Bio News – May, 2024

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

3/29　光照射で細胞を好きな場所に接着し、免疫によるがん攻撃を観察 –阪大など

光を照射して生きた細胞をひとつずつ好きな場所に瞬時・精密にくっつける技術を、大阪大学産業科学研究所の山口哲志教授（生体機能関連化学）らのグループが開発した。この技術により、免疫細胞ががん細胞を攻撃する様子をリアルタイムで観察することができた。がんなどの治療から産業まで幅広い分野で応用が期待できるという。

3/31　ビタミン D とカルシウムのサプリメントは効果なし　研究結果

ビタミン D のサプリメント摂取が骨折予防に役立つかどうかを検証するため、今から 1 年半前、2 万 6,000 人の男女を対象とした実験が行われた。結果は、ビタミン D は骨折予防に役立たないというものだった。ビタミン D を摂取している人としていない人の骨折の可能性はまったく同じだったのだ。ビタミン D の摂取量には関係なく、またカルシウムを補助的にとっても効果はなかった。（※ビタミン D はすべての人に必要な栄養素だが、ほとんどの人は通常の食事から必要量を摂取している。そうでなくとも日光を 10 分間浴びるだけで、1 日に必要とされるビタミン D 量の約 4 倍を摂取することができる）
今回新たに 3 万 6,000 人以上の閉経後の女性を対象に、ビタミン D とカルシウムの併用が及ぼす影響を 22 年間にわたって調べた大規模な研究が、医学誌「内科学紀要」に掲載された。被験者は 7 年間サプリメントを摂取し、その後 15 年間追跡調査を受けた。これは研究としては極めて長期にわたるもので、研究者らの決意と努力に敬意を表したい。この研究では、サプリメントが股関節骨折に及ぼす影響だけでなく、がんや心臓病で死亡する割合がサプリメントによって変化するかについても検証された。それによると、サプリメントを服用しても股関節骨折のリスクは低下しなかった。以前の研究で同じ結果が出ていることを考えれば、驚くべきことではない。
この研究は 20 年以上にわたって被験者を追跡する長期的なものであることから、別の問いを投げかけることもできる。ビタミン D とカルシウムは死亡率に影響を及ぼすのか？研究の結果、サプリメントの摂取でがんによる死者数はわずかに減少した一方、心臓病による死者数はわずかに増加した。

4/1　ゲノム編集ベビー「やがて世界は受け入れる」初作製の中国研究者

遺伝子を書き換えるゲノム編集を施した子どもを世界で初めて誕生させたと 2018 年に発表し、中国で収監された中国人研究者の賀建奎（がけんけい）・南方科技大元副教授が、毎日新聞のオンライン取材に応じた。賀氏は、遺伝性の難病治療のため、国際的なルールを守った上でヒト胚（受精卵）へのゲノム編集の研究を再開したことを明かし、「やがて社会が受け入れる」と主張した。

4/1　小林製薬は入社式を行わず　58人の新入社員に辞退者はなし

4/1　新型コロナワクチン廃棄へ　臨時接種終了、162 万回分　厚労省

新型コロナウイルスワクチンについて、厚生労働省は 1 日、第一三共、米モデルナ、米ファイザー各社製のワクチン計約 162 万回分を廃棄すると発表した。
予防接種法上の臨時接種が先月 31 日で終了したことに伴う措置。

4/1　ドイツで大麻所持と栽培が合法に　18 歳以上の成人が個人目的で（販売や取引は禁止）

4/2　エーザイのアルツハイマー病薬 Leqembi 皮下注射の米国承認申請に遅延

Subcutaneous Leqembi filing delayed after FDA asks Eisai for more data | FirstWord Pharma

4/3　Bavarian Nordic が米国でエムポックスワクチン Jynneos の販売開始

4/5　HER2 陽性固形癌への第一三共/AstraZeneca の Enhertu 使用を米国承認

US FDA approves Daiichi, AstraZeneca drug for treatment of solid tumors (msn.com)

4/5　テラドックの長年の CEO が辞任、暫定トップに CFO を任命

Teladoc（本社：ニューヨーク州パーチェイス市）の最高経営責任者（CEO）Jason Gorevic 氏は、バーチャルケア会社を 15 年間率いた後、即時辞任する。最高財務責任者のマラ・マーシー氏が最高経営責任者（CEO）代行に任命された。2019 年に入社したマーシー氏は、この期間中も引き続き CFO を務める。
Teladoc は、2021 年初頭の新型コロナウイルス感染症（COVID-19）パンデミックの真っ最中に、遠隔医療の人気が急上昇し、注目を集めた。しかし、同社は競争激化の中でこの勢いを維持することができず、テラドックは昨年 2 億 2,040 万ドルの損失を報告。同社株は 2021 年 2 月の最高値 294.54 ドルから金曜日時点で約 14 ドルまで約 95%急落している。

4/5　オムロンが Luscii を買収して遠隔患者モニタリングを推進

オムロン ヘルスケア（本社：京都市下京区）は、遠隔患者モニタリング サービスへのアクセスを拡大するために、オランダの Luscii Healthtech を買収した。
両社はオムロンが Luscii のシードラウンドを支援した 2018 年以来、協力してきた。スマート遠隔ケアと仮想病棟のリーダーである Luscii のカスタマイズ可能な在宅ケア プラットフォームとアプリは、150 以上の疾患に対応している。

4/6　DNA 研究で 1500 年前の中国皇帝の顔を復元

1996 年、考古学者のグループが中国北西部で武帝の墓を発見し、散乱した骨とほぼ無傷の頭蓋骨を発掘した。そして今回、頭蓋骨の輪郭と肢体から抽出した DNA を使って、中国の研究チームが武帝の容姿を現代に蘇らせた。
Current Biology 誌に掲載された最新研究で、チームは DNA の信頼性を検証した方法を含め、その研究成果と方法の詳細を発表した。

4/6　強誘電性と半導体特性両立、東北大など開発した新有機分子の効果

東北大学の三部宏平大学院生と芥川智行教授らの研究グループは、強誘電性と半導体特性を両立する新しい有機分子を開発した。これにより外部電場に応答する分子集合体を作れるようになり、有機半導体の特性をオンオフ制御できた。単一の有機分子で作る有機メモリーなど、次世代高密度メモリーへの応用が期待される。
研究グループは、高いホール移動度の半導体特性を持つ有機材料のベンゾチアノベンゾチオフェン（BTBT）骨格に極性水素結合ネットワークを導入。強誘電性を持たせ、半導体特性との両立に成功した。

4/7　国立感染症研究所、アジアで情報共有…次のパンデミックに備えインド・ベトナムなどと

4/8　新生児の遺伝子編集治療の臨床試験を米国も許可

新生児の遺伝子編集治療の臨床試験を英国とオーストラリアに次いで米国も許可した。
許可されたのは OTC-HOPE という名称の Ph1/2 試験で、フィラデルフィア拠点のバイオテック iEcure の開発品 ECUR-506 が生後 7 か月までの男性新生児に投与される。

4/8　日本初の“脂肪減少薬”きょう販売開始　薬剤師の指導のもと購入可　腹囲など条件あり

大正製薬が、8 日から販売を始めたのは肥満症になる前に服用し、内臓脂肪や腹囲の減少が期待される薬、「アライ」。摂取した脂肪のおよそ 25 パーセントが排出されるということで、処方箋なしで薬剤師の指導のもと薬局で購入でき、腹囲が男性は 85 センチ以上、女性は 90 センチ以上の人が対象。

4/8　前立腺がん、2040 年までに全世界で倍増　英ロンドン大学予測

英医学誌ランセットに 4 日に掲載された英ロンドン大学の論文は、40 年までに全世界で年間約 290 万人が前立腺がんと診断され、20 年時点の 140 万人の 2 倍以上になると予測。特に低・中所得国の男性患者の増加が著しいとしている。同疾患による死者数は、20 年時点の 37 万 5,000 人から、40 年には年間 70 万人近くにまで増加するという。

4/9　傷ついた魚から仲間への警報物質を発見 理研と東大

傷ついた魚の皮膚から出て、周りの仲間に危険を知らせる警報物質を発見したと、理化学研究所と東京大学の研究グループが発表した。1938 年に存在が指摘され、後にノーベル賞の授賞理由の一部ともなった物質の実体が、80 年あまりを経て分かった。動物が危険を回避する神経の仕組みやコミュニケーションでのにおいの役割の理解のほか、化学物質による魚の行動制御に役立ちそうだという。

4/10　Novartis がスイスと米国の開発部門の 680 職を削減

Novartis to cut up to 68o positions in Switzerland and US | FirstWord Pharma

Novartis to cut 68o jobs in product development | Reuters

4/11　悪臭拡散の原因解明　ネコのスプレー尿　岩手大

ネコが縄張りを主張したり、異性にアピールしたりするために壁などにかける「スプレー尿」は強烈な悪臭を放つが、通常の尿と化学的な成分に違いはないことが分かった。悪臭物質を生み出す酵素たんぱく質「コーキシン」に、尿を壁などに付着させやすくする作用があるため、悪臭が拡散するという。

4/11　胎児/新生児の重病予防薬を棲み分け開発する 2 社、Rallybio（本社：コネチカット州ニューヘイブン）と J&J が提携

Rallybio and J&J collaborate to tackle maternal-foetal blood disorder - Pharmaceutical Technology (pharmaceutical-technology.com)

4/14　長寿薬 4 つ発見

50 万人を超える成人の 40 年超の処方薬や死亡を記録している英国の医療情報 UK Biobank（UKBB）によると、4 つの薬いずれかの使用と死亡率の低下、すなわちより長生きすることが関連した、としている。
4 つの薬とは、勃起不全薬バイアグラ（Viagra）の成分として知られるシルデナフィル（sildenafil）、コレステロール低下薬アトルバスタチン（atorvastatin）、鎮痛薬・ナプロキセン（naproxen）、ホルモン補充薬エストラジオール（estradiol）。

These four common medicines could help prolong your life | New Scientist

4/15　日本初！先天性の難病「脊髄髄膜瘤」の胎児手術に成功　母体の開腹手術により神経障害を軽減へ　大阪大学などのグループ

4/17　ヒト胚モデルの研究規制検討へ　内閣府調査会、部会報告書受け

内閣府の生命倫理専門調査会は 17 日、ヒトの胚性幹細胞（ES 細胞）や人工多能性幹細胞（iPS 細胞）を培養して実験容器内で作る「胚モデル」の作業部会から、研究規制の導入を提言する報告書を受け取った。現行の ES 細胞や iPS 細胞の研究指針は胚モデルを想定しておらず、指針を改正して個体産生禁止などを盛り込む必要があるか、改めて検討する。

4/18　Pfizer が研究者との新薬開発提携部門 Centers for Therapeutics Innovation を閉鎖

Pfizer closes R&D unit that spawned $7.1B anti-TL1A med (fiercebiotech.com)

4/18　サルの脳に足し算・引き算細胞を発見 ヒトの脳にも関連か

足し算と引き算に強く反応する神経細胞をサルの脳で見つけたと、東北大の虫明元（むしあけはじめ）教授（神経生理学）らのチームが発表した。右手が足し算、左手が引き算と関連性があり、こうした左右の違いがヒトの脳にも備わっている可能性が示唆される。

4/19　Sanofi が米国のワクチン販売部門を合理化して職を削減

4/19　すべての人への医療提供で人材育成拠点　WHO と 2025 年に設置へ

武見敬三厚生労働相は 19 日、すべての人が負担可能な費用で、適切な保健医療サービスを受けられるようにする「ユニバーサル・ヘルス・カバレッジ（UHC）」の人材育成拠点を、2025 年に日本に設置すると発表。世界保健機関（WHO）、世界銀行と連携して準備を進め、低中所得国での UHC の実現をめざす。

4/19　WHO と専門家、コロナ禍受け「空気感染」の定義で合意

世界保健機関（WHO）は 18 日公表した技術協議文書で、約 500 人の専門家と空気感染による病気のまん延の定義について初めて合意したと明らかにした。新型コロナウイルスのパンデミック（世界的大流行）初期に起きたような混乱を今後、回避することが狙い。
WHO は、麻疹（はしか）のような既存疾患と将来のパンデミックの脅威の両方について、空気感染を防ぐより良い方法を研究する第一歩になると述べた。

4/19　プベルル酸以外に「複数の化合物検出」 紅麹サプリ原料の中間分析

小林製薬（大阪市）の紅麹（こうじ）成分を含むサプリメントをめぐる健康被害の問題で、厚生労働省は 19 日、健康被害の報告があった製品の原料から、プベルル酸に加え、本来の製品に含まれていない複数の化合物が検出されたと発表した。厚労省は引き続き、検出された物質の特定やこれらの物質が混入した原因の究明を進める。

4/20　ネッタイシマカ 蚊の大規模調査へ

国立感染症研究所は 5 月にも、東南アジアの 8 か国・地域で、デング熱などの熱帯感染症を媒介する蚊「ネッタイシマカ」の大規模な遺伝子解析調査に乗り出す。ネッタイシマカは、遺伝子変異で殺虫剤に強い耐性を持った個体が出現している。日本では航空機に紛れ込んで見つかるケースが相次いでいるため、感染研は今回の調査で生息域などを解明し、今後の水際対策に生かす考え。

4/20　武田薬品の皮下注射 Entyvio のクローン病治療を米国 FDA が承認

Pharma Industry News and Analysis | FirstWord Pharma
FDA clears Takeda's Entyvio injection for Crohn's disease

4/22　飲酒でできるアルデヒドも老化原因の可能性 名大、「早老症」の研究で判明

お酒を飲むと体内に生じるアルデヒド類が遺伝子を傷つけて老化を引き起こす可能性がある、と名古屋大学の研究グループが発表した。老化についてはこれまでの研究からさまざまな原因が指摘されてきた。今回、急速に老化が進む「早老症」の発症原因を突き止める研究からお酒がもたらす新たな「悪さ」も明らかになったという。

4/23　エーザイ/Biogen のアルツハイマー病薬 Leqembi（レケンビ；lecanemab、レカネマブ）の米国での普及が難航

Alzheimer's drug adoption in US slowed by doctors' skepticism | Reuters

4/23　Lilly が Nexus（本社：イリノイ州リンカーンシャア）の注射薬製造工場を取得

Eli Lilly to acquire manufacturing facility from Nexus Pharma | Reuters

4/24　マウスにも「目の錯覚」

東京大の研究チームは 23 日、脳が明るさを知覚する神経メカニズムの一端を解明したと発表した。目の錯覚による「錯視」の一種をマウスが見ていることを初めて確かめ、その際の脳の活動を調べた結果、より高次の視覚野の神経が明るさの知覚に関わっていることがわかったという。

4/24　「熱中症特別警戒アラート」きょうから運用開始

国内で過去に例のない危険な暑さが予想された場合に、熱中症を予防する行動の徹底を求める新しい情報、「熱中症特別警戒アラート」の運用がきょう（24 日）から始まる。

4/24　スタンフォード大学の大学長を辞した Tessier-Lavigne 氏が率いる AI 創薬会社 Xaira Therapeutics が発足

Marc Tessier-Lavigne, forced to resign as Stanford president, heading AI-focused biotech startup - San Francisco Business Times (bizjournals.com)

4/24　尿路結石の分解を iPS 細胞で再現…予防薬の開発へ弾み －名古屋市立大

耐えがたい激痛で知られる尿路結石の主成分を白血球が積極的に食べて分解する様子を、人の iPS 細胞（人工多能性幹細胞）を使って再現することに成功したと、名古屋市立大の岡田淳志准教授と岡田朋記・病院助教らのチームが発表した。予防薬の開発に役立つといい、国際科学誌に論文が掲載された。

4/24　ヤンバルクイナの羽から新種　300 枚を調べて見つけた小さな掃除屋

沖縄本島の北部に生息する飛べない鳥、ヤンバルクイナの羽毛にすむ新種のダニが見つかった。法政大などのチームが発見し、和名はヤンバルクイナウモウダニと命名された。宿主に害を与えない「良いダニ」だという。

4/25　AI 創薬の BenevolentAI が米国を退去して、従業員 30%削減

ロンドンに拠点を置く BenevolentAI が、現金を維持するために最大 180 人の従業員削減とパイプラインの再編を行うと発表。これに伴い米国支店も閉鎖。
さらに、最高財務責任者であるニコラス・ケハー氏が辞任、同社の上級副社長兼グループ財務ディレクターのトム・ホルゲート氏が暫定 CFO として就任。
彼らの苦闘はバイオテクノロジー業界で特別なものではない。2022 年以降、公開市場の低迷により資金調達が困難になる中、医薬品開発業者は引き締めを余儀なくされている。数十にも及ぶ企業が資

金を確保するために人員削減に訴えている。BioPharma Dive の集計によると、バイオテック企業は今年最初の 3 か月だけで約 3,200 人の従業員を解雇した、としている。

BenevolentAI CFO resigns as company lays off staff, restructures | BioPharma Dive

4/25　スイスの CSL の IgA 腎症薬 Filspari を欧州も承認

CSL Vifor, Travere score conditional EU approval for Filspari in IgAN | FirstWord Pharma

4/25　Cidara（本社：カリフォルニア州サンディエゴ）が J&J から取り戻すインフルエンザ薬 Ph2b 試験資金 2 億 4,000 万ドルを調達

Cidara Therapeutics Reacquires Global Development and Commercial Rights to CD388 and Announces Private Placement Financing of $240 Million (yahoo.com)

4/26　COVID-19 ワクチン技術特許の侵害で GSK が Pfizer/BioNTech を訴えた

GlaxoSmithKline sues Pfizer and BioNTech over Covid-19 vaccine technology | Reuters

4/29　「ドラッグロス」改善へ、希少疾患新薬の申請要件緩和…日本人の臨床試験なしで可能に

海外で承認された薬が日本で使えない「ドラッグロス」の問題を改善するため、厚生労働省は、小児がんなどの希少疾患の新薬について、承認申請の要件を緩和することを決めた。日本人の臨床試験データがなくても申請できる新たな仕組みを、5 月にも導入する方針だ。海外の製薬企業による申請を促し、薬の実用化の時期を早める狙いがある。

4/29　日本の HPV（ヒトパピローマウイルス）ワクチンの普及率は高所得国の中で最低

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. 骨髄移植によって家族性アルツハイマー病が感染 -マウス研究

2. アルツハイマー病の免疫療法がマウスの研究で有望性を示す

3. 科学者らが「ミニ腎臓」を成長させ、代謝異常と多発性嚢胞腎の治療法について新たな洞察を明らかに -マウス実験

4. 父親の食事が子孫の健康にどのような影響を与えるかを調査するマウス研究

5. ワクチン接種前の代謝の健康状態が抗インフルエンザ反応の有効性を決定 -マウス実験

6. 米ぬか由来ナノ粒子の抗がん作用を確認 -マウス実験
   ～未利用資源を原料とした安価で安全なナノ粒子製剤開発に期待～

7. てんかん治療薬が神経線維腫症 1 型マウスの脳腫瘍を予防

8. ビタミン D がマウスの腸内細菌を変化させて癌免疫を向上させる

1. 骨髄移植によって家族性アルツハイマー病が感染 -マウス研究

日付：2024 年 3 月 28 日
ソース：Cell Press
概要：

家族性アルツハイマー病は骨髄移植を介して感染する可能性があることを研究者らが『Stem Cell Reports』誌で発表している。
ブリティッシュ コロンビア大学の研究チームが、遺伝性アルツハイマー病を患うマウスの骨髄幹細胞を正常な実験用マウスに移植したところ、移植されたマウスはアルツハイマー病を、しかも加速度的に、発症したとしている。この研究は、アルツハイマー病の発症における脳の外で発生するアミロイドの役割を強調しており、これによりアルツハイマー病のパラダイムが脳内で独占的に生成される疾患からより全身性の疾患へと変化する。
研究者らは、この発見に基づいて、血液製剤の輸血や細胞療法中に不用意にアルツハイマー病に感染するのを防ぐため、血液、組織、臓器、幹細胞のドナーはアルツハイマー病のスクリーニングを受ける必要がある、と述べている。
研究者らは将来の研究で、正常なマウスから家族性アルツハイマー病のマウスに組織を移植することで病気が軽減できるかどうかをテストし、この病気が他の種類の移植や輸血によっても伝染するかどうかをテストし、病気伝染の研究を拡大する予定である、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＞Familial Alzheimer's disease transferred via bone marrow transplant in mice (medicalxpress.com)

MARCH 28, 2024

Editors' notes

Familial Alzheimer's disease transferred via bone marrow transplant in mice

by Cell Press

A painting representing Alzheimer's transmissibility as reported in this *Stem Cell Reports* study. Credit: Chaahat Singh

Familial Alzheimer's disease can be transferred via bone marrow transplant, researchers show in the journal *Stem Cell Reports*. When the team transplanted bone marrow stem cells from mice carrying a hereditary version of Alzheimer's disease into normal lab mice, the recipients developed Alzheimer's disease—and at an accelerated rate.

The study highlights the role of amyloid that originates outside of the brain in the development of Alzheimer's disease, which changes the paradigm of Alzheimer's from being a disease that is exclusively produced in the brain to a more systemic disease.

Based on their findings, the researchers say that donors of blood, tissue, organ, and stem cells should be screened for Alzheimer's disease to prevent its inadvertent transfer during blood product transfusions and cellular therapies.

"This supports the idea that Alzheimer's is a systemic disease where amyloids that are expressed outside of the brain contribute to central nervous system pathology," says senior author and immunologist Wilfred Jefferies, of the University of British Columbia.

"As we continue to explore this mechanism, Alzheimer's disease may be the tip of the iceberg and we need to have far better controls and screening of the donors used in blood, organ and tissue transplants as well as in the transfers of human derived stem cells or blood products."

To test whether a peripheral source of amyloid could contribute to the development of Alzheimer's in the brain, the researchers transplanted bone marrow containing stem cells from mice carrying a familial version of the disease—a variant of the human amyloid precursor protein (APP) gene, which, when cleaved, misfolded and aggregated, forms the amyloid plaques that are a hallmark of Alzheimer's disease. They performed transplants into two different strains of recipient mice: APP-knockout mice that lacked an APP gene altogether, and mice that carried a normal APP gene.

In this model of heritable Alzheimer's disease, mice usually begin developing plaques at nine to 10 months of age, and behavioral signs of cognitive decline begin to appear at 11 to 12 months of age. Surprisingly, the transplant recipients began showing symptoms of cognitive decline much earlier—at six months post-transplant for the APP-knockout mice and at nine months for the "normal" mice.

"The fact that we could see significant behavioral differences and cognitive decline in the APP-knockouts at six months was surprising but also intriguing because it just showed the appearance of the disease that was being accelerated after being transferred," says first author Chaahat Singh of the University of British Columbia.

In mice, signs of cognitive decline present as an absence of normal fear and a loss of short and long-term memory. Both groups of recipient mice also showed clear molecular and cellular hallmarks of Alzheimer's disease, including leaky blood-brain barriers and buildup of amyloid in the brain.

Observing the transfer of disease in APP-knockout mice that lacked an APP gene altogether, the team concluded that the mutated gene in the donor cells can cause the disease and observing that recipient animals that carried a normal APP gene are susceptible to the disease suggests that the disease can be transferred to health individuals.

Because the transplanted stem cells were hematopoietic cells, meaning that they could develop into blood and immune cells but not neurons, the researchers' demonstration of amyloid in the brains of APP knockout mice shows definitively that Alzheimer's disease can result from amyloid that is produced outside of the central nervous system.

Finally the source of the disease in mice is a human APP gene demonstrating the mutated human gene can transfer the disease in a different species.

In future studies, the researchers plan to test whether transplanting tissues from normal mice to mice with familial Alzheimer's could mitigate the disease and to test whether the disease is also transferable via other types of transplants or transfusions and to expand the investigation of the transfer of disease between species.

"In this study, we examined bone marrow and stem cells transplantation. However, next it will be important to examine if inadvertent transmission of disease takes

place during the application of other forms of cellular therapies, as well as to directly examine the transfer of disease from contaminated sources, independent from cellular mechanisms," says Jefferies.

More information: Conclusive Demonstration of Iatrogenic Alzheimer's Disease Transmission in a Model of Stem Cell Transplantation, *Stem Cell Reports* (2024). DOI: 10.1016/j.stemcr.2024.02.012. www.cell.com/stem-cell-reports … 2213-6711(24)00049-3

Journal information: Stem Cell Reports

Provided by Cell Press

2. アルツハイマー病の免疫療法がマウスの研究で有望性を示す

日付：2024 年 4 月 3 日
ソース：ワシントン大学医学部
概要：

アルツハイマー病は、アミロイドベータと呼ばれる粘着性タンパク質が脳内に蓄積してプラークを形成することから始まり、脳萎縮と認知機能低下を引き起こす。アルツハイマー病の経過を変えることが初めて証明された新世代のアルツハイマー病薬は、脳の免疫細胞による除去のためにアミロイドをタグ付けすることによって機能する。
今回、セントルイスのワシントン大学医学部の研究者らは、有害なプラークを除去する別の有望な方法を発見した。それは、免疫細胞を直接動員してプラークを消費することである。『Science Translational Medicine』誌に掲載されたこの研究で、研究者らは、アルツハイマー病斑内に散在する APOE タンパク質とミクログリア細胞上の LILRB4 受容体との間の相互作用をブロックする抗体でマウスを治療すると、損傷した細胞を活性化して除去することを示した。すなわち、アルツハイマー病様疾患のマウスの脳内のアミロイド斑が減少し、マウスの行動異常が軽減されることが示されたのである。
このアプローチはアルツハイマー病以外にも影響を与える可能性がある。脳タンパク質の有毒な塊は、パーキンソン病、筋萎縮性側索硬化症（ALS）、ハンチントン病など、多くの神経変性疾患の特徴だ。この研究結果に勇気づけられて、研究者らは他の病気を進行させると考えられているジャンクタンパク質を脳から除去するための他の免疫療法、つまり免疫系を利用する薬剤の可能性を模索している。

研究関連ニュース/他のトップページに戻る

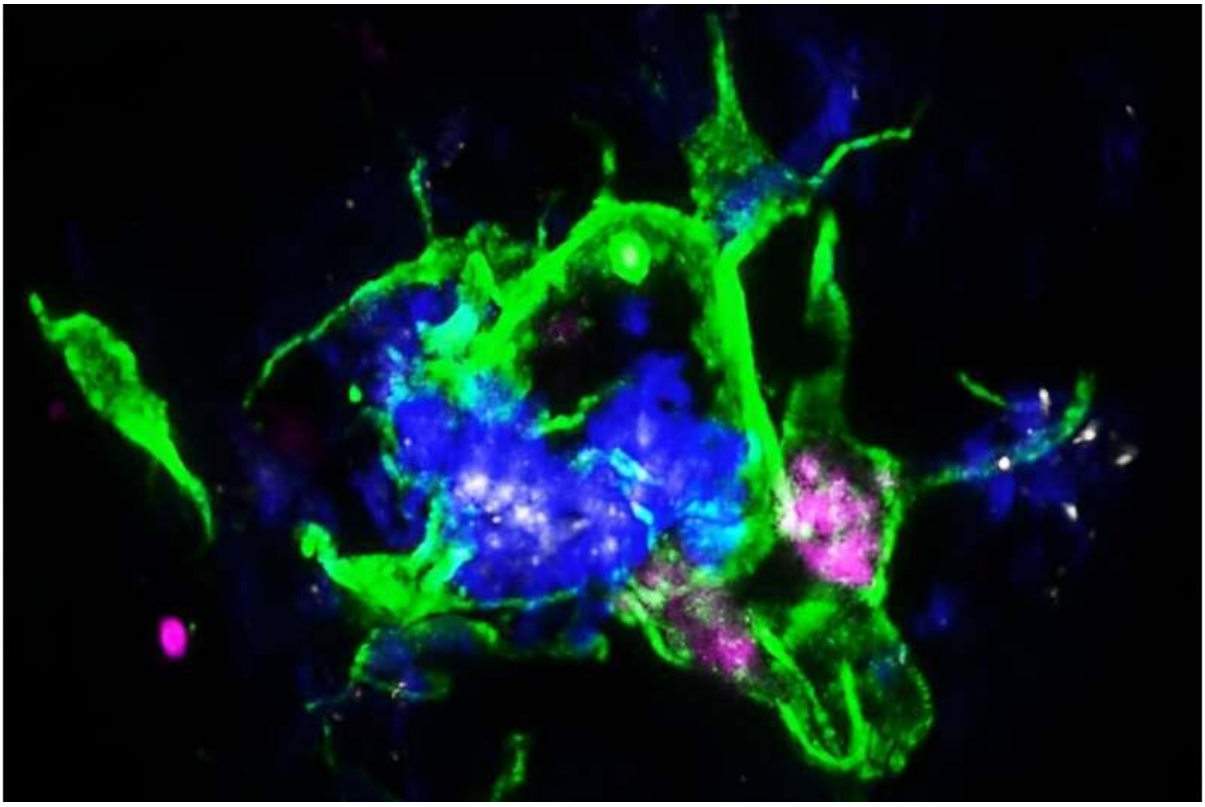
＜英文＞Immunotherapy for Alzheimer's disease shows promise in mouse study (medicalxpress.com)

APRIL 3, 2024

Editors' notes

Immunotherapy for Alzheimer's disease shows promise in mouse study

by Marta Wegorzewska, Washington University School of Medicine



Scientists at Washington University School of Medicine in St. Louis have shown that treating mice with an antibody that blocks the interaction between APOE proteins (white) sprinkled within Alzheimer's disease plaques and the LILRB4 receptor on microglia cells (purple) activates them to clean up damaging plaques (blue) in the brain. Credit: Jinchao hou

Alzheimer's disease starts with a sticky protein called amyloid beta that builds up into plaques in the brain, setting off a chain of events that results in brain atrophy and cognitive decline. The new generation of Alzheimer's drugs—the first proven to change the course of the disease—work by tagging amyloid for clearance by the brain's immune cells.

Now, researchers at Washington University School of Medicine in St. Louis have found a different and promising way to remove the noxious plaques: by directly mobilizing immune cells to consume them.

In a study published in *Science Translational Medicine*, the researchers showed that activating immune cells called microglia with an antibody reduces amyloid plaques in the brain and mitigates behavioral abnormalities in mice with Alzheimer's-like disease.

The approach could have implications beyond Alzheimer's. Toxic clumps of brain proteins are features of many neurodegenerative conditions, including Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease. Encouraged by the study results, researchers are exploring other potential immunotherapies—drugs that harness the immune system—to remove junk proteins from the brain that are believed to advance other diseases.

"By activating microglia generally, our antibody can remove amyloid beta plaques in mice, and it could potentially clear other damaging proteins in other neurodegenerative diseases, including Parkinson's disease," explained the study's senior author, Marco Colonna, MD, the Robert Rock Belliveau, MD, Professor of Pathology.

Microglia surround plaques to create a barrier that controls the damaging protein's spread. They also can engulf and destroy the plaque proteins, but in Alzheimer's disease they usually do not. The source of their passivity could result from a protein called APOE that is a component of amyloid plaques. The APOE proteins in the plaque bind to a receptor—LILRB4—on the microglia surrounding the plaques, inactivating them, Yun Chen, co-first author on the study, explained.

For reasons that are still unknown, the researchers found that in mice and people with Alzheimer's disease, microglia that surround plaques produce and position LILRB4 on their cell surface, which inhibits their ability to control damaging plaque formation upon binding to APOE. The other co-first author, Jinchao Hou, Ph.D., now a faculty member at Children's Hospital of Zhejiang University School of Medicine in Zhejiang Province, China, treated mice that had amyloid beta plaques in the brain with a homemade antibody that blocked APOE from binding to LILRB4.

After working with Yongjian Liu, Ph.D., a professor of radiology in Washington University's Mallinckrodt Institute of Radiology, to confirm that the antibody reached the brain, the researchers found that activated microglia were able to engulf and clear the amyloid beta plaques.

Clearing the amyloid beta plaques in mice also alleviates risk-taking behavior. Individuals with AD may lack memory of past experiences to inform their decisions. They may engage in risky behavior, making them vulnerable to becoming victims of fraud or financial abuse. Treating mice with an antibody to clear the plaques showed promise in altering the behavior.

After amyloid beta plaques form in the brain, another brain protein—tau—becomes tangled inside neurons. In this second stage of the disease, neurons die and cognitive symptoms arise. High levels of LILRB4 and APOE have been observed in AD patients in this later stage, Chen explained. It is possible that blocking the proteins from interacting and activating microglia could alter later stages of the disease. In future studies, the researchers will test the antibody in mice with tau tangles.

Drugs that target amyloid plaques directly can cause a potentially serious side effect. In Alzheimer's patients, amyloid proteins build up on the walls of the arteries in the brain as well as other parts of brain tissue. Removing plaques from brain blood vessels can induce swelling and bleeding, a side effect known as ARIA.

This side effect is seen in some patients receiving lecanemab, a drug approved by the Food and Drug Administration to treat Alzheimer's. The mice used in this study

lacked amyloid plaques on blood vessels, so the researchers could not evaluate what happened when blood vessel plaques were removed.

They are working with a different mouse model—one that does have plaques on brain arteries—to understand whether this new approach also carries a risk of ARIA.

"Lecanemab, as the first therapeutic antibody that has been able to modify the course of the disease, confirmed the importance of amyloid beta protein in Alzheimer's disease progression," said author David Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor of Neurology. "And it opened new opportunities for developing other immunotherapies that use different methods of removing damaging proteins from the brain."

More information: Jinchao Hou et al, Antibody-mediated targeting of human microglial leukocyte Ig-like receptor B4 attenuates amyloid pathology in a mouse model, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adj9052

Journal information: Science Translational Medicine

Provided by Washington University School of Medicine

3. 科学者らが「ミニ腎臓」を成長させ、代謝異常と多発性嚢胞腎の治療法について新たな洞察を明らかに –マウス実験

日付：2024 年 4 月 8 日
ソース：南洋理工大学（NTU シンガポール）
概要：

シンガポールの南洋理工大学の科学者らは、実験室で「ミニ腎臓」を増殖させ、生きたマウスに移植することに成功し、代謝異常と多発性嚢胞腎（PKD）の潜在的な治療法についての新たな洞察を明らかにした。
PKD 患者は 50 代から 60 代の間に末期腎臓病に進行することが多く、標準的な治療選択肢は透析または腎移植である。しかし、透析は患者の生活の質を著しく損なう一方、移植腎臓の取得は困難な場合が多い。もう 1 つの選択肢は、食品医薬品局（FDA）が承認した薬剤トルバプタンだが、これは非常に高価で、肝臓に重度の副作用がある。そんな中で PKD 患者に対するより効果的な治療の必要性に対処するために、NTU の研究チームは、新しく開発したミニ腎臓をマウスに移植することで、この病気をより深く理解しようと努めた。
科学誌『Cell Stem Cell』に掲載された研究で、研究チームは、さらなる調査のために生きたマウスから取り出した後でも、余分なストレス刺激や化学物質なしで嚢胞が維持されていたため、移植されたミニ腎臓は高品質であると言える、としている。対照的に、皿の中で培養された以前の腎臓オルガノイドは、ストレス刺激がなければ嚢胞を形成できない。
研究者らは臨床で PKD 患者を治療することを目的としているが、この可能性を確立するにはさらなる研究が必要である、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＞Scientists grow 'mini kidneys,' revealing new insights into metabolic defects and potential therapy for polycystic kidney disease | ScienceDaily

Scientists grow 'mini kidneys,' revealing new insights into metabolic defects and potential therapy for polycystic kidney disease

Date:

April 8, 2024

Source:

Nanyang Technological University

Summary:

Scientists have successfully grown 'mini kidneys' in the lab and grafted them into live mice, revealing new insights into the metabolic defects and a potential therapy for polycystic kidney disease.

FULL STORY

Scientists at Nanyang Technological University, Singapore (NTU Singapore) have successfully grown 'mini kidneys' in the lab and grafted them into live mice, revealing new insights into the metabolic defects and a potential therapy for polycystic kidney disease.

'Mini kidneys,' or kidney organoids, are kidney-like structures grown in the lab using stem cells. In the study led by NTU's Lee Kong Chian School of Medicine (LKCMedicine), researchers grew the organoids using skin cells derived from patients with polycystic kidney disease (PKD), a prevalent form of genetic condition that affects 1 in 1000 individuals across all ethnicities.*

People with PKD often progress to end-stage kidney disease between their 50s and 60s, with the standard treatment options available being dialysis or a kidney transplant. However, dialysis significantly compromises a patient's quality of life, while a transplanted kidney can be challenging to acquire. One other option is the Food and Drug Administration (FDA) approved drug Tolvaptan, which is very costly and has severe side effects on the liver.

To address the need for more effective treatment for PKD patients, the NTU research team sought to better understand the disease by engrafting their newly developed mini kidneys into mice.

Previous studies were conducted on mini kidneys grown in a dish, which could only partly mimic the kidney structure and function. The NTU scientists engrafted the mini kidneys into live mice to comprehensively replicate the pathological features of kidney disease, including blood flow, fluid movement (tubular fluid) and cellular communication with other organs.

Lead investigator Assistant Professor Xia Yun at LKCMedicine said, "Engrafting the kidney organoid in mice provided us with a physiologically sophisticated approach to studying polycystic kidney disease as we were able to successfully emulate critical disease characteristics similar to those observed in human kidney patients."

Critical disease characteristics included abnormalities like the spontaneous formation of cysts in the kidneys and the subsequent damage to its tiny tubes.

In their study, reported in the scientific journal *Cell Stem Cell*, the NTU research team said that they believed their engrafted mini kidneys were high quality because cysts sustained without extra stress stimulation or chemicals, even after they were removed from the live mice for further investigations in a dish. In contrast, previous kidney organoids grown in a dish cannot form cysts without stress stimulation.

Co-investigator Assistant Professor Foo Jia Nee at LKCMedicine said, "The similarity between the disease manifestation observed in our engrafted mini kidney model and the real-life experiences of polycystic kidney disease patients suggest that growing kidney organoids and engrafting them into live mice could be beneficial in studying the disease and a useful tool to test new treatments."

Metabolic defects in polycystic kidney disease

Scientists have long known that abnormalities in a structure on kidney cells, or the primary cilium, cause cysts to form in kidneys. However, tests to understand the regulatory mechanism and relationship between the primary cilium and cell metabolism (autophagy) in live mice with PKD, have not been possible until now.

By studying the development of PKD in live mice and testing cellular pathways, researchers found evidence that boosting autophagy could reduce the severity of cysts in the mini kidney.

After establishing that boosting autophagy could reduce cysts, the NTU scientists shortlisted 22 drugs known for their effects on cell metabolism and tested them in the lab. Results showed that minoxidil, a clinical drug widely used to cure hypertension and hair loss, effectively reduced cyst formation in the novel mouse model.

Asst Prof Xia Yun said, "Our study has demonstrated how cysts in polycystic diseased kidneys can be reduced by boosting autophagy, suggesting that this could be a promising treatment for PKD. Moreover, the proven clinical safety of minoxidil may allow it to be quickly re-purposed to treat PKD patients in clinic. However, more research will be needed to establish this potential."

Commenting as an independent expert, Associate Professor Ng Kar Hui, Senior Consultant, Division of Paediatric Nephrology, Dialysis and Renal Transplantation, Department of Paediatrics, Khoo Teck Puat -- National University Children's Medical Institute, National University Hospital, said, "Polycystic kidney disease is one of the biggest causes of chronic kidney diseases among adults. An effective treatment may potentially ameliorate the rising numbers of people with kidney failure in Singapore. The establishment of such models in live organisms brings us one step closer to finding more treatment options.

In future studies, the NTU team will test the efficacy of minoxidil and adapt the mini kidney models to investigate other burgeoning kidney diseases without a strong genetic underpinning, such as diabetic kidney disease.

* Harris, P.C., and Torres, V.E. (2009). Polycystic kidney disease. Annual Review of Medicine. Volume 60, 321-337.

Story Source:

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

Journal Reference:

1. Meng Liu, Chao Zhang, Ximing Gong, Tian Zhang, Michelle Mulan Lian, Elaine Guo Yan Chew, Angelysia Cardilla, Keiichiro Suzuki, Huamin Wang, Yuan Yuan, Yan Li, Mihir Yogesh Naik, Yixuan Wang, Bingrui Zhou, Wei Ze Soon, Emi Aizawa, Pin Li, Jian Hui Low, Moses Tandiono, Enrique Montagud, Daniel Moya–Rull, Concepcion Rodriguez Esteban, Yosu Luque, Mingliang Fang, Chiea Chuen Khor, Nuria Montserrat, Josep M. Campistol, Juan Carlos Izpisua Belmonte, Jia Nee Foo, Yun Xia. **Kidney organoid models reveal cilium-autophagy metabolic axis as a therapeutic target for PKD both in vitro and in vivo**. *Cell Stem Cell*, 2024; 31 (1): 52 DOI: 10.1016/j.stem.2023.12.003

4. 父親の食事が子孫の健康にどのような影響を与えるかを調査するマウス研究

日付：2024 年 4 月 17 日
ソース：シドニー大学
概要：

『Nature Communications』誌に掲載された新しい研究では、雄マウスの食餌における栄養素のバランスが、息子の不安様行動のレベルと娘の代謝の健康に影響を与えることが判明した。この研究は、食事の影響が父親の精子を介して世代から世代へとどのように伝わるのかを理解するための一歩となる。最終的には、次世代の代謝性疾患や気分障害のリスクを下げることを目的として、将来父親になる人のための食事ガイドラインを提供できる可能性がある。
父親マウスの食餌が彼自身の生殖上の健康だけでなく、子供の生殖上の健康にも影響を与える可能性があることは以前既に発見されている。雄マウスに餌を与えすぎたり、少なすぎたりすると、子孫の代謝や行動、さらには癌のリスクに影響を与える可能性もある。あまり理解されていないのは、受胎前の雄マウスの食餌の種類と組成に応じて、子孫の健康にさまざまな種類の健康影響があるかどうかであった。
そこで今回オーストラリアのシドニー大学チャールズ・パーキンスセンターでは、研究者らは雄マウスにタンパク質、脂肪、炭水化物の割合が異なる 10 種類の餌のうちの 1 つを与え、その後、標準的な餌で飼育された雌マウスと交尾させた。次に、得られた子マウスの行動と生理機能が研究された。
研究者らは、低タンパク質、高炭水化物の食餌を与えられた雄マウスは、より高いレベルの不安を抱える雄の子孫を産む可能性が高いことを発見した。また、高脂肪食を与えられた雄マウスは、より高いレベルの体脂肪と代謝性疾患のマーカーを持つ娘を産む可能性が高いことも発見した。

研究関連ニュース/他のトップページに戻る

＜英文＞Research explores how a father's diet could shape the health of his offspring | ScienceDaily

Research explores how a father's diet could shape the health of his offspring

Date:

April 17, 2024

Source:

University of Sydney

Summary:

A mice study suggests a father's diet may shape the anxiety of his sons and the metabolic health of his daughters before they are even conceived.

FULL STORY

New research, published in *Nature Communications*, finds that the macronutrient balance in the diet of male mice affects the level of anxiety-like behaviour of sons and the metabolic health of daughters.

The research provides a step towards understanding how the effect of diet can transmit from one generation to the next via a father's sperm. It could ultimately inform dietary guidelines for fathers-to-be, with the goal of lowering the risk of metabolic disease and mood disorders in the next generation.

Parents like to believe they can shape the interests and behaviour of their children, with mixed success. But a new study from an international team of researchers confirms this is the case for mice, with father's shaping their offspring's health through their own diet.

Scientists have already discovered that a mouse father's diet can have an impact not only on his own reproductive health but on that of his offspring. Over- or under-feeding male mice can affect their offspring's metabolism and behaviour, as well as their risk of cancer. What is less understood is whether there are diverse types of health impacts on the health of offspring, depending on the type and composition of the diet of male mice before conception.

This was the starting point for the research by scientists in the international GECKO consortium, with lead investigators in Copenhagen, Sydney, and Chicago.

At the University of Sydney's Charles Perkins Centre in Australia researchers fed male mice one of ten diets differing in the proportions of protein, fats, and carbohydrates, then allowed them to mate with females reared on standard diet. The behaviour and physiology of the resulting pups were then studied.

Dietary composition as important as number of calories

The scientists discovered that male mice fed low protein and high carbohydrate diets were more likely to have male offspring with higher levels of anxiety, as measured by time spent in the safety zones of their maze. They also found that male mice that were fed high fat diets were more likely to have daughters with higher levels of body fat and markers of metabolic disease.

"Our study shows that the type of diet eaten before conception can program specific characteristics of the next generation," says co-senior author and leader of the

GECKO consortium Professor Romain Barrès, from the University of Copenhagen and Université Côte d'Azur, Nice.

"It is extraordinary that by titrating mixtures of protein, fat and carbs in the father's diet we could influence specific features of his sons and daughters health and behaviour. There is some important biology at play here," said Professor Stephen Simpson, co-senior author and Academic Director of the Charles Perkins Centre at the University of Sydney.

The team also observed that males on a low protein diet also ate more food overall. However, thanks to the study design, they could determine that both the amount of calories, and the macronutrient composition of the males' diets, influenced the health of their offspring.

"Our study shows that it's not just eating too much or too little, but the composition of the diet that can have an impact on future children," says Professor Romain Barrès.

The work was conducted in mice and has opened the way for the team to study the molecular mechanisms involved. The mouse work is part of a broader series of studies within the GECKO consortium, involving humans and other mammals at partner institutions.

"We think our study is a step towards establishing dietary guidelines for fathers to be, with the ultimate goal of lowering the risk of metabolic disease and mood disorders in the next generation," says Professor Romain Barrès.

Story Source:

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

Journal Reference:

1. Angela Jane Crean, Alistair McNair Senior, Therese Freire, Thomas Daniel Clark, Flora Mackay, Gracie Austin, Tamara Jayne Pulpitel, Marcelo Aguiar Nobrega, Romain Barrès, Stephen James Simpson. **Paternal dietary macronutrient balance and energy intake drive metabolic and behavioral differences among offspring**. *Nature Communications*, 2024; 15 (1) DOI: 10.1038/s41467-024-46782-y

5. ワクチン接種前の代謝の健康状態が抗インフルエンザ反応の有効性を決定 –マウス実験

日付：2024 年 4 月 18 日
ソース：セント・ジュード小児研究病院
概要：

『Nature Microbiology』誌に掲載された研究で、セント・ジュード小児研究病院の研究者らは、肥満マウスをインフルエンザワクチン接種後ではなく接種前に健康的な食事に切り替えると、高 BMI 値にもかかわらず、致死量のインフルエンザウィルスから完全に保護できることを発見した。すなわち、ワクチン接種時に動物が代謝的に健康であれば、ワクチンは効果的に機能し、その逆もまた真で、マウスの外見がどのようなものであっても、代謝機能障害がある場合、ワクチンは効果を発揮しなかった。
これまでの研究では、ワクチン接種後であってもインフルエンザウィルスに曝露されると、肥満マウスの 100%が病気で死亡することが示されていた。科学者らの当初の予想に反して、肥満中にワクチン接種したマウスが健康な体重に戻っても、結果は改善しなかった。ワクチン接種の 4 週間前に健康的な食事に切り替えるだけで、BMI が高いにもかかわらず、劇的な効果で生存率が向上した。
この研究はマウスに限定されていたが、ヒトにおけるインフルエンザワクチンの有効性を改善する研究の機会を開くものだ、としている。この研究結果は、代謝の健康を改善する方法がその後のインフルエンザワクチン接種も改善する可能性があることを示唆している。

研究関連ニュース/他のトップページに戻る

＜英文＞Study shows metabolic health before vaccination determines effectiveness of anti-flu response (medicalxpress.com)

APRIL 18, 2024

Editors' notes

Study shows metabolic health before vaccination determines effectiveness of anti-flu response

by St. Jude Children's Research Hospital

Credit: Unsplash/CC0 Public Domain

Metabolic health (normal blood pressure, blood sugar and cholesterol levels, among other factors) influences the effectiveness of influenza vaccinations. Vaccination is known to be less effective in people with obesity compared to those with a healthier body mass index (BMI), but St. Jude Children's Research Hospital scientists have found it is not obesity itself, but instead metabolic dysfunction, which makes the difference.

In a study published today in *Nature Microbiology*, the researchers found switching obese mice to a healthy diet before flu vaccination, but not after, completely protected the models from a lethal dose of flu, despite BMI.

"We found that the vaccines worked effectively if at the time of vaccination an animal is metabolically healthy," said corresponding author Stacey Schultz-Cherry, Ph.D., St. Jude Department of Host-Microbe Interactions and Center of Excellence for Influenza Research and Response co-director. "And the opposite was also true: Regardless of what the mice looked like on the outside, if they had metabolic dysfunction, the vaccines did not work as well."

Prior research has shown that when exposed to influenza virus, even after vaccination, 100% of obese mice succumbed to disease. Contrary to the scientists' original expectations, when mice who were vaccinated while obese returned to a healthy weight, outcomes did not improve. These now outwardly healthy mice still all succumbed to disease when exposed to the real virus. Only switching to a healthy diet four weeks before vaccination improved survival, with drastic effect, despite high BMI.

"We were excited to see this effect because mice with obesity are so susceptible to severe disease and succumbing to the infection," Schultz-Cherry said. "Getting 100% survival with the vaccine where we had only seen 0% survival was impressive." The improved survival suggests the researchers have discovered a greater underlying principle determining influenza vaccine efficacy.

Metabolic dysfunction hinders the immune system

While studying how metabolic function influences influenza vaccine responses, the scientists found that poor metabolic health causes immune system dysfunction. T cells, the primary immune cells involved in anti-viral responses, failed to act in animals that had been in an unhealthy metabolic state at the time of vaccination, even during later viral exposure. Even when the animals ate a healthy diet after vaccination and maintained a normal BMI, the anti-flu T cells were "frozen" in that dysfunctional state.

However, a healthy diet before vaccination improved T-cell function, which resulted in a robust anti-flu response during later exposure.

"The T cells were better able to do their job in the metabolically healthy mice at the time of vaccination," Schultz-Cherry said. "It wasn't a matter of the numbers of them or the types of them. It was their functional activity. There were plenty of them in the lungs, not working. The healthy diet switched them from not working to functioning properly, but only if the switch occurred before vaccination."

The earlier healthy diet also improved inflammation. Pro-inflammatory cytokines are upregulated in obese animals. Schultz-Cherry's team found that models also returned to a lower basal cytokine level when switched to a healthy diet before vaccination.

"A healthy diet lowered some of the systemic meta-inflammation in these animals, and they regained some of the epithelial innate immune responses," said Schultz-Cherry. "We started seeing better signaling of things like interferons, which we know is problematic in obesity and in general saw the immune system starting to function the way that it should."

Improving metabolic health may improve influenza vaccine effectiveness

"What we found and are emphasizing is that it's not the phenotype of obesity that matters; it's really about metabolic health," Schultz-Cherry said. "It's metabolic health at that moment of vaccination that really makes a difference."

The study was restricted to mice, but it does open research opportunities to improve influenza vaccine efficacy in humans. The findings suggest methods of improving metabolic health may also improve subsequent influenza vaccinations. Given the recent introduction of metabolic improvement drugs, especially glucagon-like peptide 1 (GLP-1) agonists, there may be potential for a cooperative effect.

"We don't know for sure, but if the outcome of using GLP-1 drugs is weight loss and improved metabolic health, we would hypothesize that it will help," Schultz-Cherry said. "But we do know that we can do better protecting our vulnerable populations, and this study is a start for understanding how."

More information: Rebekah Honce et al, Diet switch pre-vaccination improves immune response and metabolic status in formerly obese mice, *Nature Microbiology* (2024). DOI: 10.1038/s41564-024-01677-y

Journal information: Nature Microbiology

6. 米ぬか由来ナノ粒子の抗がん作用を確認 –マウス実験
～未利用資源を原料とした安価で安全なナノ粒子製剤開発に期待～

日付：2024 年 4 月 22 日
ソース：東京理科大学
概要： https://www.tus.ac.jp/today/archive/20240422_3252.html

東京理科大学薬学部薬学科の西川 元也教授、鈴木 日向子氏（2021 年度卒業）、板倉 祥子助教、同大学薬学研究科薬科学専攻の佐々木 大輔氏（2023 年度博士後期課程修了）、同大学薬学部生命創薬科学科の草森 浩輔准教授らの研究グループは、エクソソーム様の米ぬか由来ナノ粒子（rbNPs; rice bran-derived nanoparticles）が優れた抗がん活性を有することを明らかにしました。
近年、植物由来のナノ粒子は低コストで大量に調製可能であり、医薬的に有用な生理活性を示す報告が相次いでいます。精米過程で発生する副産物である米ぬかはあまり活用されておらず、大量に廃棄されています。しかし、米ぬかにはγ-オリザノールやγ-トコトリエノールなど抗がん作用を示すさまざまな物質が含まれることから、rbNPs はがん治療の新規治療薬候補として有望であろうと期待されます。
本研究グループは、コシヒカリの米ぬかをリン酸緩衝生理食塩水に懸濁し、遠心分離後、シリンジフィルターで濾過した濾液を超遠心分離した沈殿物を懸濁することで rbNPs を得ました。
rbNPs はがん細胞にのみ特異的に細胞傷害作用を示し、マウス結腸がん colon26 細胞に対して、他の植物由来ナノ粒子や抗がん剤として用いられているドキシル®よりも高い細胞傷害作用を示しました。その背景には、β-カテニンやサイクリン D1 などの発現抑制を通じてがん細胞の細胞周期を停止させ、アポトーシスを誘導するというメカニズムがあることも突き止めました
rbNPs が培養細胞だけでなく、動物レベルでもこうした抗がん作用を示すかを確かめるために、colon26 細胞を移植した腹膜播種モデルマウスに rbNPs を腹腔内投与しました。その結果、rbNPs は副作用を示すことなく、がん細胞の増殖を顕著に抑制しました。
以上の結果から、rbNPs は新たながん治療薬候補として極めて有望であることが示唆されました。
本研究成果は、2024 年 3 月 16 日に国際学術誌「Journal of Nanobiotechnology」にオンライン掲載されました。

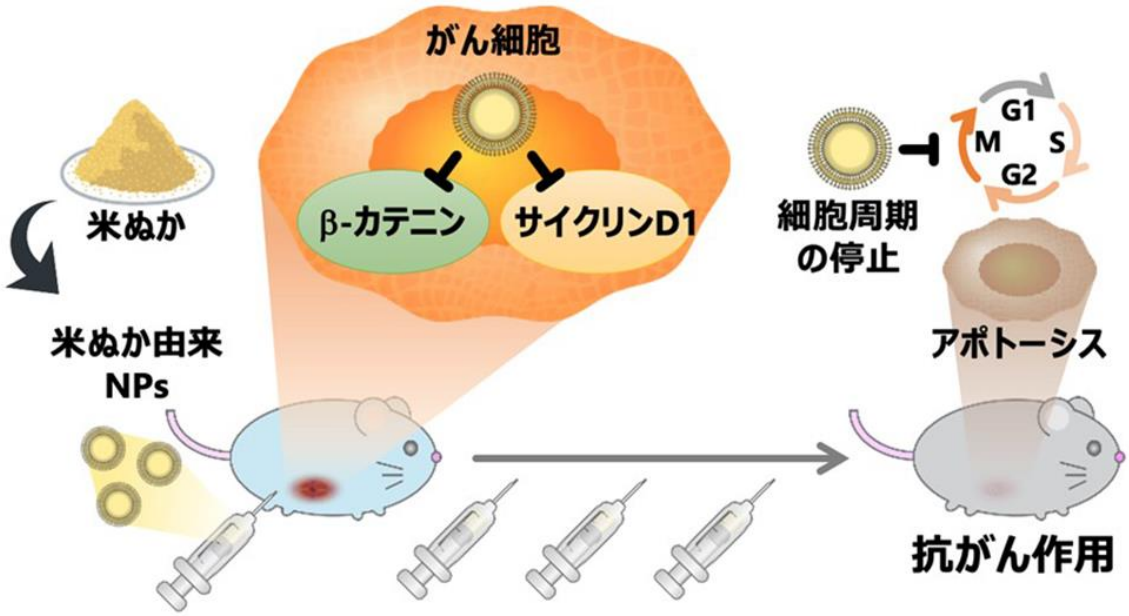


図. 本研究の概要。rbNPs は細胞周期を停止させ、アポトーシスを誘導することで抗がん作用を示すことが明らかになった。

研究関連ニュース/他のトップページに戻る

＜英文＞Breakthrough rice bran nanoparticles show promise as affordable and targeted anticancer agent | ScienceDaily

Breakthrough rice bran nanoparticles show promise as affordable and targeted anticancer agent

Researchers discover that nanoparticles derived from rice bran are both effective and safe for the treatment of cancer

Date:

April 22, 2024

Source:

Tokyo University of Science

Summary:

Plant-derived nanoparticles have demonstrated significant anticancer effects. Researchers recently developed rice bran-derived nanoparticles (rbNPs) that

efficiently suppressed cell proliferation and induced programmed cell death of only cancer cells. Furthermore, rbNPs successfully suppressed the growth of tumors in mice having aggressive adenocarcinoma in their peritoneal cavity, without any adverse effects. Given their low production costs and high efficacy, rbNPs hold great promise for developing affordable and safe anticancer agents.

FULL STORY

Plant-derived nanoparticles have demonstrated significant anticancer effects. Researchers recently developed rice bran-derived nanoparticles (rbNPs) that efficiently suppressed cell proliferation and induced programmed cell death of only cancer cells. Furthermore, rbNPs successfully suppressed the growth of tumors in mice having aggressive adenocarcinoma in their peritoneal cavity, without any adverse effects. Given their low production costs and high efficacy, rbNPs hold great promise for developing affordable and safe anticancer agents.

Several types of conventional cancer therapies, such as radiotherapy or chemotherapy, destroy healthy cells along with cancer cells. In advanced stages of cancer, tissue loss from treatments can be substantial and even fatal. Cutting-edge cancer therapies that employ nanoparticles can specifically target cancer cells, sparing healthy tissue. Recent studies have demonstrated that plant-derived nanoparticles (pdNPs) that have therapeutic effects can be an effective alternative to traditional cancer treatments. However, no pdNPs have been approved as anticancer therapeutic agents till date.

Rice bran is a byproduct generated during rice refining process that has limited utility and low commercial value. However, it contains several compounds with anticancer properties, such as γ-oryzanol and γ-tocotrienol. To explore these therapeutic properties of rice bran, a team of researchers led by Professor Makiya Nishikawa from Tokyo University of Science (TUS) in Japan developed nanoparticles from rice bran and tested their effectiveness in mice models. Their study, published in Volume 22 of Journal of Nanobiotechnology on 16 March 2024, was co-authored by Dr. Daisuke Sasaki, Ms. Hinako Suzuki, Associate Professor Kosuke Kusamori, and Assistant Professor Shoko Itakura from TUS.

"In recent years, an increasing number of new drug modalities are being developed. At the same time, development costs associated with novel therapies have increased dramatically, contributing to the burden of medical expenses. To address this issue, we used rice bran, an industrial waste with anticancer properties, to develop nanoparticles," explains Prof. Nishikawa.

The study evaluated the anticancer effects of rice bran-derived nanoparticles (rbNPs), which were obtained by processing and purifying a suspension of Koshihikari rice bran in water. When a cancer cell line named colon26 was treated with rbNPs, cell division was arrested and programmed cell death was induced,

indicating strong anticancer effects of the nanoparticles. The observed anticancer activity of rbNPs can be attributed to γ-tocotrienol and γ-oryzanol, that are easily taken up by cancer cells resulting in cell cycle arrest and programmed cell death. Additionally, rbNPs reduced the expression of proteins, such as β-catenin (a protein associated with Wnt signaling pathway involved in cell proliferation) and cyclin D1, which are known to promote cancer recurrence and metastases. Moreover, the rbNPs reduced the expression of β-catenin only in colon26 cells without affecting the non-cancerous cells.

"A key concern in the context of pdNPs is their low pharmacological activity compared to pharmaceutical drugs. However, rbNPs exhibited higher anticancer activity than DOXIL®, a liposomal pharmaceutical formulation of doxorubicin. Additionally, doxorubicin is cytotoxic to both cancer cells and non-cancerous cells, whereas rbNPs are specifically cytotoxic to cancer cells, suggesting that rbNPs are safer than doxorubicin," highlights Prof.Nishikawa.

To confirm the anticancer properties of rbNPs in the living body, the researchers injected rbNPs into mice having aggressive adenocarcinoma in their peritoneal cavity (enclosed by the diaphragm, abdominal muscles, and pelvis and houses organs like intestines, liver, and kidneys). They observed significant suppression of tumor growth with no adverse effects on the mice. Additionally, the rbNPs significantly inhibited metastatic growth of murine melanoma B16-BL6 cells in a lung metastasis mouse model.

Rice bran has several attributes that make it an excellent source of therapeutic pdNPs. Firstly, it is economic as compared to many other sources of pdNPs. Nearly 40% of the rice bran is discarded in Japan, providing a readily available source of raw material. Secondly, the preparation efficiency of rbNPs is higher than that of previously reported pdNPs. Besides being practical and safe as an anticancer therapeutic, the physicochemical properties of rbNPs are very stable. However, a few parameters, such as establishment of separation technologies at the pharmaceutical level, assessing production process control parameters, and evaluation of efficacy and safety in human cancer cell lines and xenograft animal models, must be investigated prior to clinical trials in humans.

In conclusion, rice bran, an agricultural waste product, is a source of therapeutic pdNPs that are affordable, effective, and safe, and has the potential to revolutionize cancer treatment in the future.

"By establishing a manufacturing method for rice bran nanoparticles with stable quality and confirming their safety and effectiveness, we can develop drugs for cancer treatment that are sustainable, eco-friendly, and affordable. Consequently, we may be able to help more cancer patients maintain good physical and mental health after treatment," concludes Prof. Nishikawa.

Story Source:

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

Journal Reference:

1. Daisuke Sasaki, Hinako Suzuki, Kosuke Kusamori, Shoko Itakura, Hiroaki Todo, Makiya Nishikawa. **Development of rice bran-derived nanoparticles with excellent anti-cancer activity and their application for peritoneal dissemination**. *Journal of Nanobiotechnology*, 2024; 22 (1) DOI: 10.1186/s12951-024-02381-z

7. てんかん治療薬が神経線維腫症 1 型マウスの脳腫瘍を予防

日付：2024 年 4 月 15 日
ソース：ワシントン大学医学部
概要：

セントルイスのワシントン大学医学部の研究者らの研究によると、てんかんの小児の治療に使用される薬剤が、神経線維腫症 1 型（NF1）の 2 匹のマウスモデルにおいて脳腫瘍の形成と増殖を抑制したことが明らかになった。
NF1 は、目と脳をつなぐ視神経を含む、全身の神経上で腫瘍の増殖を引き起こす遺伝的疾患である。
研究者らが、腫瘍を抱えたマウスを生後 12 週から 4 週間治療したところ、腫瘍の成長が止まり、目の網膜へのさらなる損傷も見られなかった。腫瘍が出現する前の生後 4 週目から 4 週間の薬剤投与を受けたマウスは、治療終了から 4 カ月経っても腫瘍の増殖を示さなかった。これらの発見により、研究者らは、おそらく 2 歳から 4 歳の NF1 の幼児に対する 1 年間の治療で、脳腫瘍のリスクを軽減するのに十分である可能性があると示唆している。
この発見は、薬剤ラモトリギンが NF1 患者の脳腫瘍を予防または遅延できるかどうかを評価する臨床試験の基礎となるとして、『Neuro-Oncology』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

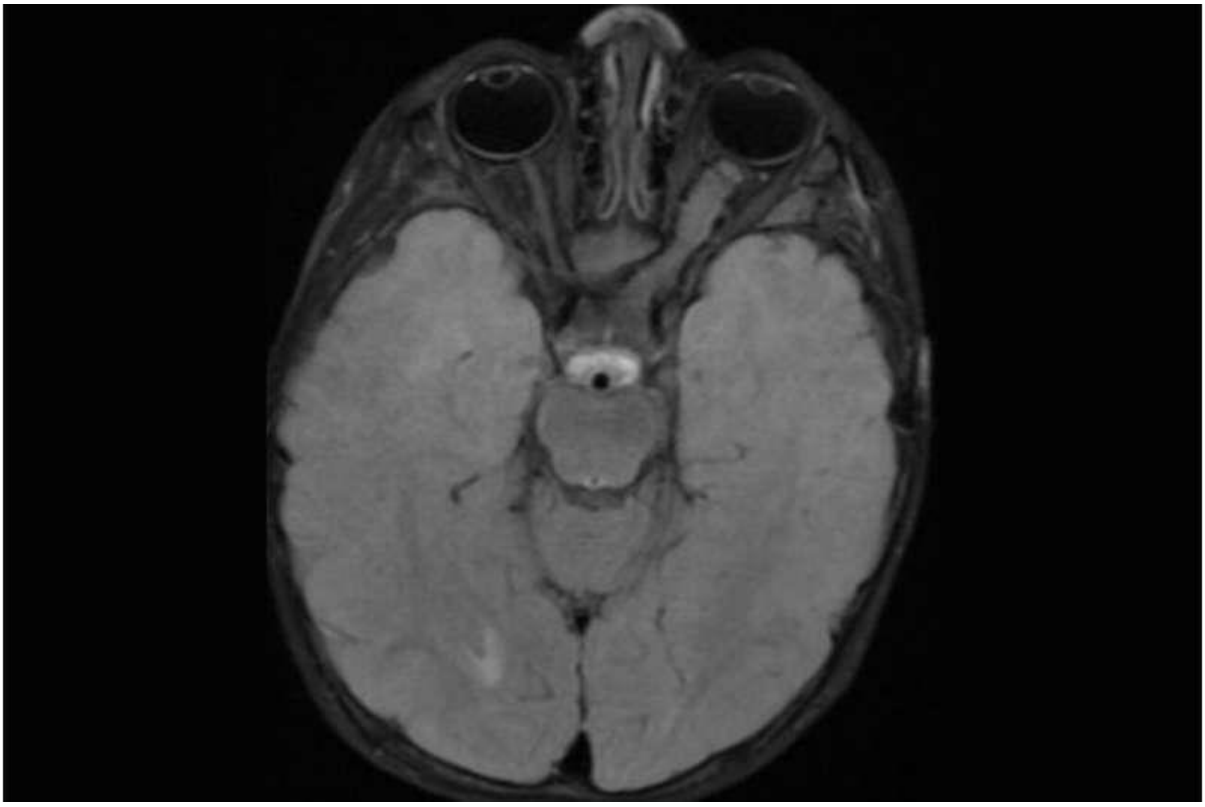
＜英文＞Epilepsy drug prevents brain tumors in mice with neurofibromatosis type 1 (medicalxpress.com)

APRIL 15, 2024

Editors' notes

Epilepsy drug prevents brain tumors in mice with neurofibromatosis type 1

by Washington University School of Medicine



A brain scan of a neurofibromatosis type 1 (NF1) patient reveals a tumor on the optic nerve connecting the left eye to the brain (right side of the image). Researchers at Washington University School of Medicine in St. Louis have discovered that an FDA-approved epilepsy drug can prevent or slow the growth of NF1-linked optic gliomas in mice, laying the groundwork for a clinical trial. Credit: Robert McKinstry/Washington University

A drug used to treat children with epilepsy prevents brain tumor formation and growth in two mouse models of neurofibromatosis type 1 (NF1), according to a study by researchers at Washington University School of Medicine in St. Louis. NF1 is a genetic condition that causes tumors to grow on nerves throughout the body, including the optic nerves, which connect the eyes to the brain.

The findings lay the groundwork for a clinical trial to assess whether the drug, lamotrigine, can prevent or delay brain tumors in children with NF1. The study is published in the journal *Neuro-Oncology*.

"Based on these data, the Neurofibromatosis Clinical Trials Consortium is considering launching a first-of-its-kind prevention trial," said senior author David H. Gutmann, MD, Ph.D., the Donald O. Schnuck Family Professor of Neurology and the director of Washington University's Neurofibromatosis Center. The clinical trials consortium is an international network of NF scientists that was formed by the U.S. Department of Defense in 2006 to find therapies for all forms of neurofibromatosis. "The plan is to enroll kids without symptoms, treat them for a limited time, and then see whether the number of children who develop tumors that require treatment goes down.

"This is a novel idea, so we took it to an NF1 patient focus group," Gutmann continued. "They said, 'This is exactly what we're looking for.' A short-term treatment with a drug that has been used safely for 30 years was acceptable to them if it reduced the chance their children would develop tumors and need chemotherapy that might have all kinds of side effects."

The most serious tumors that people with NF1 get affect the optic nerve and are known as optic gliomas. Such tumors typically appear between ages 3 and 7. While they are rarely fatal, they cause vision loss in up to a third of patients as well as other symptoms, including early puberty. Standard chemotherapy for optic gliomas is only moderately effective at preventing further vision loss and can affect children's developing brains, resulting in cognitive and behavioral problems.

In a previous study, Gutmann and Corina Anastasaki, Ph.D., an assistant professor of neurology and the first author on the new paper, showed that lamotrigine stopped optic glioma growth in NF1 mice by suppressing neuronal hyperactivity.

The Neurofibromatosis Clinical Trial Consortium found their data intriguing but demanded more evidence before they would consider launching a clinical trial. The consortium members asked Gutmann and Anastasaki to clarify the connection between Nf1 mutation, neuronal excitability and optic gliomas; assess whether lamotrigine was effective at the doses already proven safe in children with epilepsy; and conduct these studies in more than one strain of NF1 mice.

In people, NF1 is a highly variable disease. It can be caused by any one of thousands of different mutations in the NF1 gene, where different mutations could be associated with different medical problems. Repeating experiments in multiple strains of mice was a way of gauging whether lamotrigine was likely to work in people regardless of the underlying mutation.

Anastasaki and Gutmann not only showed that lamotrigine worked in two strains of NF1 mice, they also showed that the drug worked at lower doses than those used for epilepsy, meaning that it was probably safe. Even better, they found that a short course of the drug had lasting effects, both as a preventive and a treatment.

Mice that had tumors and that were treated for four weeks starting at 12 weeks of age saw their tumors stop growing and even showed no further damage to the retinas of their eyes. Mice that received a four-week course of the drug starting at 4 weeks of age, before tumors typically emerge, showed no tumor growth even four months after treatment had ended.

These findings have led Gutmann to suggest that a one-year course of treatment for young children with NF1, maybe between the ages of 2 to 4, might be enough to reduce their risk of brain tumors.

"The idea that we might be able to change the prognosis for these kids by intervening within a short time window is so exciting," Gutmann said. "If we could just get them past the age when these tumors typically form, past age 7, they may

never need treatment. I'd love it if I never again had to discuss chemotherapy for kids who aren't even in first grade yet."

More information: Corina Anastasaki et al, NF1 mutation-driven neuronal hyperexcitability sets a threshold for tumorigenesis and therapeutic targeting of murine optic glioma, *Neuro-Oncology* (2024). DOI: 10.1093/neuonc/noae054

Provided by Washington University School of Medicine

8. ビタミン D がマウスの腸内細菌を変化させて癌免疫を向上させる

日付：2024 年 4 月 25 日
ソース：フランシス・クリック研究所
概要：

英国のフランシス・クリック研究所、米国国立衛生研究所（NIH）の国立がん研究所（NCI）、デンマークのオールボー大学の研究チームは、ビタミン D がマウスの腸内細菌の一種の増殖を促進し、癌免疫力を向上させることを発見した。
4 月 22 日の『Science』誌に報告されたところによると、研究者らは、ビタミン D が豊富な食餌を与えられたマウスは、実験的に移植された癌に対する免疫抵抗力が向上し、免疫療法治療に対する反応が改善された。この効果は、血液中のビタミン D に結合して組織から遠ざけるタンパク質を遺伝子編集で除去したときにも見られた。驚くべきことに、研究チームはビタミン D が腸内の上皮細胞に作用し、その結果バクテロイデス・フラジリスと呼ばれる細菌の量を増加させることを発見した。移植された腫瘍がそれほど増殖しなかったため、この微生物はマウスに癌に対するより良い免疫を与えたが、研究者らはまだその仕組みを解明できていない。この細菌だけでより優れた癌免疫が得られるかどうかをテストするために、通常の食餌を与えたマウスにバクテロイデス フラジリスを与えたところ、これらのマウスは腫瘍の増殖にもよりよく抵抗できたが、ビタミン D 欠乏食を与えた場合はそうではなかった。これまでの研究では、ヒトにおけるビタミン D 欠乏症と癌リスクとの関連性が示唆されているが、その証拠はまだ決定的になっていない。
研究者らは、ビタミン D 欠乏症を改善することがヒトに対しても癌予防と治療に効果があると最終的に言えるようになるには、さらなる研究が必要だとしている。

研究関連ニュース/他のトップページに戻る

＜英文＞Vitamin D alters mouse gut bacteria to give better cancer immunity | ScienceDaily

Vitamin D alters mouse gut bacteria to give better cancer immunity

Date:

April 25, 2024

Source:

The Francis Crick Institute

Summary:

Researchers have found that vitamin D encourages the growth of a type of gut bacteria in mice which improves immunity to cancer.

FULL STORY

Researchers at the Francis Crick Institute, the National Cancer Institute (NCI) of the U.S. National Institutes of Health (NIH) and Aalborg University in Denmark, have found that vitamin D encourages the growth of a type of gut bacteria in mice which improves immunity to cancer.

Reported today in *Science*, the researchers found that mice given a diet rich in vitamin D had better immune resistance to experimentally transplanted cancers and improved responses to immunotherapy treatment. This effect was also seen when gene editing was used to remove a protein that binds to vitamin D in the blood and keeps it away from tissues.

Surprisingly, the team found that vitamin D acts on epithelial cells in the intestine, which in turn increase the amount of a bacteria called *Bacteroides fragilis*. This microbe gave mice better immunity to cancer as the transplanted tumours didn't grow as much, but the researchers are not yet sure how.

To test if the bacteria alone could give better cancer immunity, mice on a normal diet were given *Bacteroides fragilis*. These mice were also better able to resist tumour growth but not when the mice were placed on a vitamin D-deficient diet.

Previous studies have proposed a link between vitamin D deficiency and cancer risk in humans, although the evidence hasn't been conclusive.

To investigate this, the researchers analysed a dataset from 1.5 million people in Denmark[1], which highlighted a link between lower vitamin D levels and a higher risk of cancer. A separate analysis of a cancer patient population also suggested that people with higher vitamin D levels[2] were more likely to respond well to immune-based cancer treatments.

Although *Bacteroides fragilis* is also found in the microbiome in humans, more research is needed to understand whether vitamin D helps provide some immune resistance to cancer through the same mechanism.

Caetano Reis e Sousa, head of the Immunobiology Laboratory at the Crick, and senior author, said: "What we've shown here came as a surprise -- vitamin D can regulate the gut microbiome to favour a type of bacteria which gives mice better immunity to cancer.

"This could one day be important for cancer treatment in humans, but we don't know how and why vitamin D has this effect via the microbiome. More work is needed before we can conclusively say that correcting a vitamin D deficiency has benefits for cancer prevention or treatment."

Evangelos Giampazolias, former postdoctoral researcher at the Crick, and now Group Leader of the Cancer Immunosurveillance Group at the Cancer Research UK Manchester Institute, said: "Pinpointing the factors that distinguish a 'good' from a 'bad' microbiome is a major challenge. We found that vitamin D helps gut bacteria to elicit cancer immunity improving the response to immunotherapy in mice.

"A key question we are currently trying to answer is how exactly vitamin D supports a 'good' microbiome. If we can answer this, we might uncover new ways in which the microbiome influences the immune system, potentially offering exciting possibilities in preventing or treating cancer."

Romina Goldszmid, Stadtman Investigator in NCI's Center For Cancer Research, said: "These findings contribute to the growing body of knowledge on the role of microbiota in cancer immunity and the potential of dietary interventions to fine-tune this relationship for improved patient outcomes. However, further research is warranted to fully understand the underlying mechanisms and how they can be harnessed to develop personalized treatment strategies."

This research was funded by Cancer Research UK, the UK Medical Research Council, the Wellcome Trust, an ERC Advanced Investigator grant, a Wellcome Investigator Award, a prize from the Louis-Jeantet Foundation, the Intramural Research Program of the NCI, part of the National Institutes of Health, CCR-NCI and the Danish National Research Foundation.

Research Information Manager at Cancer Research UK, Dr Nisharnthi Duggan said: "We know that vitamin D deficiency can cause health problems, however, there isn't enough evidence to link vitamin D levels to cancer risk. This early-stage research in mice, coupled with an analysis of Danish population data, seeks to address the evidence gap. While the findings suggest a possible link between vitamin D and immune responses to cancer, further research is needed to confirm this.

"A bit of sunlight can help our bodies make vitamin D but you don't need to sunbathe to boost this process. Most people in the UK can make enough vitamin D by spending short periods of time in the summer sun. We can also get vitamin D from our diet and supplements. We know that staying safe in the sun can reduce the risk of cancer, so make sure to seek shade, cover up and apply sunscreen when the sun is strong."

Story Source:

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

Journal Reference:

1. Evangelos Giampazolias, Mariana Pereira da Costa, Khiem C. Lam, Kok Haw Jonathan Lim, Ana Cardoso, Cécile Piot, Probir Chakravarty, Sonja Blasche, Swara Patel, Adi Biram, Tomas Castro-Dopico, Michael D. Buck, Richard R. Rodrigues, Gry Juul Poulsen, Susana A. Palma-Duran, Neil C. Rogers, Maria A. Koufaki, Carlos M.

Minutti, Pengbo Wang, Alexander Vdovin, Bruno Frederico, Eleanor Childs, Sonia Lee, Ben Simpson, Andrea Iseppon, Sara Omenetti, Gavin Kelly, Robert Goldstone, Emma Nye, Alejandro Suárez-Bonnet, Simon L. Priestnall, James I. MacRae, Santiago Zelenay, Kiran Raosaheb Patil, Kevin Litchfield, James C. Lee, Tine Jess, Romina S. Goldszmid, Caetano Reis e Sousa. **Vitamin D regulates microbiome-dependent cancer immunity**. *Science*, 2024; 384 (6694): 428
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