma stimulation, they found that there was no longer an increase in arterial pulsatility and there was no more gamma-stimulated amyloid clearance.

"We think that many neuropeptides are involved," Murdock said. Tsai added that a major new direction for the lab's research will be determining what other peptides or other molecular factors may be driven by sensory gamma stimulation.

Tsai and Murdock added that while this paper focuses on what is likely an important mechanism -- glymphatic clearance of amyloid -- by which sensory gamma stimulation helps the brain, it's probably not the only underlying mechanism that matters. The clearance effects shown in this study occurred rather rapidly but in lab

experiments and clinical studies weeks or months of chronic sensory gamma stimulation have been needed to have sustained effects on cognition.

With each new study, however, scientists learn more about how sensory stimulation of brain rhythms may help treat neurological disorders.

In addition to Tsai, Murdock and Boyden, the paper's other authors are Cheng-Yi Yang, Na Sun, Ping-Chieh Pao, Cristina Blanco-Duque, Martin C. Kahn, Nicolas S. Lavoie, Matheus B. Victor, Md Rezaul Islam, Fabiola Galiana, Noelle Leary, Sidney Wang, Adele Bubnys, Emily Ma, Leyla A. Akay, TaeHyun Kim, Madison Sneve, Yong Qian, Cuixin Lai, Michelle M. McCarthy, Nancy Kopell, Manolis Kellis, Kiryl D. Piatkevich.

Support for the study came from Barbara J. Weedon, Henry E. Singleton, the Hubolow family, Robert A. and Renee E. Belfer, Eduardo Eurnekian, the Ko Hahn family, the Carol and Gene Ludwig Family Foundation, the Halis Family Foundation, Lester A. Gimpelson, the Dolby family, Jay L. and Carroll D. Miller, Lawrence and Debra Hilibrand, David B. Emmes, the Marc Haas Foundation, The Picower Institute for Learning and Memory, The JPB Foundation, and the National Institutes of Health.

Story Source:

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

Journal Reference:

1. Mitchell H. Murdock, Cheng-Yi Yang, Na Sun, Ping-Chieh Pao, Cristina Blanco-Duque, Martin C. Kahn, TaeHyun Kim, Nicolas S. Lavoie, Matheus B. Victor, Md Rezaul Islam, Fabiola Galiana, Noelle Leary, Sidney Wang, Adele Bubnys, Emily Ma, Leyla A. Akay, Madison Sneve, Yong Qian, Cuixin Lai, Michelle M. McCarthy, Nancy Kopell, Manolis Kellis, Kiryl D. Piatkevich, Edward S. Boyden, Li-Huei Tsai. **Multisensory gamma stimulation promotes glymphatic clearance of amyloid**. *Nature*, 2024; DOI: 10.1038/s41586-024-07132-6

2. 遺伝子コードの変化が、ヒトの先祖がなぜ尾を失ったかを説明する可能性 –マウス実験

日付：2024 年 2 月 28 日
ソース：NYU グロスマン医学校
概要：

古代の祖先における遺伝的変化が、人間がサルのような尾を持たない理由の一部を説明するかもしれない、というのが、NYU Grossman School of Medicine の研究者らによる新しい研究の結果だ。
この研究は、尾のない類人猿と人間の DNA を、尾のある猿と比較し、TBXT 遺伝子の挿入を見つけた。この挿入は、サルには存在せず、人間と類人猿で共有されている。研究チームが一連のマウスを調査し、TBXT 遺伝子への挿入が尾に影響を与えるかどうかを調べると、いくつかのマウスが尾なしで生まれるなど、様々な尾の影響が見られた。
この研究は、過去の研究で尾の発達に関連する 100 以上の遺伝子が特定されていたが、尾の喪失は TBXT の突然変異ではなく、類人猿と人間の祖先における DNA コードの変化（突然変異）によって起こったことを発見した。
この研究成果は『Nature』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＞Change in gene code may explain how human anc | EurekAlert!

NEWS RELEASE 28-FEB-2024

Change in gene code may explain how human ancestors lost tails

Mechanism behind change may reveal new role for parts of the genetic code

Peer-Reviewed Publication

NYU LANGONE HEALTH / NYU GROSSMAN SCHOOL OF MEDICINE

IMAGE:

TAIL LOSS IN GORILLAS, CHIMPANZEES, AND HUMANS IS BELIEVED TO HAVE OCCURRED ABOUT 25 MILLION YEARS AGO, WHEN THE GROUP EVOLVED AWAY FROM OLD WORLD MONKEYS.

view more

CREDIT: COURTESY OF NATURE (2024)

A genetic change in our ancient ancestors may partly explain why humans don't have tails like monkeys, finds a new study led by researchers at NYU Grossman School of Medicine.

Published online February 28 as the cover story of the journal *Nature*, the work compared the DNA of tail-less apes and humans to that of tailed monkeys, and found an insertion of DNA shared by apes and humans, but missing in monkeys. When the research team engineered a series of mice to examine whether the insertion, in a gene called *TBXT*, affected their tails, they found a variety of tail effects, including some mice born without tails.

"Our study begins to explain how evolution removed our tails, a question that has intrigued me since I was young," says corresponding study author Bo Xia, PhD, a student at the time of the study in the labs of study senior co-authors Jef D. Boeke, PhD, and Itai Yanai, PhD at NYU Grossman School of Medicine. Xia is now a junior fellow of the Harvard Society of Fellows, and a principal investigator at the Broad Institute of MIT and Harvard.

More than 100 genes had been linked by past work to the development of tails in various vertebrate species, and the study authors hypothesized that tail loss occurred through changes in the DNA code (mutations) of one or more of them. Remarkably, say the study authors, the new study found that the differences in tails came not from TBXT mutations, but instead from the insertion of a DNA snippet called AluY into the gene's regulatory code in the ancestors of apes and humans.

Profound Surprise

The new finding proceeds from the process by which genetic instructions are converted into proteins, the molecules that make up the body's structures and signals. DNA is "read" and converted into a related material in RNA, and ultimately into mature messenger RNA (mRNA), which produces proteins.

In a key step that produces mRNA, "spacer" sections called introns are cut out of the code, but before that guide the stitching together (splicing) of just the DNA sections, called exons, which encode the final instructions. Further, the genomes of vertebrate animals evolved to feature alternative splicing, in which a single gene can code for more than one protein by leaving out or adding exon sequences. Beyond splicing, the human genome grew more complex still by evolving to include "countless" switches, part of the poorly understood "dark matter" that turns on genes at different levels in different cell types.

Still other work has shown that half of this non-gene "dark matter" in the human genome, which lies both between genes and within the introns, consists of highly repeated DNA sequences. Further, most of these repeats consist of retrotransposons, also called "jumping genes" or "mobile elements," which can move around and insert themselves repeatedly and randomly in human code.

Pulling these details together, the "astounding" current study found that the transposon insertion of interest, *AluY*, which affected tail length, had randomly occurred in an intron within the *TBXT* code. Although it did not change a coding portion, the intron insertion, so the research team showed, influenced alternative splicing, something not seen before, to result in a variety of tail lengths. Xia found an *AluY* insertion that remained in the same location within the *TBXT* gene in humans and apes resulted in the production of two forms of *TBXT* RNA. One of these, they theorize, directly contributed to tail loss.

"This finding is remarkable because most human introns carry copies of repetitive, jumping DNAs without any effect on gene expression, but this particular *AluY* insertion did something as obvious as determine tail length," said Boeke, the Sol and Judith Bergstein Director of the Institute for System Genetics at NYU Langone Health.

Tail loss in the group of primates that includes gorillas, chimpanzees, and humans is believed to have occurred about 25 million years ago, when the group evolved away from Old World monkeys, said the authors. Following this evolutionary split, the group of apes that includes present-day humans evolved the formation of fewer tail vertebrae, giving rise to the coccyx, or tailbone. Although the reason for the tail loss is uncertain, some experts propose that it may have better suited life on the ground than in the trees.

Any advantage that came with tail loss was likely powerful, the researchers say, because it may have happened despite coming with a cost. Genes often influence more than one function in the body, so changes that bring an advantage in one place may be detrimental

elsewhere. Specifically, the research team found a small uptick in neural tube defects in mice with the study insertion in the *TBXT* gene.

“Future experiments will test the theory that, in an ancient evolutionary trade-off, the loss of a tail in humans contributed to the neural tube birth defects, like those involved in spinal bifida, which are seen today in one in a thousand human neonates,” said Yanai, also in the Institute for Systems Genetics.

In addition to Xia, Boeke and Yanai, other NYU Langone study authors were Weimin Zhang, Guisheng Zhao, Ran Brosh, Aleksandra Wudzinska, Emily Huang, Hannah Ashe, Gwen Ellis, Maayan Pour, Yu Zhao, Camila Coelho, Yinan Zhu, Alexander Miller, Jeremy Dasen, Matthew Maurano, and Sang Yong Kim. The mouse engineering work was supported by the NYU Langone Health Rodent Genetic Engineering Laboratory (RGEL) led by Dr. Sang Yong Kim. The study was funded by NYU Langone research fund and National Institutes of Health grants RM1HG009491, P01AG051449, DP5OD033430, and R35GM119703, and by NYSTEM predoctoral fellowship C322560GG.

JOURNAL

Nature

DOI

10.1038/s41586-024-07095-8

METHOD OF RESEARCH

Data/statistical analysis

SUBJECT OF RESEARCH

Not applicable

ARTICLE TITLE

On the genetic basis of tail-loss evolution in humans and apes

ARTICLE PUBLICATION DATE

28-Feb-2024

3. AI 分析によると、妊娠中の喫煙は新生児の行動障害のリスクを高める可能性がある –マウス実験

日付：2024 年 3 月 5 日
ソース：信州大学
概要：

信州大学医学部の分子細胞生理学部門の研究者らは、妊娠中の喫煙が新生児の行動障害リスクを増加させる可能性を AI 分析によって予測する研究について『Cells』誌で紹介している。
喫煙が癌、脳卒中、糖尿病などのリスク因子であることは約半世紀前から知られているが、近年の研究では妊娠中のニコチン暴露（PNE）が注意欠陥/多動性障害（ADHD）や自閉症スペクトラム障害（ASD）などの神経発達障害と関連している可能性が示唆されている。
この研究では、マウスを用いて PNE が引き起こす行動の変化を理解するために、AI ベースのシステムが導入された。DeepLabCut と Simple Behavioral Analysis（SimBA）という 2 つのオープンソースツールキットを組み合わせ、マウスの行動実験の映像を自動的に分析した。研究者らは、PNE マウスと対照群の実験を行い、ADHD および ASD の特徴的な行動の指標を探した。
実験結果によると、PNE マウスは対照群に比べて衝動的であり、ADHD 様の特徴を示した。また、迷路実験により、PNE マウスの作業記憶が変化しており、これも ADHD の特徴とされた。更に、広場での実験では、PNE マウスが ASD の特徴である社交行動の欠如と増加した不安を示したとしている。組織学的な分析も行われ、ASD の典型的な特徴である海馬の神経新生の減少が確認された。
AI ベースのシステムによる分析結果は非常に信頼性が高いとされ、将来的には ASD や ADHD などの神経発達障害のメカニズムを理解し、より良い診断ツールや治療法を開発するための手掛かりとなる可能性がある、としている。

研究関連ニュース/他のトップページに戻る

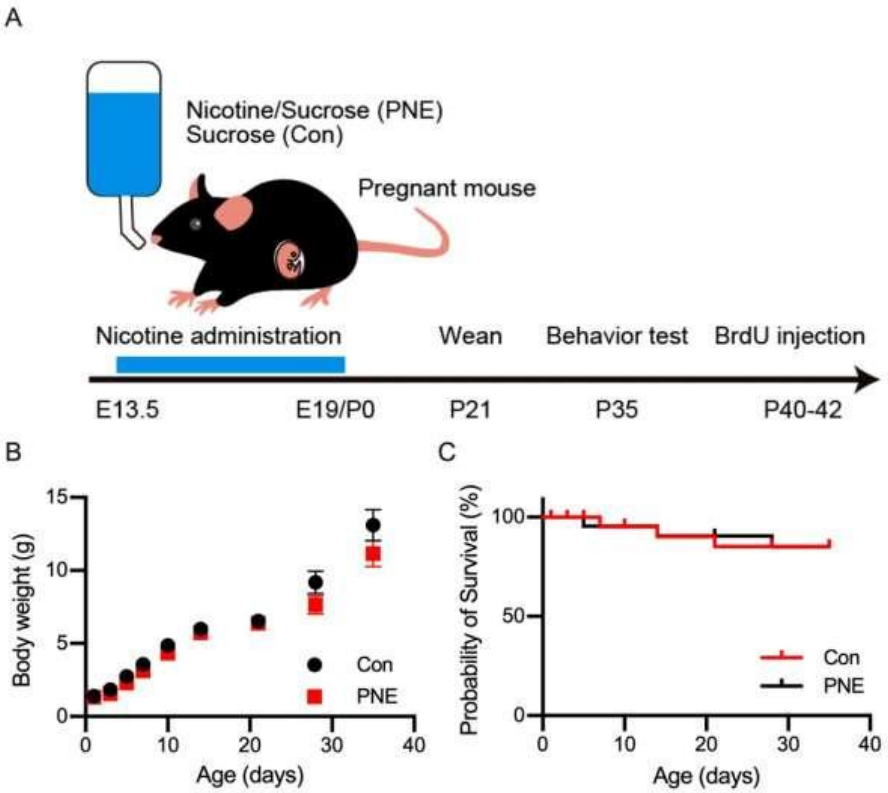
＜英文＞AI analysis predicts smoking during pregnancy may increase the risk of behavioral disorders in newborns (medicalxpress.com)

MARCH 5, 2024

Editors' notes

AI analysis predicts smoking during pregnancy may increase the risk of behavioral disorders in newborns

by Shinshu University



Establishment of nicotine exposure mice and postnatal development. (A): schematic drawing showing the experimental design of the prenatal nicotine exposure (PNE). Water with nicotine and sucrose (PNE), or sucrose only (Con), was supplied to pregnant C57BL/6J mice, starting from embryonic day 14 until delivery, postnatal day 0 (P0). Mothers and pups were supplied with normal drinking water thereafter. (B): the developmental changes in the body weight of PNE (n = 8) and Con (n = 8) pups until the date of the behavioral experiments. A slight decrease in the body weight was observed in PNE mice, but this was not statistically significant. (C): the survival curve of the PNE (n = 24) and Con (n = 24) mice indicated no change in the mortality after prenatal exposure of nicotine.

The fact that smoking is a risk factor for several diseases, including cancer, stroke, and diabetes, has been known for approximately half a century. However, over the past few decades, scientists have brought to light many of the detrimental effects of smoking during pregnancy, linking this habit to high infant mortality, failed delivery, and low body weight at birth.

In addition, recent studies suggest that prenatal nicotine exposure (PNE) may be related to neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

For a long time now, scientists have used animal models (like rodents) to understand how PNE leads to neurodevelopmental disorders. By carefully analyzing the behavior of rodents, they can infer whether PNE is causing neurological changes and the brain regions affected by it; this can later be confirmed through histological analyses.

Unfortunately, thus far, studies on behavioral changes induced by PNE in mice have shown varied results, some of which are contradictory. Although there could be multiple reasons behind these discrepancies, human error and bias are prime suspects. In general, the assessment of complex animal behaviors, especially social interactions, relies on the efforts of human observers, which introduces a baseline level of subjectivity that is hard to dispel.

But what if we can leverage artificial intelligence (AI) to produce more accurate and unbiased results from observations of PNE mice behavior?

In a study published in *Cells*, researchers from the Department of Molecular and Cellular Physiology at the Shinshu University School of Medicine, including graduate student Mengyun Zhou, Assistant Professor Takuma Mori, and Professor Katsuhiko Tabuchi, developed and trained a deep learning-based system to automatically analyze footage from behavioral experiments on mice.

They used this tool to explore the behavioral changes induced by PNE in mice without observer biases, seeking to shed light on the link between nicotine and neurodevelopmental disorders.

The proposed AI-based framework relied on a combination of two well-established open-source toolkits, namely DeepLabCut and Simple Behavioral Analysis (SimBA). "AI tools can label the body parts of animals in markerless video footage and precisely estimate their poses using supervised machine learning," explains Prof. Tabuchi.

"Since animal behaviors are defined as a specific arrangement of body parts over a short period of time, deep-learning toolkits like SimBA can use the pose estimations obtained with DeepLabCut to classify different types of animal behaviors."

After reaching an optimal training protocol for their framework using manually labeled data, the researchers conducted several experiments using PNE and control mice, looking for indicators of ADHD- and ASD-like behaviors.

First, they carried out cliff avoidance reaction tests, which are used to test impulsivity. In these tests, they placed the subject mouse on top of a slightly elevated platform and took note—both manually and with the AI system—of how long the mouse waited before jumping down the platform. The test results suggested that PNE mice are more impulsive, a behavioral feature of ADHD in humans.

They also tested the working memory of mice using a Y-shaped maze and counted the number of times each mouse spontaneously switched from one arm of the maze to another.

"We observed a decrease in the spontaneous alteration in PNE mice, suggesting that their working memory was altered, which is another behavioral feature of ADHD," comments Mengyun Zhou. "These results suggest prenatal exposure to nicotine may cause ADHD in mice, which is consistent with clinical reports in humans."

Finally, the researchers conducted open-field and social-interaction experiments, which represented the main challenge for their AI-based system. In these experiments, the researchers observed either one or two mice behaving freely in a large enclosure and looked for indicators of anxiety and social behaviors, such as grooming and following. Interestingly, PNE mice exhibited social behavioral deficits and increased anxiety, which are features of ASD.

Subsequent histological analysis of hippocampal brain tissue confirmed decreased neurogenesis, a hallmark of ASD. Thus, it appears that smoking may not only increase the risk of ADHD but also ASD.

Worth noting, the results obtained using the AI-based system were highly reliable. Prof. Tabuchi says, "We validated the accuracy of our behavioral analysis framework by drawing a careful comparison between the results generated by the model and behavior assessments made by multiple human annotators, which is considered the gold standard." These analyses cement the potential of the proposed approach and showcase its capabilities for many types of behavioral studies.

With any luck, further efforts will pave the way to a solid understanding of mechanisms behind neurodevelopmental disorders like ASD and ADHD, ultimately leading to better diagnostic tools and therapeutic methods.

More information: Mengyun Zhou et al, Deep-Learning-Based Analysis Reveals a Social Behavior Deficit in Mice Exposed Prenatally to Nicotine, *Cells* (2024). DOI: 10.3390/cells13030275

Provided by Shinshu University

4. マウスモデルで見つかったアルツハイマー病の最も早いバイオマーカーが新しい標的を指摘する可能性

日付：2024 年 3 月 6 日
ソース：イリノイ大学アーバナ・シャンペーン校
概要：

イリノイ大学アーバナ・シャンペーン校の研究者らは、アルツハイマー病のマウスモデルを研究する中で、脳内で特異的な神経タンパク質の急増がアルツハイマー病の最も早い生物学的マーカーであることを報告している。さらに、この増加したタンパク質活性が、神経変性の初期段階に関連する発作を引き起こし、マウスでこのタンパク質を抑制すると発作活動の発症と進行が遅くなった。この神経特異的なタンパク質である PSD-95 は、アルツハイマー病の研究、早期診断、治療の新しい標的となり得ると研究チームは述べている。
この研究は、アミロイド β が脳内でプラークを形成し、神経活動を妨げるアルツハイマー病の進行に関与するタンパク質を生成するマウスを対象に行われた。研究チームは他の研究が報告していないマウスの寿命の早い段階に焦点を当て、アルツハイマー病の他のマーカーや異常が報告されていない時期を対象とした。
彼らの研究結果は、『EMBO Reports』誌に掲載されている。
今後は、マウスの研究結果が人間の患者サンプルと相関するかどうかを検証し、PSD-95 が他の病状や疾患の進行段階にどのような役割を果たすか調査する予定だとしている。

研究関連ニュース/他のトップページに戻る

＜英文＞Earliest-yet Alzheimer's biomarker found in mouse model could point to new targets | ScienceDaily

Earliest-yet Alzheimer's biomarker found in mouse model could point to new targets

Date:

March 6, 2024

Source:

University of Illinois at Urbana-Champaign, News Bureau

Summary:

A surge of a neural-specific protein in the brain is the earliest-yet biomarker for Alzheimer's disease, report researchers studying a mouse model of the disease. Furthermore, the increased protein activity leads to the seizures associated with the earliest stages of neurodegeneration, and inhibiting the protein in the mice slowed

the onset and progression of seizure activity. The neural-specific protein, PSD-95, could pose a new target for Alzheimer's research, early diagnosis and treatment.

FULL STORY

A surge of a neural-specific protein in the brain is the earliest-yet biomarker for Alzheimer's disease, report University of Illinois Urbana-Champaign researchers studying a mouse model of the disease. Furthermore, the increased protein activity leads to the seizures associated with the earliest stages of neurodegeneration, and inhibiting the protein in the mice slowed the onset and progression of seizure activity.

The neural-specific protein, PSD-95, could pose a new target for Alzheimer's research, early diagnosis and treatment, said study leader Nien-Pei Tsai, an Illinois professor of molecular and integrative physiology.

Tsai's group studies mice that make more of the proteins that form amyloid-beta, which progressively aggregates in Alzheimer's disease to form plaques in the brain that hamper neural activity.

However, in the new work, the group focused on a time frame much earlier in the mouse lifespan than others have studied -- when no other markers or abnormalities have been reported, Tsai said.

"We were thinking, if we can catch anything that is happening early enough, maybe we can find a way to diagnose the disease earlier or slow down the progression," Tsai said.

"We know that Alzheimer's is irreversible. But if we can slow down the progression or even delay the onset of the disease, we can improve the quality of life for patients."

While watching early neural development, first in neuron cultures and then in live mice, the researchers saw an elevation in PSD-95 levels.

The PSD-95 protein's job is to attract and pull other receptors to the synaptic surface -- the space where two neurons pass signals to one another.

"Our data suggests that the elevated PSD-95 is contributing to hyperexcitability in the brain. That's a common phenotype is some of the early stages of Alzheimer's disease patients: They tend to have hyperexcitability or elevated seizure susceptibility in the brain, preceding and exacerbating the neurodegeneration that follows," said Tsai, who also is affiliated with the Beckman Institute of Advanced Science and Technology at the U. of I.

To confirm that increased PSD-95 was a driving force behind the seizure activity, the researchers inhibited PSD-95 in a mouse cohort.

They saw reduced receptor activity at the synapse, fewer seizures in the mice and reduced mortality from seizures.

"Our findings show that PSD-95 is a critical contributor to the hyperexcitability in the earliest stages of Alzheimer's. So we think that PSD-95 can be an early biomarker to indicate that a patient could have Alzheimer's disease or elevated seizure susceptibility. In terms of treatment, antibody inhibitors for PSD-95 could be useful in the early onset of Alzheimer's, with more clinical study."

The group published its findings in the journal *EMBO Reports*.

The researchers hope to partner with clinical research teams to determine whether their findings in mice correlate with samples from human patients.

They also plan to study other receptors that PSD-95 interacts with on the synaptic surface to see if it plays a role in other symptoms of the disease or stages of its progression.

"For example, the NMDA receptor has been shown to contribute to neural cell death in Alzheimer's disease. So we're trying to see whether by inhibiting PSD-95, we also can inhibit this particular NMDA receptor to slow down cell death."

The National Institutes of Health and the Alzheimer's Association supported this work.

The National Institute of Health supported this work through grants R01NS105615, R01MH124827 and R21AG071278.

Story Source:

Materials provided by **University of Illinois at Urbana-Champaign, News Bureau**. Original written by Liz Ahlberg Touchstone. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yeeun Yook, Kwan Young Lee, Eunyoung Kim, Simon Lizarazo, Xinzhu Yu, Nien-Pei Tsai. **Hyperfunction of post-synaptic density protein 95 promotes seizure response in early-stage aβ pathology**. *EMBO Reports*, 2024; DOI: 10.1038/s44319-024-00090-0

5. 母親の肥満が肝癌を促進する可能性 –マウス実験

日付：2024 年 3 月 12 日
ソース：ジュネーブ大学
概要：

2030 年までに特定の先進国の人口の 50%に達する可能性のある肥満は、主要な公衆衛生上の懸念である。それはそれ自体が健康に影響を与えるだけでなく、その子孫にも深刻な影響を与える可能性がある。ジュネーブ大学（UNIGE）とジュネーブ大学病院（HUG）の科学者らは、3 月 12 日に『JHEP Reports』誌に発表した研究において、母親の肥満は子供の肝臓疾患や肝癌のリスクを高める可能性があることが明らかにしている。
科学者らは 2 つのグループの雌マウスを研究した。1 つは脂肪と糖分が豊富な食餌を与えられ、すぐに肥満になった。2 番目のグループは通常通りに給餌された。彼女らの全ての子孫は通常の食餌を与えられ、肥満にはならなかった。従って、唯一の違いは、最初のグループの母親の肥満であった。
結果として、母親の肥満が子供の肝臓疾患のリスクを高めることが分かり、その主な原因の 1 つは母親からの異常な腸内細菌叢の伝播であることが示された。このリスクは、後に癌につながる可能性があることも示唆されている。ただし、これらの結果はまだ人間での確認が必要であり、子供への肥満の悪影響を制限するための警告と行動の呼びかけとなっている。

研究関連ニュース/他のトップページに戻る

＜英文＞Maternal obesity may promote liver cancer | ScienceDaily

Maternal obesity may promote liver cancer

Date:

March 12, 2024

Source:

Université de Genève

Summary:

Obesity, which could reach 50% of the population in certain developed countries by 2030, is a major public health concern. It not only affects the health of those who suffer from it, but could also have serious consequences for their offspring. Scientists have studied the impact of maternal obesity on the risk of developing liver disease and liver cancer. Using an animal model, the team discovered that this risk was indeed much higher in the offspring of mothers suffering from obesity.

FULL STORY

Obesity, which could reach 50% of the population in certain developed countries by 2030, is a major public health concern. It not only affects the health of those who suffer from it, but could also have serious consequences for their offspring. Scientists at the University of Geneva (UNIGE) and the Geneva University Hospitals (HUG) have studied the impact of maternal obesity on the risk of developing liver disease and liver cancer. Using an animal model, the team discovered that this risk was indeed much higher in the offspring of mothers suffering from obesity. One of the main causes was the transmission of a disturbed intestinal microbiota from the mother, resulting in a chronic liver disease whose effects became apparent in adulthood. These results, which have yet to be confirmed in humans, are a warning signal and a call for action to limit the deleterious effect of obesity on children. This research is published in the journal *JHEP Reports*.

The scientific community suspects that maternal obesity disrupts the metabolic balance of the unborn child, and even increases the risk of childhood cancer and colorectal cancer.

But to what extent? "We wanted to understand whether the children of mothers suffering from obesity were at greater risk of developing liver diseases, and by what biological mechanisms," explains Christian Toso, full professor at the UNIGE Faculty of Medicine and director of the Division of digestive surgery at the HUG, who led this research.

"Indeed, while the risk of liver cancer due to a hepatic virus is decreasing, obesity-related liver diseases are constantly on the rise."

The scientists studied two groups of female mice: the first fed with a diet rich in fat and sugar -- similar to junk food -- which rapidly became obese.

The second -- the control group -- was fed normally. All their offspring were fed with a normal diet and were not overweight.

The only difference was therefore the maternal obesity of the first group.

"At 20 weeks, which corresponds to adulthood in humans, we could not detect any notable differences," explains Beat Moeckli, junior staff surgeon and researcher in professor Toso's team, the first author of this work.

"However, at 40 weeks, a senior age in mice, the liver health of the first group began to deteriorate.

All the parameters of liver disease -- fat deposits, fibrosis, and inflammation -- were significantly higher in the offspring of mothers suffering from obesity.

And these are the main risk factors for liver cancer in humans".

From disease to cancer: the role of microbiota

To confirm whether these mice had a higher risk of developing liver cancer, the team injected two groups of these mice with an oncogenic product just after weaning.

And indeed, the offspring of obese mothers had an 80% risk of developing cancer, compared with 20% for the control group.

"The mother's obesity thus has an impact long after the birth of its offspring, which seem to inherit a dysfunctional microbiota despite their own living conditions," analyses Beat Moeckli.

"Obesity alters the composition and diversity of the mother's microbiota, which is passed on to the next generation and persists throughout life".

However, by placing mice from both groups in the same cage, the scientists observed a normalisation of the microbiota.

As mice are coprophagous (they eat their faeces), they quickly share the same microbiotic strains.

Bacterial diversity then increased, favouring the good bacteria.

As a result, the healthy microbiota naturally regains the upper hand, and the marker of liver disease dramatically decreased.

"We see a clear effect of the microbiota on the risk of developing liver cancer, indicating its central role in transmitting the risk of disease from mother to child."

The junk food diet encourages the proliferation of bad bacteria and reduces bacterial diversity.

This altered microbiota, transmitted at birth, then leads to greater inflammation in the liver and, over time, generates fibrosis and steatosis (an excessive presence of fat), which in turn increase the risk of developing liver cancer.

Normalising the microbiota also normalises the risk of cancer.

And in humans?

These data come from a study on an animal model, in a highly controlled environment. To be applied in a clinical context, they need to be confirmed in humans under real-life conditions. The first stage will consist of an epidemiological study based on large bodies of data obtained from following mothers and their children over several decades. "However, we already know that it is possible to modify the microbiota, for instance by using probiotics. "Having highlighted the importance of the microbiome represents a first step towards new therapies," the scientists conclude.

Story Source:

Materials provided by **Université de Genève**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Beat Moeckli, Vaihere Delaune, Benoît Gilbert, Andrea Peloso, Graziano Oldani, Sofia El Hajji, Florence Slits, Joana Rodrigues Ribeiro, Ruben Mercier, Adrien Gleyzolle, Laura Rubbia-Brandt, Quentin Gex, Stephanie Lacotte, Christian Toso. **Maternal obesity increases the risk of hepatocellular carcinoma through the transmission of an altered gut microbiome**. *JHEP Reports*, 2024; 101056 DOI: 10.1016/j.jhepr.2024.101056

6. 質の低い睡眠と片頭痛発作との関連性 –マウス実験

日付:2024 年 3 月 13 日
ソース:アリゾナ大学健康科学部
概要:

3 月 13 日に『Brain Communications』誌に発表されたアリゾナ大学健康科学部の新しい研究では、睡眠の質の低さと片頭痛の発作との関連性が特定され、睡眠の質を改善することが片頭痛を持つ人の発作を軽減する可能性があることが示唆されている。
今まで、片頭痛が睡眠の質を低下させるのか、逆に睡眠の質が低いために片頭痛が引き起こされるのかは分かっていなかった。
この研究では、研究チームがマウスの前臨床モデルを使用して睡眠の障害を評価した。マウスの睡眠構造は人のものに密接に似ており、深い睡眠、REM 睡眠、軽い睡眠のサイクルを含む。睡眠は脳波記録と視覚的な観察で評価された。
研究者は、マウスが睡眠不足の場合、片頭痛のような痛みを経験する可能性が高まることを発見したが、片頭痛のような痛みが通常の睡眠を乱すことはなく、睡眠不足によって、片頭痛患者では、片頭痛発作の可能性が高まることを発見した。
この研究から、睡眠の質を改善することが片頭痛発作の頻度を減少させる可能性があることが示唆されている。
この研究から、片頭痛患者は寝る前に電子デバイスの使用を制限し、その他の睡眠の健康に関するアドバイスに従うことが、片頭痛発作の発生の可能性を制限する簡単な方法である、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＞Poor sleep linked to migraine attacks | ScienceDaily

Poor sleep linked to migraine attacks

Date:

March 13, 2024

Source:

University of Arizona Health Sciences

Summary:

A new study has identified a link between poor sleep and migraine attacks that suggests improving sleep health may diminish migraine attacks in people with migraine.

FULL STORY

A new study by researchers at the University of Arizona Health Sciences identified a link between poor sleep and migraine attacks that suggests improving sleep health may diminish migraine attacks in people with migraine.

Many people with migraine report having sleeping disorders, including insomnia, trouble falling or staying asleep, poor sleep quality, excessive daytime sleepiness, waking up from sleep and being forced to sleep because of a migraine headache.

Until now, it was unknown whether migraine causes poor sleep or vice versa.

"It has been recognized for quite a long time that there is a relationship between sleep and migraine," said principal investigator Frank Porreca, PhD, research director for the Comprehensive Center for Pain & Addiction and professor of pharmacology at the UArizona College of Medicine -- Tucson.

"The way it has been investigated in the past has been through patient-reported information, which is subjective. We quantitatively measured sleep in preclinical models and found that migraine-like pain does not influence sleep, but if you have disrupted sleep, your chances of having a migraine attack if you're a migraine patient are much higher."

Porreca led a research team that used preclinical mouse models to evaluate sleep disruption, as the sleep architecture of mice closely matches that of people, including cycles of deep sleep, REM sleep and light sleep.

Sleep was assessed using electroencephalogram recordings and visual observations.

Researchers found that when mice were sleep deprived, they were more likely to experience migraine-like pain, but migraine-like pain did not disrupt normal sleep.

Porreca noted that sleep deprivation can happen for many reasons, including stress.

For this study, the research team ensured they were studying the effect of sleep, and not stress, on migraine by giving mice novel objects to explore to keep them awake.

"Mice are compelled to explore novel objects. They just have to go and look," Porreca said.

"It reminds me of how teenagers are often sleep deprived because they're on their phones. Anybody who studies sleep will tell you that from a sleep hygiene point of view, you don't want any devices in your bedroom where you're trying to sleep."

For people with migraine, limiting the use of electronic devices before bedtime and following other sleep health tips could be an easy way to limit the likelihood of migraine attacks.

"Early morning is one of the most common times people experience migraine attacks," Porreca said.

"Migraine is highly female prevalent -- it's 3 to 1, women to men -- and almost all the women are of childbearing age. Many people with migraine probably have children. They wake up with a migraine attack and are immediately stressed. They don't have time to take care of themselves, they have to get the kids ready for school and they have to get ready for work. That migraine attack is happening in the worst time of the day for function. Improved sleep is critically important and probably would diminish the frequency of migraine attacks."

The American Migraine Foundation estimates more than 39 million people in the U.S. live with migraine, though that number is probably higher due to the number of people who do not get a diagnosis or treatment.

Story Source:

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

Journal Reference:

1. Robson C Lillo Vizin, Caroline M Kopruszinski, Paula M Redman, Hisakatsu Ito, Jill Rau, David W Dodick, Edita Navratilova, Frank Porreca. **Unraveling the directional relationship of sleep and migraine-like pain**. *Brain Communications*, 2024; 6 (2) DOI: 10.1093/braincomms/fcae051

7. 安全で高度に効果的な癌免疫療法へ向けた DNA オリガミベースのワクチン –マウス実験

広範囲に適用可能なワクチンプラットフォームにより、アジュバント分子と様々な抗原のナノメートル単位の精密な間隔による抗腫瘍反応が向上

日付：2024 年 3 月 15 日
ソース：ハーバード大学バイオロジカルインスパイアードエンジニアリング Wyss 研究所
概要：

治療用癌ワクチンは、患者の癌細胞を破壊するだけでなく、癌の再発や拡散を防ぐ可能性がある免疫療法の一形態である。複数の治療用癌ワクチンが臨床試験で研究されているものの、臨床の癌専門医によってまだ一般的に使用されていない。治療用癌ワクチンの中心成分は抗原であり、これらは腫瘍細胞によって優先的に産生されるか新たに産生される（新抗原）もので、患者の免疫系に癌細胞を検索して破壊する機能を与える。ほとんどの場合、これらの抗原は単独では作用せず、抗原提示細胞（APC）として知られる免疫細胞内で一般的な警告信号を引き起こすアジュバント分子の助けが必要だ。APC は、抗原とアジュバント分子の両方を取り込み、さまざまなタイプの T 細胞に抗原を提示する。これらの T 細胞は、腫瘍に対する即時の攻撃を開始したり、将来の防御のために腫瘍の長期的な免疫記憶を保存したりする。がんワクチンの効果は、そのアジュバントが APC に対してどれだけのレベルと期間で「警告」を鳴らすかに依存する。
以前の研究では、DNA オリガミなどのナノ構造体を使用してアジュバント分子と抗原分子を同時に APC に送達することが APC の活性化を増加させることがわかった。しかし、これらのアプローチのいずれも、アジュバント分子の数やナノスケールでの配列が下流の腫瘍指向の免疫にどのように影響するかを系統的に調査していなかった。
今回、ハーバード大学 Wyss 工学研究所の研究者らが、DNA オリガミプラットフォームである DoriVac を作成。DoriVac ワクチンは、腫瘍を持つマウスが腫瘍の成長を制御し、対照群のマウスよりもかなり長く生存することを可能にした。この研究は、ナノ精度でアジュバント分子とさまざまな抗原の間隔を調整することで、腫瘍に対する強化された抗腫瘍反応を実現する幅広く適用可能なワクチンプラットフォームを提供する、としている。
DoriVac は、CpG として知られるアジュバントの分子を正確に 3.5 ナノメートル間隔で配置した場合、最も有益な免疫細胞（抗腫瘍性の T 細胞を含む）を誘導する抗原提示細胞（APC）の刺激をもたらす、としている。
この研究は、『Nature Nanotechnology』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＞DNA origami-based vaccines toward safe and highly-effective precision cancer immunotherapy | ScienceDaily

DNA origami-based vaccines toward safe and highly-effective precision cancer immunotherapy

Broadly applicable vaccine platform enables enhanced anti-tumor responses through nanometer-precise spacing of adjuvant molecules and a variety of antigens

Date:

March 15, 2024

Source:

Wyss Institute for Biologically Inspired Engineering at Harvard

Summary:

Researchers have created a DNA origami platform called DoriVac, whose core component is a self-assembling square block-shaped nanostructure. DoriVac vaccines enabled tumor-bearing mice to better control the growth of tumors and to survive significantly longer than control mice.

FULL STORY

Therapeutic cancer vaccines are a form of immunotherapy in the making that could not only destroy cancer cells in patients, but keep a cancer from coming back and spreading. Multiple therapeutic cancer vaccines are being studied in clinical trials, but despite their promise, they are not routinely used yet by clinical oncologists to treat their patients.

The central ingredient of therapeutic cancer vaccines is antigens, which are preferentially produced or newly produced (neoantigens) by tumor cells and enable a patient's immune system to search and destroy the cancerous cells. In most cases, those antigens cannot act alone and need the help of adjuvant molecules that trigger a general alarm signal in immune cells known as antigen-presenting cells (APCs). APCs internalize both antigen and adjuvant molecules and present the antigens to different types of T cells. Those T cells then launch an immediate attack against the tumor, or preserve a longer-lasting memory of the tumor for future defense.

A cancer vaccine's effectiveness depends on the level and duration of the "alarm" its adjuvants can ring in APCs. Previously, researchers found that delivering adjuvant and antigen molecules to APCs simultaneously using nanostructures like DNA origami can increase APC activation. However, none of these approaches systematically investigated how the number and nanoscale arrangement of adjuvant molecules affect downstream tumor-directed immunity.

Now, a research team at the Wyss Institute at Harvard University, Dana-Farber Cancer Institute (DFCI), Harvard Medical School (HMS), and Korea Institute of Science and Technology (KIST) has created a DNA origami platform called DoriVac, whose core component is a self-assembling square block-shaped nanostructure. To one face of the square block, defined numbers of adjuvant molecules can be attached in highly tunable, nanoprecise patterns, while the opposite face can bind tumor antigens. The study found that molecules of an adjuvant known as CpG spaced exactly 3.5 nanometers apart from each other resulted in the most beneficial stimulation of APCs that induced a highly-desirable profile of T cells, including those that kill cancer cells (cytotoxic T cells), those that cause beneficial inflammation (Th-1 polarized T cells), and those that provide a long-term immune memory of the tumor (memory T cells). DoriVac vaccines enabled tumor-bearing mice to better control the growth of tumors and to survive significantly longer than control mice. Importantly, the effects of DoriVac also synergized with those of immune checkpoint inhibitors, which are a highly successful immunotherapy that is already widely used in the clinic. The findings are published in *Nature Nanotechnology*.

"DoriVac's DNA origami vaccine technology merges different nanotechnological capabilities that we have developed over the years with an ever-deepening knowledge about cancer-suppressing immune processes," said Wyss Core Faculty member William Shih, Ph.D., who led the Wyss Institute team together with first-author Yang (Claire) Zeng, M.D., Ph.D.. "We envision that in the future, antigens identified in patients with different types of tumors could be quickly loaded onto prefabricated, adjuvant-containing DNA origami to enable highly effective personalized cancer vaccines that can be paired with FDA-approved checkpoint inhibitors in combination therapies." Shih is also a Professor at HMS and DFCI's Department of Cancer Biology and, as some of the other authors, a member of the NIH-funded cross-institutional "Immuno-engineering to Improve Immunotherapy" (*i3*) Center based at the Wyss.

DNA origami rationale

The CpG adjuvant is a synthetic strand of DNA made up of repeated CpG nucleotide motifs that mimic the genetic material from immune cell-invading bacterial and viral pathogens. Like its natural counterparts, CpG adjuvants bind to a "danger receptor" called TLR9 in immune cells, which in turn induces an inflammatory (innate) immune response that works in concert with the antigen-induced (adaptive) immune response.

"We knew from previous work that to trigger strong inflammatory responses, TLR9 receptors need to dimerize and aggregate into multimeric complexes binding to multiple CpG molecules. The nanoscale distances between the CpG-binding domains in effective TLR9 assemblies revealed by structural analysis fell right into the range of what we hypothesized we could mirror with DNA origami structures presenting precisely spaced CpG molecules," explained Zeng, who was an Instructor in Medicine at the time of the study and now is a senior scientist at DFCI and Harvard Medical School (HMS). In addition to Shih, Zeng was also mentored on the project by senior authors Ju Hee Ryu, Ph.D., a Principal Researcher at KIST, and Wyss Founding Core Faculty member David Mooney, Ph.D., who also is Professor at Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS), and one of the *i3* Center's Principal Investigators.

Zeng and the team fabricated DoriVac vaccines in which different numbers of CpG strands were spaced at 2.5, 3.5, 5, or 7 nanometers apart from each other on one face of the square block, and a model antigen was attached to the opposite face. They protected their structures from being degraded in the body using a chemical modification method that Shih's group had developed earlier. When internalized by different types of APCs, including dendritic cells (DCs), which orchestrate tumor-directed T cell responses, the DoriVac vaccines improved the uptake of antigens compared to controls consisting of free antigen molecules. A CpG spacing of 3.5 nanometers produced the strongest and most beneficial responses in APCs, and significantly outperformed a control vaccine containing only free CpG molecules. "We were excited to find that the DoriVac vaccine preferentially induced an immune activation state that supports anti-tumor immunity, which is what researchers generally want to see in a good vaccine," said Zeng.

Besides spacing, the numbers of CpG molecules in DoriVac vaccines also mattered. The team tested vaccines containing between 12 to 63 optimally spaced CpG molecules and found that 18 CpG molecules provided the best APC activation. This meant that their approach can also help limit the dosage of CpG molecules and thus minimize commonly observed toxic side effects observed with adjuvants.

Gained in (tumor) translation

Importantly, these *in vitro* trends translated to *in vivo* mouse tumor models. When prophylactically injected under the skin of mice, DoriVac vaccines accumulated in the closest lymph nodes where they stimulated DCs. A vaccine loaded with a melanoma antigen prevented the growth of subsequently injected aggressive melanoma cells. While all control animals had succumbed to the cancer by day 42 of the experiment, DoriVac-protected animals all were alive. DoriVac vaccines also inhibited tumor growth in mice in which the formation of melanoma tumors was already underway, with a 3.5 nanometer spacing of 18 CpG molecules again providing maximum effects on DC and T cells, and the strongest reduction in tumor growth.

Next, the team asked whether DoriVac vaccines could also boost immune responses produced by small "neoantigens" emerging in melanoma tumors. Neoantigens are ideal targets because they are exclusively made by tumor cells. However, they often are not very immunogenic themselves, which make highly effective adjuvants an important component in neoantigen vaccines. A DoriVac vaccine customized with four neoantigens enabled the researchers to significantly suppress growth of the tumor in mice that produced the neoantigens.

Finally, the researchers asked whether DoriVac could synergize with immune checkpoint therapy, which reactivates T cells that have been silenced in tumors. In mice, the two therapies combined resulted in the total regression of melanoma tumors, and prevented them from growing back when the animals were exposed to the same tumor cells again four months later. The animals had built up an immune memory of the tumor. The team obtained a similar vaccination efficiency in a mouse lymphoma model.

"We think that DoriVac's value for determining a sweet spot in adjuvant delivery and enhancing the delivery and effects of coupled antigens can pave the way to more effective clinical cancer vaccines for use in patients with a variety of cancers," said Zeng. The team is currently translating the DoriVac platform toward its clinical application, which is supported by the study's assessment of vaccine distribution and

vaccine-directed antibodies in mice, as well as cytokines produced by immune cells in response to the vaccines *in vivo*.

"The DoriVac platform is our first example of how our pursuit of what we call Molecular Robotics -- synthetic bioinspired molecules that have programmable shape and function -- can lead to entirely new and powerful therapeutics. This technology opens an entirely new path for development of designer vaccines with properties tailored to meet specific clinical challenges. We hope to see its rapid translation into the clinic," said Wyss Institute Founding Director Donald Ingber, M.D., Ph.D., who is also the *Judah Folkman Professor of Vascular Biology* at HMS and Boston Children's Hospital, and the *Hansjörg Wyss Professor of Bioinspired Engineering* at SEAS.

Other authors on the study are Olivia Young, Christopher Wintersinger, Frances Anastassacos, James MacDonald, Giorgia Isinelli, Maxence Dellacherie, Miguel Sobral, Haiqing Bai, Amanda Graveline, Andyna Vernet, Melinda Sanchez, Kathleen Mulligan, Youngjin Choi, Thomas Ferrante, Derin Keskin, Geoffrey Fell, Donna Neuberg, Cathrine Wu, and Ick Chan Kwon. The study was funded by the Wyss Institute's Validation Project and Institute Project programs, Claudia Adams Barr Program at DFCI, Korean Fund for Regenerative Medicine (award #21A0504L1), Intramural Research Program of KIST (award #2E30840), and National Institutes of Health (under the i3 Center supporting U54 grant (award #CA244726-01).

Story Source:

Materials provided by **Wyss Institute for Biologically Inspired Engineering at Harvard**. Original written by Benjamin Boettner. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yang C. Zeng, Olivia J. Young, Christopher M. Wintersinger, Frances M. Anastassacos, James I. MacDonald, Giorgia Isinelli, Maxence O. Dellacherie, Miguel Sobral, Haiqing Bai, Amanda R. Graveline, Andyna Vernet, Melinda Sanchez, Kathleen Mulligan, Youngjin Choi, Thomas C. Ferrante, Derin B. Keskin, Geoffrey G. Fell, Donna Neuberg, Catherine J. Wu, David J. Mooney, Ick Chan Kwon, Ju Hee Ryu, William M. Shih. **Fine tuning of CpG spatial distribution with DNA origami for improved cancer vaccination**. *Nature Nanotechnology*, 2024; DOI: 10.1038/s41565-024-01615-3

8. 老化した免疫系を活性化させ、ワクチンへの反応を改善するためのマウス研究

日付：2024 年 3 月 27 日
ソース：スタンフォード大学医学部
概要：

老化した免疫系の人は新型ウイルスと戦うのが難しく、ワクチンへの反応も弱い。
今回、『Nature』誌に掲載されたスタンフォード大学医学部と国立衛生研究所ロッキーマウンテン研究所によるマウスでの研究が、あるタイプの免疫細胞の組成を調節する一度の治療で高齢者の免疫系を活性化させることがいつか可能になるかもしれないことを示す誘惑的な証拠を提供している。
この治療は、老齢マウスの免疫系が新しいウイルスに直接立ち向かう能力を著しく改善し、またワクチンに活発に反応する能力を高め、数ヶ月後に新たな脅威と戦うことを可能にした。
対象となる細胞は、造血幹細胞（HSC）のサブセット。HSC は免疫系の祖先であり、B 細胞や T 細胞を含むすべての他の種類の血液と免疫細胞を生み出します。歳をとるにつれて、私たちの HSC はリンパ球と呼ばれる他の免疫細胞よりも、骨髄性細胞と呼ばれる他の免疫細胞の生成を好むようになります。この変化は、新しいウイルスや細菌の脅威に完全に反応する能力を妨げ、若い人よりもワクチンへの反応がはるかに劣るようになる。
研究者らは、年齢が 18～24 ヶ月（マウスの世界ではふらつく年齢）のマウスに、骨髄性細胞を標的とした抗体を投与することで、バランスのとれた HSC を増やし、新しい未熟な B 細胞と T 細胞を増やすことができるかどうかを検証した。この投与により、未処理の動物よりも数週間後に、バランスのとれた HSC と未熟な B 細胞と T 細胞が増加した。また、この治療は、高齢免疫系が新しい病原体に対処する際に発生することがある炎症など、いくつかの負の結果も減少させた。
さらに、研究者らは、マウスと人間の骨髄性細胞が類似しているため、将来的には同様の技術を使用して高齢の人間の免疫系を活性化させ、新しい感染症に対する脆弱性を減少させ、ワクチンへの反応を改善することが可能になるかもしれない、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞Old immune systems revitalized in mouse study, improving vaccine response | ScienceDaily

Old immune systems revitalized in mouse study, improving vaccine response

Date:

March 27, 2024

Source:

Stanford Medicine

Summary:

Those with aging immune systems struggle to fight off novel viruses and respond weakly to vaccination. Researchers were able to revitalize the immune system in mice.

FULL STORY

Planes, trains, boats, automobiles and even feet. During the past decades and centuries, global travel and human migration have made all of us more worldly -- from our broadening awareness of the world beyond our birthplaces, to our more sophisticated palates, to our immune systems that are increasingly challenged by unfamiliar bacteria and viruses.

In the elderly, these newly imported pathogens can gain the upper hand frighteningly quickly. Unfortunately, however, vaccination in this age group isn't as effective as it is in younger people.

Now a study conducted in mice by Stanford Medicine and the National Institute of Health's Rocky Mountain Laboratories provides tantalizing evidence that it may one day be possible to rev up an elderly immune system with a one-time treatment that modulates the composition of a type of immune cell.

The treatment significantly improved the ability of geriatric animals' immune systems to tackle a new virus head on, as well as to respond vigorously to vaccination -- enabling them to fight off a new threat months later.

"This is a real paradigm shift -- researchers and clinicians should think in a new way about the immune system and aging," said postdoctoral scholar Jason Ross, MD, PhD. "The idea that it's possible to tune the entire immune system of millions of cells simply by affecting the function of such a rare population is surprising and exciting."

Ross and Lara Myers, PhD, a research fellow at Rocky Mountain Laboratories, are the lead authors of the study, which will be published March 27 in *Nature*. Irving Weissman, MD, professor of pathology and of developmental biology, and Kim Hasenkrug, PhD, the chief of Rocky Mountain Laboratories' Retroviral Immunology Section, are the senior authors of the research.

A shift in the immune system

The targeted cells are a subset of what's known as hematopoietic stem cells, or HSCs. HSCs are the granddaddies of the immune system, giving rise to all the other types of blood and immune cells including B and T cells, which are collectively

known as lymphocytes. As we age, our HSCs begin to favor the production of other immune cells called myeloid cells over lymphocytes. This shift hampers our ability to fully react to new viral or bacterial threats and makes our response to vaccination much less robust than that of younger people.

"Older people just don't make many new B and T cell lymphocytes," said Weissman, who is the Virginia and D.K. Ludwig Professor in Clinical Investigation in Cancer Research. "During the start of the COVID-19 pandemic it quickly became clear that older people were dying in larger numbers than younger people. This trend continued even after vaccinations became available. If we can revitalize the aging human immune system like we did in mice, it could be lifesaving when the next global pathogen arises."

Weissman was the first to isolate HSCs in mice and humans in the late 1980s. In the years since, he and his colleagues have investigated the molecular minutiae of these cells, painstakingly tracing the complicated relationships among the scores of cell types that arise in their wake.

Some of these descendants make up what's known as the adaptive immune system: highly specialized B and T lymphocytes that each recognize just one particular three-dimensional structure -- perhaps a pointy bit here or a telltale knobby clump there -- that betrays an invading virus or bacteria. Like trained assassins once they spot their mark, B lymphocytes churn out antibodies that latch onto the telltale structures and target infected or foreign cells for destruction, while various subtypes of T lymphocytes either demolish infected cells or raise a hue and cry to summon other immune cells to finish off the enemy.

The specificity of the B and T lymphocytes allows the immune system to have memory; once you've been exposed to a specific invader, the body reacts swiftly and decisively if that same pathogen is seen again. This is the basic concept behind vaccination -- trigger an initial response to a harmless mimic of a dangerous bacteria or virus. In response, the lymphocytes that recognize the invader not only give rise to cells that eliminate the infection but also generate long-lived memory B and T cells that, in some cases, can last a lifetime. Thus, the system is primed when the threat becomes real.

Another key part of our immune system is called innate immunity, and it's much less discriminating. In the blood, it's run by a class of cells called myeloid cells. Like school janitors, these cells scour the body, gobbling up any unfamiliar cells or bits of detritus. They also trigger inflammatory responses, which recruit other cells and chemicals to infected sites. Inflammation helps the body protect itself against invaders, but it can be a major problem when triggered inappropriately or overenthusiastically, and aging has been linked to chronic inflammation in humans.

An evolutionary disadvantage

Ross and Weissman knew from previous research that during aging, the number of HSCs that make balanced proportions of lymphocytes and myeloid cells decline, while those that are myeloid-biased increase their numbers. This favors the production of myeloid cells. Early in human history, when people rarely left their birthplace and lived shorter lives, this gradual change probably had no consequences (it may even have been favorable) because people were likely to

encounter all their surrounding pathogens by young adulthood and be protected by their memory lymphocytes. But now it's distinctly disadvantageous.

The researchers wondered if they could tilt the balance back toward a younger immune system by depleting myeloid-leaning HSCs and allowing the more balanced HSCs to replace them. Their hunch was correct. Mice between 18 and 24 months old (doddering in the mouse world) that were treated with an antibody targeting the myeloid-leaning HSCs for destruction had more of the balanced HSCs -- and more new, naïve B and T lymphocytes -- than their untreated peers even several weeks later.

"These new, naïve lymphocytes provide better immune coverage for novel infections like those humans increasingly encounter as our world becomes more global," Weissman said. "Without this renewal, these new infectious agents would not be recognized by the existing pool of memory lymphocytes."

The treatment also reduced some negative outcomes like inflammation that can arise when an elderly immune system grapples with a new pathogen.

"Not only did we see a shift toward cells involved in adaptive immunity, but we also observed a dampening in the levels of inflammatory proteins in the treated animals," Ross said. "We were surprised that a single course of treatment had such a long-lasting effect. The difference between the treated and untreated animals remained dramatic even two months later."

When the treated animals were vaccinated eight weeks later against a virus they hadn't encountered before, their immune systems responded more vigorously than untreated animals', and they were significantly better able to resist infection by that virus. (In contrast, young mice used as controls passed all the challenges with flying colors.)

"Every feature of an aging immune system -- functional markers on the cells, the prevalence of inflammatory proteins, the response to vaccination and the ability to resist a lethal infection -- was impacted by this single course of treatment targeting just one cell type," Ross said.

Finally, the researchers showed that mouse and human myeloid-biased HSCs are similar enough that it may one day be possible to use a similar technique to revitalize aging human immune systems, perhaps making a person less vulnerable to novel infections and improving their response to vaccination.

"We believe that this study represents the first steps in applying this strategy in humans," Ross said.

The study also has interesting implications for stem cell biology and the way HSCs rely on biological niches, or specific neighborhoods of cells, for their longevity and function throughout our lives.

"Most people in immunology have believed that you lose these kinds of tissue-specific stem cells as you grow older," Weissman said. "But that is completely wrong. The problems arise when you start to favor one type of HSC over another. And we've shown in mice that this can be reversed. This finding changes how we think about stem cells during every stage of aging."

The study was funded by the National Institutes of Health (grants R35CA220434, R01DK115600 and R01AI143889), the Virginia and D.K. Ludwig Fund for Cancer Research, the RSNA Resident/Fellow Research Grant, a Stanford Cancer Institute Fellowship grant, and the Ellie Guardino Research Fund.

Story Source:

Materials provided by **Stanford Medicine**. Original written by Krista Conger. *Note: Content may be edited for style and length.*

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