Bio News – January, 2020

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

11/29　心不全に「細胞スプレー法」阪大が治験開始　患者の心臓表面に幹細胞を直接吹きかけ

11/29 「アイコス」(フィリップモリスインターナショナル製) 新研究～紙巻きタバコと変わらない「細胞への悪影響」

https://news.yahoo.co.jp/byline/ishidamasahiko/20191129-00152854/

11/29 電気で潤うコンタクトレンズ　ドライアイ防ぐ　東北大

11/30　脳脊髄液に毒性高いたんぱく　非遺伝性 ALS 患者で検出　慶大

https://headlines.yahoo.co.jp/hl?a=20191130-00000009-jij-sctch

11/30　Roche や Novartis 等の 17 の新薬が 61%の値引きで中国の保険支払対象の座を得る

中国は低価格大量使用の市場であり、国際製薬会社はたくさん使われるなら値下げしてもいいかという気持ちになっているということだ。

11/30　Teva がテルアビブ大学との提携を拡大～癌や脳の研究に協力して取り組む

12/2　25～64 歳の働き手の死亡率上昇により米国人の寿命短縮

米国人の寿命は 1959 年に 69.9 歳だったが、2014 年には 79.4 歳へと延びていた。しかし、主に 25～64 歳の労働年齢層の死亡率上昇によりその後 3 年間は連続して減少、2016 年は 78.9 歳に短縮している。
1990 年代に比べて米国の現在の働き手は、薬物過剰摂取・アルコール乱用・自殺による死や臓器疾患による死をより被っている。

12/2　佐賀大でがんゲノム医療　遺伝子異常検査受け治験

https://headlines.yahoo.co.jp/hl?a=20191202-03460710-saga-sctch

12/2　イルカは右利きが大多数、6 年間の研究で明らかに

12/3　アステラス製薬が神経筋疾患遺伝子治療の Audentes を 30 億ドルで買収

12/4　精子が前に進んで受精するのに必要な蛋白質 VSP を大阪大学研究者等が同定

12/5　毛染めや直毛剤を度々使うことと乳癌が関連

12/6　Eli Lilly が癌研究/開発部門を統合し、Loxo Oncology at Lilly と命名

Eli Lilly の自前の癌研究チームと同社が今年初めに買った Loxo Oncology が合体して Loxo Oncology at Lilly という名称となり、その名が示す通り Loxo の 3 人・Josh Bilenker 氏, Jacob Van Naarden 氏, Nisha Nanda 氏が新体制の舵を取る。

12/7　Biogen の元 R&D リーダーが率いる遺伝子治療会社 Limelight Bio が 7,500 万ドル調達

12/9　iPS 細胞移植で失明回復の可能性　世界初の臨床研究へ

https://headlines.yahoo.co.jp/hl?a=20191209-00000007-kobenext-sctch

12/9　iPS 備蓄事業　2022 年度まで支援を継続

https://headlines.yahoo.co.jp/hl?a=20191209-00050012-yomidr-sctch

12/10　AbbVie が Scripps Research との提携を拡大

12/10　Sanofi の新 CEO・Paul Hudson 氏の最初の買い物～25 億ドルで Synthorx 買収

12/11　バイオテックスタートアップへの投資資金 2 億 1,000 万ドルを Perceptive Advisors が調達

Perceptive Advisors がボストン拠点の起業支援会社 Xontogeny と協力してバイオテックのスタートアップ企業に投資する預り金 Perceptive Xontogeny Venture Fund（PXV Fund）として 2 億 1,000 万ドルを調達。

12/11　Sanofi が新たな戦略の元、糖尿病や心血管疾患の研究を中止

12/11　国産の新ゲノム編集手法（クリスパー・キャス 3）－編集ミス少ない長所も －大阪大学などが開発

https://headlines.yahoo.co.jp/hl?a=20191211-00010000-sportal-sctch

12/12　食べずにはいられなくする衝動性に寄与する脳回路を同定– ジョージア大学

https://eurekalert.org/pub_releases/2019-12/uog-rdb121119.php

12/13　パーキンソン病治療開発の Aspen が 650 万ドルを手に船出

パーキンソン病の自家細胞移植治療を開発する Aspen Neuroscience が Domain Associates と Axon Ventures が率いた 650 万ドルの投資を手にして発足。
個々の患者の皮膚細胞を加工して iPS 細胞を作り、続いてパーキンソン病で枯渇するドパミン放出神経細胞へと仕立てて患者に移植する治療を開発する。

12/13　Stephen Hahn 氏（The University of Texas MD Anderson Cancer Center）が FDA 長官と認められた

12/13　Juul 製を含む電子タバコから肺疾患原因と目される物質を韓国が検出/Reuters 報道

Reuters によると、韓国が 153 の電子タバコ液を調べたところ重度肺疾患との関連が強く疑われる酢酸ビタミン E（vitamin E acetate）が米国 Juul Labs 製を含む 13 品から検出された。

12/13　サルの細胞を持つブタが中国で誕生し、数日間、生存していたことが明らかに

https://headlines.yahoo.co.jp/article?a=20191213-00010004-newsweek-int

https://www.newsweekjapan.jp/stories/world/2019/12/post-13608_2.php

12/14　チョウザメを全て雌化　近大、安価なキャビアに道

https://headlines.yahoo.co.jp/hl?a=20191214-00000515-san-sctch

12/14　BMS が特許裁判で Gilead に勝利～陪審 7 億 5,200 万ドル支払いを命令

Gilead Sciences の子会社 Kite の癌治療 Yescarta が Bristol-Myers Squibb（BMS）手持ちの CAR T 特許を侵害しているとしてカリフォルニア州ロサンゼルスの陪審が BMS へ 7 億 5,200 万ドル支払いを命じた。

12/16　GSK が小児用 HIV 薬を米国と欧州に承認申請

12/17　Charles River が HemaCare を約 3 億 8,000 万ドルで買収

12/18　脳の病気、iPS 細胞使った再現成功　原因遺伝子も判明 -神戸大

https://headlines.yahoo.co.jp/hl?a=20191218-00000005-asahi-soci

12/18　ニコチン含量が少ない 22nd Century Group のタバコを FDA が承認

12/19　2030 年には米国成人の約 2 人に 1 人が肥満、約 4 人に 1 人は重度肥満になると推定

12/19　予防接種歴を皮膚下に記録、米 MIT が染料開発 ゲイツ財団支援

https://headlines.yahoo.co.jp/hl?a=20191219-00000019-jij_afp-sctch

12/19　BSE の原因を初めて解明か 研究

https://headlines.yahoo.co.jp/hl?a=20191219-00000026-jij_afp-sctch

12/20　Novartis の世界一高価な薬 Zolgensma が抽選で無料提供される(最大 100 回分)

12/20　投資会社 Deerfield がデューク大学の創薬研究支援に最大 1 億 3,000 万ドルを投じる

昨年 354 の発明を発表し、新たに 16 社を立ち上げたデューク大学内での創薬研究が治験開始可能な段階まで到達するのを最大 1 億 3,000 万ドルを投じて支援する新会社 Four Points Innovation を投資会社 Deerfield Management が設立。

12/21　寿命を長らえさせる酵素 SIRT6 の脂肪肝阻止効果が判明

12/23　ブタ体内で人のiPS膵臓　文科省、明大の研究計画を了承

https://headlines.yahoo.co.jp/hl?a=20191223-00000520-san-sctch

12/23　エボラ治療薬　研究用に輸入へ…厚労省

12/24　エーザイの睡眠薬 Dayvigo（レンボレキサント）を FDA が承認

12/24　BMS の売上の 30%を占める抗凝固薬 ELIQUIS の後発品（Micro Labs 製と Mylan Pharmaceuticals 製）を FDA が承認

12/24　アルツハイマー病予防に植物由来のセラミドが有効 マウスの実験結果から北大グループ

https://headlines.yahoo.co.jp/hl?a=20191224-00010000-sportal-sctch

12/24 Intra-Cellular の統合失調症薬 Caplyta を米国 FDA が承認、株価も 12 ドル台から 30 ドル超へと高騰

12/24 アルツハイマー病予防に植物由来のセラミドが有効 マウスの実験結果から北大グループ

https://headlines.yahoo.co.jp/hl?a=20191224-00010000-sportal-sctch

12/26 チンパンジーも音楽でリズムを取れると確認　京大霊長類研

https://headlines.yahoo.co.jp/hl?a=20191226-00000063-mai-sctch

12/27 アステラスが抗癌免疫治療の Xyphos Biosciences を最大 6 億 6,500 万ドルで買収

12/28 ダンゴムシのふんに秘密　小1から研究、11年目で解明

https://headlines.yahoo.co.jp/hl?a=20191228-00000016-asahi-soci

12/29 iPS から血小板　京大チーム…輸血時拒絶反応なし

https://headlines.yahoo.co.jp/hl?a=20191229-00050004-yomidr-sctch

12/29 「母乳バンク」全国整備へ　低体重児の病気リスク減

https://headlines.yahoo.co.jp/hl?a=20191229-00000064-kyodonews-soci

12/30 世界初とされる遺伝子編集赤ちゃんを作った研究者に中国が収監刑を課した/ロイター

https://www.reuters.com/article/china-health-babies/chinese-court-sentences-gene-editing-scientist-to-three-years-in-prison-xinhua-idUSB9N28L01Y

https://www.statnews.com/2019/12/30/he-jiankui-who-created-worlds-first-crisprd-babies-sentenced-to-three-years-in-prison-for-illegal-medical-practice/?utm_source=STAT+Newsletters&utm_campaign=4f9cb12e66-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-4f9cb12e66-150065641

https://news.yahoo.co.jp/pickup/6346820

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. HIV：初期段階でやっつける方法

2. がん細胞が結腸組織内でどのように成長して広がるかを視覚的に示す新しい手法

3. 「エピジェネティックなカウチポテト」マウス作成

4. 脳血管の健康状態改善がアルツハイマー病との闘いに役立つ可能性

5. 軽度のアルコール摂取でも癌発症リスクは増大

6. 精密エピゲノム編集法でマウスの遺伝的脳障害を修正

7. アルツハイマー病薬候補がより広範な老化を逆転

8. 植物が豊富な食餌がマウスを植物媒介感染から保護

9. クマから学ぶ

1. HIV：初期段階でやっつける方法

日付：2019 年 11 月 26 日
ソース：モントリオール大学
概要：

モントリオール大学のウィルス学者らが、HIV 感染の非常に早い段階でその感染を食い止める方法を特定した。
いったん HIV に感染すると、そのウィルスはすぐに体内に拡散はしない。最初は、主に生殖組織で局所的に増殖する必要があり、ウィルスは、この最初の局所的拡大後に初めて増殖する。
さて、免疫反応は武装闘争のようなもので、敵が侵入し、身体が自身を守る。ウィルスは侵入者であり、白血球は砦を押さえようとする兵士で、更にその白血球には、リンパ球、食細胞、顆粒球など、独自の「歩兵ユニット」が装備されている。食細胞グループには、「形質細胞様樹状細胞」（PDC）として知られるさらに専門的なユニットがある。これらの小さな円形の細胞は、内部告発者であり、それを通じて防御プロセス全体が動き出す。脅威を検出すると、形を変えて樹状突起と呼ばれる突起を発達させる。又、最も重要な働きとしては、他の細胞に感染抵抗性を引き起こすタンパク質であるインターフェロンの大量生産を開始させる。
その名前が示すように、HIV は免疫系を優先的に標的にする。つまり、HIV は身体自体の防御機能を攻撃して弱め、感染した人はわずかな感染の影響を受けやすくなる。その状態に到達するとすぐに、HIV は PDC を邪魔にならないようにし、アラームを鳴らさないようにする。そこで HIV が PDC に対して具体的に何をするか、感染前と感染中の両方で PDC レベルとその機能を高めるとどうなるか？これをテストするために、研究者らは Flt3 受容体リガンドとして知られる特別なタンパク質を使用して、ヒト化マウスの骨髄からの PDC の産生を刺激した。
この特殊なタンパク質を投与すると、これらのマウスで高レベルの PDC が維持され、いくつかの顕著な結果が得られた。
1）感染マウスの初期数が減少
2）ウィルスが血液中で検出可能になるまでの時間が長くなった
3）血液中のウィルス量（ウィルス血症とも呼ばれる）が大幅に減少
言い換えれば、初期感染時に高レベルの PDC を維持することで HIV 感染は抑制される。この独創的な研究はまた、Flt3 受容体リガンドの注射が PDC の存在量を増加させるだけでなく、ウィルスを検出し、その検出後にインターフェロンを産生する能力を高めることも示した。研究者らは、これらの新しい発見が、HIV ワクチンの設計において非常に重要だ、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/11/191126121207.htm

HIV: Overwhelming the enemy from the start

Date:

November 26, 2019

Source:

University of Montreal

Summary:

Virologists have identified a way to thwart HIV infection at its very early stages.

FULL STORY

1.7 million. That's how many people are infected with the human immunodeficiency virus (HIV) each year worldwide. 1.7 million people who are condemned to lifelong antiretroviral therapy (ART) or risk developing fatal AIDS . Out of the 37.9 million people living with HIV (PLWH), 22.3 million have access to ART, allowing them to have an almost normal lifespan. Unfortunately, however, the medications only go so far: they don't reach the cells where the virus lies dormant for years. Moreover, potential long-term adverse effects of these medications remain unknown.

Still, HIV research has been making steady strides to help the large number of PLWH. HIV laboratories around the globe are trying to unlock the "secrets" of the virus and find its weak spots in order to prevent or cure the infection. At the Montreal Clinical Research Institute (IRCM), scientists Éric A. Cohen and Tram NQ Pham have recently identified a way to thwart HIV infection at its very early stages. Their discovery is the subject of an article in the scientific journal *Cell Reports*.

The window of vulnerability: a few crucial first days

"Contrary to popular belief, HIV is not so easily transmitted," says Éric Cohen, director of the Human Retrovirology Research Unit at the IRCM and a virology professor in the Department of Microbiology, Infectious Diseases and Immunology at Université de Montréal. "We are studying the window of vulnerability of the virus, meaning the moments in the infection process when it could be weakened or attacked. We focused on the very early stages following viral invasion."

Once transmitted, HIV does not immediately spread through the body. It initially has to multiply locally, mainly in the genital tissues. It is only after this initial, local expansion that the virus spreads. This localized expansion offers a very brief window of vulnerability before the virus efficiently establishes a systemic infection.

The immune response is like an armed struggle: an enemy infiltrates and the body defends itself. Viruses are the intruders, and white blood cells are soldiers trying to hold down the fort. The white blood cells are equipped with their own "infantry units": lymphocytes, phagocytes, granulocytes and others. The phagocyte group has an even more specialized unit known as 'plasmacytoid dendritic cells' (PDCs). These small, round-shaped cells patrol the body, specializing in both pathogen detection and antiviral response orchestration. In other words, they are the whistleblowers, the ones through which the entire defence process is set into motion. When they detect a threat, they change shape and develop protuberances called dendrites. "Most importantly, they start producing large

amounts of interferon, a protein that triggers a state of infection resistance in other cells," Cohen explained.

As its name implies, HIV preferentially targets the immune system: it attacks and weakens the body's own defences, and the infected person becomes susceptible to the slightest infection. As soon as it arrives, HIV gets PDCs out of the way and prevents them from sounding the alarm. "The virus doesn't seem to kill them directly, but it makes them disappear in a way that is still not understood," said Pham, the senior research associate in the Human Retrovirology Research Unit. "The loss of PDCs from both the infection site and throughout the body helps establish the infection."

A humanized mouse model to fight HIV infection

"Given what HIV does to PDCs, we wondered what would happen if we boosted PDC levels and their function both prior to and during infection," said Cohen. To test this, the scientists used a special protein known as Flt3 receptor ligand to stimulate the production of PDCs from the bone marrow of humanized mice. These rodents are engineered to have a human immune system in place of the mouse's own machinery. Consequently, in an infected humanized mouse, HIV behaves as it otherwise would in a human host.

Administration of this special protein maintained high levels of PDCs in these mice and produced some striking results: 1) the initial number of infected mice was reduced; 2) the time it took for the virus to be detectable in the blood was lengthened; and 3) the amount of virus in the blood, also known as viremia, was significantly reduced. "We observed up to a 100-fold decrease in viremia," Pham noted. "In other words, the initial infection is suppressed by maintaining a high level of PDCs."

The Implications for designing a vaccine

This seminal work also showed that the injection of the Flt3 receptor ligand not only increased PDC abundance, but also boosted their ability to detect the virus and produce interferon following its detection.

Of course, HIV infection normally goes unnoticed and by the time the viremia is detectable, it is a little too late. In this context, the discovery by Cohen and Pham is highly important in terms of prevention and a potential cure. "These new findings will be crucial in the design of an HIV vaccine, which is basically aimed at teaching the immune system to defend itself by introducing it to a weakened form of the virus," said Cohen. "We can now focus on PDCs in order to control the seeding and expansion of the virus at the early stage of infection."

Story Source:

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

Journal Reference:

1. Tram N.Q. Pham, Oussama Meziane, Mohammad Alam Miah, Olga Volodina, Chloé Colas, Kathie Béland, Yuanyi Li, Frédéric Dallaire, Tibor Keler, Jean V. Guimond, Sylvie Lesage, Cheolho Cheong, Élie Haddad, Éric A. Cohen. **Flt3L-Mediated Expansion of Plasmacytoid Dendritic Cells Suppresses HIV Infection in Humanized Mice**. *Cell Reports*, 2019; 29 (9): 2770 DOI: 10.1016/j.celrep.2019.10.094

Cite This Page:

- MLA
- APA
- Chicago

University of Montreal. "HIV: Overwhelming the enemy from the start." ScienceDaily. ScienceDaily, 26 November 2019. <www.sciencedaily.com/releases/2019/11/191126121207.htm>.

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2. がん細胞が結腸組織内でどのように成長して広がるかを視覚的に示す新しい手法

日付:2019 年 12 月 2 日
ソース:デューク大学医療センター
概要:

デューク大学癌研究所の研究者らは、幹細胞の突然変異が静かに発生し、結腸の広い領域全体に拡大して、最終的に優勢になって悪性腫瘍になるのを観察した。
研究者らは、マウスの革新的なモデリングシステムを使用して、幹細胞を発光させることにより、結腸癌の変異を視覚的にタグ付けした。大腸癌で見つかった変異はマウスで視覚化され、1 つまたは別の変異が他の変異に勝って悪性腫瘍の原動力となることが明らかにされた。
幹細胞を発光させるには、分子染色技術を適用し、単一の腫瘍の幹細胞におけるいくつかの一般的な結腸癌変異にタグ付けした蛍光バーコードを作成した。これをマウスに移すと、蛍光性幹細胞の虹を視覚的に追跡でき、前癌性イベントの細胞および分子動力学を明らかにすることができた。
研究者らは、乳癌の癌領域を見るために蛍光バーコードを使用した追加研究を進めており、乳管がんとして知られる前がん状態が悪性と良性への変異によって引き起こされる時期についてさらに学ぶことを目指している、としている。
この研究成果は、12 月 2 日の *Nature Communications* 誌のオンライン版に掲載されている。

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/2019/12/191202081643.htm

New technique visually depicts how cancer cells grow and spread in colon tissue

Even before cancer is detectable, glow-in-the-dark cells show mutations driving malignancy

Date:

December 2, 2019

Source:

Duke University Medical Center

Summary:

Researchers have observed how stem cell mutations quietly arise and spread throughout a widening field of the colon until they eventually predominate and become a malignancy.

FULL STORY

Duke Cancer Institute researchers have observed how stem cell mutations quietly arise and spread throughout a widening field of the colon until they eventually predominate and become a malignancy.

Using an innovative modeling system in mice, the researchers visually tagged colon cancer mutations by causing stem cells to glow. Mutations found in colon cancer were then visualized in the animals, illuminating a sort of tournament-to-the-death underway in the intestine in which one or another mutation prevailed over the others to become the driving force of a malignancy.

"This study provides new insight into the previously invisible process in which mutant precancerous stem cells spread throughout the colon and seed cancer," said Joshua Snyder, Ph.D., assistant professor in the departments of Surgery and Cell Biology at Duke and corresponding and co-senior author of a study publishing online Dec. 2 in the journal *Nature Communications*.

"Our technique sets a firm foundation for testing new therapies that interrupt this early, pre-malignant process. We hope to one day target and eliminate these stealth precancerous cells to prevent cancer," Snyder said.

Snyder and colleagues -- including co-senior author H. Kim Lyerly, M.D., George Barth Geller Professor at Duke ¬ -- applied the molecular dyeing technique in a new way, tagging several common colon cancer mutations in the stem cells of a single tumor to create a fluorescent barcode.

When transferred to a mouse, the rainbow of fluorescent stem cells coul In this way, the researchers found key differences in how the intestinal habitats common to babies and adults grow pre-cancerous fields of mutant cells. At a critical period, newborns are sensitive to the effects of mutations within intestinal stem cells. This insidiously seeds large fields of premalignant mutated cells throughout the intestine -- a process called field cancerization -- that dramatically increases cancer risk. These fields of mutated cells can grow and spread for years without being detected by current screening technologies; often, they remain harmless, but under proper conditions, can rapidly become cancerous later in adults.

The researchers also observed that some colon cancer mutations found in patients can lead to a striking increase in the fertility of the environment surrounding precancerous fields. Ultimately, this leads to the rapid spread of fields throughout the intestine, with lethal consequences.

Certain common mutations that arise from external sources, such as an injury or an environmental exposure, could also disrupt the environment surrounding the stem cell and lead to the rapid growth and spread of precancerous fields. These occurrences can be especially lethal in adults and occur much more rapidly than previously expected -- as if dropping a match on a drought-stricken forest.

"Field cancerization has been suggested to be the defining event that initiates the process of cancer growth, including cancers of the breast, skin and lung," Snyder said. "Our technique allows us to model how premalignant cells compete and expand within a field by simple fluorescent imaging, potentially leading to earlier diagnosis and treatment."

Snyder said additional studies are underway using the fluorescent barcoding to view the cancer fields in breast cancer, aiming to learn more about when a pre-cancerous condition known as ductal carcinoma in situ is driven by malignant vs. benign mutations.

In addition to Snyder and Lyerly, study authors include Peter G. Boone, Lauren K. Rochelle, Veronica Lubkov, Wendy L. Roberts, P.J. Nicholls, Cheryl Bock, Mei Lang Flowers, Richard J. von Furstenberg,

Joshua D. Ginzel, Barry R. Stripp, Pankaj Agarwal, Alexander D. Borowsky, Robert D. Cardiff, Larry S. Barak and Marc G. Caron.

The work was supported by the National Cancer Institute (512-CA100639-10, 1K22CA212058, R21CA173245, 1R33CA191198, NICHD 5T32HD040372), Sage Biosciences (3U24CA209923-01S1), the Department of Defense (W81XWH-12-1-0447) and Duke Surgery.

Story Source:

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

Journal Reference:

1. Peter G. Boone, Lauren K. Rochelle, Joshua D. Ginzel, Veronica Lubkov, Wendy L. Roberts, P. J. Nicholls, Cheryl Bock, Mei Lang Flowers, Richard J. von Furstenberg, Barry R. Stripp, Pankaj Agarwal, Alexander D. Borowsky, Robert D. Cardiff, Larry S. Barak, Marc G. Caron, H. Kim Lyerly, Joshua C. Snyder. **A cancer rainbow mouse for visualizing the functional genomics of oncogenic clonal expansion**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-13330-y

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Cite This Page:

- MLA
- APA
- Chicago

Duke University Medical Center. "New technique visually depicts how cancer cells grow and spread in colon tissue: Even before cancer is detectable, glow-in-the-dark cells show mutations driving malignancy." ScienceDaily. ScienceDaily, 2 December 2019. <www.sciencedaily.com/releases/2019/12/191202081643.htm>.

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3. 「エピジェネティックなカウチポテト」マウス作成

日付：2019 年 12 月 4 日
ソース：ベイラー医科大学
概要：

運動が好きな人と嫌いな人がいるのはなぜだろう？ほとんどの人はそれがすべて遺伝によると考えるが、新しいベイラー医科大学主導のマウスの研究では、異なる分子レベルの調節−エピジェネティクス−が運動への生来の意欲を決定する上で重要な役割を果たすことが初めて示されている。
エピジェネティクスとは、さまざまな細胞型でオンまたはオフになる遺伝子を決定する分子メカニズムのことである。エピジェネティックなメカニズムは本質的に遺伝学よりも順応性があるため、この調査結果は、人々がより身体的に活発になることを「プログラム」するのを助ける潜在的な方法を示唆している。
今日、*Nature Communications* 誌で、ベイラーの研究者と同僚は、驚くべき「エピジェネティックなカウチポテト」マウス作成を報告している。研究者らは、視床下部と呼ばれる脳の一部内のニューロンにおいて、DNA メチル化の変化（DNA へのメチル化学タグの追加）が自発的な運動行動のレベルに大きな影響を与えることを発見した。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/12/191204145739.htm

Scientists create 'epigenetic couch potato' mouse

Date:

December 4, 2019

Source:

Baylor College of Medicine

Summary:

A study in mice shows for the first time that epigenetics -- the molecular mechanisms that determine which genes are turned on or off -- plays a key role in determining an individual's innate drive to exercise.

FULL STORY

Why is it that some people love to exercise, and others hate it? Most people would assume it's all due to genetics, but a new Baylor College of Medicine led study in mice shows for the first time that a different molecular level of regulation -- epigenetics -- plays a key role in determining one's innate drive to exercise. Epigenetics refers to molecular mechanisms that determine which genes are turned on or off in different cell types. Since epigenetic mechanisms are inherently more malleable than genetics, the findings suggest a potential way to help 'program' people to enjoy being more physically active.

Today, in the journal *Nature Communications*, Baylor researchers and colleagues report the surprising creation of an 'epigenetic couch potato' mouse. They found that in neurons within a part of the brain called the hypothalamus, changes in DNA methylation -- the addition of methyl chemical tags in the DNA -- have a major impact on levels of voluntary exercise behavior.

"We study developmental programming, which refers to how the environment during development can have a long term impact on risk of disease," said corresponding author, Dr. Robert A. Waterland, professor of pediatrics -- nutrition at the USDA/ARS Children's Nutrition Research Center at Baylor and Texas Children's Hospital.

Over the last several years, the researchers studied various mouse models to understand developmental programming of energy balance, that is, the balance of calories consumed vs. those burned off. A prolonged positive energy balance leads to obesity. Remarkably, whether the early environmental influence was fetal growth restriction, infant overnutrition, or maternal exercise during pregnancy, the long-term effect on energy balance was always due to persistent changes in physical activity, not food intake.

"Our earlier findings suggested that establishment of one's physical activity 'set point' can be affected by early environment, and that this may involve epigenetics," said Waterland, who also is a professor of molecular and human genetics and a member of the Dan L Duncan Comprehensive Cancer Center at Baylor.

How the brain regulates the body's energy balance

In the current study, Waterland and his colleagues designed an experiment to directly test whether DNA methylation in the brain affects energy balance. They focused on the hypothalamus, a brain region that plays a central role in energy balance, and in particular, studied a specialized subset of hypothalamic neurons called AgRP neurons, famous for their role in regulating food intake.

The researchers disrupted DNA methylation in AgRP neurons by disabling the Dnmt3a gene. Dnmt3a is responsible for adding methyl groups to DNA, particularly in the brain during early postnatal life. The results showed that, indeed, DNA methylation was dramatically reduced in AgRP neurons of these mice. The investigators then tested whether these animals gained or lost weight when compared to normal mice.

"We expected that interfering with DNA methylation in AgRP neurons would result in major changes in the animals' weight," said Dr. Harry MacKay, a postdoctoral fellow in the Waterland lab and first author of the study. "Somewhat disappointingly, however, the Dnmt3a-deficient mice were only slightly fatter than those that were not deficient."

But when the researchers explored the cause of this change in energy balance, things got more interesting. The team expected to find differences in food intake between normal and Dnmt3a-deficient mice. But there were none. Instead, they found a major difference in spontaneous physical exercise.

The researchers placed running wheels in the animals' cages for eight weeks and measured how much they ran each night. Normal male mice ran about 6 Km (3,7 miles) every night, but the Dnmt3a-deficient mice ran only half as much and, accordingly, lost less fat. Importantly, detailed

treadmill studies showed that, although they ran only half as much as normal mice, the Dnmt3a-deficient mice were just as capable of running. They had the ability, but appeared to lack the desire.

"Our findings suggest that epigenetic mechanisms, such as DNA methylation, that are established in the brain during fetal or early postnatal life, play a major role in determining individual propensity for exercise," Waterland said. "Nowadays, as decreases in physical activity contribute to the worldwide obesity epidemic, it is increasingly important to understand how all of this works."

Other authors contributing to this work include Harry MacKay, C. Anthony Scott, Jack D. Duryea, Maria S. Baker, Eleonora Laritsky, Marta L. Fiorotto, Rui Chen, Yumei Li and Cristian Coarfa (Baylor College of Medicine); Amanda E. Elson and Richard B. Simerly (Vanderbilt University) and Theodore Garland Jr. (University of California at Riverside).

This work was supported by grants from the U.S. Department of Agriculture (CRIS 3092-5-001-059) and the National Institutes of Health (NIH) (5R01DK111831). Next generation sequencing was conducted at Baylor College of Medicine Functional Genomics Core, which is partially supported by the NIH shared instrument grant S10OD023469.

Story Source:

Materials provided by **Baylor College of Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Harry MacKay, C. Anthony Scott, Jack D. Duryea, Maria S. Baker, Eleonora Laritsky, Amanda E. Elson, Theodore Garland, Marta L. Fiorotto, Rui Chen, Yumei Li, Cristian Coarfa, Richard B. Simerly, Robert A. Waterland. **DNA methylation in AgRP neurons regulates voluntary exercise behavior in mice**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-13339-3

Cite This Page:

- MLA
- APA
- Chicago

Baylor College of Medicine. "Scientists create 'epigenetic couch potato' mouse." ScienceDaily. ScienceDaily, 4 December 2019. <www.sciencedaily.com/releases/2019/12/191204145739.htm>.

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4. 脳血管の健康状態改善がアルツハイマー病との闘いに役立つ可能性

日付:2019 年 12 月 5 日
ソース:マサチューセッツ総合病院
概要:

アルツハイマー病の患者では、アミロイドベータタンパク質の断片が脳の組織と血管に蓄積している。これは、おそらくクリアランス機構の欠陥によるものとされている。
今回、マウス実験で、マサチューセッツ総合病院(MGH)の研究者らは、非常に遅い自発血管脈動(「血管運動」とも呼ばれる)が脳からの物質のクリアランスを促進することを発見、このプロセスを標的として改良することによって、アミロイドベータの蓄積を予防または治療するのに役立つのでは、としている。
今回 *Neuron* 誌で発表されたこの研究では、研究者らはマウスの脳にデキストランと呼ばれる蛍光標識炭水化物を注入し、そのクリアランスを追跡するために画像検査を実施した。彼らの実験により、脳からデキストランを除去するために血管運動が重要であり、これらの血管の脈動の振幅の増加を刺激するとクリアランスが増加する可能性があることが明らかになった。また、脳の血管壁にアミロイドベータが蓄積した状態にある脳アミロイド血管症のマウスでは、血管の拍動が妨げられ、クリアランス率が低下した。
彼らは、健康な血管系の促進に向けた治療戦略を導くことによって、脳からのアミロイドベータのクリアランスを改善すれば、アルツハイマー病の発症を予防または遅らせることができるのではないか、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/2019/12/191205073031.htm

Improving blood vessel health in brain may help combat Alzheimer's

Date:

December 5, 2019

Source:

Massachusetts General Hospital

Summary:

Researchers have found that very slow spontaneous blood vessel pulsations drive the clearance of substances from the brain, indicating that targeting and improving this process may help to prevent or treat amyloid-beta accumulation.

FULL STORY

In patients with Alzheimer's disease, amyloid-beta protein fragments accumulate in the tissue and blood vessels of the brain, likely due to a faulty clearance mechanism. In experiments conducted in mice, investigators at Massachusetts General Hospital (MGH) have found that very slow spontaneous vessel pulsations -- also known as 'vasomotion' -- drive the clearance of substances from the brain, indicating that targeting and improving this process may help to prevent or treat amyloid-beta accumulation.

In their study published in *Neuron*, the researchers injected a fluorescently labeled carbohydrate called dextran into the brains of awake mice, and they conducted imaging tests to follow its clearance. Their experiments revealed that vasomotion was critical for clearing dextran from the brain and stimulating an increase of the amplitude of these vessel pulsations could increase clearance. Also, in mice with cerebral amyloid angiopathy, a condition that causes amyloid-beta to build up in the walls of the brain's blood vessels, vessel pulsations were hindered and clearance rates were reduced.

"We were able to show for the first time that large dilations and contractions of vessels that happen spontaneously at an ultra-low frequency are a major driving force to clear waste products from the brain," said lead author Susanne van Veluw, PhD, an investigator in the department of Neurology at MGH. "Our findings highlight the importance of the vasculature in the pathophysiology of Alzheimer's disease. If we direct therapeutic strategies towards promoting healthy vasculature and therefore improve clearance of amyloid-beta from the brain, we may be able to prevent or delay the onset of Alzheimer's disease in the future."

Story Source:

Materials provided by **Massachusetts General Hospital**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Susanne J. van Veluw, Steven S. Hou, Maria Calvo-Rodriguez, Michal Arbel-Ornath, Austin C. Snyder, Matthew P. Frosch, Steven M. Greenberg, Brian J. Bacskai. **Vasomotion as a Driving Force for Paravascular Clearance in the Awake Mouse Brain**. *Neuron*, 2019; DOI: 10.1016/j.neuron.2019.10.033

- APA
- Chicago

Massachusetts General Hospital. "Improving blood vessel health in brain may help combat Alzheimer's." ScienceDaily. ScienceDaily, 5 December 2019. <www.sciencedaily.com/releases/2019/12/191205073031.htm>.

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5. 軽度のアルコール摂取でも癌発症リスクは増大

日付:2019 年 12 月 9 日
ソース:Wiley
概要:

日本で実施された研究で、アルコール摂取が軽度から中程度であっても、癌リスク上昇と関連することが示された。また、全体的な癌リスクはアルコール消費ゼロで最も低いように見えた、ともしている。この研究は、米国癌学会の査読付きジャーナルである *Cancer* においてオンライン公開された。
この問題を研究するために、東京大学とハーバード大学公衆衛生学部の財津將嘉医学博士と彼の同僚らは、日本全国の 33 の総合病院の 2005-2016 年の情報を調べた。研究チームは、63,232 人の癌患者と約同数の癌ではない患者の臨床データを調べ、すべての参加者の飲酒量や飲酒期間などを分析した。
全体的な癌のリスクは、アルコール摂取量がゼロのときに最も低くなるようであり、癌リスクとアルコール摂取量の間にはほぼ線形の関連があった。1 日ワイン 1 杯程度の少量のアルコールでも 10 年間飲酒を続けると、癌になるリスクが 5%(食道癌は 45%、喉頭癌は 22%、大腸癌は 8%、胃癌は 6%)上がることが判明。少量の飲酒は循環器病などのリスクを下げるとの報告もあるが、がんに関しては量に応じて危険性が高まる、としている。
「日本では、死亡の主な原因は癌であり、アルコール関連の癌リスクに関する公の教育の促進をさらに奨励すべきだ。」と、財津博士は言っている。

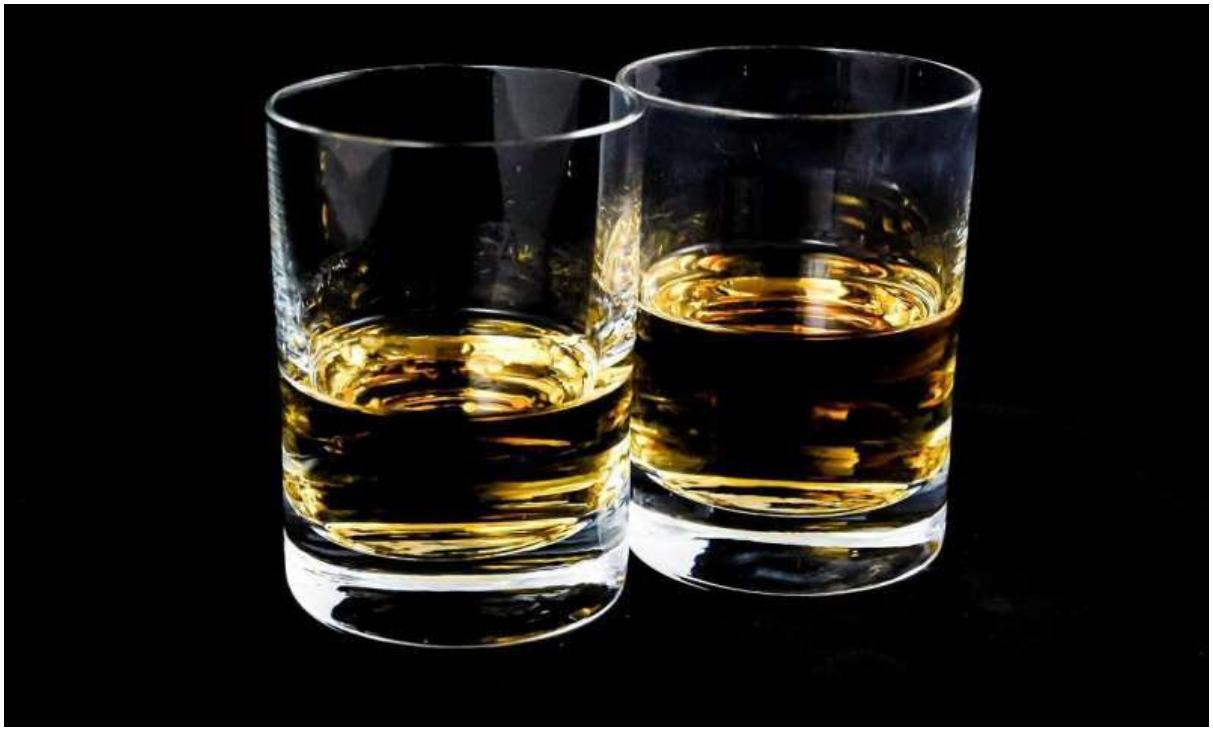
研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-12/w-ela120419.php

NEWS RELEASE 9-DEC-2019

Even light alcohol consumption linked to higher cancer risk in Japan

WILEY



Credit: CC0 Public Domain

In a study conducted in Japan, even light to moderate alcohol consumption was associated with elevated cancer risks. In the study published early online in *Cancer*, a peer-reviewed journal of the American Cancer Society, the overall cancer risk appeared to be the lowest at zero alcohol consumption.

Although some studies have linked limited alcohol consumption to lower risks of certain types of cancer, even light to moderate consumption has been associated with a higher risk of cancer overall. To study the issue in Japan, Masayoshi Zaitsu, MD, Ph.D., of The University of Tokyo and the Harvard T.H. Chan School of Public Health, and his colleagues examined 2005-2016 information from 33 general hospitals throughout Japan. The team examined clinical data on 63,232 patients with cancer and 63,232 controls matched for sex, age, hospital admission date, and admitting hospital. All participants reported their average daily amount of standardized alcohol units and the duration of drinking. (One standardized drink containing 23 grams of ethanol was equivalent to one 180-milliliter cup (6 ounces) of Japanese sake, one 500-milliliter bottle (17 ounces) of beer, one 180-milliliter glass (6 ounces) of wine, or one 60-milliliter cup (2 ounces) of whiskey.

Overall cancer risk appeared to be the lowest at zero alcohol consumption, and there was an almost linear association between cancer risk and alcohol consumption. The association suggested that a light level of drinking at a 10-drink-year point (for example, one drink per day for 10 years or two drinks per day for five years) would increase overall cancer risk by five percent. Those who drank two or fewer drinks per day had an elevated cancer risk regardless of how long they had consumed alcohol. Also, analyses classified by sex, drinking/smoking behaviors, and occupational class mostly showed the same patterns.

The elevated risk appeared to be explained by alcohol-related cancer risk across relatively common sites, including the colorectum, stomach, breast, prostate, and esophagus.

"In Japan, the primary cause of death is cancer," said Dr. Zaitsu. "Given the current burden of overall cancer incidence, we should further encourage promoting public education about alcohol-related cancer risk."

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Additional Information

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Penny Smith +44 (0) 1243 770448 (UK)
newsroom@wiley.com

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Full Citation: "Light to moderate amount of lifetime alcohol consumption and risk of cancer in Japan." Masayoshi Zaitsu, Takumi Takeuchi, Yasuki Kobayashi, and Ichiro Kawachi. *CANCER*; Published Online: December 9, 2019 (DOI: 10.1002/cncr.32590).

URL Upon Publication: http://doi.wiley.com/10.1002/cncr.32590

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About the Journal

CANCER is a peer-reviewed publication of the American Cancer Society integrating scientific information from worldwide sources for all oncologic specialties. The objective of *CANCER* is to provide an interdisciplinary forum for the exchange of information among oncologic disciplines concerned with the etiology, course, and treatment of human cancer. *CANCER* is published on behalf of the American Cancer Society by Wiley and can be accessed online. Follow us on Twitter @JournalCancer

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6. 精密エピゲノム編集法でマウスの遺伝的脳障害を修正

日付:2019 年 12 月 10 日
ソース:ジョンズ・ホプキンズ大学医学部
概要:

ジョンズ・ホプキンズ大学医学部の研究者らは、発達中のマウスの脳で標的遺伝子エピゲノム編集アプローチを使用することによって、遺伝障害 WAGR 症候群(これはヒトに知的障害や肥満をもたらす原因になる)を引き起こす遺伝子変異を逆転させた。この特定の編集は、規制対象の遺伝子の実際の遺伝暗号を変更することなく、エピゲノム(遺伝子の規制方法)を変更したという点でユニークである。
研究者らは、この遺伝子 C11orf46 が脳発達期間の重要な調節因子であることを発見、具体的には、電気信号の送信を司る新たに形成されたニューロンから成長する長い繊維を誘導し、それらが脳の 2 つの半球を接続する束内に形成するのを助ける方向感知タンパク質のオンとオフを切り替える。脳梁として知られるこの束ねられた構造を適切に形成しないと、知的障害、自閉症、または他の脳発達障害などの状態につながる可能性がある。WAGR 症候群は染色体 11p13 欠失症候群としても知られており、C11orf46 を含む染色体 11p13 の領域に位置する遺伝子の一部または全部が偶然に欠失した場合に起こる。研究者らが、マウスの脳内で生成される C11orf46 タンパク質の量を減らすと、WAGR 症候群で見られるように、C11orf46 タンパク質が少ないマウス脳のニューロンの繊維は、ニューロン束状脳梁を形成できなかった。
この研究は、*Nature Communications* 誌の 9 月 11 日号オンライン版に掲載された。また、この研究の著者の中には、Atsushi Saito, Yuto Hasegawa, Yuya Tanaka, Atsushi Kamiya など日本人研究者の名前もある。

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/2019/12/191210140410.htm

Genetic brain disorder fixed in mice using precision epigenome editing

Date:

December 10, 2019

Source:

Johns Hopkins Medicine

Summary:

Using a targeted gene epigenome editing approach in the developing mouse brain, researchers reversed one gene mutation that leads to the genetic disorder WAGR syndrome, which causes intellectual disability and obesity in people. This specific editing was unique in that it changed the epigenome -- how the genes are regulated -- without changing the actual genetic code of the gene being regulated.

FULL STORY

Using a targeted gene epigenome editing approach in the developing mouse brain, Johns Hopkins Medicine researchers reversed one gene mutation that leads to the genetic disorder WAGR syndrome, which causes intellectual disability and obesity in people. This specific editing was unique in that it changed the epigenome -- how the genes are regulated -- without changing the actual genetic code of the gene being regulated.

The researchers found that this gene, C11orf46, is an important regulator during brain development. Specifically, it turns on and off the direction-sensing proteins that help guide the long fibers growing out of newly formed neurons responsible for sending electrical messages, helping them form into a bundle, which connects the two hemispheres of the brain. Failure to properly form this bundled structure, known as the corpus callosum, can lead to conditions such as intellectual disability, autism or other brain developmental disorders.

"Although this work is early, these findings suggest that we may be able to develop future epigenome editing therapies that could help reshape the neural connections in the brain, and perhaps prevent developmental disorders of the brain from occurring," says Atsushi Kamiya, M.D., Ph.D., associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine.

The study was published online in the September 11 issue of *Nature Communications*.

WAGR syndrome is also known as chromosome 11p13 deletion syndrome, which can result when some or all of the gene located in the region of chromosome 11p13 that includes C11orf46 is deleted by chance. The researchers used a genetic tool, short hairpin RNA, to cause less of the C11orf46 protein to be made in the brains of mice. The fibers of the neurons in the mouse brains with less of the C11orf46 protein failed to form the neuron bundled corpus callosum, as is found in WAGR syndrome.

The gene that makes Semaphorin 6a, a direction-sensing protein, was turned on higher in mice with lower C11orf46. By using a modified CRISPR genome editing system, the researchers were able to edit a portion of the regulatory region of the gene for Semaphorin. This editing of the epigenome allowed C11orf46 to bind and turn down the gene in the brains of these mice, which then restored the neuron fiber bundling to that found in normal brains.

Other authors on the study include Atsushi Saito, Yuto Hasegawa, Yuya Tanaka, Mohika Nagpal, Gabriel Perez and Emily Alway of Johns Hopkins; Cyril Peter, Sergio Espeso-Gil, Tariq Fayyad, Chana Ratner, Aslihan Dincer, Achla Gupta, Lakshmi Devi and Schahram Akbarian of Mount Sinai; John Pappas of New York University; François Lalonde of the National Institute of Mental Health (NIMH), John Butman of the National Institutes of Health (NIH) Clinical Center; and Joan Han of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

This work was supported by grants from the National Institute on Drug Abuse (DA041208), NIMH (MH091230, MH094268, MH104341, MH117790), the National Center for Complementary and Integrative Health (AT008547), a Johns Hopkins Catalyst Award, the Brain & Behavior Research Foundation, NICHD (ZIAHD008898), an NIH Bench-to-Bedside Award and Office of the Director at NIH (S10OD016374).

Han received grant funding from Rhythm Pharmaceuticals.

Story Source:

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

Journal Reference:

1. Cyril J. Peter, Atsushi Saito, Yuto Hasegawa, Yuya Tanaka, Mohika Nagpal, Gabriel Perez, Emily Alway, Sergio Espeso-Gil, Tariq Fayyad, Chana Ratner, Aslihan Dincer, Achla Gupta, Lakshmi Devi, John G. Pappas, François M. Lalonde, John A. Butman, Joan C. Han, Schahram Akbarian, Atsushi Kamiya. **In vivo epigenetic editing of Sema6a promoter reverses transcallosal dysconnectivity caused by C11orf46/Arl14ep risk gene**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-12013-y

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7. アルツハイマー病薬候補がより広範な老化を逆転

日付:2019 年 12 月 10 日
ソース:ソーク研究所
概要:

先月ジャーナル *eLife* で発表されたソーク研究所の研究によると、2 つの実験的アルツハイマー病薬、CMS121 と J147、がアルツハイマー病のマウスモデルの記憶を改善し、脳細胞の変性を遅らせた、としているが、研究者らは、新しい研究で健康な高齢マウスを用いて、この化合物が老化中に発生する脳細胞の損傷をブロックし特定の分子レベルを若い脳で見られるレベルに戻すことで老化を遅らせる方法を示している。
ソークの細胞神経生物学研究所の部長である Maher と David Schubert は、以前、薬効のある植物化合物のバリアントである CMS121 と J147 を開発した。新しい研究では、異常に早く老化する系統のマウスを用いて、ヒトの中年後期に相当する 9 ヶ月齢から CMS121 または J147 を与え、4 か月後、動物の記憶と行動をテストし、脳内の遺伝マーカーと分子マーカーを分析。薬物候補のいずれかを与えられた動物は、治療を受けなかったマウスよりも記憶テストで優れた性能を示しただけでなく、脳は細胞レベルと分子レベルで違いを示した。特に、ミトコンドリアと呼ばれる細胞のエネルギー生成構造に関連する遺伝子の発現は、加齢とともに CMS121 と J147 によって保存された、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://eurekalert.org/pub_releases/2019-12/si-adc121019.php

NEWS RELEASE 10-DEC-2019

Alzheimer's drug candidates reverse broader aging, study shows

Salk researchers show how two experimental Alzheimer's drugs protect the brains of mice from other aspects of aging

SALK INSTITUTE

LA JOLLA--(December 10, 2019) In mouse models of Alzheimer's disease, the investigational drug candidates known as CMS121 and J147 improve memory and slow the degeneration of brain cells. Now, Salk researchers have shown how these compounds can also slow aging in healthy older mice, blocking the damage to brain cells that normally occurs during aging and restoring the levels of specific molecules to those seen in younger brains.

The research, published last month in the journal *eLife*, suggests that the drug candidates may be useful for treating a broader array of conditions and points out a new pathway that links normal aging to Alzheimer's disease.

"This study further validated these two compounds not only as Alzheimer's drug candidates but also as potentially more widely useful for their anti-aging effects," says Pamela Maher, a senior staff scientist at Salk and a co-corresponding author of the new paper.

Old age is the biggest risk factor for Alzheimer's disease--above the age of 65, a person's risk of developing the disease doubles about every five years. However, at a molecular level, scientists aren't sure what occurs in the brain with aging that contributes to Alzheimer's.

"The contribution of old age-associated detrimental processes to the disease has been largely neglected in Alzheimer's disease drug discovery," says Antonio Currais, a Salk staff scientist and first author of the new paper.

Maher and David Schubert, the head of Salk's Cellular Neurobiology Lab, previously developed CMS121 and J147, variants of plant compounds with medicinal properties. Both compounds tested positive for their ability to keep neurons alive when exposed to cellular forms of stress related to aging and Alzheimer's disease. Since then, the researchers have used the drug candidates to treat Alzheimer's in animal models of the disease. But experiments revealing exactly how the compounds work suggested that they were targeting molecular pathways also known to be important in longevity and aging.

In the new research, Maher, Currais and their colleagues turned to a strain of mice that ages unusually fast. A subset of these mice was given CMS121 or J147 beginning at nine months old--the equivalent of late middle age in humans. After four months, the team tested the memory and behavior of the animals and analyzed genetic and molecular markers in their brains.

Not only did the animals given either of the drug candidates perform better on memory tests than mice that hadn't received any treatment, but their brains showed differences at the cellular and molecular levels. In particular, expression of genes associated with the cell's energy-generating structures called mitochondria was preserved by CMS121 and J147 with aging.

"The bottom line was that these two compounds prevent molecular changes that are associated with aging," says Maher.

More detailed experiments showed that both drugs affected mitochondria by increasing levels of the chemical acetyl-coenzyme A (acetyl-coA). In isolated brain cells, when the researchers blocked an enzyme that normally breaks down acetyl-CoA, or when they added extra amounts of an acetyl-coA precursor, they saw the same beneficial effect on mitochondria and energy generation. The brain cells became protected against the normal molecular changes associated with aging.

"There was already some data from human studies that the function of mitochondria is negatively impacted in aging and that it's worse in the context of Alzheimer's," says Maher. "This helps solidify that link."

Maher and Currais are planning future experiments to test the effects of CMS121 and J147 on how other organs age. They also hope to use the new results to inform the development of new Alzheimer's drugs; targeting other molecules in the acetyl-coA pathway may help treat the disease, they hypothesize.

"We are now using a variety of animal models to investigate how this neuroprotective pathway regulates specific molecular aspects of mitochondrial biology, and their effects on aging and Alzheimer's," says Currais.

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Other researchers on the study were Ling Huang, Joshua Goldberg, Gamze Ates, António Pinto-Duarte, Maxim Shokhirev and David Schubert of the Salk Institute, and Michael Petrascheck of The Scripps Research Institute. The work was supported by grants from the National Institutes of Health, the Glenn Foundation for Medical Research, the Shiley Foundation and the Edward N. and Della L. Thome Memorial Foundation.

David Schubert is an unpaid advisor for Abrexa Pharmaceuticals, a company working on the development of J147 for Alzheimer's therapy. The Salk Institute holds the patents for CMS121 and J147.

About the Salk Institute for Biological Studies: Every cure has a starting point. The Salk Institute embodies Jonas Salk's mission to dare to make dreams into reality. Its internationally renowned and award-winning scientists explore the very foundations of life, seeking new understandings in neuroscience, genetics, immunology, plant biology and more. The Institute is an independent nonprofit organization and architectural landmark: small by choice, intimate by nature and fearless in the face of any challenge. Be it cancer or Alzheimer's, aging or diabetes, Salk is where cures begin. Learn more at: salk.edu.

8. 植物が豊富な食餌がマウスを植物媒介感染から保護

日付:2019 年 12 月 23 日
ソース:UT サウスウェスタン医療センター
概要:

植物が豊富な食餌を与えられたマウスは、病原体、例えば現在調査中のロメインレタスに関連する広範に発生した大腸菌のような病原体から胃腸（GI）感染の影響を受け難い、とUT Southwestern 医療センターの研究者らが報告している。
EHEC として知られる大腸菌の株は、血性下痢や嘔吐などの症状を伴い、結腸を衰弱させ時に致命的な炎症を引き起こし、毎年世界中で食物媒介性疾患発生の原因となっている。
今週 *Nature Microbiology* 誌に掲載されている EHEC のマウスモデルに関する研究によると、植物が豊富な食事には、多くの果物や野菜に見られるゲル状物質であるペクチンが多く含まれており、ペクチンが腸内微生物によってガラクツロン酸に消化され、EHEC の病原性を阻害できる、としている。
この研究では、マウスは感染に耐える約 1 週間ペクチンを与えられた。柑橘類の皮から5%の余分なペクチンを含む食事を与えられた 6 匹のマウスの結腸と典型的な食事の 4 匹のマウスを比較すると、研究者はペクチンを食べるマウスの感染率がはるかに低いことを発見した。マウスの腸内の細菌の量は、毎日の便検査と、実験終了時の盲腸と呼ばれる小腸と大腸の接合部のポーチ内の細菌の量の分析によって測定された。研究者らは、ペクチンを含む食事のマウスには盲腸に約 10,000 個のバクテリアがいるのに対し、典型的な食事では 100 万個のバクテリアがいることを発見。5%のペクチンレベルは病原体がその病原性レパートリーを活性化するのを妨げるように見えると付け加えている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/12/191223122851.htm

Plant-rich diet protects mice against foodborne infection

Date:

December 23, 2019

Source:

UT Southwestern Medical Center

Summary:

Mice fed a plant-rich diet are less susceptible to gastrointestinal (GI) infection from a pathogen such as the one currently under investigation for a widespread E. coli outbreak tied to romaine lettuce, UT Southwestern researchers report.

FULL STORY

Mice fed a plant-rich diet are less susceptible to gastrointestinal (GI) infection from a pathogen such as the one currently under investigation for a widespread *E. coli* outbreak tied to romaine lettuce, UT Southwestern researchers report. A strain of *E. coli* known as EHEC, which causes debilitating and potentially deadly inflammation in the colon with symptoms such as bloody diarrhea and vomiting, is implicated in several foodborne outbreaks worldwide each year.

"There has been a lot of hearsay about whether a plant-based diet is better for intestinal health than a typical Western diet, which is higher in oils and protein but relatively low in fruits and vegetables," says Vanessa Sperandio, Ph.D., professor of microbiology and biochemistry at UT Southwestern. "So we decided to test it."

Her study on a mouse model of EHEC is published this week in *Nature Microbiology*.

"Plant-rich diets are high in pectin, a gel-like substance found in many fruits and vegetables. Pectin is digested by the gut microbiota into galacturonic acid, which we find can inhibit the virulence of EHEC," she adds.

"This is relevant to public health because EHEC outbreaks lead to hemorrhagic colitis, which is debilitating and sometimes causes death, particularly in the very young and the elderly," she says.

Intestinal pathogens like EHEC sense the complex chemistry inside the GI tract to compete with the gut's resident microbiota to establish a foothold, Sperandio says. Over centuries, the pathogens have developed different strategies to compete against the so-called good, or commensal, microbes that normally line the gut.

Those commensals include harmless strains of *E. coli* living in the colons of humans and other mammals, where they help the host's normal digestion process, she adds. The word commensal means "eating at the same table" and that is what the symbiotic bacteria that make up the gut's microbiota do.

The commensals that line the gut present a significant barrier to intestinal pathogens, Sperandio explains. EHEC and similar gram-negative bugs overcome that barrier by deploying a secretion system called T3SS.

T3SSs act like molecular syringes to inject a mix of virulence proteins into the cells lining the host's colon, setting off inflammation and symptoms of infection. Because mice are unaffected by EHEC, researchers use a similar pathogen, Citrobacter rodentium, in mouse studies, Sperandio explains.

"Our study finds first that the good *E. coli* and the pathogenic ones like EHEC use different sugars as nutrients," she says, adding that the two types of *E. coli* may have evolved to avoid competing for the same energy sources. "Second, we find that dietary pectin protects against the pathway the pathogenic EHEC uses to become more virulent."

Another type of commensal gut bacteria breaks down dietary pectin from fruit and vegetables, creating galacturonic acid, a sugar acid that the EHEC and C. rodentium use in two ways. Initially, the pathogen uses that sugar acid as an energy source to expand in the gut, Sperandio says.

"Once the sugar acid becomes depleted, the pathogen changes its survival strategy, almost like flipping a switch," she says. Instead of using the galacturonic acid for nourishment, the infectious bacteria employs it in a signaling pathway that increases the EHEC's and similar bacteria's virulence using the syringe-like T3SS.

In the study, mice fed pectin for about a week withstood infection. Comparing the colons of six mice fed a chow diet with 5 percent extra pectin from citrus peel with four mice on a typical diet, the researchers found a much lower rate of infection in the pectin-eating mice, Sperandio says.

The amount of bacteria in the mouse gut was measured by daily stool checks and by analysis of the amount of bacteria in a pouch at the juncture of the small and large intestines, called the cecum, at the experiment's end.

The researchers found that mice on the pectin-enriched chow had about 10,000 bacteria in the cecum compared to 1 million bacteria in mice on the typical diet. The pectin group also had fewer symptoms, she says, adding that a pectin level of 5 percent appears to prevent the pathogen from activating its virulence repertoire.

She stresses that the research is one step in a journey to define the molecular mechanisms that govern how the commensal species in the gut impact the virulence of intestinal pathogens.

"This is not translatable to humans yet. We hope a better understanding of how intestinal disease develops will lead to strategies to reduce the incidence or, at least, the symptoms caused by these gram-negative pathogens, possibly through new vaccines or drugs," she says.

Story Source:

Materials provided by **UT Southwestern Medical Center**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Angel G. Jimenez, Melissa Ellermann, Wade Abbott, Vanessa Sperandio. **Diet-derived galacturonic acid regulates virulence and intestinal colonization in enterohaemorrhagic Escherichia coli and Citrobacter rodentium**. *Nature Microbiology*, 2019; DOI: 10.1038/s41564-019-0641-0

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9. クマから学ぶ

日付:2019 年 12 月 30 日
ソース:ヘルムホルツ協会マックスデルブリュック分子医学センター
概要:

グリズリーベアは冬眠に何カ月も費やすが、運動不足によって筋肉の質や量が低下する、ということはないとされている。ベルリンのマックスデルブリュック分子医学センター（MDC）の神経筋および心臓血管細胞生物学グループの責任者である Michael Gotthardt 教授率いる研究チームは、*Scientific Reports* 誌で、この筋肉機能を維持する仕組みについて報告している。また、この戦略はヒトの筋肉委縮防止にも役立つとしている。
冬眠期間中、クマの代謝と心拍数は急速に低下する。尿も糞も排泄しない。血液中の窒素量が劇的に増加し、インスリン抵抗性になる。もしヒトなら、健康な状態でこの冬眠フェーズを生き残ることはほとんどできない。血栓症または心理的変化に対処する必要があるだろうし、とりわけ、筋肉はこの長期間の不使用に退化してしまう。
クマのこのトリックを理解するために、研究者チームは、冬眠中および冬眠していない時期両方のグリズリーベアの筋肉サンプルをワシントン州立大学から譲り受けて調べた。次のステップで、彼らは、調査結果を人間、マウス、線虫の観察と比較した。その結果、冬眠中のクマの筋肉にアミノ酸代謝に強く影響するタンパク質を発見、その筋肉細胞には特定の非必須アミノ酸（NEAA）がより多く含まれていた。
アミノ酸が必要な場所に届くためには、筋肉がこれらのアミノ酸自体を生成することが重要である。従って、筋肉萎縮を示すヒトに対する治療の出発点は、適切な薬剤で対応できる代謝経路を活性化することによって、ヒトの筋肉が NEAA を生成するよう誘導することではないか、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/2019/12/191230104801.htm

Learning from the bears

Date:

December 30, 2019

Source:

Max Delbrück Center for Molecular Medicine in the Helmholtz Association

Summary:

Grizzly bears spend many months in hibernation, but their muscles do not suffer from the lack of movement. Researchers report on how they manage to do this. The grizzly bears' strategy could help prevent muscle atrophy in humans as well.

FULL STORY

Grizzly bears spend many months in hibernation, but their muscles do not suffer from the lack of movement. In the journal *Scientific Reports*, a team led by Michael Gotthardt reports on how they manage to do this. The grizzly bears' strategy could help prevent muscle atrophy in humans as well.

A grizzly bear only knows three seasons during the year. Its time of activity starts between March and May. Around September the bear begins to eat large quantities of food. And sometime between November and January, it falls into hibernation. From a physiological point of view, this is the strangest time of all. The bear's metabolism and heart rate drop rapidly. It excretes neither urine nor feces. The amount of nitrogen in the blood increases drastically and the bear becomes resistant to the hormone insulin.

A person could hardly survive this four-month phase in a healthy state. Afterwards, he or she would most likely have to cope with thromboses or psychological changes. Above all, the muscles would suffer from this prolonged period of disuse. Anyone who has ever had an arm or leg in a cast for a few weeks or has had to lie in bed for a long time due to an illness has probably experienced this.

A little sluggish, but otherwise fine

Not so the grizzly bear. In the spring, the bear wakes up from hibernation, perhaps still a bit sluggish at first, but otherwise well. Many scientists have long been interested in the bear's strategies for adapting to its three seasons.

A team led by Professor Michael Gotthardt, head of the Neuromuscular and Cardiovascular Cell Biology group at the Max Delbrueck Center for Molecular Medicine (MDC) in Berlin, has now investigated how the bear's muscles manage to survive hibernation virtually unharmed. The scientists from Berlin, Greifswald and the United States were particularly interested in the question of which genes in the bear's muscle cells are transcribed and converted into proteins, and what effect this has on the cells.

Understanding and copying the tricks of nature

"Muscle atrophy is a real human problem that occurs in many circumstances. We are still not very good at preventing it," says the lead author of the study, Dr. Douaa Mugahid, once a member of Gotthardt's research group and now a postdoctoral researcher in the laboratory of Professor Marc Kirschner of the Department of Systems Biology at Harvard Medical School in Boston.

"For me, the beauty of our work was to learn how nature has perfected a way to maintain muscle functions under the difficult conditions of hibernation," says Mugahid. "If we can better understand these strategies, we will be able to develop novel and non-intuitive methods to better prevent and treat muscle atrophy in patients."

Gene sequencing and mass spectrometry

To understand the bears' tricks, the team led by Mugahid and Gotthardt examined muscle samples from grizzly bears both during and between the times of hibernation, which they had received from Washington State University. "By combining cutting-edge sequencing techniques with mass spectrometry, we wanted to determine which genes and proteins are upregulated or shut down both during and between the times of hibernation," explains Gotthardt.

"This task proved to be tricky -- because neither the full genome nor the proteome, i.e., the totality of all proteins of the grizzly bear, were known," says the MDC scientist. In a further step, he and his team compared the findings with observations of humans, mice and nematode worms.

Non-essential amino acids allowed muscle cells to grow

As the researchers reported in the journal "*Scientific Reports*," they found proteins in their experiments that strongly influence a bear's amino acid metabolism during hibernation. As a result, its muscle cells contain higher amounts of certain non-essential amino acids (NEAAs).

"In experiments with isolated muscle cells of humans and mice that exhibit muscle atrophy, cell growth could also be stimulated by NEAAs," says Gotthardt, adding that "it is known, however, from earlier clinical studies that the administration of amino acids in the form of pills or powders is not enough to prevent muscle atrophy in elderly or bedridden people."

"Obviously, it is important for the muscle to produce these amino acids itself -- otherwise the amino acids might not reach the places where they are needed," speculates the MDC scientist. A therapeutic starting point, he says, could be the attempt to induce the human muscle to produce NEAAs itself by activating corresponding metabolic pathways with suitable agents during longer rest periods.

Tissue samples from bedridden patients

In order to find out which signaling pathways need to be activated in the muscle, Gotthardt and his team compared the activity of genes in grizzly bears, humans and mice. The required data came from elderly or bedridden patients and from mice suffering from muscle atrophy -- for example, as a result of reduced movement after the application of a plaster cast. "We wanted to find out which genes are regulated differently between animals that hibernate and those that do not," explains Gotthardt.

However, the scientists came across a whole series of such genes. To narrow down the possible candidates that could prove to be a starting point for muscle atrophy therapy, the team subsequently carried out experiments with nematode worms. "In worms, individual genes can be deactivated relatively easily and one can quickly see what effects this has on muscle growth," explains Gotthardt.

A gene for circadian rhythms

With the help of these experiments, his team has now found a handful of genes whose influence they hope to further investigate in future experiments with mice. These include the genes Pdk4 and Serpinf1, which are involved in glucose and amino acid metabolism, and the gene Rora, which contributes to the development of circadian rhythms. "We will now examine the effects of deactivating these genes," says Gotthardt. "After all, they are only suitable as therapeutic targets if there are either limited side effects or none at all."

Story Source:

Materials provided by **Max Delbrück Center for Molecular Medicine in the Helmholtz Association**. *Note: Content may be edited for style and length.*

Journal Reference:

1. D. A. Mugahid, T. G. Sengul, X. You, Y. Wang, L. Steil, N. Bergmann, M. H. Radke, A. Ofenbauer, M. Gesell-Salazar, A. Balogh, S. Kempa, B. Tursun, C. T. Robbins, U. Völker, W. Chen, L. Nelson, M. Gotthardt. **Proteomic and Transcriptomic Changes in Hibernating Grizzly Bears Reveal Metabolic and Signaling Pathways that Protect against Muscle Atrophy**. *Scientific Reports*, 2019; 9 (1) DOI: 10.1038/s41598-019-56007-8

Cite This Page:

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Max Delbrück Center for Molecular Medicine in the Helmholtz Association. "Learning from the bears." ScienceDaily. ScienceDaily, 30 December 2019. <www.sciencedaily.com/releases/2019/12/191230104801.htm>.