Bio News – October, 2019

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

8/30　WHO、遺伝子編集の追跡調査のため登録簿作成へ 中国の双子問題受け

8/30　Ajinomoto Bio-Pharma がインドの Granules OmniChem Private Limited (GOC) を完全入手

8/31　実験室で培養の「ミニ脳」に神経活動、人の脳に類似 -UC San Diego 研究

9/2　電子タバコ使用と関連する米国の呼吸器疾患の報告数が 215 に増加

9/3　コンゴでのエボラ流行の死者数が 2000 人を超えた

9/4　ここ10年間の米国 FDA 承認の癌治療薬の割合がそれ以前の 10 年間から約倍増

Tufts Center for the Study of Drug Development の解析によると、ここ 10 年ほど(2010-18 年)の米国 FDA 承認薬の 27%は癌治療で、それ以前の 2000 年代の 10 年間と比較して約 2 倍に上昇している。

9/5　感染症薬の Vir Biotechnology が 1 億ドルの IPO 調達を計画

9/5　社員に違法に新薬を試験投与していたとして韓国の大手製薬会社 Ahngook Pharmaceutical の社長が逮捕された

9/5　中国企業、飼い猫のクローン化に初成功

https://headlines.yahoo.co.jp/hl?a=20190905-00000029-jij_afp-sctch

9/6　科学研究支える博士、日本だけ減る傾向

https://headlines.yahoo.co.jp/hl?a=20190906-00010000-sportal-sctch

9/6　肉を食べない人は心疾患を被り難い～ただし菜食の人は脳卒中を被り易い -英国研究

9/6　武田薬品、コンピューター創薬の Schrodinger (本社:ニューヨーク) との提携拡大

9/8　変形性関節症を模すヒツジができた

半月板損傷ヒツジがヒトの変形性関節症(OA)とそっくりな変性に至ることが示された。半月板損傷ヒツジの軟骨と骨の分解はまず損傷部分で生じて関節全域に広まっていくことが示され、損傷から 6 か月後の変性はヒト OA の病態と似通っていた。

9/9　うつ抑制分子を特定＝予防食品の開発に期待 -神戸大など

https://headlines.yahoo.co.jp/hl?a=20190909-00000002-jij-sctch

9/9　BioNTech の HIV や結核の予防治療の開発にゲイツ財団が 5,500 万ドル投資

9/10　BeiGene が売り上げを 60%水増ししているとニューヨークの投資会社が報告

2017 年に Celgene の中国事業を引き継いで同社の薬剤の中国販売を手掛ける BeiGene は売り上げを 60%水増ししていると、投資会社 J Capital Research が報告している。

9/10　脳血管をヘビのように進むロボット糸、MIT が開発--脳卒中などの治療に

https://headlines.yahoo.co.jp/hl?a=20190910-35142316-cnetj-sci

9/11　人工血液、動物実験に成功　1年以上の常温保存も可能 −防衛医大など

https://headlines.yahoo.co.jp/hl?a=20190911-00000015-asahi-soci

9/12　米、電子たばこ禁止へ＝香りや味付き、ほぼ全て

9/12　世界初、細胞の老化を抑制する遺伝子を発見 −岡山・吉備国際大学

https://headlines.yahoo.co.jp/hl?a=20190912-00010008-ksbv-sctch

9/12　GSK、投資会社と組んで設立したセリアック病治療開発会社 Sitari を取得

9/12　UT MD Anderson の Vassiliki Papadimitrakopoulou 氏が Pfizer の癌臨床開発を率いる

University of Texas MD Anderson Cancer Center の Vassiliki Papadimitrakopoulou 氏が今月 23 日から Pfizer に加わって癌分野の臨床開発を率いる。

9/14　エーザイ/Biogen、アルツハイマー病治療 BACE 阻害薬の Ph3 試験 2 つを中止

9/15　イスラエルの Teva、Novartis に続いて医療用大麻の世界販売に舵取り

9/15　「ピザでがん予防」などが受賞、2019 年イグ・ノーベル賞

https://headlines.yahoo.co.jp/hl?a=20190915-00000021-jij_afp-sctch

9/16　電子タバコ使用と関連する米国の呼吸器疾患の報告数が 380 に増加

https://www.statnews.com/2019/09/16/vaping-related-illnesses-question/?utm_source=STAT+Newsletters&utm_campaign=b2f3070598-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-b2f3070598-150065641

9/16　Purdue Pharma が破綻＝オピオイド中毒訴訟 2,000 件以上抱え

https://www.statnews.com/2019/09/16/if-purdue-pharma-declares-bankruptcy-what-would-it-mean-for-lawsuits-against-the-opioid-manufacturer/?utm_source=STAT+Newsletters&utm_campaign=b2f3070598-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-b2f3070598-150065641

9/17　Merck & Co のエボラワクチン V920 の承認申請が FDA に受理されて優先審査中

9/18　Eleusis、5−HT2A 活性化剤の心血管疾患マウスでの治療効果を報告

9/18　ヒトの胎盤内から黒色炭素粒子を検出、大気汚染が影響か −ベルギー研究

https://headlines.yahoo.co.jp/hl?a=20190918-00000030-jij_afp-sctch

9/19　GSK に続いて Sanofi もバングラデシュから撤退

9/19　5 歳までの乳幼児が飲むなら水か乳との方針を*米国 4 学会が示した

*Academy of Nutrition and Dietetics
American Academy of Pediatric Dentistry

American Academy of Pediatrics
American Heart Association

9/20　がん細胞除去や、アンチエイジングに応用も？ 京大研究グループが「不良細胞除去する仕組み」を解明

9/20　砂糖の取り過ぎがメタボになる原因が分かった 名大グループが解明

9/20　「ゲノム」食品 表示義務なし…消費者庁決定

9/20　発癌性物質検出を背景に Novartis が Zantac 後発品の出荷を全世界で停止している

降圧薬/心不全薬に続いて Zantac 等の胃酸分泌抑制剤 ranitidine（ラニチジン）含有品からも発癌性と思しきニトロソアミン不純物 NDMA が検出されたことを受け、Novartis の Sandoz 事業部が手持ちの Zantac 後発品の出荷を全世界で停止している。

9/21　リンパ節転移がん治療に新手法！泡・超音波で効率化 −東北大学大学院医工学研究科

https://headlines.yahoo.co.jp/hl?a=20190921-00010002-newswitch-sctch

9/21　Roche 子会社 Genentech がサウスサンフランシスコの敷地倍増計画を市に提出

9/23　MIT 研究者が「最も黒い物質」を偶然発見　99.995%の光を吸収

9/23　Microsoft が GSK の CEO・Emma Walmsley 氏を取締役に指名

9/23　Zantac およびその他の胸焼け薬の販売を禁止/制限する国が増加

ニトロソアミン不純物 NDMA の痕跡が検出された後 3 日間で、スイス、キプロス、エジプトが、新たにすべての胸焼け薬を禁止。不純物は、かつてロケット燃料の製造に使用されていた有機化学物質であり、特定の化学反応の意図しない副産物であるとされる。WHO は、この NDMA を人間に対する発がん性物質として分類している。

9/23　遺伝子遮断技術の Akcea、一気に 3 人のトップエグゼクティブを失う

9/24　Innate Pharma、1 億ドル IPO 調達目論見書をアメリカ証券取引委員会に申請

9/24　Clovis Oncology、癌に使用する放射能医薬品の権利をドイツの 3B から取得

9/24　肥満薬 Mediator の情報を Servier Laboratories が隠していたと訴える裁判がフランスで開始

フランスの創薬メーカーServier Laboratories の裁判がパリで始まり、昨日、2,000 人の死者が疑われる糖尿病薬の犠牲者が正義を求める裁判が始まった。減量のために販売されているアンフェタミン起源の Mediator（benfluorex）は、2009 年に販売が停止するまでに数百万人が服用。この薬の化学的構成とそのリスクについて不都合な情報を Servier が隠していたとして、過失致死罪、詐欺罪などで訴えを受けている。

9/24　胃がん検診AI支援　22年実用化目指す

9/24　電子タバコからの蒸気吸入（ベイピング）に伴う肺損傷が米国で 530 人に増えた

電子タバコからの蒸気吸入（ベイピング）と関連または恐らく関連する肺損傷の症例数が米国で 9 月 17 日までの一週間に 380 人から 530 人に増えており、6 州での 7 人の死亡が確認されている。

9/25　AveXis の要職 2 人が Zolgensma データ捏造に手を染めたと Novartis が FDA に報告

Novartis が AveXis を買って手に入れた脊髄性筋萎縮症（SMA）遺伝子治療 Zolgensma (onasemnogene abeparvovec) のデータ捏造は AveXis の要職 2 人が直接手を染めたか他の者にそうするように指示することでなされたとの米国 FDA への 8 月 23 日付けの報告が公開された。

9/25　GW の大麻から作るてんかん薬 EPIDYOLEX が欧州でも承認された

9/25　Bayer がボストン地区に更に根付く～*2 病院と組んで肺疾患薬を調べる研究所開設

*Brigham and Women's Hospital と Massachusetts General Hospital

9/25　Biocon、Pfizer からインドの研究開発拠点を入手してバイオシミラーの開発を急ぐ

9/25　宇宙からマウス生還に成功 −阪大

9/26　マサチューセッツ州がベイピング製品販売を 4 か月間禁止

9/26　AI の創薬会社 Deep Genomics、病因解明から臨床試験候補化合物決定まで 18 か月で完了

Deep Genomics は、銅の蓄積で肝臓や神経が傷む重病・ウィルソン病を引き起こす銅輸送体 ATP7B 遺伝子変異がエクソン 6 欠損（Exon 6 Skipping）を誘発することをまず突き止め、その所業を解消する 12 の化合物を続いて同定し、臨床試験に進める化合物 DG12P1 を決定。以上に掛かった期間は 1 年半。

9/26　iPS 細胞から「ミニ多臓器」初成功 −東京医科歯科大

https://headlines.yahoo.co.jp/hl?a=20190926-00000003-asahi-soci

9/27　発癌性物質 NDMA 混入により GSK が Zantac 製品の出荷を全世界で停止、に続いて回収も開始。

9/27　GSK、米ペンシルベニア州の製造拠点に 1 億 2,000 ドル投じて拡張

9/27　パーキンソン病、脳神経の小胞膜異常が関与＝順天堂大

https://headlines.yahoo.co.jp/hl?a=20190927-00000113-jij-sctch

9/29　投資会社の Deerfield がニューヨーク市の 12 階建てビルをバイオテック養成所に作り変える

9/29　BMS が買う Celgene の炎症/免疫事業長 Terrie Curran 氏が Phathom の CEO 職確保

9/29　Pfizer、専任会長の Ian Read 氏が去り、CEO の Albert Bourla 氏が会長を兼任

10/1　ナノ粒子でがん細胞破壊　京大などのグループが新手法開発

https://headlines.yahoo.co.jp/hl?a=20191001-00000000-kyt-sctch

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. 1 型糖尿病 早期発見への道を開く研究

2. 大腸癌のマウスの尿の色を変えるツール

3. MouseLight プロジェクト

4. マウスモデルにおける統合失調症の発症予防

5. 数学で動物が夜に見える理由を説明
   生物学的実験により、マウスの網膜発達の数学的モデリングを確認

6. 身体の中の小胞は化学療法よりも効果的に癌と戦う

7. 善玉菌に好みの繊維を与えて、マウスの腸内微生物叢を改変

8. 浅い眠りで記憶が消去される仕組みを解明
   ～ なぜ夢は起きるとすぐに忘れてしまうのか ～

9. 改変されたキラーT 細胞が癌に対して長期に免疫を提供する可能性
   UCLA の研究者が幹細胞を使用して、マウスのヒト腫瘍を攻撃する細胞を操作

10. 肥満のヒトに高血圧を引き起こす治療可能な経路発見

1. 1 型糖尿病 早期発見への道を開く研究

1 型糖尿病は、通常 20 歳以前に現れる自己免疫疾患で、生命に不可欠なホルモンであるインスリンの産生能力を一掃する。アメリカでは約 125 万人の子供および大人が 1 型糖尿病を患っており、原因が充分に理解されていないため、発生率が増加している。多くの場合、症状が現れてから診断されるが、かなり初期の兆候からリスクのある患者を検査できる方法があれば、発症を遅らせることが可能かもしれない。

Science Immunology 誌に発表された新しい研究で、Scripps Research 研究所の科学者らは、以前から若年性糖尿病として知られている 1 型糖尿病の可能な限り早い生物学的マーカーである可能性があるものを発見した、と発表している。彼らが現在試みているマウス研究をヒトに再現できた場合、治療的介入のタイミングが劇的に改善される可能性がある。

長い間、1型糖尿病には明確な遺伝的特徴が常に存在することが分かっており、1型糖尿病の場合には、変異した HLA（ヒト白血病抗原）として知られるタンパク質がβ細胞によって作られたインスリンの断片に結合し免疫系の破壊を促す。というように HLA 遺伝子変異と1型糖尿病の関連は充分に確立されているものの、免疫系の T 細胞がこの問題のある分子に引き寄せられるモードを見分けることができていない。

今回、研究者らは 5 年にわたるマウス実験を通じて、非常に初期の段階の非肥満糖尿病マウスの血液サンプルを評価、また、最先端の構造・計算生物学の技術を駆使して、個々の T 細胞の DNA 配列を非常に高解像度に特定した。

その主な知見の1つは、CD4+T 細胞が変異した HLA タンパク質を認識しβ細胞を攻撃するのを可能にする「P9 スイッチ」と呼ばれる構造メカニズムであり、P9 スイッチはマウスの抗インスリン応答の早期バーストを駆動してその後急速に消失したため、この現象がヒトにもあれば、P9 スイッチ搭載免疫細胞は、疾患の発症初期段階にある人にしか検出できない。従って、これらの細胞の存在を明らかにする血液検査が、疾患の最も早い特定へとつながる可能性がある、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/08/190830150802.htm

Discovery paves the way for earlier detection of type 1 disease

Date:

August 30, 2019

Source:

Scripps Research Institute

Summary:

Scientists have discovered what may be the earliest possible biological marker of type 1 diabetes, formerly known as juvenile type 1 diabetes. If their mouse study can be replicated in humans, which they are now attempting to do, the timing of therapeutic intervention may be drastically improved for patients who are on course to develop the disease.

FULL STORY

Type 1 diabetes, an autoimmune disease that typically emerges before the age of 20, wipes out the body's ability to produce insulin -- a hormone that's essential to life. Diagnosis often comes after symptoms arise, at which point the disease has taken hold. But if there were a way to test at-risk patients for very early signs of the disease, it may be possible to delay its onset.

In new research published in *Science Immunology*, scientists at Scripps Research have discovered what may be the earliest possible biological marker of type 1 diabetes, formerly known as juvenile diabetes. If their mouse study can be replicated in humans, which they are now attempting to do, the timing of therapeutic intervention may be drastically improved for patients who are on course to develop the disease.

"The translational aspect of this study is what's most exciting to me," says Luc Teyton, MD, PhD, professor of immunology and microbiology at Scripps Research, who led the research. "By using single-cell technologies to study the prediabetic phase of disease, we have been able to mechanistically link specific anti-insulin T cells with the autoimmune response seen in type 1 diabetes. And that has given us the confirmation we needed to move into human studies."

Roughly 1.25 million American children and adults have type 1 diabetes, and the incidence rate is increasing for reasons that aren't fully understood. For those with the disease, the immune system attacks pancreatic beta cells that are solely responsible for producing insulin. Without insulin, their body is unable to move sugars out of the bloodstream and into cells, where glucose is needed for energy. Because of this, people with type 1 diabetes need to closely monitor their blood-glucose levels and inject insulin daily to survive.

The scientific community has known for a long time -- ever since a landmark genetic study of type 1 diabetes more than 25 years ago -- that among people with type 1 diabetes, a distinct genetic signature is always present among a certain class of immune-regulating molecules known as HLAs (short for human leukocyte antigens). HLA proteins sit on the surface of cells, telling the immune system whether to attack. While this signaling is normally helpful in destroying dangerous cells, it can become life-threatening when the molecule is sending the wrong messages.

In the case of type 1 diabetes, the mutated HLA protein binds to fragments of insulin made by beta cells, prompting destruction by the immune system.

While the connection between the HLA genetic mutation and type 1 diabetes is well-established, the scientific community could never discern the mode by which the immune system's T cells are drawn to this problematic molecule.

That's what Teyton's team set out to answer through experiments spanning five years. Their work involved evaluating blood samples of non-obese diabetic mice during the very early phase of disease, using cutting-edge structural and computational biology techniques to understand how the cells bring about disease.

The single-cell analysis they conducted had never been done before for these types of cells, unearthing new information, Teyton says. Working in concert with Scripps Research's Department of Integrative Structural and Computational Biology, the team sequenced the DNA of individual T

cells for an extremely high-resolution view of cell function and genetic variation. In all, the study produced more than 4 terabytes of data.

Among their key findings was a structural mechanism they dubbed the "P9 switch" that allows CD4+ T cells to recognize the mutated HLA protein and attack beta cells. They also discovered that the dangerous anti-insulin T cells always reside in islets, which are small tissue structures in the pancreas where beta cells are located. Previously, it was not known where the anti-insulin T cells originated, and some suspected they may be produced in pancreatic lymph nodes.

Notably, the P9 switch drove an early burst of anti-insulin response in mice, then rapidly disappeared. If this phenomenon carries over to humans, immune cells equipped with the P9 switch would be detectable only in those who are in early stages of developing the disease. Thus, a blood test that reveals the presence of these cells could provide the earliest-possible indication of disease and enable intervention.

Armed with this research, Teyton has received approval to move forward with a study in humans. His team will collect blood samples from up to 30 at-risk individuals per year and analyze the samples for precursors to disease. Type 1 diabetes has a strong genetic link; those who have an immediate relative with disease are up to 20 times more likely than the general population to get it themselves, making this a well-defined group to monitor for biomarkers, Teyton says.

An early diagnosis during the five years of pre-clinical progression and the ability to monitor beta cell destruction in real time will allow a series of new therapeutic interventions aimed at preventing type 1 diabetes and insulin dependence, Teyton says.

Authors of the study, "Position B57 of I-A controls early anti-insulin responses in NOD mice, linking an MHC susceptibility allele to type 1 diabetes onset," include Louis Gioia, Marie Holt, Anne Costanzo, Siddhartha Sharma, Brian Abe, Lisa Kain, Maki Nakayama, Xiaoxiao Wan, Andrew Su, Clayton Mathews, Yi-Guang Chen, Emil Unanue and Luc Teyton.

This work was supported by the National Institutes of Health Clinical and Translational Science Award issued to the Scripps Translational Science Institute UL1TR002550, TL1TR002551 to S.S. and L.G. and KL2TR001112 to B.A., and the National Institute of Health RO1DK058177 to E.U., R01DK099317 to M.N., RO1DK097605 and DK107541 to Y.C., and 1R01DK117138 to L.T. B.A was a resident of the Scripps Clinic & Green Hospital Internal Medicine Residency ABIM Research pathway during the course of the study.

Story Source:

Materials provided by **Scripps Research Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ouis Gioia, Marie Holt, Anne Costanzo, Siddhartha Sharma, Brian Abe, Lisa Kain, Maki Nakayama, Xiaoxiao Wan, Andrew Su, Clayton Mathews, Yi-Guang Chen, Emil Unanue and Luc Teyton. **Position B57 of I-A controls early anti-insulin responses in NOD mice, linking an MHC susceptibility allele to type 1 diabetes onset**. *Science Immunology*, 2019 DOI: 10.1126/sciimmunol.aaw6329

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2. 大腸癌のマウスの尿の色を変えるツール

イギリスのインペリアル カレッジ ロンドンと MIT のエンジニアによって、マウスの腫瘍の成長を尿の色の変化で示すシンプルな尿検査法が開発された。
癌を初期段階で検出するツールは、患者の生存率と生活の質を高めることができる。ただ、癌検診には、多くの場合、高価な機器が必要で、診療所に自ら出向く必要もあるため、ポイントオブケア診療の新分野では、より安価で迅速かつ使い易いテストが取り組まれている。
今日 *Nature Nanotechnology* 誌に掲載された論文によると、研究チームはマウスにナノセンサーを注入するが、このセンサーがプロテアーゼとして知られる腫瘍によって放出される酵素によって切断される。この切断が起きると、ナノセンサーが腎臓を通過し、青色の変化を生み出し、尿検査によって肉眼で識別することができる、というものである。
研究チームは、この初期の技術を大腸癌のマウスに応用し、腫瘍を持つマウスの尿が健康なマウスの尿に比べて明るい青色になることを発見した。
プロテアーゼは、癌だけでなく、感染症、炎症、血栓症など多くの疾患で機能的な役割を果たすため、異なるプロテアーゼで切断できるセンサーのバージョンを設計することで様々な条件を検出できる、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-09/icl-cut090219.php

NEWS RELEASE 3-SEP-2019

Color-change urine test for cancer shows potential in mouse study

IMPERIAL COLLEGE LONDON

A simple and sensitive urine test developed by Imperial and MIT engineers has produced a colour change in urine to signal growing tumours in mice.

Tools that detect cancer in its early stages can increase patient survival and quality of life. However, cancer screening approaches often call for expensive equipment and trips to the clinic, which may not be feasible in rural or developing areas with little medical infrastructure. The emerging field of point-of-care diagnostics is therefore working on cheaper, faster, and easier-to-use tests.

An international pair of engineering labs have now developed a tool that changes the colour of mouse urine when colon cancer is present. The findings from testing the fast, non-invasive cancer test are published today in *Nature Nanotechnology*.

The early stage technology, developed by teams led by Imperial's Professor Molly Stevens and MIT professor and Howard Hughes Medical Institute investigator Sangeeta Bhatia, works by injecting nanosensors into mice, which are cut up by enzymes released by the tumour, known as proteases.

When the nanosensors are broken up by proteases, they pass through the kidney, and can be seen with the naked eye after a urine test that produces a blue colour change.

The researchers applied this technology to mice with colon cancer, and found that urine from tumour-bearing mice becomes bright blue, relative to test samples taken from healthy mice.

Professor Stevens, of Imperial's Departments of Materials and Bioengineering, said: "By taking advantage of a chemical reaction that produces a colour change, this test can be administered without the need for expensive and hard-to-use lab instruments.

"The simple readout could potentially be captured by a smartphone picture and transmitted to remote caregivers to connect patients to treatment."

Sensing signals

When tumours grow and spread, they often produce biological signals known as biomarkers that clinicians use to both detect and track disease. However, not all biomarkers play an active role in tumour growth, and most are present in such small quantities that they can be challenging to find.

One family of tumour proteins known as matrix metalloproteinases (MMPs) have attracted attention as potential biomarkers, since these enzymes help promote the growth and spread of tumours by chewing up the tissue scaffolds that normally keep cells in place.

Many cancer types, including colon tumours, produce high levels of several MMP enzymes, including one called MMP9.

In this study, the Imperial-MIT team developed nanosensors where ultra-small gold nanoclusters (AuNCs) were connected to a protein carrier through linkages that are broken by MMP9s

To develop the colour-changing urine test, the researchers used two AuNC properties - their very small (<2 nanometre) size, and their ability to cause a blue colour change when treated with a chemical substrate and hydrogen peroxide.

The researchers designed the AuNC-protein complexes to disassemble after being cut by MMPs in the tumour microenvironment or blood. When broken apart, the released AuNCs travel via the blood and are small enough to be filtered through the kidneys into the urine.

In healthy mice without high MMP levels, the complexes remain intact, and are too large to pass into the urine. If AuNCs have been concentrated in the urine, a chemical test will produce a blue colour change that is visible with the naked eye.

For this study, the researchers developed sensors that are cut apart by particular MMPs and tested them in mice. The researchers demonstrated that their colour change test could accurately detect which urine samples came from mice with colon tumours in a study of 28 mice injected with the sensors, where 14 mice were healthy and 14 had tumours.

Within half an hour of the chemical treatment, only the urine from mice with colon tumours had a strong blue colour. By contrast, urine from the healthy control mice exhibited no colour change.

The team also designed the AuNC surfaces to go 'unseen' by the immune system to prevent immune reactions or toxic side effects, and to prevent abundant serum proteins from sticking to them, which would make the nanosensors too large to be filtered by the kidneys.

During a four-week follow up after nanosensor administration, the mice showed no signs of side effects, and there was no evidence that the protein-sensor complex or free AuNCs lingered in the bodies of the mice.

Co-first author Dr Colleen Loynachan, of Imperial's Department of Materials, said: "The AuNCs are similar to materials already used in the clinic for imaging tumours, but here we are taking advantage of their unique properties to give us additional information about disease. However, there's still a lot of optimisation and testing needed before the technology can move beyond the lab."

Accessible diagnostics

Next, the team will work to increase the specificity and sensitivity of the sensors by testing them in additional animal models to investigate diagnostic accuracy and safety.

"Proteases play functional roles in a number of diseases such as cancer, infectious diseases, inflammation, and thrombosis," said co-first author Ava Soleimany, of Harvard and MIT. "By designing versions of our sensors that can be cut by different proteases, we could apply this colour-based test to detect a diversity of conditions."

The researchers are now working on a formulation that is easier to administer, and identifying ways to make the sensors responsive to multiple biomarkers in order to distinguish between cancers and other diseases.

###

SMC Labelling system: Peer-reviewed / Experimental / Animals

3. MouseLight プロジェクト

2017 年 10 月、MouseLight と呼ばれるマウスのニューロントレーシングプロジェクトチームは、最初の 300 個のニューロンのデータを発表した。今回そのデータセットが大幅に拡張され、コレクションに 700 を超えるデータが追加された。
ハワード・ヒューズ医学研究所のジェネリア・リサーチ・キャンパスの研究者らは、これらニューロンのもつれを注意深く解明し、脳を横切る核細胞の分岐経路をたどり、どこに行きどの細胞を繋ぐかを特定し、この成果を 9 月 5 日の *Cell* 誌に発表している。
約 7,000 万個のニューロンを含むとされるマウスの脳は、まだまだ未知の荒野であるが、このプロジェクトは成長しており、MouseLight チームは、拡大し続けるデータセットをオンラインで共有して、他の科学者がニューロントレースの取り組みに参加することを期待している。

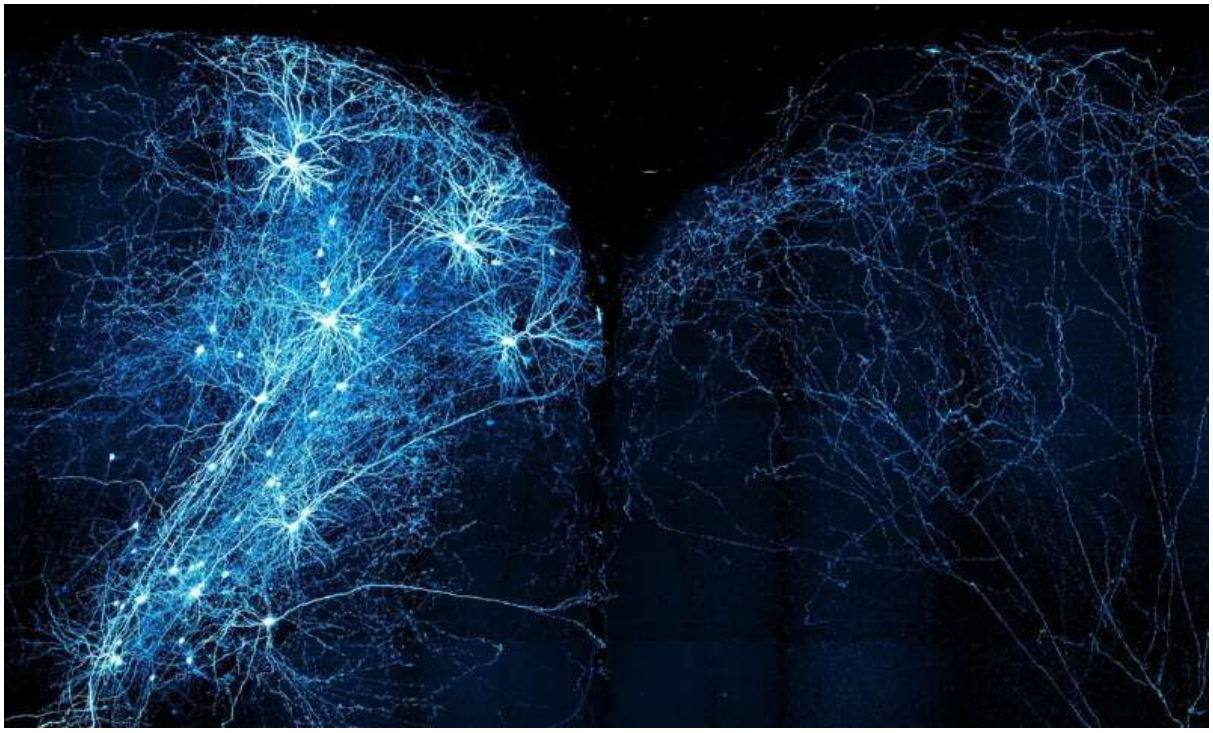
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-09-mouselight-neurons-mouse-brain.html

SEPTEMBER 5, 2019

MouseLight project maps 1,000 neurons (and counting) in the mouse brain

by Howard Hughes Medical Institute



The MouseLight team is mapping neurons in the mouse brain, revealing just how complex the brain's wiring really is. Credit: MouseLight/Janelia Research Campus

Scientists are batting a thousand in a project to reconstruct the mouse brain's wiring diagram.

Researchers at the Howard Hughes Medical Institute's Janelia Research Campus have now carefully unraveled a tangle of more than 1,000 neurons, tracing each cell's branching route across the brain to pinpoint where it goes and to which cells it connects. If laid end-to-end, the neurons would stretch more than 80 meters, roughly the length of two school buses, the team reports September 5, 2019, in the journal *Cell*.

When Jayaram Chandrashekar and his colleagues began their neural cartography effort two years ago, neuroscientists had a general idea about which areas of the mammalian brain talked to one other. But what the messaging infrastructure actually looked like was largely a mystery. A fleshed-out picture of that circuitry could help scientists better understand how the brain is wired and how messages travel through it. In October 2017, the neuron-tracing project team, called MouseLight, released data for the first 300 neurons. Now, they've vastly expanded the data set, adding over 700 more to the collection.

By tracing the paths of individual neurons, MouseLight has created the most detailed map of the mouse brain yet. This video layers on newly-traced neurons one at a time. Credit: MouseLight/Janelia Research Campus

"It's by far the largest digital collection of such neurons," says Chandrashekar.

Over time, the team has streamlined their neuron-tracing process. First, the team injects a virus into mouse brains that makes a handful of neurons glow. Then, they use a light microscope to capture high-resolution images of the illuminated neurons. A computer program stitches together the 20,000 resulting images to make a three-dimensional map of the brain. "It's like putting together 20,000 Lego blocks," Chandrashekar says. Algorithms and software developed in collaboration with Janelia's Scientific Computing group then help scientists follow the intertwined paths of individual neurons. Currently, it takes about one day to trace a single neuron, but a few years ago, it took a week or two.

The preliminary data are revealing new clues about how the mouse brain is wired. In some regions, neurons cluster into discrete categories. In other regions, neurons can't be easily delineated into specific types. What that means for the way messages travel around the brain isn't yet clear, Chandrashekar says, but it's a target for future research.

By tracing the paths of individual neurons, MouseLight has created the most detailed map of the mouse brain yet. This video layers on newly-traced neurons one at a time, and the counter keeps track of the total length of mapped neurons. Credit: MouseLight/Janelia Research Campus

Still, much of the mouse brain, which contains about 70 million neurons, remains uncharted wilderness. For even a fuzzy view of the whole brain's wiring scheme to emerge—the equivalent of a tourist map that captures major landmarks—you'd need to trace about 100,000 neurons, estimates Janelia Group Leader Karel Svoboda.

So far, MouseLight has focused on reconstructing neurons in a few areas of the brain that Janelia scientists are studying: the motor cortex, the subiculum, the hypothalamus, and the thalamus. For example, Svoboda has used MouseLight data to identify distinct motor control pathways in mice.

The project is still growing, though. The MouseLight team has shared their ever-expanding data set online, and Chandrashekar hopes that other scientists will join their neuron-tracing efforts.

Explore further

300 neurons traced in extensive brain wiring map

More information: Johan Winnubst, Erhan Bas, Tiago A. Ferreira, Zhuhao Wu, Michael N. Economo, Patrick Edson, Ben J. Arthur, Christopher Bruns, Konrad Rokicki, David Schauder, Donald J. Olbris, Sean D. Murphy, David G. Ackerman, Cameron Arshadi, Perry Baldwin, Regina Blake, Ahmad Elsayed, Mashtura Hasan, Daniel Ramirez, Bruno Dos Santos, Monet Weldon, Amina Zafar, Joshua T. Dudmann, Charles R. Gerfen, Adam W. Hantman, Wyatt Korff, Scott M. Sternson, Nelson Spruston, Karel Svoboda, Jayaram Chandrashekar, "Reconstruction of 1,000 projection neurons reveals new cell types and organization of long-range connectivity in the mouse brain." *Cell*. Published online September 5, 2019. DOI: 10.1016/j.cell.2019.07.042

Journal information: Cell

Provided by Howard Hughes Medical Institute

4. マウスモデルにおける統合失調症の発症予防

統合失調症は、世界の人口の約 1%の人々に影響を及ぼしている精神障害であり、その症状の多くが青年期後期から若年成人期の移行期間に現れることで知られる。統合失調症の原因は複雑で、ほとんどの場合は遺伝的要因が含まれるとされている。
そこで、フリードリヒ・ミッシャー生物医学研究所（FMI）の研究者らは、この根本原因に関する研究を行うために、病気を遺伝的に発症する「統合失調症マウス」を開発した。さらにそのマウスモデルを用いて、それが示す欠損を調査し、これらをどのように治療、および予防できるか調査した。
研究者らは、先ず、ヒト患者と同様に、これらのマウスモデルでも統合失調症の認知機能障害が青年期後期以降に出現すること、また、成体マウスは、ヒト患者と同様に、ニューラルネットワークの重要なオーケストレーターである PV ニューロンと呼ばれる特定のタイプのニューロンにおいて重度の機能不全を示すことを発見した。この機能不全が、統合失調症の特徴であるネットワーク同期の欠損に繋がり、抗精神病薬が、成人統合失調症マウスにおけるネットワークおよび認知障害を一時的に抑制した。
さて、PV ニューロン機能障害は、成人マウスの脳内にのみ広がったが、それらは既に思春期統合失調症マウスの海馬に存在しており、青年期後期は、海馬と皮質 PV ニューロンに応じて協調活動が後期の脳成熟に重要な時間枠であるため、研究者らは思春期の海馬機能障害が統合失調症マウスの適切な脳成熟に干渉する可能性があると仮定。最も重要な時間枠の間のネットワーク機能不全を制御することによって統合失調症の発症を防ぐことに成功した。
この研究成果は、*Cell* 誌に掲載されている。

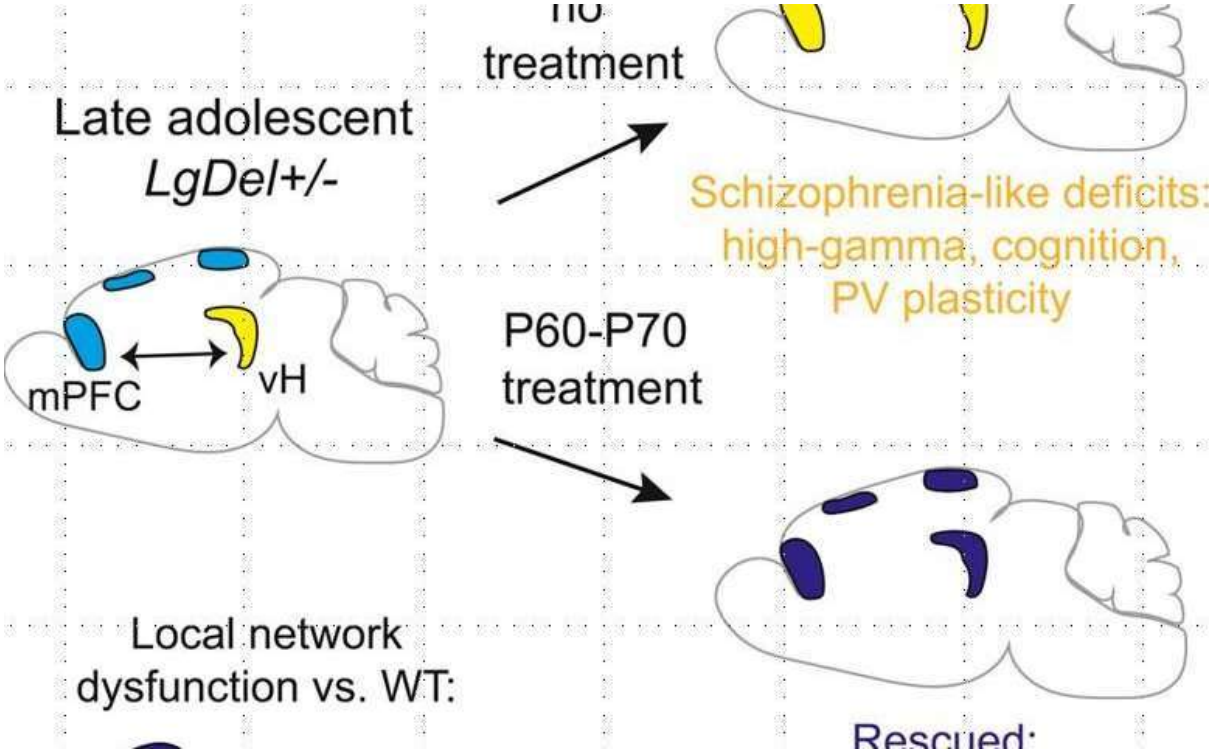
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-09-onset-schizophrenia-mouse.html

SEPTEMBER 9, 2019

Preventing the onset of schizophrenia in a mouse model

by Friedrich Miescher Institute for Biomedical Research



Progression to disease in schizophrenia-model mice can be prevented by treatments supporting PV network function during a sensitive time window late in adolescence. Credit: Caroni group

Although predisposing processes occur earlier, schizophrenia emerges at young adulthood, suggesting it might involve a pathological transition during late brain development in predisposed individuals. Using a genetic mouse model of schizophrenia, researchers from the Caroni group at the Friedrich Miescher Institute for Biomedical Research (FMI) showed that, like in patients, characteristic network and cognitive deficits only emerge in adult mice. They then demonstrated that these deficits could all be permanently prevented by specific treatments during a late adolescence sensitive time window. Their study has been published in *Cell*.

Schizophrenia—affecting about 1% of the worldwide population—is a mental disorder characterized by disorganized thoughts, false beliefs, difficulty in social relationships, cognitive deficits, abnormal motor behavior, as well as blunted emotions and motivation. A notable feature of this severe, chronic condition is that its symptoms first emerge at the transition between late adolescence and young adulthood. Schizophrenia treatments focus on the symptoms and often consist of antipsychotic medications.

The causes of schizophrenia are complex. They include comparable contributions by environmental factors—such as problems during birth, psychosocial factors, stress, and the consumption of cannabis during adolescence—and genetic factors, which in most cases involve mutations in large numbers of genes, each making a small contribution to the condition.

In order to do research on the root causes of a condition with a complex genetic component, researchers need to focus, if possible, on simpler 'genetic models'—people or animals with well-defined mutations exhibiting a strongly elevated risk of developing the disease. In schizophrenia, such models include people with the 22Q11DS syndrome, caused by

deletions within a segment of chromosome 22, who have a 20 to 30-fold increased risk of developing schizophrenia. This led researchers to develop mice carrying a corresponding deletion in order to use them as a model of schizophrenia for lab research. (These mice are called "LgDel mice" but for simplicity reasons we will call them "schizophrenia mice" here.)

Using the schizophrenia mouse model, researchers from the Caroni group set out to investigate the deficits exhibited by the schizophrenia mice, and how these could be treated and perhaps prevented. The researchers showed that what was already known in human patients was also true in the schizophrenia mice: network and cognitive dysfunctions emerged after late adolescence. Like patients, adult mice showed profound dysfunctions in a particular type of neurons called PV neurons, which are important orchestrators of neural networks. The dysfunctions led to network synchronization deficits, a hallmark of schizophrenia. Notably, antipsychotic drugs temporarily suppressed network and cognitive deficits in adult schizophrenia-mice.

Although PV neuron dysfunctions only spread through the brain in the adult, they were already present in the hippocampus of adolescent schizophrenia mice. Since late adolescence represents a time window when coordinated activity depending on hippocampal and cortical PV neurons is important for late brain maturation, the Caroni group hypothesized that adolescent hippocampal dysfunctions might interfere with proper brain maturation in schizophrenia mice. The researchers investigated whether they could prevent the onset of schizophrenia by suppressing the network dysfunctions during the most critical time window, long enough to allow for transition to normal adult brain function, in spite of a strongly predisposing genetic background.

The researchers succeeded in this. They showed that repeated treatments targeting the hippocampal PV network with common antipsychotic drugs or with more specific genetic activators of PV neurons, during 6-10 days, at the transition between late adolescence and adulthood, produced a complete and long-lasting rescue of network dysfunctions, as well as cognitive deficits in adult schizophrenia-mice.

"Our findings in a genetic mouse model support the hypothesis that a critical developmental time window influences the emergence of schizophrenia at the transition between late adolescence and adulthood—and that it is possible to prevent the progression of schizophrenia by treatment during that time window," says Pico Caroni. "It might be possible to build on our study to develop therapeutic strategies to prevent the outbreak of schizophrenia in at risk individuals."

Explore further

The neurobiological mechanisms behind schizophrenia may depend on gender

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More information: Arghya Mukherjee et al, Long-Lasting Rescue of Network and Cognitive Dysfunction in a Genetic Schizophrenia Model, *Cell* (2019). DOI: 10.1016/j.cell.2019.07.023

Journal information: Cell

5. 数学で動物が夜に見える理由を説明
生物学的実験により、マウスの網膜発達の数学的モデリングを確認

https://www.hiroshima-u.ac.jp/ilife/news/53440

【研究成果】細胞核の動的変形が核構造の再編成を引き起こすことを世界で初めて発見！ ～夜行性の桿体細胞の核内構造は細胞核の動的変形によって昼行性型の核内構造から導かれる～

本研究成果のポイント

- 夜行性哺乳類の光受容細胞の大々的な核構造の再編成が起きる仕組みを解明
- Phase-field の数理手法と実験の新規融合アプローチによって、細胞核の動的変形が核構造の再編成を引き起こすことを発見
- 細胞の物理的性質や、細胞核内 DNA の空間構造制御機構の解明に期待

概要

JST 戦略的創造研究推進事業において、広島大学大学院統合生命科学研究科の李聖林准教授と落合博講師らは、夜行性の哺乳類の桿体細胞(※1)が持つクロマチンの空間構造形成に細胞核の動的変形が重要に関わることを解明しました。

夜行性の哺乳類であるマウスの桿体細胞が持つクロマチンの空間構造形成は昼行性の哺乳類の桿体細胞が持つクロマチンの空間構造から再構築（リモデリング）されることが知られていましたが、その仕組みは大きな謎として残っていました。その謎を、新しい数理モデリングアプローチ手法を用いて理論で提案し、生体内外の実験でその仮説を証明することに成功しました。

本研究では、非常に複雑な仕組みに基づいていると考えられてきたクロマチン構造のリモデリング現象が、細胞の自然な物理的現象とも言える細胞の動的挙動に由来する細胞核のランダムな動的変形が関与していることを見出しました。

本研究は、名古屋大学の小坂田文隆准教授と共同で行いました。

本研究成果は、科学誌「PLOS Computational Biology」のオンライン版で公開されました。

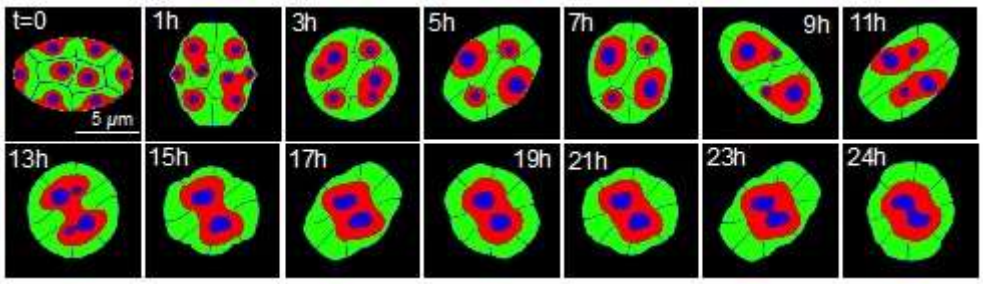
本成果は、以下の事業・研究領域・研究課題によって得られました。

- 戦略的創造研究推進事業 個人型研究（さきがけ）
- 研究領域：「社会的課題の解決に向けた数学と諸分野の協働」
  （研究総括：國府 寛司　京都大学 大学院理学研究科　教授）
- 研究課題名：「動的変形空間による細胞機能決定機構の解明及び In vitro 実験への検証」
- 研究者：李　聖林（広島大学 大学院理学研究科 准教授）
- 研究実施場所：広島大学
- 研究期間：平成 28 年 10 月～令和 2 年 3 月

上記研究課題では、空間(ドメイン)の動的変形が遺伝子あるいは生体分子の空間パターン形成を制御することを明らかにし、細胞の物理・幾何学的性質により細胞機能が制御できる可能性を提示することを目指します。遺伝子あるいは生体分子の動態をそれらが置かれている環境(細胞核または細胞)との関連性に注目していく本研究は、遺伝子操作を使わずに細胞機能を制御可能にする新しい枠組みを数学的手法から提案し、In vitro 実験で検証していきます。

用語解説

(※1) 桿体細胞（かんたいさいぼう）は、視細胞の一種である。眼球の網膜上に存在し、光の強弱に応じた明暗の認識に関わり、色覚にはほとんど関与しない。



Phase-filed 法の数理モデルを用いた細胞核の動的変形による核構造の再編成過程のシミュレーション

論文情報

- 掲載雑誌: PLOS Computational Biology
- 論文題目: Role of dynamic nuclear deformation on genomic architecture reorganization
- 著者: 李聖林 [1,2†*], 小坂田文隆 [2,3], 竹田淳一 [3], 田代聡 [4], 小林亮 [5], 山本卓 [5], 落合博 [2,5†*]
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  4. 広島大学原爆放射線医科学研究所
  5. 広島大学大学院理学研究科 数理分子生命理学専攻
- DOI: 10.1371/journal.pcbi.1007289

- 報道発表資料（455.37KB）
- 論文掲載ページ (PLOS Computational Biology に移動します)
- 広島大学研究者総覧 (李 聖林 准教授)
- 広島大学研究者総覧 (落合 博 講師)

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掲載日：2019 年 09 月 14 日

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/2019/09/190911142841.htm

Math shows why animals can see at night

Biological experiments confirm mathematical modeling of retina development in mice

Date:

September 11, 2019

Source:

Hiroshima University

Summary:

By combining mathematics with science, an interdisciplinary team found how changes in the shape of DNA structure affect the nuclei of nocturnal animals. Their findings could help explain how nocturnal animals, such as mice, see at night.

FULL STORY

Nocturnal and diurnal mammals see the same -- but only for a brief time. When mice are born, the chromatin in the cells of their eyes has a diurnal structure. Day by day, the layout of this chromatin slowly inverts, allowing the mice to see at night. How this change happens was a mystery.

Sungrim Seirin-Lee, Associate Professor, and Hiroshi Ochiai, Lecturer, in the Graduate School of Integrated Sciences for Life at HU, suspected that the chromatin was making the shape of the nuclei change shape. "When we started this research, our hypothesis was based 100 percent on

mathematics," Seirin-Lee said. "Because of our mathematical modeling, we found that nuclear deformation might be a key point in DNA's structure change."

If we could see inside of the nucleus, we would see that chromatin comes in different types and territories. Around the center of the nucleus is euchromatin, or DNA that is largely active. Heterochromatin, on another hand, is a kind of DNA that lies around the envelope or ceiling of the nucleus. Unlike euchromatin, the gene activation of heterochromatin is low.

Between nocturnal and diurnal animals, though, the differences in nuclear architecture get bigger -- especially around the retina. The DNA is in the center of the nucleus in nocturnal mammals. Usually, heterochromatin stays put in the nuclear envelope. In the case of nocturnal animals, though, Seirin-Lee and Ochiai found it can be moved by the nucleus changing shape.

To describe the movement of chromatin, Seirin-Lee and her colleagues used a type of mathematical modeling called phase-field modeling. A method commonly used in physics; phase-field modeling can be used to do things like telling apart ice from water. However, according to Seirin-Lee, "it is not common in the biological sciences. In chromatin dynamics, it is the first trial in the world!" Using this function, the group could see the movement of chromatin and nucleus by determining and defining the inside and outside of the nucleus, as well as euchromatin versus heterochromatin.

When the group observed heterochromatin in the mouse's eyes, they found that conditional architecture triggered dynamic deformation, which resulted in an inverted nuclear architecture. In the inverted architecture case, two proteins are removed, which allows heterochromatin to move.

Then, with the assistance Ochiai, they put their model to the test on neural stem cells, which mimic retinal cells. After treating the cells with proteins that keep heterochromatin at the nuclear periphery, deformation stopped. Chromatin clustering increased, and nuclear architecture could not finish inverting. This finding was consistent with Lee's mathematical modeling.

Ultimately, Seirin-Lee and her colleagues want to see if their findings are universal to mammal cells. "At this stage, we think it is just mouse eyes," Seirin-Lee said, "but we don't know! Maybe humans could have such structures by dynamic nuclear deformation." Next, Seirin-Lee is looking to tackle the intermediate structure, or a sort of hybrid between conventional and inverted architecture of the nucleus.

Story Source:

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

Journal Reference:

1. Sungrim Seirin-Lee, Fumitaka Osakada, Junichi Takeda, Satoshi Tashiro, Ryo Kobayashi, Takashi Yamamoto, Hiroshi Ochiai. **Role of dynamic nuclear deformation on genomic architecture reorganization**. *PLOS Computational Biology*, 2019; 15 (9): e1007289 DOI: 10.1371/journal.pcbi.1007289

- APA
- Chicago

Hiroshima University. "Math shows why animals can see at night: Biological experiments confirm mathematical modeling of retina development in mice." ScienceDaily. ScienceDaily, 11 September 2019. <www.sciencedaily.com/releases/2019/09/190911142841.htm>.

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6. 身体の中の小胞は化学療法よりも効果的に癌と戦う

我々の身体の健康な細胞は、DNA や RNA などの遺伝物質を他の細胞に移すナノサイズの泡を放出する。ミシガン州立大学とスタンフォード大学の新しい研究によると、これらの気泡のある細胞外小胞は、癌細胞を標的にしてそれらを殺す治療薬と遺伝子の組み合わせを運ぶミニ治療トランスポーターになる可能性がある、としている。
マウスの乳癌細胞に焦点を合わせたこの研究は、*Molecular Cancer Therapeutics* 誌に掲載されている。
研究チームが行ったことは、特定の薬物を毒性物質やターゲットとなる腫瘍の中で変換させることのできる酵素産生遺伝子を伝達する治療的アプローチを改善することだった。プロドラッグと呼ばれるこれらの薬物は、不活性な化合物として始まるが、体内で代謝されるとすぐに活性化され、癌から頭痛に至るまでの全ての戦いに参戦する。
研究者らは細胞外小胞（EV）を使用して、乳癌細胞におけるガンシクロビルと CB1954 のプロドラッグ併用療法を活性化できる酵素産生遺伝子を伝達した。ミニサークル DNA と通常のプラスミド（DNA の追加の伝達メカニズムとして機能する 2 つの異なる遺伝子ベクター）が小胞にロードされ、どちらが輸送治療に役立つかを確認した。これは、遺伝子指向酵素、プロドラッグ療法として知られている。彼らは、ミニサークル DNA が伝達時に 14 倍、癌性腫瘍を殺すのにより効果的であることを発見した。
この研究論文の主執筆者である MSU の金田助教授によると、この新しいアプローチは、腫瘍と正常組織を区別できず全てを攻撃する従来の化学療法よりも、今後より効果的な癌治療の選択肢になる可能性がある、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/09/190913111345.htm

Tiny bubbles in our body could fight cancer better than chemo

Date:

September 13, 2019

Source:

Michigan State University

Summary:

Healthy cells in our body release nano-sized bubbles that transfer genetic material such as DNA and RNA to other cells. It's your DNA that stores the important information necessary for RNA to produce proteins and make sure they act accordingly. These bubbly extracellular vesicles could become mini treatment transporters, carrying a combination of therapeutic

drugs and genes that target cancer cells and kill them, according to new research from Michigan State University and Stanford University.

FULL STORY

Healthy cells in our body release nano-sized bubbles that transfer genetic material such as DNA and RNA to other cells. It's your DNA that stores the important information necessary for RNA to produce proteins and make sure they act accordingly.

These bubbly extracellular vesicles could become mini treatment transporters, carrying a combination of therapeutic drugs and genes that target cancer cells and kill them, according to new research from Michigan State University and Stanford University.

The study, which focused on breast cancer cells in mice, is published in *Molecular Cancer Therapeutics*.

"What we've done is improve a therapeutic approach to delivering enzyme-producing genes that can convert certain drugs into toxic agents and target tumors," said Masamitsu Kanada, lead author and an assistant professor of pharmacology and toxicology in MSU's Institute for Quantitative Health Science and Engineering.

These drugs, or prodrugs, start out as inactive compounds. But once they metabolize in the body, they're immediately activated and can get to work on fighting everything from cancer to headaches. Aspirin is an example of a common prodrug.

In this case, researchers used extracellular vesicles, or EVs, to deliver the enzyme-producing genes that could activate a prodrug combination therapy of ganciclovir and CB1954 in breast cancer cells. Minicircle DNA and regular plasmid -- two different gene vectors that act as additional delivery mechanisms for DNA -- were loaded into the vesicles to see which was better at helping transport treatment. This is known as a gene-directed enzyme, prodrug therapy.

They found that the minicircle DNA was 14 times more effective at delivery and even more successful at killing cancerous tumors.

"Interestingly, the plasmid delivery method didn't show any tumor cell killing," Kanada said. "Yet the minicircle DNA-based therapy killed more than half of the breast cancer cells in the mice."

According to Kanada, this new approach could effectively become a better cancer treatment option than chemotherapy down the road.

"Conventional chemotherapy isn't able to differentiate between tumors and normal tissue, so it attacks it all," Kanada said. "This non-specificity can cause severe side effects and insufficient drug concentration in tumors."

With EVs, treatment can be targeted and because of their compatibility with the human body, this type of delivery could minimize the risk of unwanted immune responses that can come with other gene therapies.

"If EVs prove to be effective in humans, it would be an ideal platform for gene delivery and it could be used in humans sooner than we expect," Kanada said.

A phase-one clinical trial, separate from Kanada's work, is set to start soon in the U.S. and will use EVs and a type of therapeutic RNA molecule for the treatment of metastatic pancreatic cancer.

While that trial moves forward, Kanada and his team will continue to further engineer and test EVs, improving their effectiveness and safety so using them as a cancer-fighting gene therapy in humans becomes reality.

Story Source:

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

Journal Reference:

1. Masamitsu Kanada, Bryan D Kim, Jonathan W Hardy, John A. Ronald, Michael H Bachmann, Matthew P Bernard, Gloria I Perez, Ahmed A Zarea, T Jessie Ge, Alicia Withrow, Sherif A Ibrahim, Victoria Toomajian, Sanjiv S Gambhir, Ramasamy Paulmurugan, Christopher H Contag. **Microvesicle-mediated delivery of minicircle DNA results in effective gene-directed enzyme prodrug cancer therapy**. *Molecular Cancer Therapeutics*, 2019; molcanther.0299.2019 DOI: 10.1158/1535-7163.MCT-19-0299

Cite This Page:

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Michigan State University. "Tiny bubbles in our body could fight cancer better than chemo." ScienceDaily. ScienceDaily, 13 September 2019. <www.sciencedaily.com/releases/2019/09/190913111345.htm>.

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7. 善玉菌に好みの繊維を与えて、マウスの腸内微生物叢を改変

9 月 19 日に *Cell* 誌で発表された研究で、セントルイスのワシントン大学医学部の研究者らはマウスの腸内の有益な微生物の成長と代謝作用を促進する食物繊維の特定成分を発見した。この研究の最終目標は、腸内微生物の中で健康促進に役立つ持続可能で手頃な食物繊維源を特定し、次世代の栄養価の高い食品に組み込むことである。
研究者らは、先ず無菌条件下で飼育されたマウスを使用し、その後ヒト腸内微生物を定着させた。マウスにはシーケンスされたゲノムを持つヒト腸内細菌が定着していたため、すべての遺伝子は分かっていた。これにより、テストした様々な繊維タイプに応じて発現が変化したすべての細菌たんぱく質の包括的高解像度のプロテオミクス研究を実施することができた。これらの結果を遺伝子スクリーニングと組み合わせて、特定の繊維源、その生物活性分子成分、および異なる繊維に遭遇した時に異なるバクテロイデス種に対して増加した細菌遺伝子を特定することができた、としている。
また、プロテオミクス分析と遺伝子スクリーニングにより、この細菌群に存在する種の間で繊維消費の階層があることも確認された。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/09/190919142342.htm

Researchers alter mouse gut microbiomes by feeding good bacteria their preferred fibers

Date:

September 19, 2019

Source:

Cell Press

Summary:

Humans choose food based on the way it looks, smells, and tastes. But the microbes in our guts use a different classification system -- one that is based on the molecular components that make up different fibers. Investigators found particular components of dietary fiber that encourage growth and metabolic action of beneficial microbes in the mouse gut.

FULL STORY

Humans choose food based on the way it looks, smells, and tastes. But the microbes in our guts use a different classification system -- one that is based

on the molecular components that make up different fibers. In a study published September 19 in the journal *Cell*, investigators found particular components of dietary fiber that encourage growth and metabolic action of beneficial microbes in the mouse gut.

The research aims to develop ways to identify compounds that can enhance the representation of health-promoting members of the gut microbial community. The goal is to identify sustainable, affordable dietary fiber sources for incorporation into next-generation, more nutritious food products.

"Fiber is understood to be beneficial. But fiber is actually a very complicated mixture of many different components," says senior author Jeffrey Gordon, a microbiologist at the Washington University School of Medicine in St. Louis. "Moreover, fibers from different plant sources that are processed in different ways during food manufacturing have different constituents. Unfortunately, we lack detailed knowledge of these differences and their biological significance. We do know that modern Western diets have low levels of fiber; this lack of fiber has been linked to loss of important members of the gut community and deleterious health effects."

The researchers started by testing 34 food-grade fiber preparations, many purified from byproducts of food manufacturing such as peels from fruits and vegetables that are thrown out during production of processed foods and drinks. They used mice initially raised under sterile conditions and then colonized with human gut microbes. The animals were fed a high-fat, low-fiber diet representative of diets typically consumed in the United States, with or without different types of supplemental fibers. The goal was to identify those fibers that were best at boosting the levels of key fiber-degrading bacterial species and promoting the expression of beneficial metabolic enzymes in the microbiome.

Since the mice had been colonized with a defined collection of human gut bacteria with sequenced genomes, the researchers knew all the genes that were present in their model human gut microbial community. This allowed them to perform a comprehensive, high-resolution proteomics study of all bacterial proteins whose expression changed in response to the different fiber types they tested. Combining these results with genetic screens, they were able to identify particular fiber sources, their bioactive molecular components, and the bacterial genes that increased for different Bacteroides species when they encountered different fibers. They focused on Bacteroides because members of this group of bacterial species contain genes responsible for metabolizing dietary fiber that are not present in the human genome.

For the second phase of the study, the investigators wanted to determine how different members of the microbial community interact with each other as they dine on dietary fiber. First author Michael Patnode, a postdoctoral fellow in Gordon's lab, developed fluorescently labeled artificial food particles with different types of bound carbohydrates from different fibers. Collections of these nutrient-containing particles were fed to mice colonized with defined microbial communities containing different combinations of Bacteroides species.

"We were excited to see how these 'biosensors' could be used to assess the processing of particular fiber components by particular bacterial species," Patnode says. By feeding these particles to mice that either carried or did not carry a dominant fiber-consuming species, the authors found that subordinate species were waiting in line to step up and consume the fiber.

"We had suspected there might be competition going on among the different strains and that some would be stronger competitors than others," Patnode says. Proteomics analyses and genetic screens confirmed that there was a hierarchy of fiber consumption among the species present in this model bacterial community.

Gordon explains that "it's important to understand how the presence of a particular organism affects the dining behavior of other organisms -- in this case, with regard to different fibers. If we are going to develop microbiota-directed foods aimed at providing benefits to human health, it's important to

find ways to determine which food staples will be the best source of nutrients and how the microbiota will respond."

Story Source:

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

Journal Reference:

1. Michael L. Patnode, Zachary W. Beller, Nathan D. Han, Jiye Cheng, Samantha L. Peters, Nicolas Terrapon, Bernard Henrissat, Sophie Le Gall, Luc Saulnier, David K. Hayashi, Alexandra Meynier, Sophie Vinoy, Richard J. Giannone, Robert L. Hettich, Jeffrey I. Gordon. **Interspecies Competition Impacts Targeted Manipulation of Human Gut Bacteria by Fiber-Derived Glycans**. *Cell*, 2019; 179 (1): 59 DOI: 10.1016/j.cell.2019.08.011

Cite This Page:

- MLA
- APA
- Chicago

Cell Press. "Researchers alter mouse gut microbiomes by feeding good bacteria their preferred fibers." ScienceDaily. ScienceDaily, 19 September 2019. <www.sciencedaily.com/releases/2019/09/190919142342.htm>.

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8. 浅い眠りで記憶が消去される仕組みを解明
～ なぜ夢は起きるとすぐに忘れてしまうのか ～

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_190920.pdf

名古屋大学 環境医学研究所の山中 章弘 教授らの研究グループは、脳のメラニン凝集ホルモン産 生神経（MCH神経）注１）がレム睡眠注２）中に記憶を消去していることを明らかにしました。
これまでの研究から、MCH神経が摂食行動や睡眠覚醒の調節に関わっていることは分かっていま したが、記憶への影響は不明でした。
本研究グループは、超小型顕微鏡を用いた神経活動の記録をマウスに適用して、MCH神経にはレム睡眠中に活動するもの、覚醒中に活動するもの、レム睡眠と覚醒中の両方で活動するものの３種類があ ることが分かりました。さらに、特定の神経の活動を操作することができる光遺伝学注３）や化学遺伝学 注４）の手法を用いて、このMCH神経活動が記憶に重要な海馬の神経活動を抑制すること、さらにレム 睡眠中に活動するMCH神経が記憶を消去していることを明らかにしました。
私たちの睡眠リズムは、浅い眠りであるレム睡眠を起床前に繰り返すのが一般的ですが、今回明らかになったレム睡眠中に活動するMCH神経は、目覚める直前の夢の内容をすぐに忘れさせる一因として働いていると考えられます。この仕組みの応用によって、トラウマとして残っている恐怖心や怖い体験などの記憶を消去することで、心的外傷後ストレス障害（PTSD）を治療する臨床応用への貢献が 期待されます。
本研究は、北海道大学の木村 和弘 教授、寺尾 晶 准教授（現 東海大学 教授）、吉岡 充弘 教 授、大村 優 講師、SRI インターナショナルのキルドフ博士の協力を得て行いました。
本研究成果は、２０１９年９月１９日（米国東部夏時間）に米国科学誌「Science」のオンライン版で公開されます。
本研究は、国立研究開発法人科学技術振興機構（JST） 戦略的創造研究推進事業 チーム型研究 （CREST） 研究領域：「光の特性を活用した生命機能の時空間制御技術の開発と応用」の支援のも とで行われたものです。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.statnews.com/2019/09/20/scientists-pinpoint-neurons-control-memory-dreaming/?utm_source=STAT+Newsletters&utm_campaign=81c2014f07-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-81c2014f07-150065641

To sleep, perchance to forget? Scientists pinpoint in mice the neurons that control memory while dreaming

By ELIZABETH COONEY @cooney_liz

SEPTEMBER 20, 2019

ADOBE

If you wonder why we forget our dreams, new research in mice might answer that question and others related to memory. U.S. and Japanese scientists discovered that when certain neurons fire during REM sleep — when most dreams occur — they control whether the brain remembers new information.

Thomas Kilduff, director of the Center for Neuroscience at SRI International and a co-author of the paper, talked with STAT about the study and its implications. This interview has been condensed and edited.

What prompted you to study forgetting while dreaming?

Well, we didn't start out to study dreaming, although that ends up being an implication of our results. There were four threads that motivated this study. There is a lot of societal concern about neurodegenerative diseases such as Alzheimer's disease, there is a lot of research interest in the neural bases of learning and memory, there is research controversy about the role of sleep in learning and memory, specifically whether REM sleep, slow wave sleep, or both types of sleep are important for memory consolidation. And there is a lot of recent research in animal models of Alzheimer's disease suggesting sleep disruption may accelerate the accumulation of beta-amyloid in the brain and, conversely, if you enhance sleep, that may slow this process.

Related:

SCIENTISTS ROUTINELY CURE BRAIN DISORDERS IN MICE BUT NOT US. A NEW STUDY HELPS EXPLAIN WHY

In collaboration with my Japanese colleagues Akihiro Yamanaka and Akira Terao at Hokkaido University, we published a paper in 2014 that described a transgenic mouse in which we could eliminate the melanin-concentrating hormone neurons in the hypothalamus. These mice showed a partial insomnia. Because of the links between sleep and memory, we wanted to evaluate whether learning and memory were affected in these mice.

What did you find?

The very surprising result was that mice without MCH neurons performed better on learning and memory tasks than mice with intact brains. And intact mice performed more poorly on the memory tasks when MCH neurons were activated — as they are during REM sleep — and better on the memory tasks when these cells are turned off during REM. These results suggest that activation of the MCH neurons during REM sleep may interfere with memory consolidation — that is, MCH neurons may facilitate forgetting.

So melanin helps forgetting? And it promotes REM? Also, appetite?

Actually, we studied hypothalamic melanin-concentrating hormone neurons, not melanin. Which is in skin – that is another story.

How do you test memory in a lab mouse?

There are standard behavioral tests of learning and memory you can use. One is novel object recognition, one is contextual fear, and another is navigating a maze. You can look at whether the animal learns better or retains information better than control animals.

Why would mice — or people — need a mechanism to forget?

The brain has an information storage problem: We can't — and need not — remember everything.

Scientists have made good progress in identifying the neural bases of learning and memory and have found that a brain region called the hippocampus plays a particularly important role. Less effort has been spent studying forgetting than learning, but forgetting is important to eliminate useless information. It's also an active process. Some memories are consolidated during sleep but other information must be forgotten to prevent information overload.

Most dreams have informational content that is not useful for waking activity and are probably best forgotten. We and others have shown that most MCH neurons are active only during REM sleep, which is when most dreams are reported in humans. Since we have shown that activation of MCH neurons interferes with memory consolidation, activation of this neural circuit during REM sleep may indeed make it more difficult to remember our dreams.

What's new in what you found?

The mice in which the MCH neurons had degenerated actually performed better on learning and memory tasks than intact mice. Our results are consistent with previous studies that supported a role for REM sleep in forgetting, but now we identify the particular neural circuit that is responsible.

Trending Now:

WHAT TO KNOW ABOUT EEE, A MOSQUITO-BORNE VIRUS ON THE RISE

What's next?

Understanding the neural basis of learning and memory is a huge area of neuroscience research because of its implications for our everyday lives, as well as conditions with cognitive dysfunction such as Alzheimer's disease. Prior to this work, no one suspected that MCH neurons had anything to do with forgetting.

What about making the leap to humans?

Selective activation of the MCH neuron-hippocampus neural circuit could result in elimination of unpleasant memories as occur in PTSD.

What are limitations of your work to keep in mind?

The study was conducted in laboratory rodents, not humans, so we can't ask them about their dreams. Mice are nocturnal (active at night) with sleep and wake throughout the day and night, whereas most humans have a single "consolidated" sleep period that usually occurs at night.

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https://science.sciencemag.org/content/365/6459/1308

REPORT

REM sleep–active MCH neurons are involved in forgetting hippocampus-dependent memories

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DOI: 10.1126/science.aax9238

A BRAIN PATHWAY FOR ACTIVE FORGETTING

Sleep affects memories via several mechanisms. Izawa et al. identified a possible new pathway in the brain: REM sleep–active hypothalamic melanin-concentrating hormone (MCH)–producing neurons, which, among others, project to the hippocampus. Surprisingly, genetic ablation of MCH

neurons increased memory performance in mice. Conversely, pharmacogenetic activation of MCH neurons impaired memory. In vitro physiological experiments showed that activation of MCH fibers in hippocampal slices suppressed spiking activity of pyramidal cells. These findings indicate that the MCH pathway may become a target for memory modulation.

Science, this issue p. 1308

ABSTRACT

The neural mechanisms underlying memory regulation during sleep are not yet fully understood. We found that melanin concentrating hormone–producing neurons (MCH neurons) in the hypothalamus actively contribute to forgetting in rapid eye movement (REM) sleep. Hypothalamic MCH neurons densely innervated the dorsal hippocampus. Activation or inhibition of MCH neurons impaired or improved hippocampus-dependent memory, respectively. Activation of MCH nerve terminals in vitro reduced firing of hippocampal pyramidal neurons by increasing inhibitory inputs. Wake- and REM sleep–active MCH neurons were distinct populations that were randomly distributed in the hypothalamus. REM sleep state–dependent inhibition of MCH neurons impaired hippocampus-dependent memory without affecting sleep architecture or quality. REM sleep–active MCH neurons in the hypothalamus are thus involved in active forgetting in the hippocampus.

9. 改変されたキラーT 細胞が癌に対して長期に免疫を提供する可能性

UCLA の研究者が幹細胞を使用して、マウスのヒト腫瘍を攻撃する細胞を操作

インバリアントナチュラルキラーT 細胞（iNKT 細胞）：それらは免疫系の「特別な力」と呼ばれている。体内には比較的少ない（ほとんどの場合、血液細胞の 0.1%未満とされる）が、他の多くの免疫細胞よりも強力だ。

今回、UCLA の研究者らは、マウスを使った実験で、この iNKT 細胞の力を利用して腫瘍細胞を攻撃し、癌を治療できることを示した。*Cell Stem Cell* 誌に記載されている新しい方法は、動物に移植された複数のタイプのヒト腫瘍の成長を抑制した。

研究者らは、以前の臨床研究で、iNKT 細胞のレベルが自然に高い癌患者は、一般に iNKT 細胞のレベルが低い癌患者よりも長生きすることを示していた。

そこで今回の目標は、より多くの iNKT 細胞を自然に産生する身体の能力を永続的に高める治療法を作り出すことであった。骨髄に見られる造血幹細胞は自分自身で複製でき、iNKT 細胞を含むあらゆる種類の血液および免疫細胞になる。研究者らは、iNKT 細胞に発達するようプログラムされるように、幹細胞を遺伝子操作した。

彼らは、ヒト骨髄とヒト癌−多発性骨髄腫（血液がん）またはメラノーマ（固形腫瘍がん）−の両方を有するマウスで、造血幹細胞改変 iNKT 細胞（または HSC−iNKT 細胞）をテストし、マウスの免疫系、癌、および骨髄に統合された後の HSC−iNKT 細胞に何が起こったかを調べた。彼らは、幹細胞が iNKT 細胞に正常に分化し、マウスの残りの期間（一般に約 1 年）にわたって iNKT 細胞を産生し続けることを発見した。

また、人工幹細胞移植を行っていないマウスは、iNKT 細胞のレベルをほとんど検出できなかったのに対して、人工幹細胞移植を受けたマウスでは、iNKT 細胞が免疫系の総 T 細胞数の 60%を占めていた。さらに、研究者らは、元の造血幹細胞をどのように設計したかによって、これらの数を制御できることも発見した。

最後に、チームは、多発性骨髄腫とメラノーマの両方で、HSC−iNKT 細胞が腫瘍成長を効果的に抑制したことも発見した。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-09/uoc--ekt092319.php

NEWS RELEASE 23-SEP-2019

Engineered killer T cells could provide long-lasting immunity against cancer

UCLA researchers use stem cells to engineer cells that attack human tumors in mice

UNIVERSITY OF CALIFORNIA – LOS ANGELES HEALTH SCIENCES

IMAGE: Lili Yang, PhD view more

Credit: UCLA Broad Stem Cell Research Center

They've been called the "special forces" of the immune system: invariant natural killer T cells. Although there are relatively few of them in the body, they are more powerful than many other immune cells.

In experiments with mice, UCLA researchers have shown they can harness the power of iNKT cells to attack tumor cells and treat cancer. The new method, described in the journal *Cell Stem Cell*, suppressed the growth of multiple types of human tumors that had been transplanted into the animals.

"What's really exciting is that we can give this treatment just once and it increases the number of iNKT cells to levels that can fight cancer for the lifetime of the animal," said Lili Yang, a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA and the study's senior author.

Scientists have hypothesized that iNKT cells could be a useful weapon against cancer because it has been shown that they are capable of targeting many types of cancer at once -- a difference from most immune cells, which recognize and attack only one particular type of cancer cell at a time. But most people have very low quantities of iNKT cells; less than 0.1% of blood cells are iNKT cells in most cases.

Still, Yang and her colleagues knew that previous clinical studies have shown that cancer patients with naturally higher levels of iNKT cells generally live longer than those with lower levels of cells.

"They are very powerful cells but they're naturally present in such small numbers in the human blood that they usually can't make a therapeutic difference," said Yang, who also is a UCLA assistant professor of microbiology, immunology and molecular genetics and a member of the UCLA Jonsson Comprehensive Cancer Center. ¬¬

The researchers' goal was to create a therapy that would permanently boost the body's ability to naturally produce more iNKT cells. They started with hematopoietic stem cells -- cells found in the bone marrow that can duplicate themselves and can become all types of blood and immune cells, including iNKT cells. The researchers genetically engineered the stem cells so that they were programmed to develop into iNKT cells.

They tested the resulting cells, called hematopoietic stem cell-engineered invariant natural killer T cells, or HSC-iNKT cells, on mice with both human bone marrow and human cancers -- either multiple myeloma (a blood cancer) or melanoma (a solid tumor cancer) -- and studied what happened to the mice's immune systems, the cancers and the HSC-iNKT cells after they had integrated into the bone marrow.

They found that the stem cells differentiated normally into iNKT cells and continued to produce iNKT cells for the rest of the animals' lives, which was generally about a year.

"One advantage of this approach is that it's a one-time cell therapy that can provide patients with a lifelong supply of iNKT cells," Yang said.

While mice without the engineered stem cell transplants had nearly undetectable levels of iNKT cells, in those that received engineered stem cell transplants, iNKT cells made up as much as 60% of the immune systems' total T cell count. Plus, researchers found they could control those numbers by how they engineered the original hematopoietic stem cells.

Finally, the team found that in both multiple myeloma and melanoma, HSC-iNKT cells effectively suppressed tumor growth.

The study's co-first authors are Yanni Zhu, a UCLA project scientist, and Drake Smith, a UCLA doctoral student.

More work is needed to determine how HSC-iNKT cells might be useful for treating cancer in humans and whether increasing the number of HSC-iNKT cells could cause long-term side effects. But Yang said hematopoetic stem cells collected either from a person with cancer or a compatible donor could be used to engineer HSC-iNKT cells in the lab. The procedure for transplanting stem cells into patients' bone marrow is already well-established as a treatment for many blood cancers.

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Funding for the study was provided by the National Institutes of Health, the California Institute for Regenerative Medicine, the Concern Foundation, the STOP CANCER Foundation, a UCLA Broad Stem Cell Research Center Rose Hills Foundation Innovator Grant, and the center's training program, supported by the Sherry, Dave and Sheila Gold Foundation.

10.　肥満のヒトに高血圧を引き起こす治療可能な経路発見

体重が増加するにつれて、血圧も高くなるのは間違いない。今回、マウス研究で、ジョンズ・ホプキンズ大学医学部の研究者らは、肥満と血圧が関係する原因となっている可能性がある分子を特定した。これらの分子の 1 つをブロックすると、肥満マウスの血圧が効果的に低下する、と *Circulation Research* 誌で報告している。
この新しい研究は、食物に反応して代謝と食欲を制御する分子、レプチン、を中心に展開する。肥満のヒトはしばしばレプチンに耐性を持つようになるため、食事後の分子レベルの上昇が、代謝促進を阻害したり、満腹感を引き起こしたりしなくなる。この耐性に応じて、レプチンのレベルは肥満と共に上昇し続ける。レプチンは血圧を上昇させることでも知られており、代謝と食欲に対するレプチンの効果に人々が抵抗している場合でも、血圧が分子に反応して上昇することが分かっている。
以前の研究で、頸動脈小体 –喉の両側の頸動脈に沿った小さな細胞集団– に高レベルのレプチン受容体が存在し、これらが血中の酸素と二酸化炭素のレベルの変化に反応することが明らかになったが、研究者らは、これがレプチンが血圧に影響を及ぼす場所であり、脳の代謝や食欲への影響と完全に分離するのではないかと考えた。
今回の研究で、研究チームは、痩せたマウスに高用量のレプチンを与えると、心拍数や摂食量に影響を与えずに血圧が上昇することを最初に確認、その後、頸動脈小体を機能させずにマウス実験を繰り返した。その場合、マウスの血圧は変化しなかった。
次に、レプチン受容体を持たない肥満マウスを調べたところ、肥満しているにも関わらず血圧値は正常であった。これらのマウスの頸動脈にレプチン受容体を直接注入した場合、マウスの血圧が上昇した、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＞https://www.sciencedaily.com/releases/2019/09/190926083544.htm

Researchers discover new, treatable pathway known to cause hypertension in obese people

Date:

September 26, 2019

Source:

Johns Hopkins Medicine

Summary:

There's no question that as body weight increases, so too does blood pressure. Now, in a study of mice, researchers have revealed exactly which molecules are likely responsible for the link between obesity and blood pressure. Blocking one of these molecules -- a signaling

channel that's found in a tiny organ on the side of your neck -- effectively lowers blood pressure in obese mice.

FULL STORY

There's no question that as body weight increases, so too does blood pressure. Now, in a study of mice, Johns Hopkins researchers have revealed exactly which molecules are likely responsible for the link between obesity and blood pressure. Blocking one of these molecules -- a signaling channel that's found in a tiny organ on the side of your neck -- effectively lowers blood pressure in obese mice, the researchers reported recently in the journal *Circulation Research*.

"Obesity leads to a lot of bad cardiovascular outcomes, and a significant portion of those are related to poorly controlled blood pressure," says Vsevolod Polotsky, M.D., Ph.D., professor of medicine at the Johns Hopkins University School of Medicine and a senior author of the new paper. "We've identified what may be a new way to lower blood pressure in obese patients and improve these outcomes."

Nearly a third of American adults have high blood pressure, and only about half of those people have their blood pressure under control through medications and lifestyle changes. Hypertension can be especially difficult to treat in obese patients, Polotsky says.

The new work revolves around leptin, a molecule that controls appetite and metabolism in response to food. Obese people often become resistant to leptin, so rising levels of the molecule after a meal no longer boost metabolism or cause a feeling of fullness. In response to this resistance, leptin levels continue to rise with obesity. Leptin has also been shown to increase blood pressure and, surprisingly, obesity doesn't change that link -- even when people are resistant to leptin's effects on metabolism and appetite, their blood pressure rises in response to the molecule. Until now, researchers weren't sure why.

"It didn't make a lot of sense why obese people were only resistant to some of the effects of leptin," says Polotsky. "It suggested to us that maybe leptin was having a peripheral effect outside the brain."

Previous studies had revealed that there were high levels of leptin receptors in the carotid bodies -- tiny clusters of cells along the carotid arteries on either side of the throat that respond to changing levels of oxygen and carbon dioxide in the blood. Polotsky wondered whether this could be where leptin affects blood pressure, completely separate from its effects on appetite and metabolism in the brain.

Blood pressure is measured in millimeters of mercury (mm Hg) and has two readings -- systolic and diastolic. According to the American Heart Association, the risk of dying from a heart attack or stroke doubles with every 20 mm Hg systolic or 10 mm Hg diastolic increase among older adults.

In the new paper, Polotsky's group first confirmed that giving high doses of leptin to lean mice triggered a rise in blood pressure of 10.5 to 12.2 mm Hg, while having no effect on heart rate or food intake. Then, they repeated the experiment in mice without functioning carotid bodies. This time, the animals' blood pressure didn't change in response to leptin. Next, the team studied obese mice that had no leptin receptors -- despite their weight, they had normal blood pressure. But when the researchers injected the genes for leptin receptors directly into the carotid bodies of these mice, the animals' blood pressure readings rose by 9.4 to 12.5 mm Hg.

"This is a completely new mechanism of hypertension in obesity," says Polotsky.

After establishing that the carotid body is required for leptin to cause hypertension, the researchers wanted to know what other signaling molecules in the carotid body might be involved. By sifting through previously collected data on what molecules are in the carotid body, they honed in on the transient receptor potential (TRPM7) calcium channel. Polotsky and his team treated mice with the multiple sclerosis drug FTY720 (fingolimod), which blocks channels typically involved in the immune system, including TRPM7 (the drug's mechanism to treat multiple sclerosis is due to blocking a receptor called S1PR1). In this current study, the drug effectively stopped extra doses of leptin from increasing blood pressure in lean mice, both when given systemically and when applied as a topical gel on the skin directly above the carotid bodies.

"We are now working with biochemists to develop a long-acting drug that acts specifically on TRPM7 in the carotid body," says Polotsky. More research is needed to determine whether such a drug could effectively treat hypertension in obese people.

The work and researchers were funded by the National Institutes of Health (R01 HL133100, R01 HL128970, R01 HL138983), the National Institute of Environmental Health Sciences (P50 ES018176), the U.S. Environmental Protection Agency (83615201, 83451001), the American Heart Association (19CDA34700025) and Consejería de Salud de Andalucía (EF-0128-2016).

Story Source:

Materials provided by **Johns Hopkins Medicine**. *Note: Content may be edited for style and length.*
