Bio News – October, 2020

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

8/28　接触者の COVID-19 検査は必須ではないとの米国の方針変更を学会が懸念

https://www.nytimes.com/2020/08/27/us/politics/trump-coronavirus-testing.html

8/29　トランプ大統領曰く、今年中に米国で COVID-19 ワクチンが使えるようになる

https://www.livemint.com/news/world/will-produce-covid-vaccine-by-this-year-end-or-sooner-says-donald-trump-11598588571781.html

9/1　オプジーボが効きやすい人を予測　がんセンター指標発見

9/1　「食べたい…」仕組み解明　福岡・久留米大教授 -食欲不振の治療へ応用期待

久留米大分子生命科学研究所（福岡県久留米市）の児島将康教授（内分泌学）の研究グループが、食欲を増進するホルモン「グレリン」が活性化する仕組みを解明した。がんなどの病気による体重減少や食欲不振症の治療のため、グレリンと同じ作用の化合物を使った薬が開発されており、成果は製薬への応用も期待される。8 月 19 日付の英科学誌ネイチャー・コミュニケーションズで発表。

9/1　Nestle が Aimmune Therapeutics を買ってピーナツアレルギー治療を手に入れる

9/1　難病「ALS」を引き起こすたんぱく質の新機能を発見　阪大などの研究グループ

9/2　米国屈指の研究者が米国 FDA 長官 Stephen Hahn 氏に自白か辞任を求めている

米国 FDA 長官 Stephen Hahn 氏に対して、新型コロナウイルス感染症（COVID-19）治療 2 つ・ヒドロキシクロロキンと回復者血漿を許可し、更に第 3 相試験完了前に COVID-19 ワクチンを承認する準備をしている事について、全て詳しく説明するか辞任することを Scripps Research Translational Institute の設立者 Eric Topol 氏が求めている。

9/2　Boston Pharmaceuticals が Novartis から脂肪肝薬の権利を取得

9/3　米国 FDA は回復者血漿を COVID-19 に使えるとしたが NIH は何とも言えないと判断

9/3　マウスの ES 細胞でミニ心臓 -東京医科歯科大チーム

https://www.yomiuri.co.jp/science/20200903-OYT1T50237/

9/3　受精卵のゲノム編集「当面禁止を」 国際委員会が勧告

9/3　微生物、宇宙空間で年単位での生存を確認

9/4　GSK がロンドンの Kings Cross に人工知能（AI）研究所を開設

9/4　アリゾナ大学が寮からの下水検査で新型コロナウイルス感染流行を阻止

9/4　新型コロナの抗体は 4 カ月以上持続される可能性がある。アイスランドの大規模研究で発見

9/4　新型コロナワクチンの接種、無料化を検討　政府の分科会

9/4　がん「光免疫療法」薬剤　厚労省部会が了承　楽天系が開発

https://www.nikkei.com/article/DGXMZO63483770U0A900C2916M00/

9/6　ゆっくり長く効く水溶性レムデシビル皮下注射剤を Starpharma（オーストラリア メルボルン）が開発

9/6　Samsung Biologics が約 20 億ドルを費やして超特大生物薬工場を建設

9/7　仕事でセクシャルハラスメントを受けた人の自殺死亡率はおよそ 3 倍高い -スウェーデン

9/8　新 ECMO の臨床研究開始　新型コロナの治療に貢献 -国立循環器病研究センター

9/8　肝臓に薬の副作用が出るリスク、ゲノム情報から予測 -東京医科歯科大と武田薬品工業など

9/9　AstraZeneca のワクチン治験が中断　深刻な副作用疑い

9/9　富士フイルム、ワクチン原薬を3倍に増産へ…米政府の資金活用しテキサス工場で

9/10　AstraZeneca の COVID-19 ワクチン試験中断を招いた病気は横断性脊髄炎らしい、治験は来週にも再開

9/10　米国の COVID-19 小児が 50 万人を超えた～全感染者の約 10%

9/11　新日本科学から独立した Satsuma Pharmaceuticals の片頭痛薬 Ph3 失敗～株価暴落

9/11　がん化のリスクある iPS 細胞を除去　肥満治療薬で -慶應大など

9/14　AstraZeneca が Ph3 段階の新型コロナウイルス感染予防ワクチンの英国試験再開

9/14　「プラズマクラスター」が空気中の新型コロナ減少に有効と実証…シャープ

9/15　金星に生命の痕跡か　微生物が作るガス、大気から検出

9/15　シンガポール、全住人への新型コロナウイルス感染接触者追跡装置の配布開始

9/16　武田薬品が米国の細胞治療製造拠点を開設（マサチューセッツ州ボストンの R&D 拠点敷地内）

https://www.businesswire.com/news/home/20200915005224/en/

9/16　BioNTech 社の COVID-19 ワクチン開発にドイツ政府が最大 3 億 7,500 万ユーロ提供

BioNTech が Pfizer や Fosun Pharma と共同開発している新型コロナウイルス感染（COVID-19）予防ワクチン BNT162 の開発をドイツが最大 3 億 7,500 万ユーロ（約 4 億 5,000 万ドル）を出して支援。

9/16　幹細胞でマウスの肺線維化を抑制、新型コロナにも期待？ -順天堂大

9/16　iPS 視細胞、今秋移植へ　世界初、中枢神経再生目指す　神戸アイセンター病院

9/16　高濃度の柿渋、新型コロナ感染抑える効果　食品化に期待 -奈良県立医大

9/16　騒音ストレスで魚が短命に、寄生虫への免疫低下 -英カーディフ大研究

9/16　AstraZeneca の COVID-19 ワクチンの米国での試験はまだ再開されていない

英国での第 3 相試験での安全性懸念を受けて中断された AstraZeneca の新型コロナウイルス感染（COVID-19）予防ワクチン AZD1222（ChAdOx1 nCoV-19）の試験は英国、ブラジル、南アフリカで再開されているが、米国ではまだ再開されていない。

9/17　嗅覚異常はなぜ起こる？　久留米大や京大などが原因解明

9/17　アメリカ西部の山火事の煙ヨーロッパに到達　世界一周も

9/18　Amgen が Lilly の COVID-19 治療抗体の製造を手伝う

9/18　ワニにヘリウム吸わすと鳴き声が変わる！京大准教授 -「イグ・ノーベル賞」

日本人がノーベル賞のパロディ版とも言える、ユニークな研究に贈られる「イグ・ノーベル賞」を受賞するのは、これで14年連続。

9/18　新型コロナ、欧州で「驚くべき速さ」で拡大 WHO が警鐘

世界保健機関（WHO）は 17 日、欧州各国で新型コロナウイルスの感染が「驚くべき速さ」で拡大していると警鐘を鳴らした。自主隔離期間を短縮する動きもけん制。

9/19　新型コロナウイルスは空気を介して感染しうる　米CDCが確認

9/19　RegenxBio とペンシルベニア大学が遺伝子治療技術無断使用で Sarepta を訴えた

RegenxBio とペンシルベニア大学が、Sarepta（マサチューセッツ州ケンブリッジ）が開発中の筋ジストロフィー遺伝子治療一式について特許を侵害しているとの訴えを起こした。
因みに、最近 Roche は Sarepta のデュシェンヌ型筋ジストロフィー（DMD）遺伝子治療 SRP-9001 の米国外権利を 11 億ドル超も払って手に入れている。

9/20　コロナ治療薬候補のアビガン、承認申請へ　有効性確認か

新型コロナウイルスの治療薬候補「アビガン」について、富士フイルム富山化学が近く国に製造販売の承認を申請することがわかった。9 月中旬まで実施した臨床試験（治験）のデータを 20 日に精査し、一定の有効性が確認できたもよう。承認されれば、日本で開発された新型コロナ治療薬としては初めてとなる。

9/22　米CDC、エアロゾル感染警告を撤回 「草案を誤掲載」

9/22　トランプ大統領、国連演説で中国批判　コロナ巡り「責任を取らせねば」

9/23　パーキンソン病で傷む脳領域に光を照射する試験がフランスでまもなく始まる

9/23　手足口病を引き起こすエンテロウイルス 71 の複製を安全に阻害する化合物を同定 -デューク大

9/23　微生物成分の治療薬を開発する Siolta（カリフォルニア州サンカルロス）が 3,000 万ドル調達

9/23　J＆J、コロナワクチン大規模治験を開始－1回接種で効果と期待

9/23　富士フイルム、アビガンで有効性確認　10 月中に製造販売承認を申請

富士フイルム富山化学は今年3月、重篤ではない肺炎の症状を示した新型コロナ患者を対象にアビガンの国内臨床第 III 相試験を始め、アビガンの投与で早期の症状改善を確認。本試験でも、安全性上の新たな懸念はなかったという。今後、富士フイルム富山化学は、本試験の詳細なデータ解析および申請に必要な業務を進め、10月中にもアビガンの製造販売承認事項一部変更承認申請を行う予定。

9/23　論文引用栄誉賞に中村氏ら日本人2人受賞　ノーベル賞の登竜門

医学・生理学部門で、がん研究会がんプレシジョン医療研究センターの中村祐輔所長（67）
化学部門で東京大学大学院工学系研究科の藤田誠・卓越教授（62）

9/24　米国 FDA、COVID-19 ワクチン認可の新たなガイドラインを準備

FDA は COVID-19 ワクチンの効果は少なくとも 50%必要との方針を既に 6 月 30 日に示しており、準備されている新たな方針では更なる認可要件が示される。

9/25　イヌに新型コロナウイルスを嗅ぎ分けさせる試験がフィンランドの空港で開始

9/26　“回復患者の血しょう投与”倫理委で初承認

新型コロナウイルス患者の治療法の候補である回復した人の血液の成分「血しょう」を別の患者に投与する臨床研究が、国内の医療機関の倫理委員会で初めて承認された。アメリカでは緊急の使用が許可されているが、日本でも、国立国際医療研究センターで研究が進められ、今月15日に内部の倫理委員会で、実際の患者へ投与する臨床研究が正式に承認され、これを受けて厚生労働省が17日に受理。

9/27　J&J の COVID-19 ワクチン Ph1/2a 報告～1 回投与の確かな免疫反応が認められた

9/28　Pfizer の研究者が、COVID-19 ワクチン認可申請を 11 月後半まで待つべきと要請している

BioNTech が Pfizer と開発している新型コロナウイルス感染（COVID-19）予防ワクチン BNT162 の第 3 相試験の効果は 10 月中に恐らく判明するとの見通しを背景にして、Bloomberg が得た情報によると、少なくとも 11 月の終わりまで米国 FDA への認可申請は待つべきと研究者 60 人以上が要請している。

9/29　新型コロナ、世界で死者 100 万人超　毎日 5 千人ペース

世界の死者数は 29 日午後 1 時現在で 100 万 867 人、感染者数は 3328 万 2969 人。国別にみると、死者は米国（約 20 万 5 千人）が最も多く、ブラジル（約 14 万 2 千人）、インド（約 9 万 6 千人）、メキシコ（約 7 万 7 千人）、英国（約 4 万 2 千人）と続く。この 5 カ国で世界全体の半分以上を占めている。日本の死者は 1561 人。

9/29　新型コロナの人工抗体を作製 治療や検査、感染防止薬に期待 -名大など

新型コロナウイルスを捕まえ、不活性化する「人工抗体」を作製することに成功したと、名古屋大学と国立病院機構名古屋医療センターの研究グループが発表した。この人工抗体が付いたウイルスは細胞に感染しなくなることなども確認されている。新たな治療薬や抗原検査キット、さらにワクチンに代わる感染防止薬の開発につながる成果と期待される。

9/29　迫るノーベル賞、日本人 3 年連続なるか、有力候補者は？

【生理学医学賞】 EPR 効果、個別化がん治療の先駆
効率的にがん組織だけに作用する治療法の開発に貢献した、バイオダイナミックス研究所（熊本市中央区）の前田浩理事長と国立がん研究センター研究所の松村保広客員研究員

【物理学賞】 強相関電子系の第一人者
東京大学の十倉好紀卓越教授（理化学研究所創発物性科学研究センター長）

【化学賞】 自己集合やルイス酸触媒開発
分子が自発的に構造体を形成する「自己集合」を化学合成に応用した東京大学の藤田誠卓越教授
酸・塩基の反応で、かさ高い構造を持つ「ルイス酸触媒」を開発した中部大学の山本尚教授

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. 薬剤耐性菌感染症の新治療法

2. ハダカデバネズミの難聴が有利に働くワケ

3. 脳形成における必須脂肪酸の役割 -マウス実験

4. 熱と微生物叢がより強い骨を作る -マウス実験

5. アレルギー性免疫反応が細菌感染との闘いを助ける -マウス実験

6. ヒトとマウスの生化学反応速度の違い

7. インフルエンザが妊婦にとって壊滅的になり得る理由 -マウス実験

8. 星型の脳細胞が睡眠の鍵を握る
   自由に行動するマウスの睡眠中の星状細胞カルシウムの活性を、ミニチュア顕微鏡を使用して初めて研究

9. パーキンソン病で損傷したマウスの脳の回路を幹細胞が修復

1. 薬剤耐性菌感染症の新治療法

日付：2020 年 9 月 2 日
ソース：ダートマス大学セイヤーエンジニアリング
概要：

ダートマス大学の研究者らは、ヒトの免疫系から本質的に隠れるように新しい抗菌剤を設計、この抗菌剤が生命を脅かすメチシリン耐性黄色ブドウ球菌（MRSA）感染を治療する可能性がある、としている。今日 *Science Advances* 誌で発表された新しい論文にこの薬剤の詳細が述べられている。
Centers for Disease Control and Prevention（CDC）は、MRSA、最も一般的な細菌性病原体の 1 つであり、米国で最も致命的な薬剤耐性細菌の 1 つ、を効果的に治療することを優先している。が、そんな中今回のダートマスエンジニアリング学部が率いる新しい研究は、リシンをベースとした人工抗菌剤が MRSA およびその他の黄色ブドウ球菌による生命にかかわる感染症を治療するための安全な反復投与を可能にする可能性を示している。
この論文は、ウサギ、部分的にヒト化された免疫系を持つマウス、および抽出されたヒト免疫細胞を用いた研究における治療の肯定的結果について詳述している。また、研究者らは、抗菌剤の 2023 年からのヒト臨床試験に向けての準備はできている、と言っている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/09/200902182421.htm

NEW TREATMENT FOR DRUG-RESISTANT BACTERIAL INFECTIONS

Date:

September 2, 2020

Source:

Thayer School of Engineering at Dartmouth

Summary:

A new antibacterial agent that has been engineered to essentially hide from the human immune system may treat life-threatening MRSA infections. A new article provides details on the agent, which is the first lysin-based treatment with the potential to be used multiple times on a single patient, making it ideal to treat particularly persistent drug-resistant and drug-sensitive infections.

FULL STORY

A new antibacterial agent that has been engineered by researchers at Dartmouth to essentially hide from the human immune system may treat life-threatening MRSA infections. A new paper, published today in *Science Advances*, provides details on the agent, which is the first lysin-based treatment with the potential to be used multiple times on a single patient, making it ideal to treat particularly persistent drug-resistant and drug-sensitive infections.

The Centers for Disease Control and Prevention (CDC) has prioritized finding effective treatment of Methicillin-resistant Staphylococcus aureus (MRSA), one of the most common bacterial pathogens and the single most deadly drug-resistant bacteria in the United States. Now, a new study led by Dartmouth Engineering faculty shows promise for an engineered lysin-based antibacterial agent that may enable safe, repeated dosing to treat life-threatening infections by MRSA and other types of S. aureus.

In recent years, lysins -- enzymes naturally produced by microbes and associated viruses -- have shown potential to treat S. aureus, which can rapidly acquire resistance to other types of antibiotic drugs.

"Lysins are one of the most promising next-generation antibiotics. They kill drug-sensitive and drug-resistant bacteria with equal efficacy, they can potentially suppress new resistance phenotypes, and they also have this laser-like precision," said Karl Griswold, corresponding author and associate professor of engineering at Dartmouth.

While there is promise in lysins, development has been slowed due to concerns that they prompt humans' immune systems to develop antidrug antibodies, which can have negative side effects including life-threatening hypersensitivity reactions.

That's why the Dartmouth Engineering team -- which also included researchers in Dartmouth's computer science department, The Lundquist Institute at Harbor-UCLA Medical Center, Lyticon, and Stealth Biologics -- engineered and patented F12, a new lysin-based antibacterial agent. F12 is essentially able to hide from the human immune system (due to T cell epitope deletion), and therefore does not cause the same negative side effects as unmodified, natural lysins.

F12 is the first lysin-based treatment with the potential to be used multiple times on a single patient, making it ideal to treat particularly persistent drug-resistant and drug-sensitive infections. Preclinical studies showed the efficacy of F12 does not diminish with repeated doses, while two other anti-MRSA lysin treatments currently in clinical trials are only designed to be used a single time.

"We have engineered this super potent, super effective anti-MRSA biotherapeutic, and we've done it in a way that renders it compatible with and largely invisible to the human immune system. By making it a safer drug, we've enabled the possibility of dosing multiple times in order to treat even the most highly refractory infections," said Griswold.

The team's paper, "Globally deimmunized lysostaphin evades human immune surveillance and enables highly efficacious repeat dosing," was published earlier today by *Science Advances*. The work was the result of two grants from the National Institutes of Health (NIH) totaling $1.7 million.

The paper details the treatment's positive results in rabbits, mice with partially-humanized immune systems, and studies with extracted human immune cells. Griswold believes the antibacterial agent could be ready for human clinical trials as soon as 2023.

"This is the first report of a translation-ready deimmunized lysin, and F12 has serious, bonafide clinical potential," said Griswold.

Further studies of F12 will examine synergy with standard-of-care antibacterial chemotherapies; preliminary results suggest the combinations are extremely potent and suppress drug-resistance phenotypes.

Story Source:

Materials provided by **Thayer School of Engineering at Dartmouth**. Original written by Julie Bonette. *Note: Content may be edited for style and length.*

Journal Reference:

1. Hongliang Zhao, Seth A. Brooks, Susan Eszterhas, Spencer Heim, Liang Li, Yan Q. Xiong, Yongliang Fang, Jack R. Kirsch, Deeptak Verma, Chris Bailey-Kellogg, and Karl E. Griswold. **Globally deimmunized lysostaphin evades human immune surveillance and enables highly efficacious repeat dosing**. *Science Advances*, 2020
DOI: 10.1126/sciadv.abb9011

Cite This Page:

- MLA
- APA
- Chicago

Thayer School of Engineering at Dartmouth. "New treatment for drug-resistant bacterial infections." ScienceDaily. ScienceDaily, 2 September 2020. <www.sciencedaily.com/releases/2020/09/200902182421.htm>.

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2. ハダカデバネズミの難聴が有利に働くワケ

日付：2020 年 9 月 3 日
ソース：イリノイ大学シカゴ校
概要：

イリノイ大学シカゴ校の生物科学および神経科学の教授であり、論文の筆頭著者の一人である Thomas Park 教授らは、何十年にもわたってハダカデバネズミを研究しており、地下の低酸素条件下で繁殖する能力や痛みに対する高い耐性など、奇妙な特性のいくつかについて以前に説明している。
今回彼らが *Current Biology* 誌に発表した新しい調査結果によると、ハダカデバネズミは聴覚に関連する遺伝子に 6 つの変異があるため、互いに通信するために使用される絶え間ないきしみ音をほとんど聞くことができない。研究者らは、このような聴覚障害は、社会的で声のある動物にとっては奇妙であるが、適応的で有益な特性だ、と結論している。
研究者らは、聴覚に関連する遺伝子に 6 つの変異について、これらが何らかの形で適応的であるために選択されたはずだ、という考えから研究を深めていった。
彼らは、ハダカデバネズミが内耳の蝸牛増幅機能 –内耳の特殊化した細胞が音信号を脳に送信する前に増幅するのを助けるプロセス– を欠いていることを発見。蝸牛増幅は、内耳にある有毛細胞によって助けられるが、これらの細胞が適切に機能しないと音は激しく減衰する。ただ、本当に大きな音は、実際には有毛細胞を殺してしまう。有毛細胞は、他のタイプの細胞とは異なり、再生不可能で、これにより、ほとんどの哺乳類の難聴が進行する。ハダカデバネズミには機能的な蝸牛増幅がないため、聞こえる音は有毛細胞に対して致命的なレベルには達しない。そのため、ハダカデバネズミはコミュニティーの絶え間ない不協和音に耐えることができる。
ハダカデバネズミはこの特性を持つ唯一の哺乳類であり、新しい発見は、ハダカデバネズミがヒトの難聴を調査するための良い動物モデルであるかもしれない、と示唆している。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/09/200903145006.htm

HEARING LOSS IN NAKED MOLE-RATS IS AN ADVANTAGE, NOT A HARDSHIP

Date:

September 3, 2020

Source:

University of Illinois at Chicago

Summary:

With six mutations in genes associated with hearing, naked mole-rats can barely hear the constant squeaking they use to communicate with one another. This hearing loss, which is strange for such social, vocal animals, is an adaptive, beneficial trait, according to new findings.

FULL STORY

If naked mole-rats were human, they would be prescribed hearing aids. With six mutations in genes associated with hearing, naked mole-rats can barely hear the constant squeaking they use to communicate with one another. This hearing loss, which is strange for such social, vocal animals, is an adaptive, beneficial trait, according to new findings published in the journal *Current Biology*.

Naked mole-rats are East African hairless mammals that are bald and wrinkly with buck teeth. They live in underground colonies and their social structure resembles that of bees -- there are soldiers, workers and a queen. A lot of cooperation is required for a mole-rat colony to function. Naked mole-rats need to decide where to dig, how to defend the colony, and how to convey the location of food sources, and much of this is accomplished by vocal communication.

"Naked mole-rats are constantly chirping and squeaking," said Thomas Park, professor of biological sciences and neuroscience at the University of Illinois Chicago and one of the lead authors on the paper.

Park has been studying naked mole-rats for decades and has described some of their odd traits, such as their ability to thrive under conditions of low oxygen underground and their high tolerance for pain.

"We were curious about their hearing since they are so vocal, but research had suggested that their hearing is actually quite bad," Park said.

Park and colleagues tested the hearing of mole-rats using technology similar to that used for testing human hearing. They performed an auditory brain stem response test, during which electrodes placed on the scalp pick up signals indicative of sound being processed in the brain. The researchers found the signals were weak, confirming naked mole-rats have poor hearing. In fact, "their hearing is so bad that they would be candidates for hearing aids if they were people," Park said.

Once the hearing loss was confirmed, Park and colleagues turned to the mole-rats' genetics and found six mutations in genes associated with hearing loss in humans.

"The fact that there were so many of these mutations strongly suggests that these mutations were selected for because they are adaptive in some way," Park explained.

The researchers also found the naked mole-rats lacked cochlear amplification, a process by which specialized cells in the inner ear help amplify sound signals before those signals are sent to the brain. Cochlear amplification is aided by cells called outer hair cells, which are located in the inner ear. Without proper functioning of these cells, sounds are severely dampened.

"If the naked mole-rats didn't have these mutations, the constant noise they produce could actually kill the hair cells responsible for hearing," Park said.

Hair cells receive auditory vibrations and send signals to the brain where they are interpreted as sound. Really loud sounds actually kill hair cells, which, unlike other types of cells, can't regenerate. Park said this is why hearing loss in most mammals is progressive.

"Because the naked mole-rats lack functional cochlear amplification, the sounds they hear don't ever get up to a level where they are lethal to hair cells, and so the naked mole-rats can withstand this constant cacophony without going totally deaf," Park said. "They are the only mammals we know of that lack cochlear amplification."

The new findings suggest that mole rats may be a good animal model to investigate hearing loss in humans.

Story Source:

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

Journal Reference:

1. Sonja J. Pyott, Marcel van Tuinen, Laurel A. Screven, Katrina M. Schrode, Jun-Ping Bai, Catherine M. Barone, Steven D. Price, Anna Lysakowski, Maxwell Sanderford, Sudhir Kumar, Joseph Santos-Sacchi, Amanda M. Lauer, Thomas J. Park. **Functional, Morphological, and Evolutionary Characterization of Hearing in Subterranean, Eusocial African Mole-Rats**. *Current Biology*, 2020; DOI: 10.1016/j.cub.2020.08.035

Cite This Page:

- MLA
- APA
- Chicago

University of Illinois at Chicago. "Hearing loss in naked mole-rats is an advantage, not a hardship." ScienceDaily. ScienceDaily, 3 September 2020. <www.sciencedaily.com/releases/2020/09/200903145006.htm>.

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3. 脳形成における必須脂肪酸の役割 –マウス実験

日付：2020 年 9 月 4 日
ソース：広島大学
概要：

広島大学の研究者らによると、オメガ 6 脂肪が多く、オメガ 3 脂肪が少ない食餌を与えられた妊娠中のマウスは、ドーパミン産生ニューロンのレベルが高い子孫を生み出す。これらのマウスは高カロリー食を追跡し続けることから、妊娠中の母親の食事が子供の食生活を制御している可能性がある、としている。また、このことが新しい肥満防止戦略を提供する可能性がある、としている。
オメガ 6 脂肪は、グレープシードオイル、コーン油、ゴマ油に含まれており、世界の料理のいくつかのサラダドレッシングの定番であり、オメガ 3 脂肪は、魚、シソ油、アマニ油に含まれている。これらの脂肪とバランスの取れた食事は、健康な脳の成長に不可欠であると考えられている。
研究者らは、マウスの胎児が中脳のドーパミン産生ニューロンの子宮内成長を示すことを発見した。この高オメガ 6/低オメガ 3 食への曝露が、妊娠中の特定の期間に胎児の脳のこれらのニューロンの成長を増加させ、子孫の脳でのドーパミン放出を促進し、その結果子孫に砂糖や脂肪分の多い食事の快楽的消費を刺激する、としている。
調査結果は、8 月 28 日に、査読付きジャーナル *Communications Biology* 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＞https://www.eurekalert.org/pub_releases/2020-09/hu-oom090320.php

NEWS RELEASE 4-SEP-2020

OFFSPRING OF MICE FED IMBALANCED DIETS SHOWN TO BE NEUROLOGICALLY 'PROGRAMMED' FOR OBESITY

HIROSHIMA UNIVERSITY

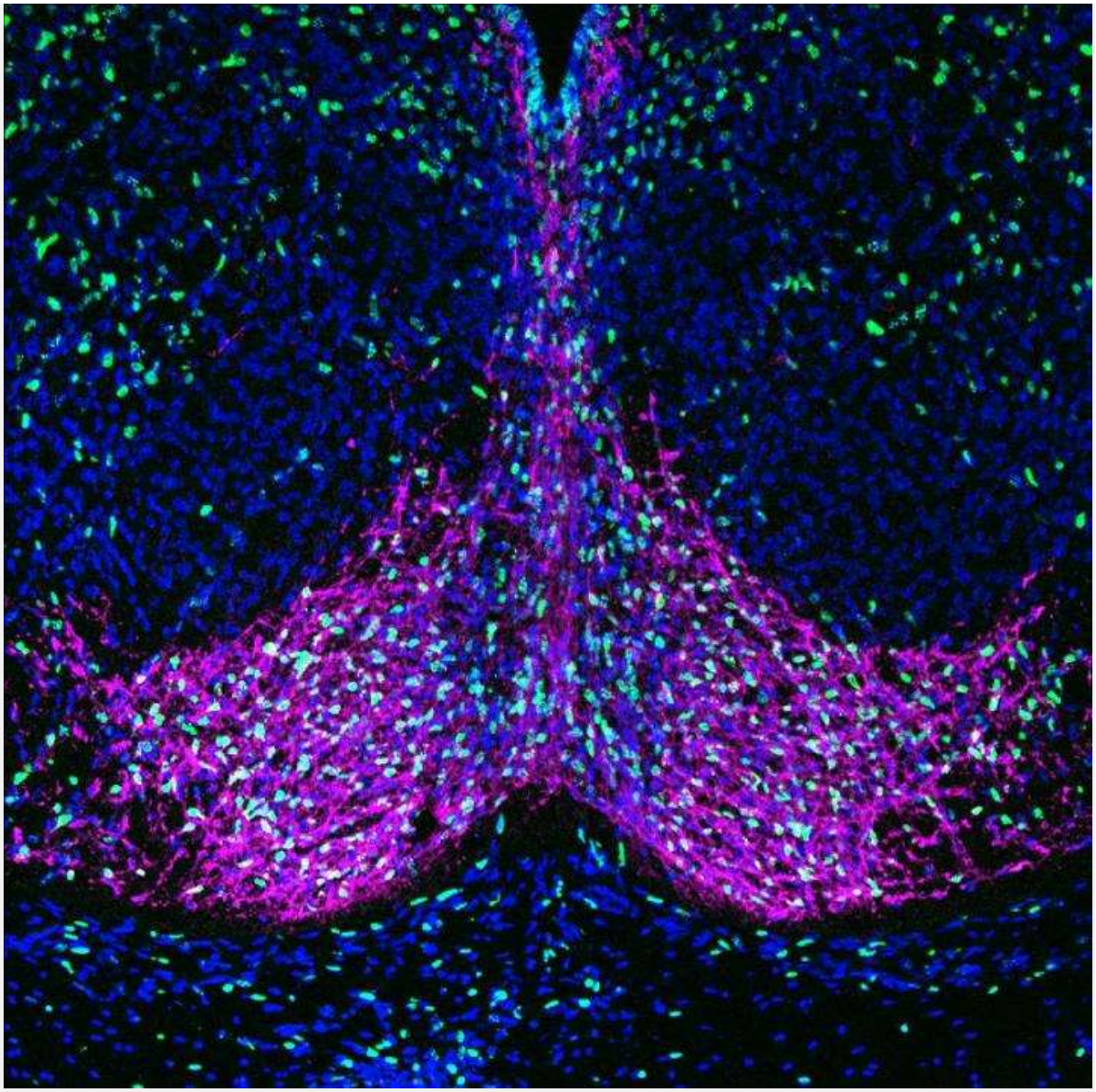

IMAGE: THE MAGENTA STAINING SHOWS BRAIN CELLS THAT RELEASE DOPAMINE. THE GREEN STAINING SHOWS NEWLY GENERATED CELLS. THE BLUE STAINING SHOWS ALL CELLS. **view more**

CREDIT: NOBUYUKI SAKAYORI, HIROSHIMA UNIVERSITY

Pregnant mice fed a diet high in omega-6 fats and low in omega-3 fats produce offspring that go on to exhibit "hedonic"--pleasurable but excessive--levels of consumption of hyper-caloric diets, according to researchers at Hiroshima University.

Omega-6 fats are found in grapeseed oil, corn oil and sesame oil, and are a staple of several salad dressings in world cuisine. Omega-3 fats are found in fish, perilla oil, and linseed oil. A diet balanced with these fats is considered essential for healthy brain growth.

The researchers also found that the offspring exhibit increased in utero growth of dopamine-producing neurons in the midbrain--the neurological reward system. They believe that exposure to this high omega-6/low omega-3 diet increases growth in these neurons in the fetus's brain during a specific period during pregnancy, driving dopamine release in the offspring's brain, and thus primes the offspring for hedonic consumption of sugar- or fat-rich diets over the course of their life.

The findings were published in the peer-reviewed journal *Communications Biology*, on August 28.

Meanwhile, mice whose mothers had not consumed the imbalanced omega-6/omega-3 diet did not exhibit as much overeating behavior, even when tempted by the presence of such food.

Since the 1960s, the Western diet has experienced a significant uptick in the presence of polyunsaturated omega-6 fats, and in ratios to polyunsaturated omega-3 fats that historically humans had never experienced before.

The ratio between these two types of fats is important because biochemically they compete with each other for incorporation into cell membranes, and an omega-6/omega-3 imbalance in the membranes of red blood cells is correlated with weight gain. An earlier study on mice had found that consumption of an imbalanced omega-6/omega-3 diet by the pregnant mother replicates this imbalance in the offspring's brain and even impairs brain development.

The Hiroshima researchers also found that a dopamine-inhibiting drug eliminates the hedonic consumption of the offspring, further supporting the notion that the dopamine signaling plays a critical role in driving this behavior.

"This suggests that adult mice gorging themselves on hyper-caloric diets were in effect neurologically programmed to do so by their mother's own consumption patterns," said Nobuyuki Sakayori, paper author and assistant professor from the Graduate School of Biomedical and Health Sciences at Hiroshima University.

The scientists were keen to stress that the ratio of omega-6 to omega-3 fat in the mouse diet is much higher than that experienced by most humans, and that their work lays the foundation for further, epidemiological studies on humans to see if the pattern holds for us.

But if it does, this could provide a new strategy for preventing obesity in children by managing the type of fats that pregnant mothers consume, akin to how mothers today generally avoid consumption of alcohol.

"This could work much better than existing anti-obesity campaigns or food taxes," Sakayori continued, "because instead of fighting against the brain's reward system, such a strategy focuses right from the start on the development of that system."

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Since its foundation in 1949, Hiroshima University has striven to become one of the most prominent and comprehensive universities in Japan for the promotion and development of scholarship and education. Consisting of 12 schools for undergraduate level and 4 graduate schools, ranging from natural sciences to humanities and social sciences, the university has grown into one of the most distinguished comprehensive research universities in Japan. English website: https://www.hiroshima-u.ac.jp/en

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4. 熱と微生物叢がより強い骨を作る –マウス実験

日付：2020 年 9 月 11 日
ソース：ジュネーブ大学
概要：

老化に関連する骨疾患である骨粗しょう症は、骨密度の低下、骨の微細構造の劣化、および骨折のリスクの増加を特徴とする。閉経後の女性の 3 分の 1 が影響を受けており、大きな公衆衛生問題となっている。
スイスのジュネーブ大学（UNIGE）の研究チームは、疫学分析、実験室実験、最先端のメタゲノムおよびメタボロミクスツールを通じて、より暖かい周囲温度（34℃）への曝露が骨の強度を高めることを観察、骨粗しょう症に典型的な骨密度の低下を防いだ、としている。さらに、熱によって引き起こされる腸内細菌叢の組成の変化に関連するこの現象は、骨粗しょう症に苦しんでいるマウスに暖かい環境に住んでいるマウスの微生物叢を移植することによって再現できた。実際、移植後、彼らの骨はより強く、より密になった。
細胞代謝で発見されたこれらの結果は、骨粗しょう症の予防と治療のための効果的で革新的な介入を想像させてくれるものだとしている。
この研究成果は、*Cell Metabolism* 誌で発表された。

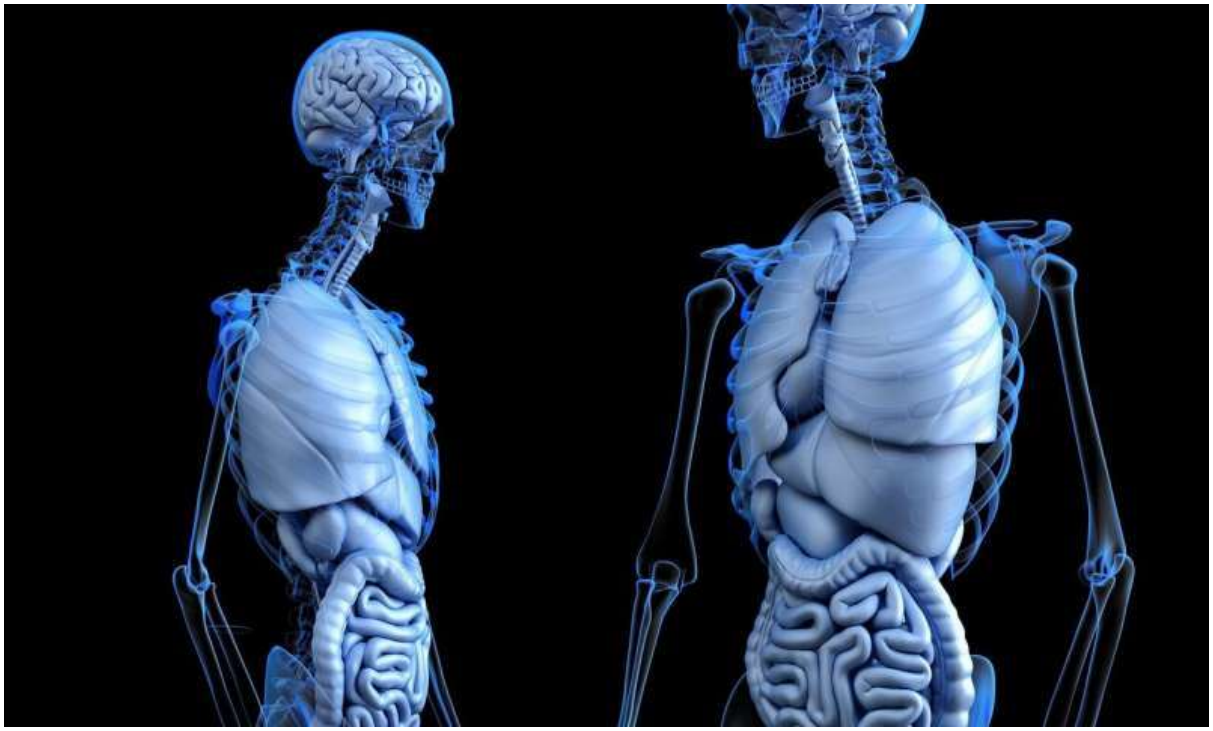
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2020-09-stronger-bones-microbiota.html

SEPTEMBER 11, 2020

STRONGER BONES THANKS TO HEAT AND MICROBIOTA

By University of Geneva



Credit: CC0 Public Domain

Osteoporosis, a bone disease linked to aging, is characterized by a loss of bone density, micro-architectural deterioration of the bones and an increased risk of fractures. With one third of postmenopausal women affected, it is a major public health problem. Through epidemiological analyses, laboratory experiments and state-of-the-art metagenomic and metabolomics tools, a research team from the University of Geneva (UNIGE), in Switzerland, has observed that exposure to warmer ambient temperatures (34 °C) increases bone strength, while preventing the loss of bone density typical of osteoporosis. Moreover, this phenomenon, linked to a change in the composition of gut microbiota triggered by heat, could be replicated by transplanting the microbiota of mice living in a warm environment to mice suffering from osteoporosis. Indeed, after the transplant, their bones were stronger and denser. These results, to be discovered in *Cell Metabolism*, make it possible to imagine effective and innovative interventions for prevention and treatment of osteoporosis.

Many biologists are familiar with Allen's Rule, from 19th-century naturalist Joel Asaph Allen, according to which animals living in warm areas have a larger surface area in relation to their volume than animals living in colder environment. Indeed, a larger skin surface allows better evacuation of body heat. "In one experiment, we placed newborn mice at a temperature of 34 °C in order to minimize the heat shock associated with their birth. We found that they had longer and stronger bones, confirming that bone growth is affected by ambient temperature," explains Mirko Trajkovski, Professor at the Department of Cell Physiology and Metabolism and at the Diabetes Centre of the UNIGE Faculty of Medicine, who led the study. But what about adulthood?

Consistent epidemiological data

By placing several groups of adult mice in a warm environment, the scientists observed that while bone size remained unchanged, bone strength and density were largely improved. They then repeated their experiment with mice after an ovariectomy modeling post-menauposal osteoporosis. "The effect was very interesting," says Claire Chevalier, then a researcher in Professor Trajkovski's laboratory and the first author of this work. "The simple fact of warming the living environment of our mice protected them from the bone loss typical of osteoporosis!"

What about human beings? The research team analyzed global epidemiological data on the incidence of osteoporosis in relation to the average temperature, latitude, calcium consumption and vitamin D levels. Interestingly, they found that the higher the temperature, the fewer hip fractures—one of the main consequences of osteoporosis— regardless of other factors. "We found a clear correlation between geographical latitude and hip fractures, meaning that in the northern countries the incidence is higher compared to the warmer south," says Mirko Trajkovski. "Normalizing the analysis of the known players such as vitamin D or calcium did not modify this correlation. However, when we excluded the temperature as the determinant, the correlation was lost. This is not to say that calcium or vitamin D do not play a role, either alone or in combination. However, the determining factor is heat—or lack thereof."

How the microbiota adapts

Specialists in the microbiota, the Geneva scientists wanted to understand its role in these metabolic modifications. To this end, they transplanted the microbiota of mice living in a 34° environment to osteoporotic mice, whose bone quality was rapidly improved. "These findings may imply an extension to Allen's rule, suggesting elongation-independent effects of the warmth, which predominantly favors bone density and strength during adulthood through microbiota alterations," says Mirko Trajkovski.

Thanks to the state-of-the-art metagenomic tools developed in their laboratory, the scientists then succeeded in understanding the role played by microbiota. When adapts to heat, it leads to a disruption in the synthesis and degradation of polyamines, molecules that are involved in aging, and in particular in bone health. "With heat, the synthesis of polyamines increases, while their degradation is reduced. They thus affect the activity of osteoblasts (the cells that build bones) and reduce the number of osteoclasts (the cells that degrade bones). With age and menopause, the exquisite balance between the osteoclast and osteoblast activity is disrupted," explains Claire Chevalier. "However, heat, by acting on the polyamines, which we found to be partly regulated by the microbiota, can maintain the balance between these two cell groups." These data therefore indicate that exposure to warmth could be a prevention strategy against osteoporosis.

Developing new treatments

The influence of microbiota on metabolism is being better understood. However, in order to be able to use this knowledge to develop therapeutic strategies, scientists must identify precisely the role of particular bacteria in particular diseases. In the context of their work on osteoporosis, Professor Trajkovski's team has been able to

identify certain important bacteria. "We still need to refine our analyses, but our relatively short-term goal would be to identify candidate bacteria, and develop several 'bacterial cocktails' to treat metabolic and bone disorders, such as osteoporosis, but also to improve insulin sensitivity, for example," the authors conclude.

Explore further

Modulating bone cell recruitment to prevent osteoporosis

More information: Claire Chevalier et al, Warmth Prevents Bone Loss Through the Gut Microbiota, *Cell Metabolism* (2020). DOI: 10.1016/j.cmet.2020.08.012

Journal information: Cell Metabolism

Provided by University of Geneva

5. アレルギー性免疫反応が細菌感染との闘いを助ける –マウス実験

日付：2020 年 9 月 9 日
ソース：オーストリア科学アカデミーCeMM 分子医学研究センター
概要：

オーストリア科学アカデミーCeMM 分子医学研究センター、ウィーン医科大学、スタンフォード大学医学部の研究者らは、アレルギー反応を引き起こすことで最もよく知られている免疫系のモジュールが、黄色ブドウ球菌によって引き起こされる感染に対する生体防御を獲得する上で重要な役割を果たすことを発見した。このアレルギーモジュールは、マスト細胞と免疫グロブリン E で構成されており、体内の二次細菌感染に対する保護と耐性の向上をもたらす。
科学者らは、軽度の黄色ブドウ球菌皮膚感染症のマウスが、適応免疫応答と細菌成分に対する特異的 IgEs 抗体を発生させることを発見した。この免疫応答は、これらのマウスが重度の二次肺または皮膚や軟部組織感染に直面した場合に、これらのマウスに高い耐性を与える。ただし、機能的な IgE エフェクターメカニズムまたはマスト細胞を欠いているマウスは、そのような保護を構築することができない。
これらの発見は、バクテリアに対する「アレルギー」免疫反応は病理的ではなく、防御的であることを示している。
したがって、毒素産生病原菌に対する防御は、「アレルギーモジュール」の重要な生物学的機能である、として *Immunity* 誌に発表している。

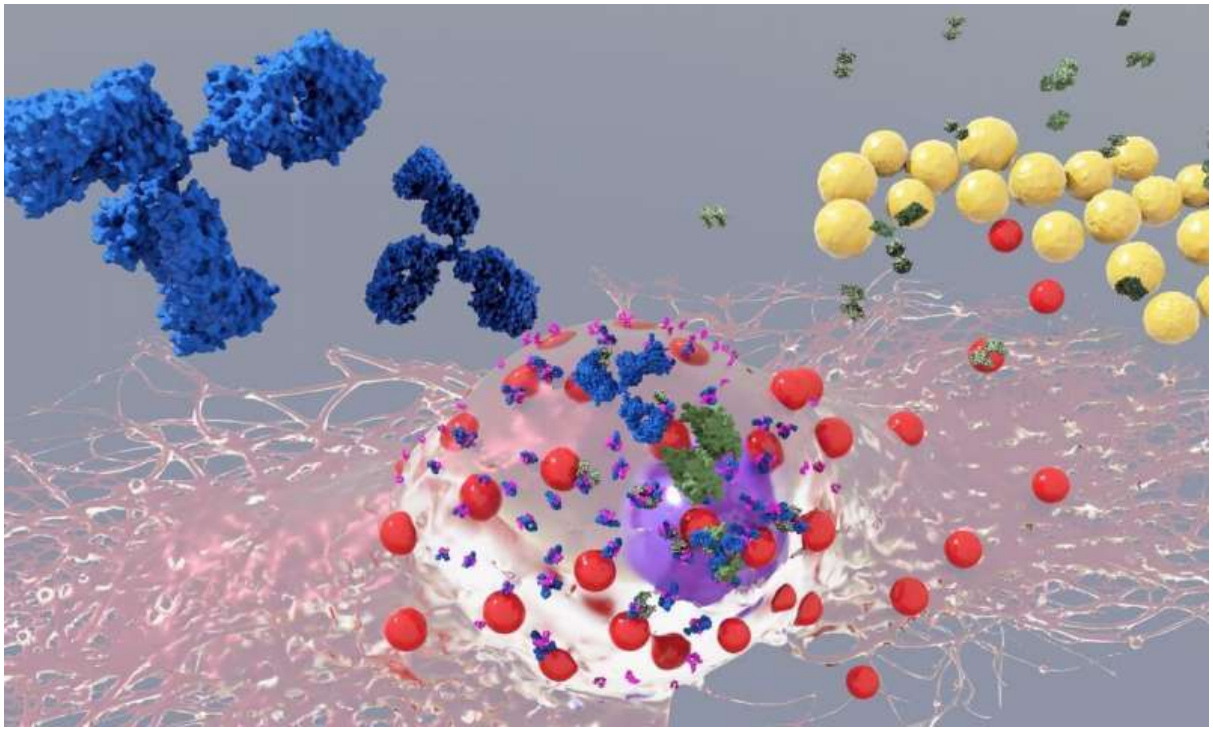
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2020-09-allergic-immune-responses-bacterial-infections.html

SEPTEMBER 9, 2020

ALLERGIC IMMUNE RESPONSES HELP FIGHT BACTERIAL INFECTIONS

by CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences



Artistic 3D of a mast cell (in the center of the picture) with IgE antibodies (in blue), which bound to the receptor Fc?RI (in pink) on the cell surface and Staphylococcus aureus bacteria (in gold). The IgE antibodies were induced during an earlier S. aureus infection and recognize bacterial toxins (in green). Upon re-infection with S. aureus (as shown) the IgE antibodies increase the mast cell response to S. aureus toxins (in green), leading to enhanced release of mast cell granules (in red) and antibacterial activity Credit: Bobby R. Malhotra/CeMM

Allergy is one of the most common diseases in Europe, it is estimated that more than 150 million Europeans suffer from recurring allergies and by 2025 this could have increased to half of the entire European population.1 Allergic patients initially undergo a process of 'sensitization,' meaning that their immune system develops a specific class of antibodies, so called Immunoglobulin E antibodies (IgE), which can recognize external proteins, referred to as allergens. IgEs bind and interact with cells that express a specific receptor called FcεR1. There are only a few cell types in the body that express the FcεR1 receptor and probably the most important ones are mast cells, a type of immune cell found in most tissues throughout the body.

When re-exposed to the allergen, mast cells (with IgE bound to their FcεR1 receptors) immediately react by rapidly releasing different mediators (e.g. histamine, proteases or cytokines) that cause the classic allergic symptoms. These symptoms depend on the tissue where the contact with the allergen happens and can range from sneezing/wheezing (respiratory tract) to diarrhea and abdominal pain (gastrointestinal tract) or itching (skin). Systemic exposure to allergens can activate a large number of mast cells from different organs at the same time, causing anaphylaxis, a serious and life-threatening allergic reaction.

Despite decades of research and detailed knowledge of the critical role of IgEs and mast cells in allergies, the physiological, beneficial function of this "allergy module" is still not completely understood. In 2006, Stephen J. Galli, senior co-author of this study, and his laboratory at Stanford University revealed the importance of mast cells

for innate resistance against venoms of certain snakes and the honeybee. Subsequent work from the Galli laboratory showed the critical role of the 'allergy module' in acquired host defense against high doses of venom: this finding (to which Philipp Starkl, first author of the current study, contributed importantly) represented the first clear experimental evidence supporting the 'Toxin Hypothesis' postulated by Margie Profet in 1991. This hypothesis proposed a beneficial function for allergic reactions against noxious substances.

Following up on this discovery, Philipp Starkl, Senior Postdoctoral fellow at the Medical University of Vienna and CeMM, together with Sylvia Knapp, Professor at the Medical University of Vienna and CeMM PI, and Stephen J. Galli, Professor at Stanford University School of Medicine, and colleagues, set out to investigate whether this phenomenon could be relevant in defense against other toxin-producing organisms, in particular, pathogenic bacteria. The authors selected the bacterium *Staphylococcus aureus* as pathogen model due to its enormous clinical relevance and broad repertoire of toxins. This bacterium is a prototypic antibiotics-resistant pathogen and is also associated with the development of allergic immune responses in diseases such as asthma and atopic dermatitis. For their research, they used different experimental *S. aureus* infection models in combination with genetic approaches and in vitro mast cell models to reveal the functions of selected components of IgE effector mechanisms.

The scientists found that mice with a mild *S. aureus* skin infection develop an adaptive immune response and specific IgEs antibodies against bacterial components. This immune response grants these mice an increased resistance when they are confronted with a severe secondary lung or skin and soft tissue infection. However, mice that are lacking functional IgE effector mechanisms or mast cells are unable to build such protection. These findings indicate that the "allergic" immune response against bacteria is not pathological, but instead protective. Hence, defense against toxin-producing pathogenic bacteria might be an important biological function of the allergy module.

This study is an important collaboration initiated by Philipp Starkl at the laboratory of Stephen J. Galli at Stanford University together with other colleagues and then continued at the laboratory of Sylvia Knapp at CeMM and the Medical University of Vienna. This exciting discovery not only advances the general understanding of the immune system and most notably allergic immune responses, but it could also explain why the body has maintained the allergy module throughout evolution. Despite their dangerous contributions to allergic diseases, IgEs and mast cells can exert beneficial functions that the immune system can capitalize on to protect the body against venoms and infections with toxin-producing bacteria, such as *S. aureus*.

Explore further

Bee sting allergy could be a defense response gone haywire, scientists finds

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More information: Philipp Starkl et al, IgE Effector Mechanisms, in Concert with Mast Cells, Contribute to Acquired Host Defense against Staphylococcus aureus, *Immunity* (2020). DOI: 10.1016/j.immuni.2020.08.002

Journal information: Immunity

Provided by CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences

6. ヒトとマウスの生化学反応速度の違い

日付：2020 年 9 月 17 日
ソース：理化学研究所
概要：https://www.riken.jp/press/2020/20200918_1/index.html

ヒトの時間とネズミの時間
－タンパク質の合成と分解速度が体節時計周期の多様性を生む－

理化学研究所（理研）生命機能科学研究センター再構成生物学研究ユニットの戎家美紀ユニットリーダー(研究当時、現欧州分子生物学研究所（EMBL） Barcelona グループリーダー)、松田充弘研究員(研究当時、現 EMBL Barcelona 研究員)、ポンペウ・ファブラ大学のジョルディ・ガルシア教授、京都大学ウイルス・再生医科学研究所の影山龍一郎教授、京都大学 iPS 細胞研究所のジャンタシュ・アレヴ助教（研究当時、現京都大学高等研究院ヒト生物学高等研究拠点（ASHBi）准教授）、戸口田淳也教授、池谷真准教授らの国際共同研究グループは、ヒトの発生時間がマウスよりも遅いのは、遺伝子発現やタンパク質分解などの速度が、ヒトではマウスに比べて遅いことに起因することを発見しました。
本研究成果は、「ヒトとマウスの時間の違いがどのように生じるのか」という生物学上の根本的な問いを解き明かしたものです。
脊椎動物の発生期における重要イベントである「**体節時計**[1]」は、遺伝子発現の振動現象であり、規則的な体節形成の中心原理です。
今回、国際共同研究グループは、培養皿上で**多能性幹細胞**[2]から体節時計を再現し、マウスとヒトの体節時計周期の時間スケールが異なる理由を調べました。体節時計の中心となる遺伝子をヒトとマウスで入れ替えた細胞を作製したところ、マウスの遺伝子を持ったヒト細胞はヒトの時間（5 時間周期）、ヒトの遺伝子を持ったマウス細胞はマウスの時間（2 時間周期）を示しました。またこの違いは、タンパク質の分解速度や遺伝子発現の遅れなどの生化学反応が、ヒトの細胞ではマウスよりも 2 倍から 3 倍程度遅いために生じることが分かりました。すなわち、ヒトとマウスの時間の違いは体節時計遺伝子の違いではなく、細胞内環境の違いにより生じることが明らかになりました。
本研究は、科学雑誌『Science』（9 月 18 日号）の掲載に先立ち、オンライン版（9 月 17 日付：日本時間 9 月 18 日）に掲載されます。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/09/200917181243.htm

HUMANS DEVELOP MORE SLOWLY THAN MICE BECAUSE OUR CHEMISTRY IS DIFFERENT

Date:

September 17, 2020

Source:

RIKEN

Summary:

Scientists have found that the 'segmentation clock' -- a genetic network that governs the body pattern formation of embryos -- progresses more slowly in humans than in mice because the biochemical reactions are slower in human cells. The differences in the speeds of biochemical reactions may underlie differences between species in the tempo of development.

FULL STORY

Scientists from the RIKEN Center for Biosystems Dynamics Research, European Molecular Biology Laboratory (EMBL) Barcelona, Universitat Pompeu Fabra, and Kyoto University have found that the "segmentation clock" -- a genetic network that governs the body pattern formation of embryos -- progresses more slowly in humans than in mice because the biochemical reactions are slower in human cells. The differences in the speeds of biochemical reactions may underlie differences between species in the tempo of development.

In the early phase of the development of vertebrates, the embryo develops into a series of "segments" that eventually differentiate into different types of tissues, such as muscles or the ribs. This process is known to be governed by an oscillating biochemical process, known as the segmentation clock, which varies between species. For example, it is about two hours in mice, and about five hours in humans. Why the length of this cycle varies between species has remained a mystery, however.

To solve this mystery, the group began experiments using embryonic stem cells for mice and induced pluripotent stem (iPS) cells which they transformed into presomitic mesoderm (PSM) cells, the cells that take part in the segmentation clock.

They began by examining whether something different was happening in the network of cells or whether there was a difference in the process within cells. They found, using experiments that either blocked important signals or put cells in isolation, that the latter is true.

With the understanding that processes within cells were key, they suspected that the difference might be within the master gene -- HES7 -- which controls the process by repressing its own promoter, and did a number of complex experiments where they swapped the genes between the human and mouse cells, but this did not change the cycle.

According to corresponding author Miki Ebisuya, who performed the work both at RIKEN BDR and EMBL Barcelona, "Failing to show a difference in the genes left us with the possibility that the difference was driven by different biochemical reactions within the cells." They looked at whether there were differences in factors such as the degradation rate of the HES7 protein, an important factor in the cycle. They looked at a number of processes including how quickly mouse and human proteins were degraded and found, confirming the hypothesis, that both proteins were degraded more slowly in human cells than in mouse cells. There were also differences in the time it took to transcribe and translate HES7 into proteins, and the time it took for HES7 introns to be spliced. "We could thus show," says Ebisuya, "that it was indeed the cellular environment in human and mouse cells that is the key to the differential biochemical reaction speeds and thus differential time scales."

She continues, "Through this we have come up with a concept that we call developmental allochrony, and the present study will help us to understand the complicated process through which vertebrates develop. One of the key remaining mysteries is exactly what is difference between the human and mouse cells that drives the difference in reaction times, and we plan to do further studies to shed light on this."

Story Source:

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

Journal Reference:

1. Mitsuhiro Matsuda, Hanako Hayashi, Jordi Garcia-Ojalvo, Kumiko Yoshioka-Kobayashi, Ryoichiro Kageyama, Yoshihiro Yamanaka, Makoto Ikeya, Junya Toguchida, Cantas Alev, Miki Ebisuya. **Species-specific segmentation clock periods are due to differential biochemical reaction speeds**. *Science*, 2020; 369 (6510): 1450 DOI: 10.1126/science.aba7668

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7. インフルエンザが妊婦にとって壊滅的になり得る理由 –マウス実験

日付：2020 年 9 月 22 日
ソース：RMIT 大学
概要：

RMIT 大学が主導する新しい研究は、なぜインフルエンザが妊娠中に生命を脅かす合併症を引き起こす可能性があるのか、その理由を説明するのに役立つ。
今まで妊娠中のインフルエンザが母体と胎児の深刻な合併症の原因になることが知られていたが、それがどのように起こるか明確には理解されていなかった。
妊娠中、インフルエンザは母体から胎児に直接伝染するわけではないが、インフルエンザを発症した妊婦は、肺炎やその他の合併症による入院のリスクが高く、インフルエンザの影響を強く受けた母親の赤ちゃんは、胎児発育の制限、流産、早産のリスクが高くなる。
インフルエンザ A に関するこの研究では、ウイルスが妊娠中のマウスと妊娠していないマウスの体内で非常に異なる動作をすることを示した。妊娠していないマウスでは、インフルエンザ感染は肺に限局したままなのに対して、妊娠中のマウスでは、ウイルスは血管を介して循環系に広がる。
胎盤はタンパク質を分泌し、胎児の DNA を母親の血液中に放出する。これによって、ウイルスは肺にとどまらず母親の体全体に広がるのではないかとしている。
この研究は、米科学アカデミー紀要に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/09/200921151321.htm

NEW STUDY REVEALS WHY FLU CAN BE DEVASTATING FOR PREGNANT WOMEN

PRE-CLINICAL STUDY SUGGESTS VIRUS DOES NOT STAY IN THE LUNGS BUT SPREADS THROUGHOUT THE MOTHER'S BODY

Date:

September 22, 2020

Source:

RMIT University

Summary:

New research overturns current scientific thinking on flu infection in pregnancy. The study helps explain why influenza can lead to life-threatening complications during pregnancy.

The research also has implications for our understanding of how COVID-19 may be affecting the vascular system.

FULL STORY

New research helps explain why flu can lead to life-threatening complications during pregnancy, suggesting the virus does not stay in the lungs but spreads throughout the mother's body.

The pre-clinical study has overturned current scientific thinking on the reasons why flu infections affect pregnant women and their babies so severely.

The findings could also help researchers working to understand the fundamental biology of how COVID-19 spreads from the lungs into the body.

The research, in animal models, showed that during pregnancy flu spreads from the lungs through the blood vessels into the circulatory system, triggering a damaging hyperactive immune response.

Led by RMIT University in collaboration with researchers and clinicians from Ireland and Australia, the new study is published in the *Proceedings of the National Academy of Sciences*.

Lead author Dr Stella Liong said the research suggests the vascular system is at the heart of the potentially devastating complications caused by influenza during pregnancy.

"We've known for a long time that flu can cause serious maternal and fetal complications, but how this happens has not been clearly understood," Liong, a Vice-Chancellor's Postdoctoral Fellow at RMIT, said.

"Conventional thinking has blamed the suppressed immune system that occurs in pregnancy but what we see is the opposite effect -- flu infection leads to a drastically heightened immune response.

"The inflammation we found in the circulatory system is so overwhelming, it's like a vascular storm wreaking havoc throughout the body.

"We need further research to clinically validate our findings but the discovery of this new mechanism is a crucial step towards the development of flu therapies designed specifically for pregnant women."

Professor John O'Leary, Trinity College Dublin, said the study represented a landmark advance in our understanding of viral infections and pregnancy.

"The discovery of an influenza-induced 'vascular storm' is one of the most significant developments in inflammatory infectious diseases over the last 30 years and has significant implications for other viral infections, including COVID-19," he said.

Understanding flu and pregnancy

Influenza is not directly passed from mother to baby, but its potentially devastating effect on the mother is closely connected to the complications suffered by the baby.

Pregnant women who develop influenza are at higher risk of hospitalisation with pneumonia and other complications, while babies of mothers severely affected by flu are at increased risk of fetal growth restriction, miscarriage and preterm births.

Scientists have previously thought the reason flu has such serious health impacts is because the immune system is suppressed during pregnancy to enable the fetus to thrive, making it harder to fight infections.

But the new research on Influenza A shows the virus behaves very differently in the bodies of pregnant and non-pregnant mice.

In non-pregnant mice, the flu infection remains localised to the lungs. But in pregnant mice, the virus spreads into the circulatory system via the blood vessels.

This leads to intense inflammation that drastically affects the function of large blood vessels, which severely impacts on the health of the mother and can also restrict blood flow to the growing fetus.

Flu-induced vascular storm

In the new study, researchers found pregnant mice with flu had severe inflammation in the large blood vessels and the aorta, the major conduit artery from the heart.

While a healthy blood vessel dilates 90-100% to let blood flow freely, the flu-infected blood vessels functioned at only 20-30% of capacity.

Lead investigator Associate Professor Stavros Selemidis, RMIT, said even a small change in the diameter of a blood vessel could have profound changes to blood flow.

"We found a dramatic difference in these inflamed blood vessels, which can seriously affect how much blood makes it to the placenta and all the organs that help support the growing baby," Selemidis said.

"We've known that flu infection in pregnancy results in an increased risk of babies being smaller and suffering oxygen starvation.

"Our research shows the critical role that the vascular system could be playing in this, with inflammation in the blood vessels reducing blood flow and nutrient transfer from mum to baby."

While the researchers did not directly measure blood flow, the study found an increase in biomarkers for oxygen starvation in the fetuses of the flu-infected mice.

Why pregnancy makes a difference

During pregnancy, the placenta secretes proteins and releases fetal DNA into the mother's blood, which can cause underlying inflammation.

The new study suggests the influenza infection may tip that underlying inflammation in the mother's body over the edge, into a full-blown systemic inflammatory event.

Selemidis said the research also revealed a new connection to pre-eclampsia, a dangerous pregnancy complication characterised by high blood pressure.

"We found the same protein that is elevated in pre-eclampsia is also significantly elevated with flu," he said.

"While it will take further research to unpack this link, it could mean drugs targeting vascular inflammation that are currently being tested could potentially be repurposed in future for flu infection in pregnancy."

Coronavirus connection

Liong said the research also has implications for our understanding of how the COVID-19 virus may be affecting the vascular system.

"Flu and coronavirus are different but there are parallels and we do know that COVID-19 causes vascular dysfunction, which can lead to strokes and other cardiovascular problems," she said.

"Our studies in pregnancy offer new insights into the fundamental biology of how respiratory viruses can drive dysfunction in the vascular system.

"This could be valuable knowledge for those scientists working directly on treatments and vaccines for COVID-19."

The new study is the culmination of over 10 years' work by researchers in the School of Health and Biomedical Sciences at RMIT, leading a global collaboration.

The research was supported by an Australian Research Council (ARC) Future Fellowship and funding from the National Health and Medical Research Council of Australia (NHMRC).

Story Source:

Materials provided by **RMIT University**. Original written by Gosia Kaszubska. *Note: Content may be edited for style and length.*

Journal Reference:

1. Stella Liong, Osezua Oseghale, Eunice E. To, Kurt Brassington, Jonathan R. Erlich, Raymond Luong, Felicia Liong, Robert Brooks, Cara Martin, Sharon O'Toole, Antony Vinh, Luke A. J. O'Neill, Steven Bozinovski, Ross Vlahos, Paris C. Papagianis, John J. O'Leary, Doug A. Brooks, Stavros Selemidis. **Influenza A virus causes maternal and fetal pathology via innate and adaptive vascular inflammation in mice**. *Proceedings of the National Academy of Sciences*, Sept. 21, 2020; DOI: 10.1073/pnas.2006905117

Cite This Page:

- MLA
- APA
- Chicago

RMIT University. "New study reveals why flu can be devastating for pregnant women: Pre-clinical study suggests virus does not stay in the lungs but spreads throughout the mother's body." ScienceDaily. ScienceDaily, 22 September 2020. <www.sciencedaily.com/releases/2020/09/200921151321.htm>.

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8. 星型の脳細胞が睡眠の鍵を握る

自由に行動するマウスの睡眠中の星状細胞のカルシウムの活性を、ミニチュア顕微鏡を使用して初めて研究

日付：2020 年 9 月 24 日
ソース：ワシントン州立大学
概要：

Current Biology 誌に今日発表されたワシントン州立大学の新しい研究は、神経より 5 倍多勢の星型の脳細胞・アストロサイト（星状細胞）の通信手段・カルシウムは覚醒時には多く、睡眠中には少なく、睡眠がすぐにも必要な状態では急増し、眠れるようにすると減少することがマウス実験で示された。私達が眠る理由や如何に眠るかを理解し、睡眠疾患の治療を開発するにはアストロサイトに目を向ける必要がある、としている。
睡眠における星状細胞の役割をより深く掘り下げるために、研究者らは、げっ歯類モデルを使用して、睡眠と覚醒の間、および睡眠不足後の星状細胞のカルシウム活性を記録した。彼らは、マウスが動き回って通常どおりに行動するときに、マウスの脳を直接観察する小さなヘッドマウント顕微鏡を介して画像化される蛍光カルシウムインジケーターを使用した。これらの小型顕微鏡を使用した独自の方法論により、チームは自由に行動するマウスの睡眠中の星状細胞のカルシウム活性に関する初めての研究を実施することができた。
彼らは、睡眠不足が星状細胞のカルシウム活性の増加を引き起こし、それがマウスを眠らせた後に減少することを発見。また、星状細胞のカルシウム活性を遺伝的に操作することが睡眠調節に影響を与えるかどうかを見つけるために、彼らは星状細胞で選択的に STIM1 として知られているタンパク質を欠いているマウスを研究した。これらのマウスは、睡眠を奪われた後一度眠ることができた通常のマウスほど長く眠らなかったか、眠くならなかった、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/09/200924141550.htm

TWINKLING, STAR-SHAPED BRAIN CELLS MAY HOLD THE KEY TO WHY, HOW WE SLEEP

RESEARCHERS USED MINIATURE MICROSCOPES TO CONDUCT FIRST-EVER STUDY OF ASTROCYTE CALCIUM ACTIVITY IN SLEEP IN FREELY BEHAVING ANIMALS

Date:

September 24, 2020

Source:

Washington State University

Summary:

A new study suggests that star-shaped brain cells known as astrocytes could be as important to the regulation of sleep as neurons. The study builds new momentum toward ultimately solving the mystery of why we sleep and how sleep works in the brain. The discovery may also set the stage for potential future treatment strategies for sleep disorders and neurological diseases and other conditions associated with troubled sleep.

FULL STORY

A new study published today in the journal *Current Biology* suggests that star-shaped brain cells known as astrocytes could be as important to the regulation of sleep as neurons, the brain's nerve cells.

Led by researchers at Washington State University's Elson S. Floyd College of Medicine, the study builds new momentum toward ultimately solving the mystery of why we sleep and how sleep works in the brain. The discovery may also set the stage for potential future treatment strategies for sleep disorders and neurological diseases and other conditions associated with troubled sleep, such as PTSD, depression, Alzheimer's disease, and autism spectrum disorder.

"What we know about sleep has been based largely on neurons," said lead author and postdoctoral research associate Ashley Ingiosi. Neurons, she explained, communicate through electrical signals that can be readily captured through electroencephalography (EEG). Astrocytes -- a type of glial (or "glue") cell that interacts with neurons -- do not use electrical signals and instead use a process known as calcium signaling to control their activity.

It was long thought that astrocytes -- which can outnumber neurons by five to one -- merely served a supportive role, without any direct involvement in behaviors and processes. Neuroscientists have only recently started to take a closer look at their potential role in various processes. And while a few studies have hinted that astrocytes may play a role in sleep, solid scientific tools to study their calcium activity have not been available until recently, Ingiosi said.

To delve deeper into astrocytes' role in sleep, she and her coauthors used a rodent model to record astrocytes' calcium activity throughout sleep and wake, as well as after sleep deprivation. They used a fluorescent calcium indicator that was imaged via tiny head-mounted microscopes that looked directly into the brains of mice as they moved around and behaved as they normally would. This indicator allowed the team to see calcium-driven fluorescent activity twinkling on and off in astrocytes during sleep and waking behaviors. Their one-of-a-kind methodology using these miniature microscopes allowed the team to conduct the first-ever study of astrocytes' calcium activity in sleep in freely behaving animals.

The research team set out to answer two main questions: do astrocytes change dynamically across sleep and wake states like neurons do? And do astrocytes play a role in regulating sleep need, our natural drive to sleep?

Looking at astrocytes in the frontal cortex, an area of the brain associated with measurable EEG changes in sleep need, they found that astrocytes' activity changes dynamically across the sleep-wake cycle, as is true for neurons. They also observed the most calcium activity at the beginning of the rest phase -- when sleep need is greatest -- and the least calcium activity at the end of the test phase, when the need for sleep has dissipated.

Next, they kept mice awake for the first 6 hours of their normal rest phase and watched calcium activity change in parallel with EEG slow wave activity in sleep, a key indicator of sleep need. That is, they found that sleep deprivation caused an increase in astrocyte calcium activity that decreased after mice were allowed to sleep.

Their next question was whether genetically manipulating astrocyte calcium activity would impact sleep regulation. To find out, they studied mice that lacked a protein known as STIM1 selectively in astrocytes, which reduced the amount of available calcium. After being sleep deprived, these mice did not sleep as long or get as sleepy as normal mice once allowed to sleep, which further confirmed earlier findings that suggest that astrocytes play an essential role in regulating the need for sleep.

Finally, they tested the hypothesis that perhaps astrocyte calcium activity merely mirrors the electrical activity of neurons. Studies have shown that the electrical activity of neurons becomes more synchronized during non-REM sleep and after sleep deprivation, but the researchers found the opposite to be true for astrocytes, with calcium activity becoming less synchronized in non-REM sleep and after sleep deprivation.

"This indicates to us that astrocytes are not just passively following the lead of neurons," said Ingiosi. "And because they don't necessarily display the same activity patterns as neurons, this might actually implicate a more direct role for astrocytes in regulating sleep and sleep need."

More research is needed to further unravel the role of astrocytes in sleep and sleep regulation, Ingiosi said. She plans to study astrocytes' calcium activity in other parts of the brain that have been shown to be important for sleep and wake. In addition, she would like to look at astrocytes' interactions with different neurotransmitters in the brain to start to tease out the mechanism by which astrocytes might drive sleep and sleep need.

"The findings of our study suggest that we may have been looking in the wrong place for more than 100 years," said senior author and professor of biomedical sciences Marcos Frank. "It provides strong evidence that we should be targeting astrocytes to understand why and how we sleep, as well as for the development of therapies that could help people with sleep disorders and other health conditions that involve abnormal sleep."

Support for the study came from the National Institutes of Health.

Story Source:

Materials provided by **Washington State University**. Original written by Judith Van Dongen. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ashley M. Ingiosi, Christopher R. Hayworth, Daniel O. Harvey, Kristan G. Singletary, Michael J. Rempe, Jonathan P. Wisor, Marcos G. Frank. **A Role for Astroglial Calcium in Mammalian Sleep and Sleep Regulation**. *Current Biology*, 2020; DOI: 10.1016/j.cub.2020.08.052

Cite This Page:

- MLA
- APA
- Chicago

Washington State University. "Twinkling, star-shaped brain cells may hold the key to why, how we sleep: Researchers used miniature microscopes to conduct first-ever study of astrocyte calcium activity in sleep in freely behaving animals." ScienceDaily. ScienceDaily, 24 September 2020. <www.sciencedaily.com/releases/2020/09/200924141550.htm>.

9. パーキンソン病で損傷したマウスの脳の回路を幹細胞が修復

日付：2020 年 9 月 26 日
ソース：ウィスコンシン大学マディソン校
概要：

ウィスコンシン大学マディソン校の研究者らは、パーキンソン病のマウスモデルにおける概念実証幹細胞治療を実証した。彼らは、幹細胞に由来するニューロンが脳の正しい領域にうまく統合され、元々のニューロンと接続して運動機能を回復できることを発見した。パーキンソン病で損傷した脳の回路を修復するために、研究者らは、パーキンソン病のマウスモデルで死ぬ細胞の一種であるドーパミン産生ニューロンに分化するようにヒト胚性幹細胞を誘導することから始めた。彼らは、これらの新しいニューロンを、パーキンソン病の変性によって最も影響を受けた脳領域であるマウスの中脳に移植したところ、数ヶ月後、マウスは運動能力の改善を示した。また移植されたニューロンが長距離成長して脳の運動制御領域に接続していることが確認できた。
移植されたニューロンがパーキンソン病で損傷した回路を修復したことを最終的に確認するために、研究者らは遺伝子のオンとオフのスイッチを幹細胞に挿入した。これらのスイッチは、食餌または注射によって特殊なデザイナードラッグにさらされると、細胞の活動を上下させる。幹細胞がシャットダウンされると、マウスの運動の改善は消え、パーキンソン病で損傷した脳を回復するために幹細胞が不可欠であることが示唆された。また、この遺伝子スイッチ技術を使用して、移植された細胞の活動を微調整し、治療を最適化できることも示した。
研究者らは、*Cell Stem Cell* 誌で、この研究によって神経幹細胞治療が現実的な目標であることが示されている、と述べている。しかし、マウスからの発見を人々に翻訳するには、さらに多くの研究が必要だ、ともしている。

研究関連/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2020-09/uow-scc092520.php

NEWS RELEASE 25-SEP-2020

STEM CELLS CAN REPAIR PARKINSON'S-DAMAGED CIRCUITS IN MOUSE BRAINS

UNIVERSITY OF WISCONSIN-MADISON

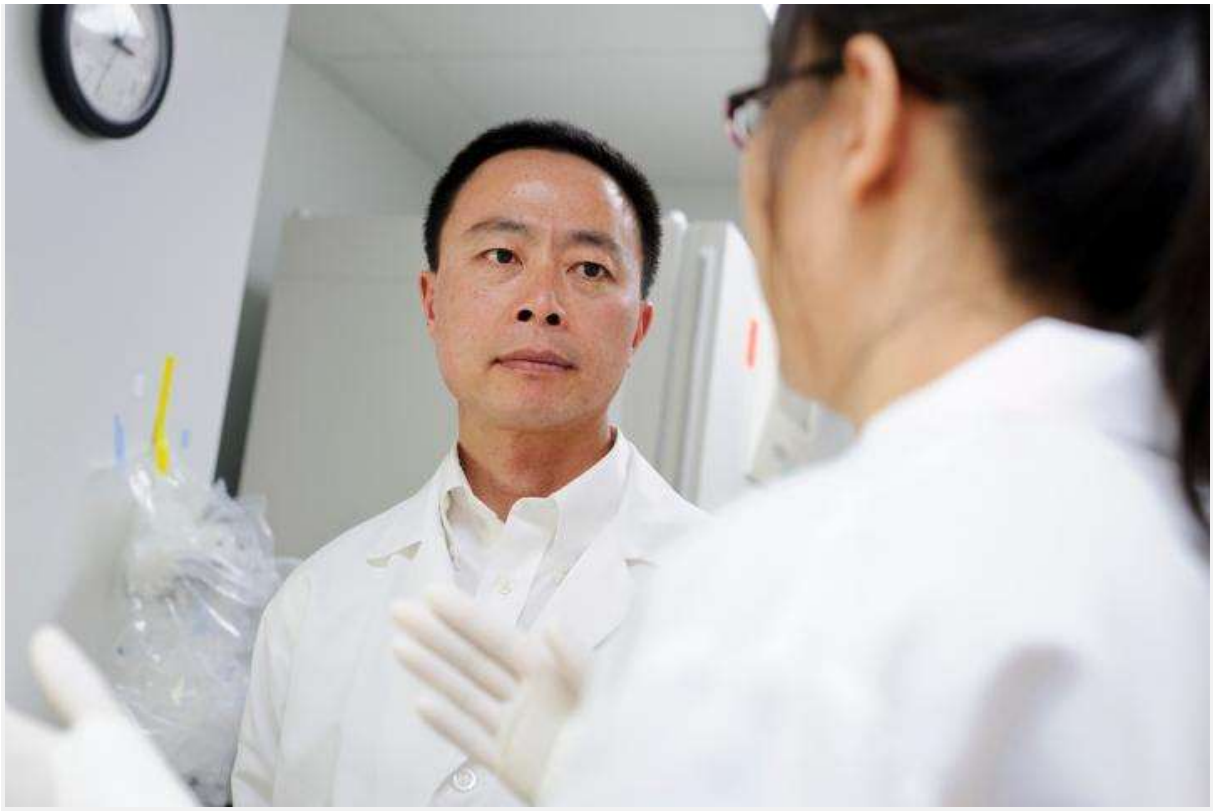

IMAGE: SU-CHUN ZHANG TALKING TO A RESEARCHER IN HIS LABORATORY AT THE WAISMAN CENTER OF THE UNIVERSITY OF WISCONSIN-MADISON. **view more**

CREDIT: UW-MADISON

MADISON, Wis. -- The mature brain is infamously bad at repairing itself following damage like that caused by trauma or strokes, or from degenerative diseases like Parkinson's. Stem cells, which are endlessly adaptable, have offered the promise of better neural repair. But the brain's precisely tuned complexity has stymied the development of clinical treatments.

In a new study addressing these hurdles, University of Wisconsin-Madison researchers demonstrated a proof-of-concept stem cell treatment in a mouse model of Parkinson's disease. They found that neurons derived from stem cells can integrate well into the correct regions of the brain, connect with native neurons and restore motor functions.

The key is identity. By carefully tracking the fate of transplanted stem cells, the scientists found that the cells' identity -- dopamine-producing cells in the case of Parkinson's -- defined the connections they made and how they functioned.

Coupled with an increasing array of methods to produce dozens of unique neurons from stem cells, the scientists say this work suggests neural stem cell therapy is a realistic goal. However, much more research is needed to translate findings from mice to people.

The team, led by UW-Madison neuroscientist Su-Chun Zhang, published its findings Sept. 22 in the journal *Cell Stem Cell*. The research was led by Zhang lab postdoctoral researchers Yuejun Chen, Man Xiong and Yezheng Tao, who now hold faculty positions in China and Singapore.

"Our brain is wired in such an accurate way by very specialized nerve cells in particular locations so we can engage in all our complex behaviors. This all depends on circuits that are wired by specific cell types," says Zhang, a professor of neuroscience and neurology at UW-Madison's Waisman Center. "Neurological injuries usually affect specific brain regions or specific cell types, disrupting circuits. In order to treat those diseases, we have to restore these circuits."

To repair those circuits in the Parkinson's disease mouse model, the researchers began by coaxing human embryonic stem cells to differentiate into dopamine-producing neurons, the kind of cells that die in Parkinson's. They transplanted these new neurons into the midbrains of mice, the brain region most affected by Parkinson's degeneration.

Several months later, after the new neurons had time to integrate into the brain, the mice showed improved motor skills. Looking closely, Zhang's group was able to see that the transplanted neurons grew long distances to connect to motor-control regions of the brain. The nerve cells also established connections with regulatory regions of the brain that fed into the new neurons and prevented them from being overstimulated.

Both sets of connections -- feeding in and out of the transplanted neurons -- resembled the circuitry established by native neurons. This was only true for dopamine-producing cells. Similar experiments with cells producing the neurotransmitter glutamate, which is not involved in Parkinson's disease, did not repair motor circuits, revealing the importance of neuron identity in repairing damage.

To finally confirm that the transplanted neurons had repaired the Parkinson's-damaged circuits, the researchers inserted genetic on-and-off switches into the stem cells. These switches turn the cells' activity up or down when they are exposed to specialized designer drugs in the diet or through an injection.

When the stem cells were shut down, the mice's motor improvements vanished, suggesting the stem cells were essential for restoring Parkinson's-damaged brains. It also showed that this genetic switch technology could be used to fine-tune the activity of transplanted cells to optimize treatment.

The Zhang group and other researchers have spent years developing methods to turn stem cells into the many different types of neurons within the brain. Each neurological disease or injury would require its own specialized nerve cells to treat, but the treatment plans would likely be broadly similar. "We used Parkinson's as a model, but the principle is the same for many different neurological disorders," says Zhang.

The work has personal meaning to Zhang. As a physician and scientist, he often receives letters from families desperate for help treating neurological disorders or brain trauma. It's also an experience he can relate to. Six years ago, Zhang was in a bike accident and broke his neck. When he awoke partially paralyzed in the hospital, his first thought was of how stem cells -- which he had already researched for years -- could help him recover.

Now, largely rehabilitated after years of physical therapy, Zhang still believes that the right stem cell treatments could, in the future, help people like him and the families he hears from.

To that end, Zhang's group is currently testing similar treatments in primates, a step toward human trials.

"There is hope, but we need to take things one step at a time," he says.

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This work was supported in part by the National Institutes of Health (grants NS096282, NS076352, and NS086604, MH099587 and MH100031).

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