Bio News – January, 2023

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

12/1　Pfizer が 13 億ドル近くを投じてアイルランドの工場を拡張

12/2　世界人口の 9 割はコロナに免疫 -WHO 推定

世界保健機関（WHO）のテドロス・アダノム・ゲブレイェスス（Tedros Adhanom Ghebreyesus）事務局長は 2 日、世界人口の少なくとも 90%は感染やワクチン接種により新型コロナウイルスに対してある程度の免疫を獲得していると推定されるが、懸念される変異株（VOC）が新たに出現する余地はまだ残っていると警告した。

12/4　Y 染色体なしでなぜオスに？　奄美大島のトゲネズミの謎、明らかに

オスになることを決める「Y 染色体」がないのに、オスが生まれる哺乳類「アマミトゲネズミ」。その性別が決まるしくみを北海道大などの研究グループが明らかにした。哺乳類で、Y 染色体が関与せず性別が決まる仕組みの解明は世界初という。進化を先取りしているとも言え、ヒトを含む哺乳類の未来の姿を考える手がかりになるという。

12/4　iPS 細胞を活用し化学物質の安全評価…動物実験の代替へ期待

厚生労働省は来年度から、iPS 細胞（人工多能性幹細胞）で作った人の神経などの細胞や、ミニ臓器「オルガノイド」を使い、化学物質が人体にとって有害かどうかを調べる新手法の開発に乗り出す。人に近い条件で確認できる利点を生かした手法を国際標準とするのが狙い。日本発の再生医療技術の有用性を世界に広くアピールし、ミニ臓器量産など新産業の育成にもつなげたい考えだ。

12/4　米国の M 痘（mpox）緊急事態が来年 1 月末で終わる見込み

12/5　JCR ファーマが本庶佑氏の基金に 100 万株寄付　年間 2 千万円の配当見込み

京都大と医薬品メーカーの JCR ファーマ（兵庫県芦屋市）は 5 日、ノーベル賞受賞者の本庶佑(ほんじょたすく)特別教授が京大に創設した若手研究者支援などの基金に、同社が自社株式 100 万株を寄付することで合意したと発表した。年間約 2 千万円の配当金が充てられる見通しで、民間企業による国立大への株式での寄付は全国で初めてだとしている。

12/7　腕前は熟練技術者並み　AI ロボットで iPS 細胞培養　理研

人工知能（AI）で制御したロボットが、試行錯誤を重ねながら人工多能性幹細胞（iPS 細胞）を培養する実験の一部を、理化学研究所などの研究チームが 7 日までに公開した。AI が試薬濃度や処理時間などを少しずつ変えながら最適な方法を自ら見つけ出し、熟練技術者並みの成功率を出したという。

12/8　第一三共/AstraZeneca のエンハーツが HER2+転移性乳癌患者の生存を有意に改善

12/9　世界初 「ひも状」の iPS 細胞を目の難病患者に移植　神戸アイセンター

12/9　痛風の炎症、細胞内たんぱく質が関与　新たなメカニズムを解明　大阪大

12/9　ウイルス増殖に必要な因子　おたふくかぜで発見　東大

おたふくかぜ（流行性耳下腺炎）の原因となるムンプスウイルス（MuV）の増殖に必要なたんぱく質を発見したと、東京大の加藤大志准教授らの研究チームが 8 日付の米科学誌電子版に発表した。

12/9　睡眠の量と深さ、脳の別々の場所で制御　筑波大など研究チーム解明

睡眠の量（時間）と深さは脳の別々の場所で制御されていることをマウスの実験で明らかにしたと、筑波大などの研究チームが 7 日付の英科学誌「ネイチャー」で発表した。睡眠の深さは、脳の表層部の「大脳皮質」で、睡眠時間は生理機能をつかさどる脳の中枢「視床下部」で制御されていた。また、眠気を引き起こす脳内での分子の情報伝達経路も分かったという。

12/9　生物多様性保全、報告と検証の新しい仕組み導入へ　COP15 で議論

カナダのモントリオールで開かれている、国連の生物多様性条約締約国会議（COP15）で、2030 年までの生物多様性に関する国際目標に、取り組み状況を報告・評価する新たな仕組みが作られる方向になった。透明性を高めて、目標達成に向けた対策強化を促す狙いがある。今後、具体的な内容を調整する。

12/9　欧州が武田薬品のデング熱ワクチン Qdenga を承認

https://www.reuters.com/business/healthcare-pharmaceuticals/urgent-takedas-dengue-vaccine-wins-eu-approval-2022-12-08/

12/10 英近衛兵の帽子を人工毛皮に PETA が国防省提訴

動物愛護団体「動物の倫理的扱いを求める人々の会（PETA）」は 9 日、英国の近衛兵らが使用するベアスキン（熊の毛皮）製帽子について、フェイクファー製の代用品への切り替えを拒否している英国防省を提訴したと発表した。

12/10　サイ iPS から卵子のもと作製　世界初、「絶滅防ぐ一手に」

世界に雌 2 頭しかおらず、絶滅の危機にあるキタシロサイの人工多能性幹細胞（iPS 細胞）から、卵子と精子のもとになる細胞を作製することに世界で初めて成功したと、大阪大の林克彦教授（生殖遺伝学）らの国際チームが 9 日、米科学誌に発表した。

12/12　ニュージーランド、2025 年までの喫煙根絶を目指す

ニュージーランドでの喫煙を 2025 年までに実質的に根絶するための法案の成立の可否が今週同国の議会で決まる。
法案の枠組みは大きく分けて 3 つ：
1、2009 年以降に生まれた人に燃やしタバコ（combustible tobacco）を売るのを違法とすること
2、タバコを売る店を 95%まで減らすこと
3、タバコのニコチン含量を少なくすること
このタバコ根絶法案が成立したら来年 2023 年から実行に移される。

12/12　慢性心不全を遺伝子治療　マウスの心臓ポンプ回復　筑波大など

慢性心不全となったマウスの心臓の細胞で、心臓を形作るのに必要な四つの遺伝子が機能するようにしたところ、血管の詰まった「梗塞（こうそく）巣」の部分が半分に縮み、心機能を改善させることに成功したと、筑波大などの研究チームが明らかにした。 研究チームの家田真樹・筑波大教授は「ポンプの働きがなくなる『心臓の線維化』は、元の状態に戻らないと考えられていたので、新たな治療法に道が開ける可能性がある」と話す。研究結果は、12 日付の米医学専門誌「サーキュレーション」で発表された。

12/13　固形がん抑制する細胞作製　マウスで iPS 細胞を活用　京都大

人工多能性幹細胞（iPS 細胞）を使い、マウスで固形がんの増大を抑制するリンパ球「T 細胞」を作製したと、京都大 iPS 細胞研究所の研究グループが発表した。免疫療法では、血液がんより難易度が

高い固形がんの治療への応用が期待されるという。論文は 13 日、国際科学誌ネイチャー・バイオメディカル・エンジニアリング電子版に掲載される。

12/13　気候難民化が進む先住民の移住資金としてバイデン政権が約 102 億円を拠出

12/13　Amgen がアイルランドの Horizon を 278 億ドルで買収

12/14　若手研究者ら支援する学術賞「神戸賞」創設　生命科学と理工学にまたがる分野
－シスメックス創業者の財団

公益財団法人中谷医工計測技術振興財団（東京、代表理事＝家次恒・シスメックス会長兼社長）は14日、新たな学術賞「神戸賞」を創設すると発表した。バイオメディカルエンジニアリング（生命科学と理工学の融合境界領域）分野で独創的な研究に取り組む日本人が対象。医療産業都市を抱える神戸発の賞として、成長産業育成を後押しする。

12/15　大麻由来のてんかん薬、治験で国内初投与　実用化の可能性

大麻由来の成分を使った医薬品について、英製薬企業の日本法人「GW ファーマ」が 15 日、国内の治験で患者に薬を初投与したと発表した。この薬は海外では「エピディオレックス」と呼ばれて使われている難治性てんかん薬。国内で大麻由来薬が実用化される可能性が出てきた。

12/15　キャベツの葉にアミノ酸を吹きかけ、気孔狭めて細菌病予防 筑波大

キャベツなどの葉にアミノ酸を吹きかけると、空気や水分の出入り口である気孔を狭めて細菌の侵入を抑え、葉が黄色くなったり壊死したりする「黒斑細菌病」の予防に効果があることを発見した。筑波大学の研究グループが発表した。被害が深刻になる中、耐性菌の心配のない対策として有望という。

12/16　米国の製薬業界代表団体 PhRMA を AbbVie が脱退

AbbVie は米国のもう 1 つの主要な製薬業界団体 Biotechnology Innovation Organization も脱退する、とされている。

12/16　糖尿病性認知症の発症を予測するバイオマーカーを発見、世界初

認知症のリスクが高いとされる糖尿病の患者について、認知機能の低下がみられない超早期に将来の発症を予測できる血液中のバイオマーカー（指標）を世界で初めて発見したと、京都医療センター（京都市）などの研究グループが発表。指標の変化をもとに早期治療に取り組むことで、糖尿病性認知症を予防したり発症を遅らせたりすることに役立てられる可能性があるとしている。

12/17　武田薬品が協力する Poseida Therapeutics（本社：カリフォルニア州サンディエゴ）のウイルス要らず血友病遺伝子治療がマウスで有効

12/19　COP15、生物多様性の回復目指す歴史的な目標を採択

カナダ・モントリオールで開催中の国連生物多様性条約第 15 回締約国会議（COP15）は 19 日、環境破壊の影響を受けた生物多様性の回復を目指し、歴史的となる目標を採択した。

12/20　エーザイ、抗てんかん剤の米国での権利譲渡

エーザイは 20 日、抗てんかん剤「フィコンパ」について、米国での商業化の権利を米製薬企業 Catalyst Pharmaceuticals（本社：フロリダ州）に譲渡する契約を結んだと発表した。契約に伴い一時金 1 億 6,000 万ドルを受け取るが、2023 年 3 月期の業績予想に変更はないと説明している。

12/21　耳病薬の試験失敗続きの Otonomy（本社：カリフォルニア州アラモ）が廃業

メニエール病、耳鳴り、難聴の試験の失敗を立て続けに喫した Otonomy が店じまいし、資産を売って得る分を含む現金を株主に配分する。

12/22　Pfizer の潰瘍性大腸炎薬 etrasimod の承認申請を米国と欧州が受理

12/22　査読偽装関与の福井大教授、国の大型研究事業の責任者を辞任

12/22　ヒトの体節形成を再現　iPS 細胞活用　京都大

人工多能性幹細胞（iPS 細胞）を使い、ヒトの背骨などのもとになる体節の形成を再現する細胞培養モデルを作製したと、京都大高等研究院の研究グループが発表した。先天性脊椎疾患などの研究に役立つことが期待されるという。論文は 22 日、英科学誌ネイチャー電子版に掲載される。

12/23　エーザイのアルツハイマー病薬レカネマブと関連しうる 3 人目の死亡例が発生

アルツハイマー病患者の認知機能低下を遅らせることを示して脚光を浴びるエーザイの抗 Aβ 抗体 lecanemab（レカネマブ）投与後の同剤と関連しうる死亡 3 例目が発生したと Science が報じた。
Science が入手した医療記録によると、同剤の進行中の試験の 79 歳の女性被験者が広範囲に及ぶ脳浮腫、出血、発作を起こしてこの 9 月中旬に死亡した。Science の要請でその医療記録を検討した複数の神経科学者はその死亡が lecanemab によって生じたようだと見ている。
エーザイは同剤のプラセボ対照第 3 相試験結果詳細を報告した先月のアルツハイマー病学会でその死亡例を打ち明けなかった。これについてバンダービルト大学の神経科学者 Matthew Schrag 氏は、エーザイとその提携会社 Biogen がその死亡例を学会で知らせなかったことは問題であり、安全性情報が隈なく報告されたという信頼を揺るがす事態だと言っている。

12/23　Gilead の年 2 回投与で事足りる HIV 薬 Sunlenca を米国も承認

12/23　米 CDC が子供の侵襲性 Strep A 症例の増加を警告

12/24　BioNTech がマラリアワクチンの臨床試験開始

12/26　PeptiDream（本社：神奈川県川崎市）が米 Eli Lilly と更なる提携

Eli Lilly は目指す標的へのペプチドをペプチドリームから手に入れ、殺細胞剤付きの薬剤へと誂えてその後の開発の一切を担当。ペプチドリームは Eli Lilly に提供した成果の開発進捗や販売目標達成に応じて最大 12.35 億ドルを得うる権利を手にする。

12/27　感染症研究、日本は世界 12 位　2019～21 年の論文など解析

デジタルサイエンス社によると、日本の 2019～21 年の論文発表などでみた世界ランキングは 12 位で、G7 参加国で最下位だった。研究力の解析などを行う同社は論文、プレプリント（第三者のチェックを受ける前の論文）、抄録（学会発表の要旨）などの刊行物約 130 万のデータベース「ディメンジョンズ」を利用して調べた。ランキング 1 位は米国で、中国、英国などと続いた。米国の刊行物が 17 万 9,465 件あったのに対して、日本は 1 万 8,737 件だった。感染症以外の分野についても調べると、15～21 年の研究分野全体では 5 位、がん研究は 4 位で、感染症研究との差が目立った。質が高いとして研究者が選んだ 82 雑誌のデータベース「ネイチャーインデックス」でみると、感染症研究分野では、スイスやオランダより低調だった。

12/28　香港の Insilico Medicine が全て AI 任せで乳癌薬候補を仕上げた

ER+/HER2−乳癌治療を目指すヒストンアセチル化酵素 KAT6A 阻害剤候補を Insilico Medicine が全部 AI（人工知能）任せの段取りで決定し、治験開始申請に向けた取り組みを始めている。

12/29　あまりの寒さにコウモリ大量落下、救出作戦決行 米テキサス州

寒波に見舞われた米テキサス州ヒューストン（Houston）で、橋の下にすみ着いているコウモリが「低体温でショック状態」になり地面に落ちる出来事があった。動物愛護団体が保護し、28 日には大部分が橋のもといた場所に返された。

12/30　Biogen のアルツハイマー病薬を FDA は内規不遵守で承認したと米国議会が報告

Biogen のいわくつきのアルツハイマー病薬 Aduhelm（アデュヘルム；aducanumab、アデュカヌマブ）を米 FDA は内規に違反して承認し、その承認過程はでたらめだらけだったと米国議会下院の 2 つの委員会・Committee on Oversight and Reform と Committee on Energy and Commerce が報告した。報告によると FDA と Biogen の付き合いは普通ではなく、FDA は自ら定める記録の決まりに従っていなかった。

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. 免疫療法で、MS 様疾患のマウスから疾患の原因となる細胞を除去

2. 子マウスの腸内微生物叢は、母マウスがその子の授乳中に低繊維食を与えられると、永久的に変化する

3. 甘味料と不安の関連性 -マウス研究

4. 腸内細菌が運動へのモチベーションを高める可能性 -マウス研究

5. すぐれた 2 型糖尿病動物モデル -ナイルラット

6. 脂肪肝疾患は脳の健康を危険にさらす -マウス研究

7. 脳が過去の恐怖体験の記憶を保存する方法
   このマウス研究が PTSD 新治療法に繋がる可能性

1. 免疫療法で、MS 様疾患のマウスから疾患の原因となる細胞を除去

日付：2022 年 12 月 5 日
ソース：ワシントン大学医学部
概要：

CAR-T として知られる癌治療は、2017 年に導入されて以来、一部の血液癌の治療に革命をもたらした。
セントルイスにあるワシントン大学医学部の研究者らは、多発性硬化症（MS）に似た自己免疫疾患のマウスを研究しており、同じアプローチを使用して、自己免疫を引き起こす不要な細胞を除去できることを示している。「Science Immunology」誌のオンライン版で入手できるこの調査結果は、免疫療法の強力なツールを、しばしば治療が困難な疾患に拡張するものだ、としている。
CAR-T 癌治療では、医師が患者自身の T 細胞を採取し、特定の癌を認識して積極的に攻撃するように改変し、体内に戻して破壊する。このアプローチに着想を得て、研究者らは、MS を引き起こすローグ T 細胞を探し出して破壊する機能を備えた CAR-T 細胞の作成に着手した。そして MS 様マウスを操作された CAR-T 細胞で治療すると、まだ問題が発生していないマウスの疾患が予防され、神経学的影響を既に示しているマウスに対してはその疾患の兆候が減少した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞Immunotherapy eliminates disease-causing cells in mice with MS-like disease: Successful cancer treatment approach extended to autoimmune disease -- ScienceDaily

Immunotherapy eliminates disease-causing cells in mice with MS-like disease

Successful cancer treatment approach extended to autoimmune disease

Date:

December 5, 2022

Source:

Washington University School of Medicine

Summary:

Researchers have shown that the cancer therapy known as CAR-T can be applied to multiple sclerosis (MS), an autoimmune disease of the nervous system. The findings extend the powerful tool of immunotherapy to autoimmune diseases, a class of diseases that are often debilitating and difficult to treat.

FULL STORY

The cancer therapy known as CAR-T has revolutionized treatment of some blood cancers since it was introduced in 2017. The therapy uses genetically altered immune cells to home in on cancer cells and destroy them.

Now, studying mice with an autoimmune disease similar to multiple sclerosis (MS), researchers at Washington University School of Medicine in St. Louis have shown that the same approach can be used to eliminate unwanted cells that cause autoimmunity. The findings, available online in *Science Immunology*, extend the powerful tool of immunotherapy to a class of diseases that are often debilitating and difficult to treat.

"We were able to use CAR-T cells to eliminate just the immune cells that are causing the autoimmunity and not other immune cells you might need to protect against viruses or other infection," said co-senior author Chyi-Song Hsieh, MD, PhD, the Alan A. and Edith L. Wolff Professor of Rheumatology and a professor of medicine and of pathology & immunology. "Our CAR-T cells were very effective at treating mice that have an MS-like disease."

At the heart of CAR-T therapy are the immune system's T cells, crucial elements of the body's defense force. T cells respond to threats such as bacteria, viruses and cancerous cells by coordinating an immune assault and killing foreign organisms and infected or cancerous cells.

But every once in a while, T cells mistake healthy cells for infected cells and turn their weapons on the body's own cells and tissues, triggering an autoimmune disease. MS is marked by rogue T cells that trigger the destruction of myelin, the protective covering over nerves. As myelin is eaten away, communication between the brain and spinal cord and the rest of the body becomes unreliable, and people begin experiencing symptoms such as fatigue, pain, tingling, vision problems and loss of coordination. Immunosuppressive drugs can quash the self-destructive activity of rogue T cells, but such drugs also suppress helpful T cells and put people at risk of severe infections.

In CAR-T cancer therapies, doctors take a patient's own T cells, modify them to recognize and vigorously attack his or her specific cancer, and then put them back in the body on a seek-and-destroy mission. Inspired by this approach, the researchers set out to create CAR-T cells equipped to seek out and destroy the rogue T cells that cause MS. The idea was to make CAR-T cells that would function akin to a police department's internal affairs office, rooting out the bad apples in the T cells defense force while leaving good T cells in place to protect the body.

"Having MS can really erode your quality of life, and while current therapies slow down the course of the disease, they don't cure it and they have side effects," said co-senior author Gregory F. Wu, MD, PhD, an associate professor of neurology and of pathology & immunology. "I believe that this is a fully treatable disease, and CAR-T cells may be the way toward much better therapeutics."

Along with Hsieh and Wu, the research team included co-authors Nathan Singh, MD, an assistant professor of medicine, and Takeshi Egawa, MD, PhD, an associate professor of pathology & immunology.

First, the researchers made some bait. They designed a molecule by combining a fragment of a protein found in myelin with a protein that activates T cells. Only T cells that target myelin -- the

bad apples, so to speak -- would respond to this hybrid molecule. Then, they loaded the bait molecule onto a kind of T cell known as killer T cells. Any rogue T cells that took the bait would be eliminated by the killer T cells.

That was the idea, at least. To see whether it worked, the researchers turned to mice with an MS-like condition. Treating such mice with the engineered CAR-T cells prevented disease in those that had yet to develop problems, and reduced signs of disease in those that were already showing neurological effects.

"We're working on improving the CAR-T cells, to get them to kill more efficiently and last longer so that we can get better treatment outcomes," Hsieh said. "Right now, there's no way to tell who is going to get MS or when, so preventing disease in people isn't realistic, but we could treat it, and I think the CAR-T approach looks very promising."

The beauty of the CAR-T approach is that by swapping out the protein fragment in the bait molecule, killer T cells can be redirected toward different rogue immune cells to treat different diseases.

"I see patients in the clinic who have a rare disease known as myelin oligodendrocyte glycoprotein (MOG) antibody disease that is very similar to MS," Wu said. "Unlike MS, which is complicated, we know exactly what the target is in MOG antibody disease. I wish I could just get rid of these self-reactive cells for my patients, but we've had no way to do that. Now, we are working toward using the patient's own immune cells to create CAR-T cells that would eliminate those self-reactive T cells."

Story Source:

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

Journal Reference:

1. Jaeu Yi, Aidan T. Miller, Angela S. Archambault, Andrew J. Jones, Tara R. Bradstreet, Sravanthi Bandla, Yu-Sung Hsu, Brian T. Edelson, You W. Zhou, Daved H. Fremont, Takeshi Egawa, Nathan Singh, Gregory F. Wu, Chyi-Song Hsieh. **Antigen-specific depletion of CD4 + T cells by CAR T cells reveals distinct roles of higher- and lower-affinity TCRs during autoimmunity**. *Science Immunology*, 2022; 7 (76) DOI: 10.1126/sciimmunol.abo0777

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2. 子マウスの腸内微生物叢は、母マウスがその子の授乳中に低繊維食を与えられると、永久的に変化する

日付：2022 年 12 月 8 日
ソース：Cell Press
概要：

マウスの新生児が最初に触れたり食べたりするものは、固有の微生物叢を確立し、それは出生時および授乳中の母親の影響を受けることが多い。食事は人生のあらゆる段階で肥満の原因となることが知られているが、授乳中の母親の食事の影響については現在も調査が続けられている。「Cell Host and Microbe」誌で 12 月 8 日に発表されたジョージア州立大学の研究者らによる論文で、研究者らは、授乳中の母マウスに低繊維食を与えると、子マウスの微生物叢が恒久的に変化し、腸の炎症と肥満につながることを発見した。
この論文の上級著者の Andrew Gewirtz 氏と彼のチームは、規則正しいレベルの繊維が微生物叢に燃料を供給し、多様なバクテリアが繁栄できるようにすると信じており、食物繊維がなくなると、食物繊維を必要としていたバクテリアが死滅し、食物繊維を食べないプロテオバクテリアが無防備に増殖する可能性がある、としている。プロテオバクテリアは大規模な細菌群で、これが活性化すると炎症を引き起こす化学物質の放出を引き起こす。細菌はまた、食事からの脂質の取り込みを促進するように腸を変化させ、肥満の増加に寄与する。
さらに、低繊維食の母親によって育てられた子の腸の破壊は、長期にわたる影響を受け、離乳後 9 週間、母マウスが伝統的な食餌を摂った後でも、繊維の少ないマウスの内臓には異常に高い数のプロテオバクテリアが残っており、子マウスの体重は増え続けてた、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞Gut microbiomes of mouse pups are permanently | EurekAlert!

NEWS RELEASE 8-DEC-2022

Gut microbiomes of mouse pups are permanently altered when moms are fed a low-fiber diet while nursing

Peer-Reviewed Publication

CELL PRESS

The first things that mouse newborns touch and eat establishes their native microbiome, which is often influenced by their mother during birth and throughout nursing. Although diet has been a known contributor to obesity in all stages of life, the effects of nursing mothers' diets is an ongoing investigation. In a paper publishing December 8th in the journal *Cell Host and Microbe*, researchers find that when nursing mouse mothers are fed a low-fiber diet, their offspring's microbiome is permanently altered, leading to gut inflammation and obesity.

"We wanted to see what would happen if we gave a low-fiber diet to the mothers at the time their pup's microbiome is being wired," says senior author Andrew Gewirtz, a microbiologist at Georgia State University. "Would we see an increase in obesity in the pups due to an altered gut from their moms' diets?"

Obesity is often attributed to diet, and the consumption of energy-dense meals, such as "fast foods." However, so called "junk food" has been around for decades, but obesity rates continue to climb. Gewirtz and his team sought to learn whether the early microbiome could be an underlying factor that changed one's susceptibility to the ill effects of these diets.

The researchers gave nursing mother mice two different diets, either a fiber-balanced "chow" traditionally used in research mouse studies or a low-fiber food. After three weeks of nursing, the pups were weened, and their microbiome was analyzed through fecal samples.

There was an abundance of Proteobacteria in both the pups and the mothers who were fed low-fiber diets when these were compared to mice fed a traditional diet. Along with altered microbiomes, both mothers and pups had intestinal disruptions, and the pups nearly doubled in weight.

"I was shocked at how quickly the mice gained weight when they were exposed to this diet," says Gewirtz. "The data was striking, and I didn't believe it at first. It took many replications to convince me."

Proteobacteria is a large, well-studied group of bacteria that have surface proteins that can easily activate the innate immune system. This activation alerts the body of an illness and triggers the release of chemicals that cause inflammation. The bacteria also alter the intestines in a way that causes greater uptake of lipids from the diets, contributing to a rise in obesity.

Gewirtz and his team believe that regular levels of fiber help fuel the microbiome in a way that allows diverse bacteria to thrive. It may be that when the fiber is gone, the bacteria that needed it for nourishment die off and Proteobacteria, who don't eat fiber, can grow unchecked.

The gut disruption in the pups nursed by mothers on low-fiber diets had long-lasting effects. After being on the traditional diet for nine weeks after weening, the guts of the low-fiber mice still had unusually high numbers of Proteobacteria, and the pups continued to gain weight.

“I hope this work can shed light onto how complex our metabolism and microbiome really are and how our early life experiences can shape us for the rest of our lives,” says Gewirtz.

###

Financial support was provided by the National Institute of Diabetes and Digestive and Kidney Diseases and the American Diabetes Association.

Cell Host & Microbe, Zou et al., “Maternal fiber deprivation alters microbiota in offspring resulting in low grade inflammation and predisposition to obesity” https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(22)00527-3

Cell Host & Microbe (@cellhostmicrobe), published by Cell Press, is a monthly journal that publishes novel findings and translational studies related to microbes (which include bacteria, fungi, parasites, and viruses). The unifying theme is the integrated study of microbes in conjunction and communication with each other, their host, and the cellular environment they inhabit. Visit http://www.cell.com/cell-host-microbe. To receive Cell Press media alerts, contact press@cell.com.

JOURNAL

Cell Host & Microbe

DOI

10.1016/j.chom.2022.10.014

METHOD OF RESEARCH

Experimental study

SUBJECT OF RESEARCH

Animals

ARTICLE TITLE

Maternal fiber deprivation alters microbiota in offspring resulting in low grade inflammation and predisposition to obesity

ARTICLE PUBLICATION DATE

8-Dec-2022

Media Contact

Megan Keller
Cell Press
press@cell.com

3. 甘味料と不安の関連性 –マウス研究

日付:2022 年 12 月 8 日
ソース:フロリダ州立大学
概要:

フロリダ州立大学医学部の研究者らは、約 5,000 種類のダイエット食品や飲料に含まれる人工甘味料アスパルテームを、マウスの不安様行動と関連付けている。
アスパルテームの影響は、それを摂取したマウスに不安を引き起こすだけでなく、甘味料にさらされたオスから 2 世代にまで広がった、としている。この研究成果は、米国科学アカデミー紀要に掲載されている。
米国食品医薬品局（FDA）は、1981 年にアスパルテームを甘味料として承認し、現在では毎年 5,000 トン近くが生産されている。アスパルテームが消費されると、アスパラギン酸、フェニルアラニン、メタノールになり、これらはすべて中枢神経系に強力な影響を与える可能性がある。この研究において、アスパルテームにさらされたオスから派生した複数の世代で行われたさまざまな迷路テストを通じて、マウスで顕著な不安様行動が観察された。また、ヒトの不安障害の治療薬であるジアゼパムを投与すると、すべての世代のマウスが不安様行動を示さなくなった。
研究者らは、今後の研究により、世代を超えたアスパルテームの効果の伝達に影響を与える分子メカニズムを特定したい、としている。

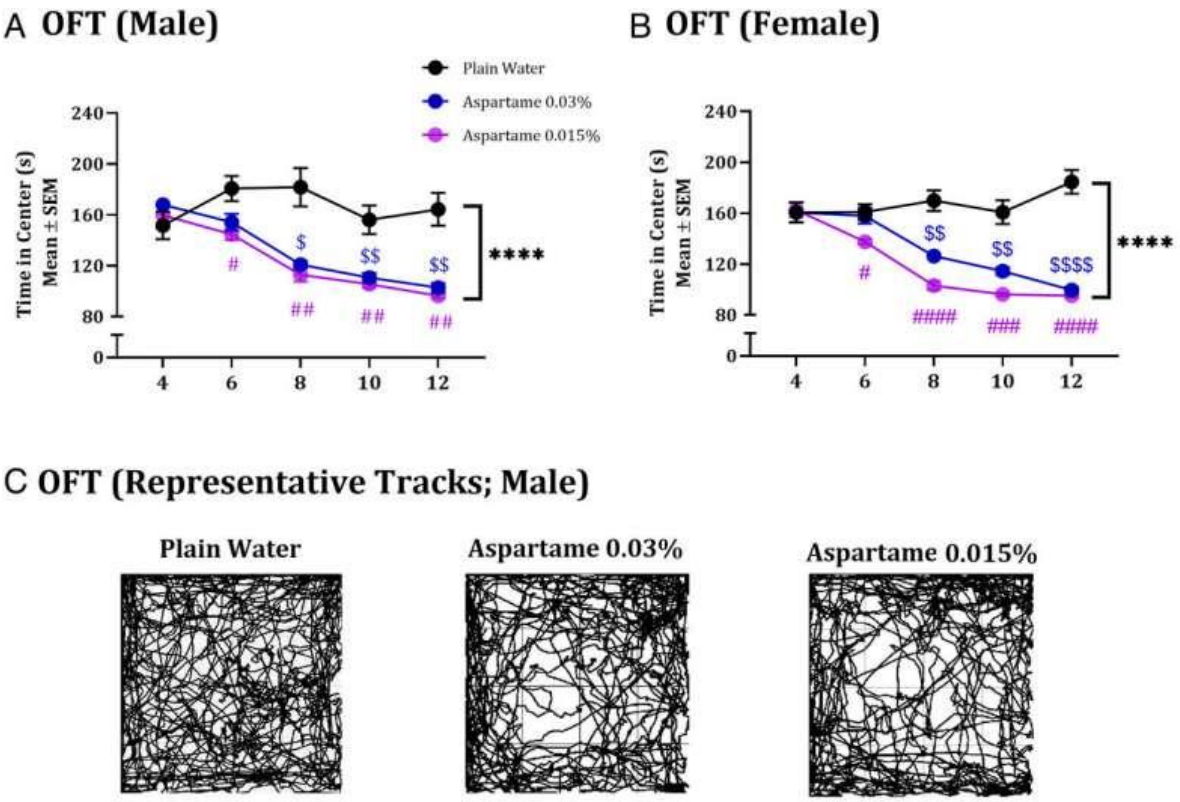
研究関連ニュース/他のトップページに戻る

＜英文＞New research links common sweetener with anxiety (medicalxpress.com)

DECEMBER 8, 2022

New research links common sweetener with anxiety

by Florida State University



Anxiety and its response to diazepam in mice exposed to aspartame-containing drinking water. Anxiety-like responses were analyzed in male and female mice exposed daily to drinking water containing 0.03% aspartame, 0.015% aspartame or to plain drinking water for 12 wk using open field test (OFT; A and B) and elevated zero maze (EZM; D). In the OFT analysis (A and B), two-way ANOVA showed that male (A) and female (B) mice in the 0.03% aspartame group (blue line) and 0.015% aspartame (purple line) groups spent significantly shorter time in the center areas in the OFT compared to their counterparts in the plain drinking water (black) group (**** in A and B). Dunnett's multiple comparisons test showed that significant differences emerged between 0.015% aspartame and plain water groups at 6 wk in males and females and persisted at 8 wk, 10 wk, and 12 wk (A and B). Significant differences between 0.03% aspartame and plain water groups emerged at 8 wk in males and females and persisted at 10 wk and at 12 wk (A and B). Typical tracks of open field exploration by one male mouse in each of the plain water, 0.03% aspartame and 0.015% aspartame groups showing differences in exploration of the center areas (C). The male and female mice in the 0.015% aspartame and plain water groups were examined in the EZM (D). Two-way ANOVA of the EZM data showed no significant effect of sex (E). Therefore, the data from male and female mice were analyzed together. The aspartame group spent significantly shorter time in the open areas of the EZM (E). Response of male and female mice in the 0.03% aspartame group to diazepam was analyzed in the OFT (E). Initially, baseline parameters were established 30 min following a single intraperitoneal administration of saline. Next, 48 h. later, the same mice received diazepam (3 mg/kg, i.p.) and 30 min following the diazepam administration, the mice were re-examined in the OFT (E). Repeated Measures ANOVA showed no significant effect of sex (E). Therefore, data from male and female mice were combined and analyzed. The time spent in the center areas was significantly increased following the diazepam administration compared to the saline administration at baseline (E). Typical tracks of open field exploration by one male mouse each in the saline and diazepam groups (F). Notes on symbols: # = comparison between 0.015% aspartame and plain water group; $ = comparison between 0.015% aspartame and plain water group. #; $ = P < 0.05; ##; $$ = P < 0.01; ###; $$$ = P < 0.001; ****, ####; $$$$ = P < 0.0001.

Credit: *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2213120119

Florida State University College of Medicine researchers have linked aspartame, an artificial sweetener found in nearly 5,000 diet foods and drinks, to anxiety-like behavior in mice.

Along with producing anxiety in the mice who consumed aspartame, the effects extended up to two generations from the males exposed to the sweetener. The study is published in the *Proceedings of the National Academy of Sciences*.

"What this study is showing is we need to look back at the environmental factors, because what we see today is not only what's happening today, but what happened two generations ago and maybe even longer," said co-author Pradeep Bhide, the Jim and Betty Ann Rodgers Eminent Scholar Chair of Developmental Neuroscience in the Department of Biomedical Sciences.

The study came about, in part, because of previous research from the Bhide Lab on the transgenerational effects of nicotine on mice. The research showed temporary—or epigenetic—changes in mice sperm cells. Unlike genetic changes (mutations), epigenetic changes are reversible and don't change the DNA sequence; however, they can change how the body reads a DNA sequence.

"We were working on the effects of nicotine on the same type of model," Bhide said. "The father smokes. What happened to the children?"

The U.S. Food and Drug Administration (FDA) approved aspartame as a sweetener in 1981. Today, nearly 5,000 metric tons are produced each year. When consumed, aspartame becomes aspartic acid, phenylalanine and methanol, all of which can have potent effects on the central nervous system.

Led by doctoral candidate Sara Jones, the study involved providing mice with drinking water containing aspartame at approximately 15% of the FDA-approved maximum daily human intake. The dosage, equivalent to six to eight 8-ounce cans of diet soda a day for humans, continued for 12 weeks in a study spanning four years.

Pronounced anxiety-like behavior was observed in the mice through a variety of maze tests across multiple generations descending from the aspartame-exposed males.

"It was such a robust anxiety-like trait that I don't think any of us were anticipating we would see," Jones said. "It was completely unexpected. Usually you see subtle changes."

When given diazepam, a drug used to treat anxiety disorder in humans, mice in all generations ceased to show anxiety-like behavior.

Researchers are planning an additional publication from this study focused on how aspartame affected memory. Future research will identify the molecular mechanisms that influence the transmission of aspartame's effect across generations.

Other co-authors were Department of Biomedical Sciences faculty members Deirdre McCarthy, Cynthia Vied and Gregg Stanwood, and FSU Department of Psychology Professor Chris Schatschneider.

More information: Sara K. Jones et al, Transgenerational transmission of aspartame-induced anxiety and changes in glutamate-GABA signaling and gene expression in the amygdala, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2213120119

Journal information: Proceedings of the National Academy of Sciences

Provided by Florida State University

4. 腸内細菌が運動へのモチベーションを高める可能性 –マウス研究

日付：2022 年 12 月 14 日
ソース：ペンシルベニア大学医学部
概要：

ペンシルベニア大学ペレルマン医学部の研究者らが主導したマウス研究によると、腸内細菌のいくつかの種類は、腸内の神経を活性化して運動への欲求を促進する。この研究は本日の「Nature」誌に掲載され、一部の細菌が運動パフォーマンスを向上させる理由を腸から脳への経路を明らかにすることで説明している。
この研究で、研究者らは、実験用マウスの大規模なランニングパフォーマンスの違いは、パフォーマンスの高い動物における特定の腸内細菌種の存在に大きく起因することを発見した。研究者らは、この効果を細菌が産生する代謝産物と呼ばれる小分子にまで遡り、この代謝産物が、腸内の感覚神経を刺激して、運動中の動機を制御する脳領域の活動を強化することを示した。
最終的に、ペンシルベニア大学やその他の場所にある 10 を超える個別の研究所が関与する何年にもわたる科学的調査研究の過程で、研究者らは、より良いパフォーマンスに密接に関係している 2 つの細菌種、Eubacterium rectale と Coprococcus eutactus が脂肪酸アミド（FAA）として知られる代謝物を生成することを発見した。
この調査結果は、一般人がランニングを始めたり、エリートアスリートのパフォーマンスを最適化するための方法を提供するだけでなく、依存症やうつ病などの状況でモチベーションや気分を修正するためのより簡単な方法も生み出す可能性がある、と付け加えている。

研究関連ニュース/他のトップページに戻る

＜英文＞Gut microbes can boost the motivation to exercise, research finds (medicalxpress.com)

DECEMBER 14, 2022

Gut microbes can boost the motivation to exercise, research finds

by Perelman School of Medicine at the University of Pennsylvania

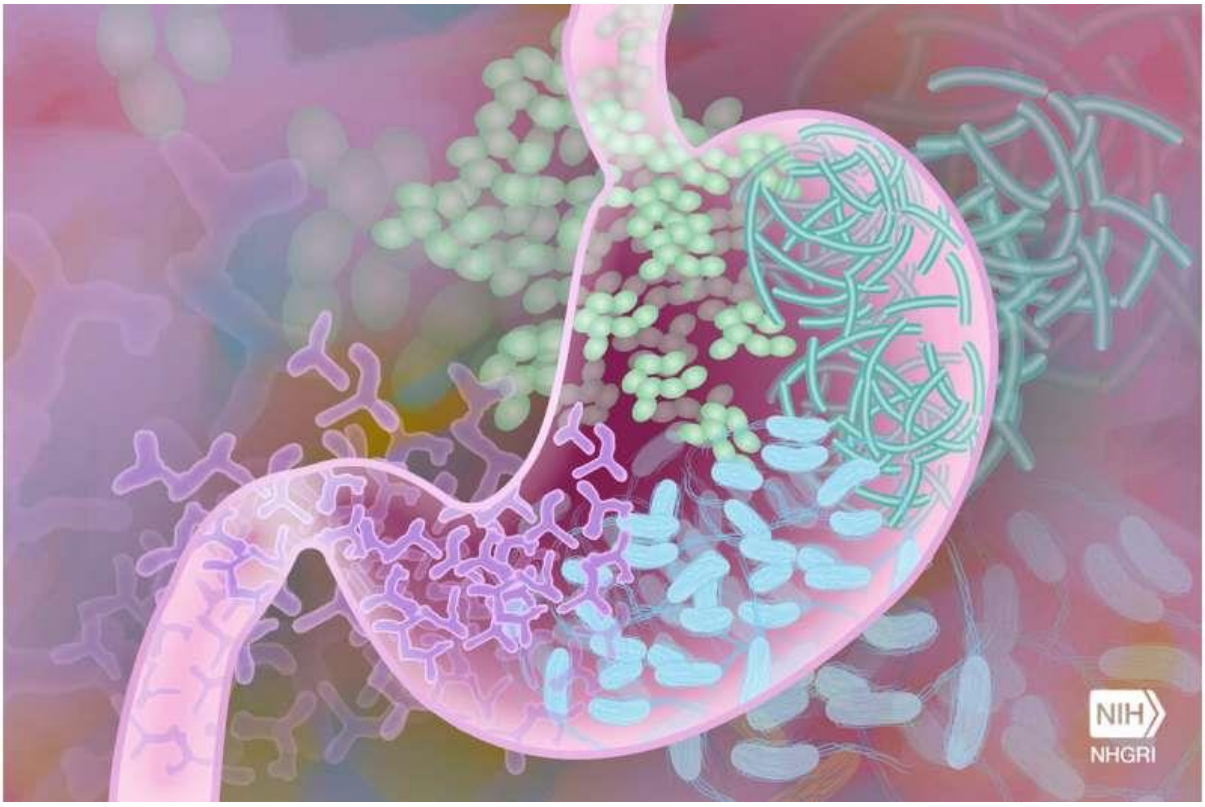


Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

Some species of gut-dwelling bacteria activate nerves in the gut to promote the desire to exercise, according to a study in mice that was led by researchers at the Perelman School of Medicine at the University of Pennsylvania. The study was published today in *Nature*, and reveals the gut-to-brain pathway that explains why some bacteria boost exercise performance.

In the study, the researchers found that differences in running performance within a large group of lab mice were largely attributable to the presence of certain gut bacterial species in the higher-performing animals. The researchers traced this effect to small molecules called metabolites that the bacteria produce—metabolites that stimulate sensory nerves in the gut to enhance activity in a motivation-controlling brain region during exercise.

"If we can confirm the presence of a similar pathway in humans, it could offer an effective way to boost people's levels of exercise to improve public health generally," said study senior author Christoph Thaiss, Ph.D., an assistant professor of Microbiology at Penn Medicine.

Thaiss and colleagues set up the study to search broadly for factors that determine exercise performance. They recorded the genome sequences, gut bacterial species, bloodstream metabolites, and other data for genetically diverse mice. They then measured the amount of daily voluntary wheel running the animals did, as well as their endurance.

The researchers analyzed these data using machine learning, seeking attributes of the mice that could best explain the animals' sizeable inter-individual differences in running performance. They were surprised to find that genetics seemed to account for only a small portion of these performance differences—whereas differences in gut bacterial populations appeared to be substantially more important. In fact, they observed that giving mice broad-spectrum antibiotics to get rid of their gut bacteria reduced the mice's running performance by about half.

Ultimately, in a years-long process of scientific detective work involving more than a dozen separate laboratories at Penn and elsewhere, the researchers found that two bacterial species closely tied to better performance, *Eubacterium rectale* and *Coprococcus eutactus,* produce metabolites known as fatty acid amides (FAAs). The latter stimulate receptors called CB1 endocannabinoid receptors on gut-embedded sensory nerves, which connect to the brain via the spine. The stimulation of these CB1 receptor-studded nerves causes an increase in levels of the neurotransmitter dopamine during exercise, in a brain region called the ventral striatum.

The striatum is a critical node in the brain's reward and motivation network. The researchers concluded that the extra dopamine in this region during exercise boosts performance by reinforcing the *desire* to exercise.

"This gut-to-brain motivation pathway might have evolved to connect nutrient availability and the state of the gut bacterial population to the readiness to engage in prolonged physical activity," said study co-author, J. Nicholas Betley, Ph.D., an associate professor of Biology at the University of Pennsylvania's School of Arts and Sciences. "This line of research could develop into a whole new branch of exercise physiology."

The findings open up many new avenues of scientific investigation. For example, there was evidence from the experiments that the better-performing mice experienced a more intense "runner's high"—measured in this case by a reduction in pain sensitivity—hinting that this well-known phenomenon is also at least partly controlled by gut bacteria. The team now plans further studies to confirm the existence of this gut-to-brain pathway in humans.

Apart from possibly offering cheap, safe, diet-based ways of getting ordinary people running and optimizing elite athletes' performance, he added, the exploration of this pathway might also yield easier methods for modifying motivation and mood in settings such as addiction and depression.

The study was led by Penn Medicine scientist Lenka Dohnalová. Other Penn Medicine authors include: Patrick Lundgren, Jamie Carty, Nitsan Goldstein, Lev Litichevskiy, Hélène Descamps, Karthikeyani Chellappa, Ana Glassman, Susanne Kessler, Jihee Kim, Timothy Cox, Oxana Dmitrieva-Posocco, Andrea Wong, Erik Allman, Soumita Ghosh, Nitika Sharma, Kasturi Sengupta, Mark Sellmyer, Garret FitzGerald, Andrew Patterson, Joseph Baur, Amber Alhadeff, and Maayan Levy.

More information: A microbiome-dependent neuronal pathway regulates the motivation for exercise in mice, *Nature* (2022). doi.org/10.1038/s41586-022-05525-z

Journal information: Nature

5. 癌細胞を溶かす DNA

日付：2022 年 12 月 21 日
ソース：東京大学
概要：https://www.t.u-tokyo.ac.jp/press/pr2022-12-22-001

東京大学大学院工学系研究科の森廣邦彦助教、岡本晃充教授らの研究グループは、1 対のヘアピン型 DNA が、癌で過剰発現するマイクロ RNA を起点にして集合体を形成し、癌細胞が死滅する現象を発見した。
癌治療には、外科手術のほかに、薬物や放射線による治療が試みられる。これまでにもさまざまな抗がん剤が開発されてきたが、効きにくいなどの理由で、従来型とは異なるメカニズムで機能する抗がん剤が求められている。
本研究グループは、1 対のヘアピン型 DNA がマイクロ RNA をきっかけにして集合体を形成することに着目し、これを癌に特徴的なマイクロ RNA に作用させることによってその癌細胞を死滅させることができることを発見した。さらに、その細胞死をきっかけに免疫細胞を誘導し、がん組織の成長を妨げることができることがわかった。
今回の結果は、従来型の抗がん剤とは全く異なる作用メカニズムをもつ新規の抗がん剤設計のアイデアを提供するものである。また、コロナ禍以降に着目されている核酸医薬と比較しても、今回の人工 DNA 集合体はこれまでにないメカニズムによる効き方であり、新しいカテゴリーの核酸医薬をもたらすことが期待される。
本研究成果は、2022 年 12 月 20 日（米国東部標準時）に米国化学会誌「Journal of The American Chemical Society」のオンライン版に掲載された。

研究関連ニュース/他のトップページに戻る

＜英文＞Artificial DNA kills cancer: Hairpin-shaped DNA binds with microRNA in cancer cells to trigger an immune response -- ScienceDaily

Artificial DNA kills cancer

Hairpin-shaped DNA binds with microRNA in cancer cells to trigger an immune response

Date:

December 21, 2022

Source:

University of Tokyo

Summary:

Researchers have used artificial DNA to target and kill cancer cells in a completely new way. The method was effective in lab tests against human cervical cancer- and breast cancer-derived cells, and against malignant melanoma cells from mice. The team created

a pair of chemically synthesized, hairpin-shaped, cancer-killing DNA. When the DNA pairs were injected into cancer cells, they connected to microRNA (miRNA) molecules that are overproduced in certain cancers. Once connected to the miRNA, they unraveled and joined together, forming longer chains of DNA which triggered an immune response. This response not only killed the cancer cells but prevented further growth of cancerous tissue. This method is different from conventional anticancer drug treatments and is hoped to bring about a new era of drug development.

FULL STORY

Researchers at the University of Tokyo have used artificial DNA to target and kill cancer cells in a completely new way. The method was effective in lab tests against human cervical cancer- and breast cancer-derived cells, and against malignant melanoma cells from mice. The team created a pair of chemically synthesized, hairpin-shaped, cancer-killing DNA. When the DNA pairs were injected into cancer cells, they connected to microRNA (miRNA) molecules that are overproduced in certain cancers. Once connected to the miRNA, they unraveled and joined together, forming longer chains of DNA which triggered an immune response. This response not only killed the cancer cells but prevented further growth of cancerous tissue. This method is different from conventional anticancer drug treatments and is hoped to bring about a new era of drug development.

Cancer is a sadly familiar global health concern and current methods of treatment have their limitations. However, drugs based on nucleic acids -- namely DNA and RNA, the vital information-carrying molecules -- can control the biological functions of cells, and are expected to transform the future of medicine and provide a significant boost towards efforts to overcome cancer and other hard-to-treat illnesses, caused by viruses and genetic diseases.

A research group at the University of Tokyo, led by Assistant Professor Kunihiko Morihiro and Professor Akimitsu Okamoto from the Graduate School of Engineering, were inspired to create a new anticancer drug using artificial DNA. "We thought that if we can create new drugs that work by a different mechanism of action from that of conventional drugs, they may be effective against cancers that have been untreatable up to now," said Okamoto.

Nucleic acid drug use for cancer treatment has been challenging because it is difficult to make the nucleic acids distinguish between cancer cells and other healthy cells. This means there is a risk of adversely affecting the patient's immune system if healthy cells are inadvertently attacked. However, for the first time, the team was able to develop a hairpin-shaped DNA strand that can activate a natural immune response to target and kill specific cancerous cells.

Cancer cells can overexpress, or make too many copies of, certain DNA or RNA molecules, causing them to not function normally. The team created artificial oncolytic (cancer-killing) hairpin DNA pairs called oHPs. These oHPs were triggered to form longer DNA strands when they encountered a short (micro) RNA called miR-21, which is overexpressed in some cancers. Typically, oHPs don't form longer strands due to their curved hairpin shape. However, when the artificial oHPs enter a cell and encounter the target microRNA, they open up to combine with it and form a longer strand. This then causes the immune system to recognize the presence of the overexpressed miR-21 as dangerous and activate an innate immune response, which ultimately leads to the death of the cancer cells.

The tests were effective against overexpressed miR-21 found in human cervical cancer-derived cells, human triple-negative breast cancer-derived cells, and mouse malignant melanoma-derived cells. "The formation of long DNA strands due to the interaction between short DNA oHPs and overexpressed miR-21, found by this research group, is the first example of its use as a selective immune amplification response which can target tumor regression, providing a new class of nucleic acid drug candidates with a mechanism that is completely different from known nucleic acid drugs," said Okamoto.

"The results of this study are good news for doctors, drug discovery researchers and cancer patients, as we believe it will give them new options for drug development and medication policies. Next, we will aim for drug discovery based on the results of this research, and examine in detail the drug efficacy, toxicity and potential administration methods." This research still has many steps to go before a treatment can be made available, but the team is confident in the benefits of nucleic acids for new drug discovery.

Funding:

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Story Source:

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

Journal Reference:

1. Kunihiko Morihiro, Hiraki Osumi, Shunto Morita, Takara Hattori, Manami Baba, Naoki Harada, Riuko Ohashi, Akimitsu Okamoto. **Oncolytic Hairpin DNA Pair: Selective Cytotoxic Inducer through MicroRNA-Triggered DNA Self-Assembly**. *Journal of the American Chemical Society*, 2022; DOI: 10.1021/jacs.2c08974

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6. 脂肪肝疾患は脳の健康を危険にさらす −マウス研究

日付:2022 年 12 月 22 日
ソース:キングズカレッジロンドン
概要:

非アルコール性脂肪性肝疾患（NAFLD）と脳機能障害との関連性を調べる研究で、キングスカレッジロンドンとローザンヌ大学に所属するロジャー ウィリアムズ肝臓学研究所の科学者らは、肝臓に脂肪が蓄積すると、脳への酸素の減少と脳組織への炎症を促進し、どちらも深刻な脳疾患の発症につながることを証明している。
NAFLD は、人口の約 25%、病的肥満の 80%以上が罹患している。不健康な食事と肥満が脳機能に及ぼす悪影響については、いくつかの研究で報告されているが、この研究は、NAFLD と脳の機能低下を明確に関連付け、潜在的な治療標的を特定した最初の研究であると考えられる。
Inserm（フランス国立衛生医学研究所）およびフランスのポワティエ大学との共同で実施されたこの研究では、マウスに 2 つの異なる食餌を与えた。マウスの半分は、カロリー摂取量の脂肪が 10%以下の食餌を摂取したが、残り半分のマウスのカロリー摂取量には 55%の脂肪が含まれていた。
16 週間後、研究者らは一連のテストを実施して、これらの食餌が体、より具体的には肝臓と脳に及ぼす影響を比較した。彼らは、高レベルの脂肪を消費する全てのマウスが肥満と見なされ、NAFLD、インスリン抵抗性、および脳機能障害を発症したことを発見した。また、NAFLD のマウスの脳が酸素レベルの低下に苦しんでいることも示された。これは、病気が脳血管の数と太さに影響を与え、組織に酸素を供給する量が少なくなるためであるが、脳が炎症を起こしている間、特定の細胞がより多くの酸素を消費するためでもある。これらのマウスはまた、より不安であり、うつ病の兆候を示した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞ Fatty liver disease endangers brain health -- ScienceDaily

Fatty liver disease endangers brain health

Date:

December 22, 2022

Source:

King's College London

Summary:

People with liver disease caused by eating too much sugar and fat could be at increased risk of developing serious neurological conditions like depression or dementia.

FULL STORY

In a study examining the link between non-alcoholic fatty liver disease (NAFLD) and brain dysfunction, scientists at the Roger Williams Institute of Hepatology, affiliated to King's College London and the University of Lausanne, found an accumulation of fat in the liver causes a decrease in oxygen to the brain and inflammation to brain tissue -- both of which have been proven to lead to the onset of severe brain diseases.

NAFLD affects approximately 25% of the population and more than 80% of morbidly obese people. Several studies have reported the negative effects of an unhealthy diet and obesity can have on brain function however this is believed to be the first study that clearly links NAFLD with brain deterioration and identifies a potential therapeutic target.

The research, conducted in collaboration with Inserm (the French National Institute of Health and Medical Research) and the University of Poitiers in France, involved feeding two different diets to mice. Half of the mice consumed a diet with no more than 10% fat in their calorie intake, while the other half's calorie intake contained 55% fat; intended to resemble a diet of processed foods and sugary drinks.

After 16 weeks researchers conducted a series of tests to compare the effects of these diets on the body and more specifically, on the liver and the brain. They found that all mice consuming the higher levels of fat were considered obese, and developed NAFLD, insulin resistance and brain dysfunction.

The study which was funded by the University of Lausanne and Foundation for Liver Research also showed that the brain of mice with NAFLD suffered from lower oxygen levels. This is because the disease affects the number and thickness of the brain blood vessels, which deliver less oxygen to the tissue, but also due to specific cells consuming more oxygen while the brain is becoming inflamed. These mice were also more anxious and showed signs of depression.

By comparison, the mice consuming the healthy diet did not develop NAFLD or insulin resistance, they behaved normally, and their brain was completely healthy.

"It is very concerning to see the effect that fat accumulation in the liver can have on the brain, especially because it often starts off mild and can exist silently for many years without people knowing they have it," said lead author Dr Anna Hadjihambi, sub-team lead in the Liver-Brain Axis group at the Roger Williams Institute of Hepatology and honorary lecturer at King's College London.

To try and combat the dangerous effect that NAFLD has on the brain, the scientists bred mice with lower levels of a whole-body protein known as Monocarboxylate Transporter 1 (MCT1) -- a protein specialised in the transport of energy substrates used by various cells for their normal function.

When these mice were fed the same unhealthy fat- and sugar-rich diet as those in the initial experiment, they had no fat accumulation in the liver and exhibited no sign of brain dysfunction -- they were protected from both ailments.

"Identifying MCT1 as a key element in the development of both NAFLD and its associated brain dysfunction opens interesting perspectives," said Professor Luc Pellerin, director of the Inserm U1313 research unit at the University of Poitiers in France and senior researcher in the study. "It

highlights potential mechanisms at play within the liver-brain axis and points to a possible therapeutic target."

Dr Hadjihambi added: "This research emphasises that cutting down the amount of sugar and fat in our diets is not only important for tackling obesity, but also for protecting the liver to maintain brain health and minimise the risk of developing conditions like depression and dementia during ageing, when our brain becomes even more fragile.

Story Source:

Materials provided by **King's College London**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Anna Hadjihambi, Christos Konstantinou, Jan Klohs, Katia Monsorno, Adrien Le Guennec, Chris Donnelly, I. Jane Cox, Anjali Kusumbe, Patrick S. Hosford, Ugo Soffientini, Salvatore Lecca, Manuel Mameli, Rajiv Jalan, Rosa Chiara Paolicelli, Luc Pellerin. **Partial MCT1 invalidation protects against diet-induced non-alcoholic fatty liver disease and the associated brain dysfunction**. *Journal of Hepatology*, 2023; 78 (1): 180 DOI: 10.1016/j.jhep.2022.08.008

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7. 脳が過去の恐怖体験の記憶を保存する方法
このマウス研究が PTSD 新治療法に繋がる可能性

日付:2022 年 12 月 26 日
ソース:カリフォルニア大学リバーサイド校
概要:

遠隔恐怖記憶とは、数ヶ月から数十年前の遠い過去に起こったトラウマ的な出来事の記憶のことである。今回「Nature Neuroscience」誌に掲載されたカリフォルニア大学リバーサイド校のマウス研究で、研究者らは脳が遠隔恐怖記憶を統合する基本的なメカニズムを明らかにしている。
脳は異なるメカニズムを使用して、最近の恐怖記憶と遠い過去の恐怖記憶を保存する。以前の研究では、恐怖記憶の最初の形成には海馬が関与しているが、時間と共に徐々に成熟し、海馬への依存度が低下することが示唆されている。現在、多くの研究により、最近の恐怖記憶がどのように保存されるかが説明されているが、脳が遠隔恐怖記憶をどのように統合するかはよく分かっていない。そこで、研究者らは、以前の研究で遠隔記憶の統合に関与しているとされている大脳皮質の一部である前頭前皮質(PFC)に注目した。彼らは、記憶ニューロンと呼ばれる PFC 内の神経細胞を発見、そしてこれらが、最初の外傷的出来事時に活性化され、遠隔恐怖記憶の想起中に再活性化されることを発見。また PFC のこれらの記憶ニューロンを選択的に阻害すると、マウスは遠隔恐怖記憶を思い出すことができなかった(ただし、最近の恐怖記憶は思い出せた)。これは、遠隔恐怖記憶の想起における PFC 記憶ニューロンの重要な役割を示唆している。
PTSD 患者が遠い過去に形成された恐怖の記憶に苦しんでいることを考えると、彼らの研究は、PTSD 患者の慢性的な恐怖を抑制するための治療戦略を開発する上で重要な洞察を提供するものだ、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞How the brain stores remote fear memory: Mouse study could lead to novel therapies for people living with PTSD -- ScienceDaily

How the brain stores remote fear memory

Mouse study could lead to novel therapies for people living with PTSD

Date:

December 26, 2022

Source:

University of California - Riverside

Summary:

A remote fear memory is a memory of traumatic events that occurred in the distant past -- a few months to decades ago. A mouse study has now spelled out the fundamental mechanisms by which the brain consolidates remote fear memories. The study demonstrates that remote fear memories formed in the distant past are permanently stored in connections between memory neurons in the prefrontal cortex.

FULL STORY

A remote fear memory is a memory of traumatic events that occurred in the distant past -- a few months to decades ago. A University of California, Riverside, mouse study published in *Nature Neuroscience* has now spelled out the fundamental mechanisms by which the brain consolidates remote fear memories.

The study demonstrates that remote fear memories formed in the distant past are permanently stored in connections between memory neurons in the prefrontal cortex, or PFC.

"It is the prefrontal memory circuits that are progressively strengthened after traumatic events and this strengthening plays a critical role in how fear memories mature to stabilized forms in the cerebral cortex for permanent storage," said Jun-Hyeong Cho, an associate professor of molecular, cell and systems biology, who led the study. "Using a similar mechanism, other non-fear remote memories could also be permanently stored in the PFC."

The brain uses distinct mechanisms to store recent versus remote fear memories. Previous studies have suggested that while the initial formation of fear memory involves the hippocampus, it progressively matures with time and becomes less dependent on the hippocampus. Much research now explains how recent fear memory is stored, but how the brain consolidates remote fear memories is not well understood.

The researchers focused on the PFC, a part of the cerebral cortex that has been implicated in remote memory consolidation in previous studies.

"We found a small group of nerve cells or neurons within the PFC, termed memory neurons, were active during the initial traumatic event and were reactivated during the recall of remote fear memory," Cho said. "When we selectively inhibited these memory neurons in the PFC, it prevented the mice recalling remote but not recent fear memory, suggesting the critical role of PFC memory neurons in the recall of remote fear memories."

In the experiments, the mice received an aversive stimulus in an environment called a context. They learned to associate the aversive stimulus with the context. When exposed to the same context a month later, the mice froze in response, indicating they could recall remote fear memories. The researchers showed that connections (synapses) between memory neurons in the PFC, termed prefrontal memory circuits, were gradually strengthened with time after fear learning, and such strengthening helped the PFC permanently store remote fear memories.

Next, to extinguish the remote fear memory in the mice, the researchers repeatedly exposed the mice to the same fear-predictive context but without the aversive stimulus. The result was a reduced fear response to the context.

"Interestingly, the extinction of remote fear memory weakened the prefrontal memory circuits that were previously strengthened to store the remote fear memory," Cho said. "Moreover, other manipulations that blocked the strengthening of the PFC memory circuits also prevented the recall of remote fear memory."

Cho explained that a dysregulation of fear memory consolidation can lead to chronic maladaptive fear in PTSD, which affects about 6% of the population at some point in their lives.

"Considering that PTSD patients suffer from fear memories formed in the distant past, our study provides an important insight into developing therapeutic strategies to suppress chronic fear in PTSD patients," he said.

Next, Cho's team plans to selectively weaken the prefrontal memory circuits and examine whether this manipulation suppresses the recall of remote fear memories.

"We expect the results will contribute to developing a more effective intervention in PTSD and other fear-related disorders," Cho said.

The study was supported by grants from the National Institutes of Mental Health.

Cho was joined in the study by Ji-Hye Lee, Woong Bin Kim, and Eui Ho Park.

Story Source:

Materials provided by **University of California - Riverside**. Original written by Iqbal Pittalwala. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ji-Hye Lee, Woong Bin Kim, Eui Ho Park, Jun-Hyeong Cho. **Neocortical synaptic engrams for remote contextual memories**. *Nature Neuroscience*, 2022; DOI: 10.1038/s41593-022-01223-1
