BIO NEWS

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目次

2019 年 3 月のニュース

＝研究編（詳細については各番号をクリックして下さい)＝

2019 年 3 月のニュース

＝企業関連ニュース他＝

・「タウリン」、難病の治療薬に -川崎医大（2/28）

・がん細胞を攻撃する「キラーT 細胞」 働きが悪くなる仕組みを解明 -慶応大（2/28）

・大統領元弁護士 Cohen 氏、大統領/米政府との接触役を Novartis に求められたと証言（2/28）

米国大統領 Donald Trump（ドナルド・トランプ）氏の元弁護士 Michael Cohen 氏へ前 CEO・Joe Jimenez 氏の頃の Novartis が 120 万ドルを払った契約の動機に大統領を含む米国政府との接触役の要求があったと Cohen 氏が議会で証言。

・乳癌薬でごたごたの Immunomedics の CEO が辞任（2/28）

先月末、乳癌薬 Sacituzumab Govitecan（IMMU-132）の米国 FDA 承認を逃し、改ざんを含む工場の欠陥を指摘する FDA 査察結果が今月に入って明らかになった Immunomedics の CEO・Michael Pehl 氏が私用で同社を辞任し欧州に引越し。

・Bristol-Myers Squibb の大株主が Celgene 買収不支持（2/28）

・米国の HIV 感染数の減少は 2013 年に伸び止まり、以降年間 39,000 人で横ばい（3/1）

・投資会社 Actares が Novartis の細胞/遺伝子治療の高価な値付けを疑問視している（3/1）

・Endo、無菌注射剤の Somerset Therapeutics を買う合意を破棄（3/1）

・変異の穴埋め遺伝子に学んで薬を開発する新会社 Maze Therapeutics が発足（3/1）

・ヒトの臓器もった動物の出産、解禁 文科省が指針改定（3/4）

・iPS から角膜、世界初の移植へ＝阪大の臨床研究を大筋了承－厚労省（3/5）

・Lilly がインスリン Humalog の同一成分半額品を米国で販売（3/5）

薬価への風当たりが米国で強くなっていることを背景にして、昨年売り上げ 30 億ドルの Eli Lilly のインスリン注射剤 Humalog の半額の同一成分品 insulin lispro を米国で発売。

・非 CRISPR/Cas9 ゲノム編集治療の Precision、1 億ドルの IPO 調達を計画（3/5）

・Biogen、網膜患遺伝子治療のイギリスの Nightstar を 8 億ドルで買収（3/5）

・莫大なオピオイド訴訟を何とかすべく Purdue Pharma が破産を検討/ロイター（3/5）

・英国の男性、ベルリン患者に続いて 2 人目、長期 HIV 寛解達成（3/6）

・Gilead の癌研究開発長 Alessandro Riva 氏が退任してインドの Glenmark がニュージャージー州に設立する新会社を率いる（3/7）
・iPS、拒絶反応少なくゲノム編集、京都大開発（3/8）
・Turing Pharmaceuticals での薬値上げで米国一の嫌われ者となった Martin Shkreli 氏は収監されても活躍（3/8）

Turing Pharmaceuticals で駆虫薬 Daraprim（pyrimethamine）を 50 倍も値上げしてアメリカ人が最も嫌う男性になった Martin Shkreli 氏は、別会社 Retrophin に居た時の罪でニュージャージー州 Fort Dix に収監されているが、Turing が 2 度社名変更して今は Phoenixus AG になった会社に電話をして今も采配を振るっている模様。ウォールストリートジャーナル（WSJ）によると、その為 FBI が Shkreli 氏と Phoenixus の契約を捜査中。

・マンモスの細胞核動いた　化石から抽出、分裂直前の動き　-近畿大（3/11）
・IBM、アルツハイマー病が生じ易い脳状態を言い当てる血液検査開発（3/12）
・塩野義のインフル治療薬ゾフルーザ、未使用患者から耐性ウィルス（3/12）
・富士フィルム、Biogen のデンマーク生物薬大規模製造工場を買う～従業員 800 人の雇用維持（3/13）
・時期米国 FDA を米国立癌研究所（NCI）長の Norman Sharpless 氏が率いる（3/13）
・錠剤サイズの「飲む体温計」、動物実験に成功　レモンと同じ原理で胃酸発電　-東北大（3/13）
・ハーバードの創薬発明から臨床試験までの橋渡しを Deerfield が 1 億ドルで支援（3/14）
・裏口入学で娘を有名大学にねじ込んだとされる投資会社 Hercules Capital の CEO 兼会長が辞任（3/14）

Yale、Georgetown、Stanford、UCLA などの有名大学に不正な金を払って子供を入学させたとして逮捕された親の一人 Manuel Henriquez 氏が Hercules Capital の CEO 兼会長を辞任。ただ、Henriquez 氏は同社と完全に縁を切るわけではなく、取締役とアドバイザーを続ける。
Henriquez 氏は 2017 年に 800 万ドル超を稼ぎ、娘を Georgetown 大学に入れるのには 40 万ドル超を払ったとされている。
関連記事：https://headlines.yahoo.co.jp/hl?a=20190313-00000003-jij_afp-int

・Biogen に続いてインド Sun Pharma も低分子化合物同定を中国の HitGen に依頼（3/15）
・去年の売り上げ上位 10 以内の薬剤～EvaluatePharma が集計（3/17）

AbbVie の Humira（adalimumab）の去年の売り上げは 199 億ドルで引き続き最も売れた薬だった。次は Bristol-Myers Squibb（BMS）が買う予定の Celgene の REVLIMID

（lenalidomide）で 97 億ドル、3 位は Merck & Co の用途拡大が順調な抗 PD-1/L1 薬 Keytruda（pembrolizumab）で 72 億ドルだった。

・Samsung BioLogics の会計不正疑いに関連して韓国検察が証券取引所を強制捜査（3/17）

・常識を覆す、脊椎損傷治療に光明 自分の細胞で神経再生 -札幌医大（3/18）

・ゲノム編集食品、日本で夏にも流通（3/18）

参照：研究編 10（以下のリンクへ）

遺伝子組み換え食品は安全である、日本のパネルが結論

・卵の摂取量が多いと心血管疾患をより生じやすくなる -米研究（3/19）

・人間の「第六感」 磁気を感じる能力発見 -東大＆カリフォルニア工科大など研究チーム（3/19）

・Aimmune のピーナツアレルギー薬の承認申請、FDA が受理（3/19）

・毎年米国小児 283,000 人が運動や遊びで外傷性脳損傷を被って救急科を受診（3/20）

・Biogen/Eisai、途中解析の無効判定でアルツハイマー病薬 aducanumab の Ph3 中止（3/22）

主要目標を達成できそうにないとの途中解析結果を受けて Biogen/Eisai（エーザイ）のアルツハイマー病薬 aducanumab 第 3 相試験 2 つ・ENGAGE と EMERGE が中止となった。大きく期待されていただけに、これを受けて Biogen の行く末に不安定要素も。

参照：研究編 9（以下のリンクへ）

有力とされた「アルツハイマー病治療薬」の失敗 苦戦が続く認知症薬の開発、今後の見通しは

・HIV の新規感染のおよそ 8 割は HIV 感染無自覚か無治療の人由来（3/22）

・大麻常用者は精神症状を 3 倍発症しやすい（3/22）

大麻常用者は精神症状を 3 倍発症しやいことが示された。

テトラヒドロカンナビノール（THC）含量 10%以上の強力大麻製品常用の場合、精神症状は更に高く 5 倍近く発症しやすくなる。強力大麻製品を禁止にすれば今回調べた欧州/ブラジル 11 地区全体の精神症状初発の 12%を防げると推定された。また、ロンドンとアムステルダムではその効果はより高く、強力大麻禁止で精神症状初発をそれぞれ 30%と 50%防げる、としている。

・自閉症予防対策の一つとして、妊婦/乳児に農薬が及ばないようにすべき（3/22）

・Biogen/Eisai、Ph3 中止 aducanumab とは別のアルツハイマー病治療抗 Aβ 抗体の Ph3 開始（3/23）

Biogen と Eisai の共同開発抗 Aβ 抗体 aducanumab のアルツハイマー病 Ph3 試験中止が明らかになった翌日 3 月 22 日、別の両社共同開発抗 Aβ 抗体 BAN2401 のアルツハイマー病患者 1,566 人参加プラセボ対象第 3 相試験（Clarity AD/Study 301）開始が発表された。

・流産リスクが最も低い年齢は 27 歳、30 歳を超えると急激に増加 -ノルウェー研究（3/23)

・株価低迷の Allergan、次の経営体制で CEO の Brent Saunders 氏が兼任している会長職の独立を約束（3/24)

続き：次の体制時に会長職を独立させるとの Allergan の意向にヘッジファンド Appaloosa は納得せず（3/26)

・2019 年発売の 7 つの薬が 2023 年までに年間売り上げ 10 億ドルに達する（3/25)

情報解析の Clarivate Analytics によると、今年 2019 年に世に出る薬の 7 つが 2023 年までに年間売り上げ 10 億ドルの大台（ブロックバスター）に達するとの予想。

以下が Clarivate Analytics が予想する今年発売のブロックバスター薬候補。（ ）内は 2023 年の売り上げ予想額。

- ・AbbVie の関節リウマチ（RA）治療 JAK1 阻害剤 Upadacitinib（22 億ドル）
- ・Novartis の脊髄性筋萎縮症（SMA）遺伝子治療 ZOLGENSMA（20 億 9,000 ドル）
- ・AstraZeneca の腎性貧血薬 roxadustat（19 億 7,000 ドル）
- ・Alexion の発作性夜間ヘモグロビン尿症（PNH）治療補体阻害剤 ULTOMIRIS（19 億 3,000 ドル）
- ・Boehringer Ingelheim の乾癬治療 IL-23 p19 抗体 Skyrizi（17 億 4,000 ドル）
- ・Aimmune のピーナツアレルギー治療 AR101（11 億 7,000 ドル）
- ・bluebird bio の β サラセミア遺伝子治療 LentiGlobin（11 億 2,000 ドル）

・J&J、4 年前 17 億 5,000 万ドルで買った Alios の RSV 薬開発中止（3/25)

・世界の 10-24 歳青少年の健康状態～4 人に 1 人が貧血、5 人に 1 人が太り過ぎ/肥満（3/25)

・歯周炎で壊れた骨の再生、患者自身の幹細胞で…順大など臨床研究を開始（3/25)

・iPS で網膜治療、理研チームが申請へ…サルで成果、臨床目指す（3/25)

・大塚製薬の子会社 Avanir Pharmaceuticals、アルツハイマー型認知症患者不穏の Ph3 で 2 用量のうち 1 つが有意効果示す（3/26)

・Thermo Fisher、ウイルスベクター製造会社 Brammer Bio を 17 億ドルで買収（3/26)

・凍結した精巣使い出産、サルで成功、不妊治療に光明 -米国研究（3/26)

・京大のグループが ALS の治験開始 がん治療薬から iPS 創薬（3/27)

目次に戻る

1．老齢マウスの脳内で幹細胞の活性化に成功

2019 年 3 月 1 日

ルクセンブルク大学のルクセンブルクシステムバイオメディシンセンター （LCSB）およびドイツ癌研究センター（DKFZ）の科学者らは、老齢マウスの脳内の幹細胞を活性化することに成功した。この活性化された幹細胞は、老齢マウスの脳内の障害や罹患領域の再生を改善した。
臓器を構成する全ての細胞は幹細胞に由来する。それらは分裂し、そして生じる細胞は特定の組織細胞に発達し、脳、肺または骨髄を形成する。しかし、年齢と共に、それらの幹細胞は増殖する能力を失い、それらの多くは恒久的な静止状態に陥る。
そこで、幹細胞の挙動に関するできるだけ正確な計算モデルを作成するために、LCSB の Computational Biology Group は新しいアプローチを適用し、新しい計算モデルを開発した。
老齢マウスの脳内の幹細胞の大部分がなぜ静止状態のままであるのかは、以前は分からなかったが、LCSB の研究者らは、この計算モデルから、老齢マウスにおいて神経幹細胞を不活性に保ち、細胞分化に重要な Wnt 経路を遮断することによって増殖を妨げる sFRP5 と呼ばれる分子を同定した。この sFRP5 の作用を中和すると、静止状態の幹細胞がより活発に増殖し始めた、としている。
彼らはこのアプローチが再生医療に新たな推進力をもたらし、幹細胞療法の開発を促進することを期待している。この研究結果は、3 月 1 日の *Cell* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2019/03/190301101812.htm

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Scientists rejuvenate stem cells in the aging brain of mice

Regenerative medicine

Date:

March 1, 2019

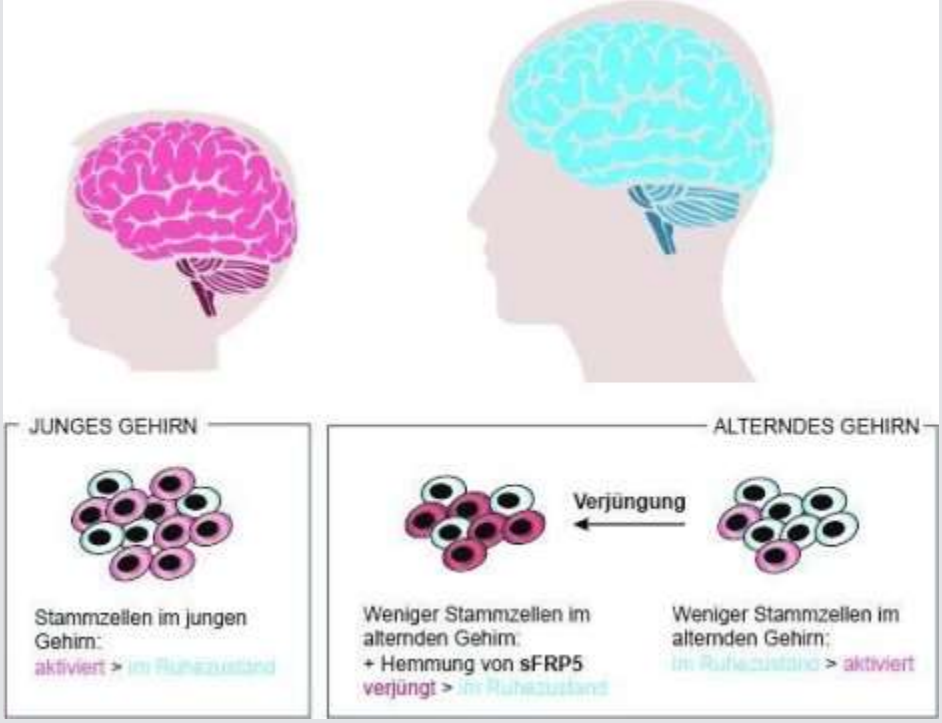
Source:

University of Luxembourg

Summary:

Scientists have been able to rejuvenate stem cells in the brain of aging mice. The revitalized stem cells improve the regeneration of injured or diseased areas in the brain of old mice. The researchers expect that their approach will provide fresh impetus in regenerative medicine and facilitate the development of stem cell therapies.

FULL STORY



Scientists from the Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg and from the German Cancer Research Center (DKFZ) have been able to rejuvenate stem cells in the brain of aging mice. The revitalized stem cells improve the regeneration of injured

or diseased areas in the brain of old mice. The researchers expect that their approach will provide fresh impetus in regenerative medicine and facilitate the development of stem cell therapies.

Credit: University of Luxembourg

Scientists from the Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg and from the German Cancer Research Center (DKFZ) have been able to rejuvenate stem cells in the brain of aging mice. The revitalised stem cells improve the regeneration of injured or diseased areas in the brain of old mice. The researchers expect that their approach will provide fresh impetus in regenerative medicine and facilitate the development of stem cell therapies.

Their results were published today in the journal *Cell*. All cells making up our organs originate from stem cells. They divide and the resulting cells develop into specific tissue cells, forming the brain, lungs or bone marrow. With age, however, the stem cells of living organisms lose their ability to proliferate. Many of them lapse into a permanent state of quiescence.

In order to create as accurate as possible computational models of stem cell behaviour, the LCSB's Computational Biology Group led by Prof. Antonio del Sol applied a novel approach. "Stem cells live in a niche where they constantly interact with other cells and extra-cellular components. It is extremely difficult to model such a plethora of complex molecular interactions on the computer. So we shifted perspective. We stopped thinking about what external factors were affecting the stem cells, and started thinking about what the internal state of a stem cell would be like in its precisely defined niche."

The novel approach led to in a new computational model developed by Dr. Srikanth Ravichandran of the Computational Biology Group: "Our model can determine which proteins are responsible for the functional state of a given stem cell in its niche -- meaning whether it will divide or remain in a state of quiescence. Our model relies on the information about which genes are being transcribed. Modern cell biology technologies enable profiling of gene expression at single cell resolution."

It was previously unknown why most of the stem cells in the brain of old mice remain in a state of quiescence. From their computational model, the researchers at the LCSB identified a molecule

called sFRP5 that keeps the neuronal stem cells inactive in old mice, and prevents proliferation by blocking the Wnt pathway crucial for cell differentiation.

A rejuvenation for cells

Then the long-standing expertise in neural stem cells of the collaborators at the German Cancer Research Center (DKFZ) came in: Studying stem cells first in a dish and then later directly in mice, they could experimentally validate the computational prediction. When neutralising the action of sFRP5, the quiescent stem cells did indeed start proliferating more actively. Thus, they were available again to be recruited for the regeneration processes in the aging brain. "With the deactivation of sFRP5, the cells undergo a kind of rejuvenation," del Sol says: "As a result, the ratio of active to dormant stem cells in the brain of old mice becomes almost as favourable as in young animals."

"Our results constitute an important step towards the implementation of stem cell-based therapies, for instance for neurodegenerative diseases," Antonio del Sol says. "We were able to show that, with computational models, it is possible to identify the essential features that are characteristic of a specific state of stem cells." This approach is not limited to studying the brain. It can also be used to model stem cells of other organs in the body. "The hope is that this will open avenues for regenerative medicine," says del Sol.

Story Source:

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

Journal Reference:

1. Georgios Kalamakis, Daniel Brüne, Srikanth Ravichandran, Jan Bolz, Wenqiang Fan, Frederik Ziebell, Thomas Stiehl, Francisco Catalá-Martinez, Janina Kupke, Sheng Zhao, Enric Llorens-Bobadilla, Katharina Bauer, Stefanie Limpert, Birgit Berger, Urs Christen, Peter Schmezer, Jan Philipp Mallm, Benedikt Berninger, Simon Anders, Antonio del Sol, Anna Marciniak-Czochra, Ana

Martin-Villalba. **Quiescence Modulates Stem Cell Maintenance and Regenerative Capacity in the Aging Brain**. *Cell*, 2019; DOI: 10.1016/j.cell.2019.01.040

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目次に戻る

2. TIGER マウスが神経疾患のモデルとしてデビュー

2019 年 3 月 4 日

Scientific Reports 誌に本日発表された新しい研究は、脳内の小さなメッセージ伝達者を追跡する方法を考案した。そしてこれが、怪我、感染、病気の診断と治療に役立つことが証明された。

この研究は、サウスキャロライナ州のクレムソン科学大学の研究者らによるもので、「TIGER マウス」と名付けられた輝くマウスを使って、体中の体液中に見られる情報豊富な粒子 -細胞外小胞（EV）と呼ばれる- の動きを追跡する。Transgenic Inducible Green fluorescent protein EV Receptor (TIGER -大学のマスコットが tiger であることにも繋げている？)マウスは、様々な EV の機能を理解するために機能する。EV は「メッセージ」 -短い RNA シーケンスあるいはマイクロ RNA の形で- を含み、免疫応答の誘導からニューロン形成の補助まで全てにおいて細胞間コミュニケーションのための指示役として働く。TIGER マウスを使用することによって、研究者らは EV を放出するこれらの細胞型をより容易に特定できることに期待している。

このマウスの作り方としては、研究者らは Cre-lox 組換え、カセットと呼ばれる一連の遺伝的指示をマウス胚の単一細胞に注入することによって特定の遺伝子を活性化または不活性化することができる遺伝子編集方法を使用した。また、緑色蛍光タンパク質と呼ばれるタンパク質を介して EV を緑色に発光させることができるカセットを設計し、TIGER マウスを他のユニークな酵素（Cre リコンビナーゼ）を持つマウスと交配させると、その仔マウスで緑色の蛍光が発せられる、としている。

英文記事：

https://www.sciencedaily.com/releases/2019/03/190304182133.htm

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TIGER mouse debuts as model for neurological ailments

Date:

March 4, 2019

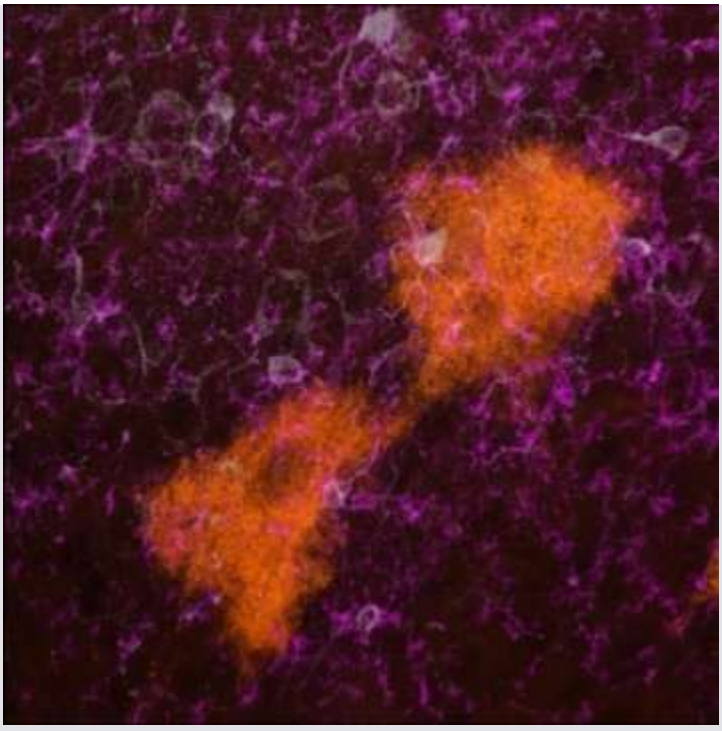
Source:

Clemson University

Summary:

The study uses a glowing mouse to track tiny message-carriers in the brain that could prove useful in diagnosing and treating injuries, infections or diseases.

FULL STORY



This is a 63X image from a TIGER mouse brain demonstrating release of CD9-GFP (orange) extracellular vesicles from astrocytes that are taken up by IBA1 (purple)/CD11b (white) neuroimmune cells called microglia.

Credit: David Feliciano / Victoria Neckles

New research published today in *Scientific Reports* has devised a way to track tiny message-carriers in the brain that could prove useful in diagnosing and treating injuries, infections or diseases.

The study, from assistant professor David Feliciano's lab in Clemson's College of Science, uses a glowing mouse -- appropriately dubbed the "TIGER mouse" -- to trace the movement of information-rich particles found in bodily fluids throughout the body, called extracellular vesicles (EVs).

The Transgenic Inducible Green fluorescent protein EV Reporter (TIGER) mouse serves as one small step for researchers toward understanding the variety of EV functions. The vesicles contain "messages" -- in the form of short RNA sequences, or microRNAs -- that act as instructions for intercellular communication in everything from inducing an immune response to assisting in neuron formation. The potential functions of EVs are endless, as the instructions doled out by the vesicles are dependent on the cells in which they originate.

By employing the TIGER mouse, the researchers hope to more easily pinpoint these cell types that release EVs.

"Up until this point, the most that someone could do is study EVs in cell lines, study them in vitro or transplant them into mice and study them that way. This way, we can study a more internal effect that EVs have in a model system because these mice are bred with a reporter system in their genes," said Victoria Neckles, a graduate student and first author on the study.

To generate the mouse, the researchers relied on Cre-lox recombination, a type of gene editing that can activate or inactivate specific genes by injecting a set of genetic instructions, called a cassette, into a single cell of a mouse embryo. Once injected, the cassette can integrate into the mouse's genome, and as the cells multiply, the cassette becomes one with the maturing mouse.

In Neckles' study, the researchers engineered a cassette that can cause EVs to glow green via a protein called green fluorescent protein. When the TIGER mouse is mated with another mouse that has a unique enzyme -- Cre recombinase -- then the green fluorescence is activated in the mice's pups. The process can become more precise by mating the TIGER mouse to a Cre mouse in which the Cre recombinase is only activated in certain cell-types, meaning only certain cells will glow in the pair's offspring while others will not. In a third case, the researchers can control when

the cells begin to glow by supplementing the pups' diet with a drug called tamoxifen, which turns on the fluorescence. While the change isn't visible to the naked eye, the florescence can be seen by photographing the mouse pups with a fluorescent scanner or an ultraviolet flashlight.

"The utility of this is that instead of having a pea soup of lots of different things, you have individual components that are labeled, and we know where they came from," Feliciano said. "The reason that's important is because it allows us to see how different cells contribute in different physiological or pathophysiological states."

Previous research in the Feliciano lab found that extracellular vesicles are released by neural stem cells and then taken up by microglia, the immune cells of the central nervous system that are the first line of defense against infection, damage or inflammation in the brain. That study signified that extracellular vesicles could potentially be engineered to direct microglia to diseased or damaged portions of the brain, where they could aid in the immune response.

With the development of the TIGER mouse, Neckles was able to uncover another cell-type that releases EVs: astrocytes, the glial cells of the brain and spinal cord that pass nutrients, maintain ion balance and repair nervous system injuries, among other functions.

"What we figured out using the mouse is that the astrocytes release EVs that help the microglia mature," Neckles said. "We don't know the precise mechanism by which this occurs, but thanks to the mouse, we can identify at least a few different sources of EVs and interpret how they function differently."

The significance of this work, Feliciano says, is to generate an "atlas" that could aid in the diagnosis and treatment of a variety of diseases.

"If you have a cell type, and you know how it is changing in any disease and how the EVs that it releases change, then you basically have an atlas -- a map of information for each vesicle for each source," Feliciano said. "So, somebody comes into the clinic, and they have a certain disease with certain symptoms. You could imagine taking their vesicles from a blood sample, and you basically have a barcode or a fingerprint that matches our known barcodes. And we could say, 'This looks like a lot of astrocyte EVs, a lot of sick EVs.' And we could diagnose disease based on that."

After five years since the study's conception, and after thoroughly vetting every piece of data to develop a transgenic mouse, Feliciano says his team is in a regrouping phase.

"Now that we've figured things out, we get to ask, 'What do we want to study the most?' We have the tool that nobody has, so what question is the most important question that we can answer and contribute to?" Feliciano said.

"The goal is to help everybody reach their goals. When everybody wins, you win. Now, other labs that study EVs can benefit from this tool," he added.

Story Source:

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

Journal Reference:

1. Victoria N. Neckles, Mary C. Morton, Jennie C. Holmberg, Aidan M. Sokolov, Timothy Nottoli, Don Liu, David M. Feliciano. **A transgenic inducible GFP extracellular-vesicle reporter (TIGER) mouse illuminates neonatal cortical astrocytes as a source of immunomodulatory extracellular vesicles**. *Scientific Reports*, 2019; 9 (1) DOI: 10.1038/s41598-019-39679-0

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- Chicago

Clemson University. "TIGER mouse debuts as model for neurological ailments." ScienceDaily. ScienceDaily, 4 March 2019. <www.sciencedaily.com/releases/2019/03/190304182133.htm>.

目次に戻る

3. ヒトを肥満にさせる遺伝的要因

2019 年 3 月 6 日

肥満は米国だけでなく世界中の主要公衆衛生問題であり、推定で 6 億 5,000 万人が肥満に苦しんでいる。この益々悪化する状態の最大の課題の 1 つは、そもそもなぜヒトは肥満になるのか、なぜ一部の人が他の人よりも肥満に弱いのか、を導き出すことだ。
ロックフェラー大学の科学者らは、全ての肥満症例のうち少なくとも 10 パーセントで役割を果たす可能性がある遺伝的メカニズムを特定、この発見は治療可能な人を特定する助けになるとしている。又、今週 *Nature Medicine* 誌に発表されたこの報告は、脂肪細胞で産生されて空腹をコントロールするホルモンであるレプチンの生物学に新たな光を投げかけるものである。
ロックフェラー大学の科学者によって 25 年前に発見されたレプチンは、その構造と機能を探求する何千もの研究の主題となっている。レプチンをコードする遺伝子は、脂肪細胞内で遺伝子を作動させる DNA 配列および調節因子によって調節され、作られるレプチンの量を制御する。今回研究者らは、長いノンコーディング RNA、すなわち IncRNA と呼ばれるこれらの規制要因に焦点を当てた。この特定の IncRNA を含まないマウスでは高脂肪食で肥満化し、脂肪細胞のレプチン生産量は少なかった。これら低レプチンマウスがレプチン注射を受けた場合、これらのマウスの体重が減少した。このレプチンホルモン療法が本質的に肥満を治癒した、としている。

英文記事：
https://www.sciencedaily.com/releases/2019/03/190306125341.htm

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Scientists identify genetic factors that may cause some people to become obese

Date:

March 6, 2019

Source:

Rockefeller University

Summary:

New research on leptin, a hormone that regulates appetite, reveals a previously unknown mechanism that may be responsible for at least 10 percent of obesity cases. The findings could help identify individuals with treatable forms of the condition.

FULL STORY

Obesity is a major public-health problem in the United States and around the world, with an estimated 650 million people suffering from the condition. One of the biggest challenges of this ever-worsening condition is figuring out why people become obese in the first place, and why some people are more vulnerable to obesity than others.

Now, scientists at The Rockefeller University and collaborators have identified a genetic mechanism that may play a role in at least 10 percent of all obesity cases. The findings, which could help identify individuals with treatable forms of the condition, shed new light on the biology of the hormone leptin, which is produced in fat cells and controls hunger. The amount of leptin in the bloodstream, and how the brain responds to it, help determine how much weight a person will gain.

The scientists report this week in *Nature Medicine* that, in mice, alterations in the cellular machinery that regulates leptin production can lead to a form of obesity treatable with leptin therapy. Evidence from human genetics studies further suggests that a similar mechanism may contribute to obesity in a subset of patients.

How leptin is finetuned

Discovered 25 years ago by Rockefeller scientist Jeffrey M. Friedman, the Marilyn M. Simpson Professor, leptin has been the subject of many thousands of studies exploring its structure and function. "We've learned a lot about leptin," says Olof Dallner, research associate and lead author

of the new report, "but we didn't actually understand the basic biology of what regulates the leptin gene."

The gene coding for the leptin hormone is regulated by adjacent DNA sequences and regulatory factors that turn the gene on in fat cells, and that also controls the amount of leptin being made. As they explored this process, Dallner and his colleagues zeroed in on one of these regulatory factors, called a long non-coding RNA, or lncRNA, which they identified together with colleagues at the University of Pennsylvania.

When the researchers engineered mice without this specific lncRNA and fed them a high-fat diet, the mice became obese, but their fat cells produced significantly lower amounts of leptin. This unusual finding suggested to the scientists that the leptin gene could not express normal levels of the hormone without the lncRNA to help it along. In comparison, a group of unaltered control mice fed the same diet gained weight and produced the expected amount of leptin.

Moreover, when these low-leptin mice were treated with injections of leptin, they lost weight -- in other words, the hormone essentially cured them. And that, the researchers say, raises the exciting possibility that some humans whose obesity is caused by a similar genetic anomaly could also lose weight with leptin therapy. (A pharmaceutical form of leptin was approved by the U.S. Food and Drug Administration in 2014.)

The fact that there may be obese people with such potentially leptin-curbing mutations was suggested by analyzing data from a large study, known as a genome-wide association study (GWAS), that included the complete genetic profiles of more than 46,000 people. Together with collaborators at the Mount Sinai School of Medicine, the Rockefeller team found that people with alterations in the human version of the lncRNA had lower leptin levels.

A potentially-treatable subtype of obesity

The number of obese people whose disease may be the result of the dysregulation of the leptin gene is not known, Dallner says, but there is reason to believe it could contribute to as many as 10 percent of all obesity cases.

For Dallner, who spent the better part of nine years working on the project, the heterogeneity of the obese population -- the fact that different people are obese for different reasons -- is the most interesting takeaway from the research. "The important part for me is that we set out to study the leptin gene in mice, and we ended up concluding that different mechanisms can cause obesity in humans," he says.

Most obese people, he explains, become resistant to leptin (which would normally curb their appetites) because they have a lot of fat. Fat cells produce high amounts of leptin and, as the hormone accumulates, the brain appears to stop responding to it.

"But there is a large subset of humans who are obese and still are relatively low in leptin," Dallner says. "We now think that many of them may have these or similar gene variants that affect the expression of the leptin gene. This gives them less leptin from an early age, making them a little bit hungrier than everyone else."

These people remain sensitive to the hormone, however, and early clinical studies have shown that obese people with low leptin levels do in fact lose a significant amount of weight when treated with leptin. But the possible mechanisms underlying such cases were not understood, until now.

Dallner says that while the exact interplay between lncRNA and the leptin gene remains unclear, there is no doubt that the two are connected. "When we studied the lncRNA, we realized it was completely co-regulated with leptin. It's expressed where leptin is expressed. When leptin is down the lncRNA is down, and vice versa. That was really the key moment, when I saw that and thought, 'Something is really going on here.'"

Story Source:

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

Journal Reference:

1. Olof S. Dallner, Jill M. Marinis, Yi-Hsueh. Lu, Kivanc Birsoy, Emory Werner, Gulya Fayzikhodjaeva, Brian D. Dill, Henrik Molina, Arden Moscati, Zoltán Kutalik, Pedro Marques-Vidal, Tuomas O. Kilpeläinen, Niels Grarup, Allan Linneberg, Yinxin Zhang, Roger Vaughan, Ruth J. F. Loos, Mitchell A. Lazar, Jeffrey M. Friedman. **Dysregulation of a long noncoding RNA reduces leptin leading to a leptin-responsive form of obesity**. *Nature Medicine*, 2019; DOI: 10.1038/s41591-019-0370-1

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Rockefeller University. "Scientists identify genetic factors that may cause some people to become obese." ScienceDaily. ScienceDaily, 6 March 2019. <www.sciencedaily.com/releases/2019/03/190306125341.htm>.

目次に戻る

４．マウス用の「スマートハウス」

2019 年 3 月 7 日

Francis Crick Institute の研究者らが、マウス用の「スマートハウス」を開発。これにより最長で 18 か月間、最小限の障害で動物の行動を調べることができる、としている。この‘Autonomouse’システムは、動物の福祉改善と同時に研究結果の効率と信頼性を高めるため、他のラボでも構築できるようにと、*PLOS ONE* でシステムの設計とソフトウェアを公表した。‘Autonomouse’では、ランニングホイール、はしご、そして食べ物や水への無制限のアクセスなど、豊かな環境の中でマウスのグループが一緒に暮らす。研究者が慎重にその活動レベル、体重と水の消費量を監視することができるように、各マウスは独特のマイクロチップでタグ付けされる。マイクロチップは、トレーニングにアクセスするための ID パスとしても機能し、マウスがトレーニング室に入ると、ドアがその後ろで閉じて、他のマウスが入るのを一時的に防ぐ。学習課題からのデータは自動的に記録され、固有のマウス ID にリンクされる。

英文記事：
https://www.sciencedaily.com/releases/2019/03/190307103137.htm

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Scientists engineer mouse 'smart house' to study behavior

Date:

March 7, 2019

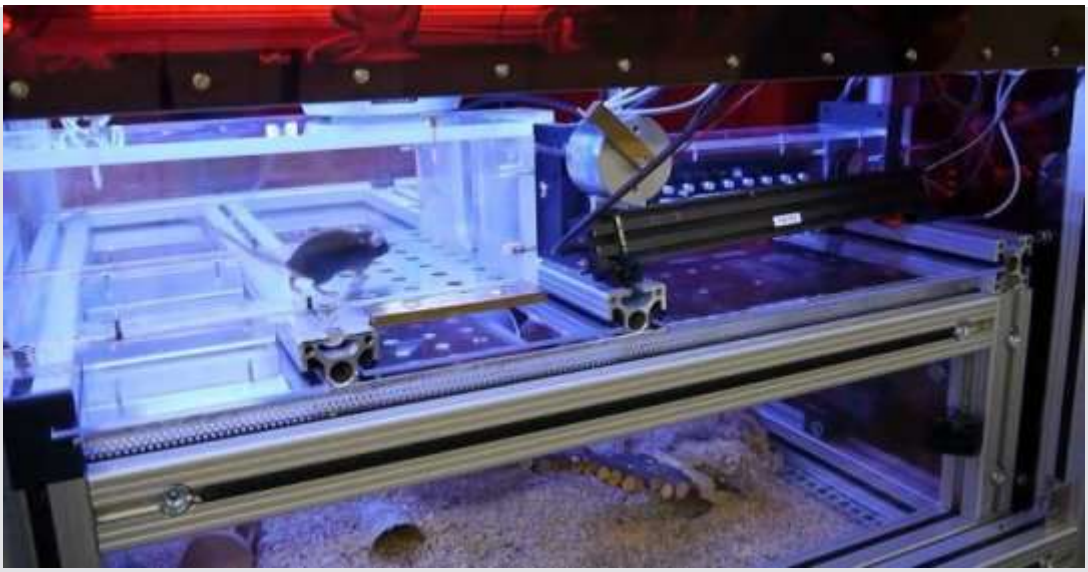
Source:

The Francis Crick Institute

Summary:

Researchers have developed a 'smart house' for mice, that allows them to study the animals' behavior with minimal disturbance for periods of up to 18 months.

FULL STORY



Autonomouse.

Credit: Andrew Erskine

Researchers at the Francis Crick Institute have developed a 'smart house' for mice, that allows them to study the animals' behaviour with minimal disturbance for periods of up to 18 months.

The 'Autonomouse' system improves animal welfare whilst simultaneously enhancing the efficiency and reliability of research findings. The team of scientists and engineers behind it have openly published the design and software of the system in *PLOS ONE* so that other labs can build their own.

"We want to understand how the brain works, and for that we need to measure behaviour," explains Andreas Schaefer, Group Leader at the Crick who led the project. "In mice, this is normally

done in a very manual and laborious way, which limits the amount of questions we can ask. So we thought of a more efficient way of doing this by getting animals to train themselves."

In Autonomouse, groups of mice live together in an enriched environment with running wheels, ladders and unlimited access to food and water. Each mouse is tagged with a unique microchip -- like those used for household pets -- so that researchers can carefully monitor its activity levels, weight and water consumption.

The microchip also acts as an ID pass to access training: When a mouse enters the training room, a door closes behind it, temporarily preventing other mice from entering while it carries out a learning task for a reward. Data from the learning task is automatically recorded, and linked to the unique mouse ID.

"Working with an unstressed, group-housed cohort of mice that train themselves at the time of day that suits them, without the intervention of researchers over long periods of time, makes our experiments better and more efficient," says Andreas.

People from the Crick's Biological Research Facility, Mechanical Engineering, Electronics and the Making lab, who helped create this system were recently awarded a Crick prize for improving animal welfare.

Story Source:

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

Journal Reference:

1. Andrew Erskine, Thorsten Bus, Jan T. Herb, Andreas T. Schaefer. **AutonoMouse: High throughput operant conditioning reveals progressive impairment with graded olfactory bulb lesions**. *PLOS ONE*, 2019; 14 (3): e0211571 DOI: 10.1371/journal.pone.0211571

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The Francis Crick Institute. "Scientists engineer mouse 'smart house' to study behavior." ScienceDaily. ScienceDaily, 7 March 2019. <www.sciencedaily.com/releases/2019/03/190307103137.htm>.

目次に戻る

5. 単一遺伝子の挿入で盲目マウスが視力を回復

2019 年 3 月 15 日

網膜変性による盲目患者には電子アイインプラントという 1 つの選択肢しかない。今回カリフォルニア大学バークレー校の神経科学者らによる代替法が開発された。この方法によるテストで、盲目のマウスが視力を回復させた、として *Nature Communications* 誌に掲載されている。網膜内の特定の細胞を標的とするように設計されたアデノ随伴ウィルス（AAV）は、眼の硝子体に直接注入できるため、網膜の下に直接注入されなければならない野生型 AAV よりも正確に遺伝子を送達できる。科学者らは、神経節細胞を標的とする AAV をとり、緑色オプシンの遺伝子をそれらに付加し、神経節細胞を光に対して感受性にすることに成功した。
この新しい治療法は、既に承認されている既存の AAV 眼科治療を考えると、3 年後には臨床試験の準備ができている可能性がある。

英文と記事：
https://www.sciencedaily.com/releases/2019/03/190315095808.htm

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With single gene insertion, blind mice regain sight

Opsins make 'blind' cells light-sensitive; potential human treatment within three years

Date:

March 15, 2019

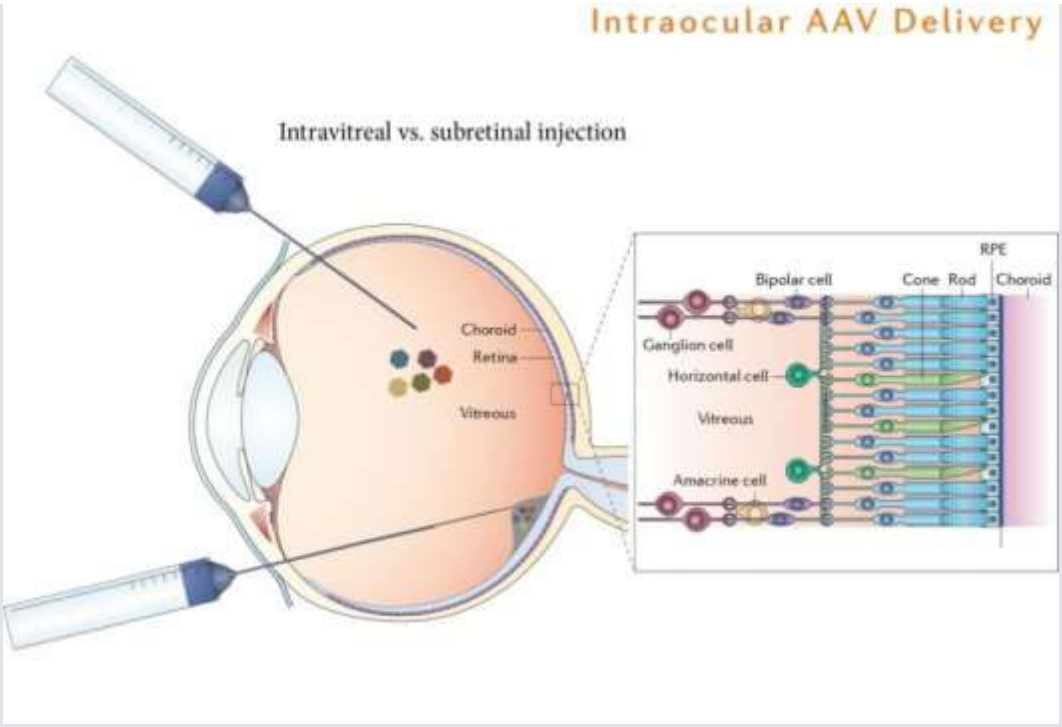
Source:

University of California - Berkeley

Summary:

People left blind by retinal degeneration have one option: electronic eye implants. Neuroscientists have now developed an alternative: gene therapy that, in tests, restored vision in blind mice. A gene for green opsin delivered via virus gave blind mice enough sight to discern patterns on an iPad at a resolution sufficient for humans to read. Given existing AAV eye therapies already approved, this new therapy could be ready for clinical trials in three years.

FULL STORY



Adeno-associated viruses (AAV) engineered to target specific cells in the retina can be injected directly into the vitreous of the eye to deliver genes more precisely than can be done with wild type AAVs, which have to be injected directly under the retina. UC Berkeley neuroscientists have taken AAVs targeted to ganglion cells, loaded them with a gene for green opsin, and made the normally blind ganglion cells sensitive to light.

Credit: John Flannery, UC Berkeley

It was surprisingly simple. University of California, Berkeley, scientists inserted a gene for a green-light receptor into the eyes of blind mice and, a month later, they were navigating around obstacles as easily as mice with no vision problems. They were able to see motion, brightness changes over a thousandfold range and fine detail on an iPad sufficient to distinguish letters.

The researchers say that, within as little as three years, the gene therapy -- delivered via an inactivated virus -- could be tried in humans who've lost sight because of retinal degeneration, ideally giving them enough vision to move around and potentially restoring their ability to read or watch video.

"You would inject this virus into a person's eye and, a couple months later, they'd be seeing something," said Ehud Isacoff, a UC Berkeley professor of molecular and cell biology and director of the Helen Wills Neuroscience Institute. "With neurodegenerative diseases of the retina, often all people try to do is halt or slow further degeneration. But something that restores an image in a few months -- it is an amazing thing to think about."

About 170 million people worldwide live with age-related macular degeneration, which strikes one in 10 people over the age of 55, while 1.7 million people worldwide have the most common form of inherited blindness, retinitis pigmentosa, which typically leaves people blind by the age of 40.

"I have friends with no light perception, and their lifestyle is heart-wrenching," said John Flannery, a UC Berkeley professor of molecular and cell biology who is on the School of Optometry faculty. "They have to consider what sighted people take for granted. For example, every time they go to a hotel, each room layout is a little different, and they need somebody to walk them around the room while they build a 3D map in their head. Everyday objects, like a low coffee table, can be a falling hazard. The burden of disease is enormous among people with severe, disabling vision loss, and they may be the first candidates for this kind of therapy."

Currently, options for such patients are limited to an electronic eye implant hooked to a video camera that sits on a pair of glasses -- an awkward, invasive and expensive setup that produces an image on the retina that is equivalent, currently, to a few hundred pixels. Normal, sharp vision involves millions of pixels.

Correcting the genetic defect responsible for retinal degeneration is not straightforward, either, because there are more than 250 different genetic mutations responsible for retinitis pigmentosa alone. About 90 percent of these kill the retina's photoreceptor cells -- the rods, sensitive to dim light, and the cones, for daylight color perception. But retinal degeneration typically spares other layers of retinal cells, including the bipolar and the retinal ganglion cells, which can remain healthy, though insensitive to light, for decades after people become totally blind.

In their trials in mice, the UC Berkeley team succeeded in making 90 percent of ganglion cells light sensitive.

Isacoff, Flannery and their UC Berkeley colleagues will report their success in an article appearing online March 15 in *Nature Communications*.

'You could have done this 20 years ago'

To reverse blindness in these mice, the researchers designed a virus targeted to retinal ganglion cells and loaded it with the gene for a light-sensitive receptor, the green (medium-wavelength) cone opsin. Normally, this opsin is expressed only by cone photoreceptor cells and makes them sensitive to green-yellow light. When injected into the eye, the virus carried the gene into ganglion cells, which normally are insensitive to light, and made them light-sensitive and able to send signals to the brain that were interpreted as sight.

"To the limits that we can test the mice, you can't tell the optogenetically-treated mice's behavior from the normal mice without special equipment," Flannery said. "It remains to be seen what that translates to in a patient."

In mice, the researchers were able to deliver the opsins to most of the ganglion cells in the retina. To treat humans, they would need to inject many more virus particles because the human eye contains thousands of times more ganglion cells than the mouse eye. But the UC Berkeley team has developed the means to enhance viral delivery and hopes to insert the new light sensor into a similarly high percentage of ganglion cells, an amount equivalent to the very high pixel numbers in a camera.

Isacoff and Flannery came upon the simple fix after more than a decade of trying more complicated schemes, including inserting into surviving retinal cells combinations of genetically engineered neurotransmitter receptors and light-sensitive chemical switches. These worked, but did not achieve the sensitivity of normal vision. Opsins from microbes tested elsewhere also had lower sensitivity, requiring the use of light-amplifying goggles.

To capture the high sensitivity of natural vision, Isacoff and Flannery turned to the light receptor opsins of photoreceptor cells. Using an adeno-associated virus (AAV) that naturally infects ganglion cells, Flannery and Isacoff successfully delivered the gene for a retinal opsin into the genome of the ganglion cells. The previously blind mice acquired vision that lasted a lifetime.

"That this system works is really, really satisfying, in part because it's also very simple," Isacoff said. "Ironically, you could have done this 20 years ago."

Isacoff and Flannery are raising funds to take the gene therapy into a human trial within three years. Similar AAV delivery systems have been approved by the FDA for eye diseases in people with degenerative retinal conditions and who have no medical alternative.

It can't possibly work

According to Flannery and Isacoff, most people in the vision field would question whether opsins could work outside their specialized rod and cone photoreceptor cells. The surface of a photoreceptor is decorated with opsins -- rhodopsin in rods and red, green and blue opsins in cones -- that are embedded in a complicated molecular machine. A molecular relay -- the G-protein coupled receptor signaling cascade -- amplifies the signal so effectively that we are able to detect single photons of light. An enzyme system recharges the opsin once it has detected the photon and becomes "bleached." Feedback regulation adapts the system to very different background brightnesses. And a specialized ion channel generates a potent voltage signal. Without transplanting this entire system, it was reasonable to suspect that the opsin would not work.

But Isacoff, who specializes in G protein-coupled receptors in the nervous system, knew that many of these parts exist in all cells. He suspected that an opsin would automatically connect to the signaling system of the retinal ganglion cells. Together, he and Flannery initially tried rhodopsin, which is more sensitive to light than cone opsins.

To their delight, when rhodopsin was introduced into the ganglion cells of mice whose rods and cones had completely degenerated, and who were consequently blind, the animals regained the ability to tell dark from light -- even faint room light. But rhodopsin turned out to be too slow and failed in image and object recognition.

They then tried the green cone opsin, which responded 10 times faster than rhodopsin. Remarkably, the mice were able to distinguish parallel from horizontal lines, lines closely spaced versus widely spaced (a standard human acuity task), moving lines versus stationary lines. The

restored vision was so sensitive that iPads could be used for the visual displays instead of much brighter LEDs.

"This powerfully brought the message home," Isacoff said. "After all, how wonderful it would be for blind people to regain the ability to read a standard computer monitor, communicate by video, watch a movie."

These successes made Isacoff and Flannery want to go a step farther and find out whether animals could navigate in the world with restored vision. Strikingly, here, too, the green cone opsin was a success. Mice that had been blind regained their ability to perform one of their most natural behaviors: recognizing and exploring three-dimensional objects.

They then asked the question, "What would happen if a person with restored vision went outdoors into brighter light? Would they be blinded by the light?" Here, another striking feature of the system emerged, Isacoff said: The green cone opsin signaling pathway adapts. Animals that were previously blind adjusted to the brightness change and could perform the task just as well as sighted animals. This adaptation worked over a range of about a thousandfold -- the difference, essentially, between average indoor and outdoor lighting.

"When everyone says it will never work and that you're crazy, usually that means you are onto something," Flannery said. Indeed, that something amounts to the first successful restoration of patterned vision using an LCD computer screen, the first to adapt to changes in ambient light and the first to restore natural object vision.

The UC Berkeley team is now at work testing variations on the theme that could restore color vision and further increase acuity and adaptation.

The work was supported by the National Eye Institute of the National Institutes of Health, the Nanomedicine Development Center for the Optical Control of Biological Function, the Foundation for Fighting Blindness, the Hope for Vision Foundation and the Lowy Medical Research Institute.

Story Source:

Materials provided by **University of California - Berkeley**. Original written by Robert Sanders.
Note: Content may be edited for style and length.

Journal Reference:

1. Michael H. Berry, Amy Holt, Autoosa Salari, Julia Veit, Meike Visel, Joshua Levitz, Krisha Aghi, Benjamin M. Gaub, Benjamin Sivyer, John G. Flannery, Ehud Y. Isacoff. **Restoration of high-sensitivity and adapting vision with a cone opsin**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-09124-x

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University of California - Berkeley. "With single gene insertion, blind mice regain sight: Opsins make 'blind' cells light-sensitive; potential human treatment within three years." ScienceDaily. ScienceDaily, 15 March 2019. <www.sciencedaily.com/releases/2019/03/190315095808.htm>.

目次に戻る

6. 健康的脂肪で肥満マウスの神経機能を改善

2019 年 3 月 18 日

2 型糖尿病は、大量の飽和脂肪を特徴とする高脂肪食に関連している。対照的に、一価不飽和脂肪酸を多く含む食事は健康上の利点を持つことが示されている。今回ミシガン大学の研究者らは、これら 2 種類の脂肪が糖尿病の最も一般的な合併症である糖尿病性ニューロパチーの進行にどのように影響するかを調査し、その結果が *JNeurosci* 誌に発表された。
この研究で、研究者らは、マウスを飽和脂肪ベースの食事からヒマワリ油由来の一価不飽和脂肪に富む食事に切り替えることで、肥満マウスの神経機能を回復させ保護することを見出した。これらの結果は、食事性脂肪を標的とする介入が糖尿病性ニューロパチーの治療のための新しい治療法を提供するかもしれないことを示唆している。

英文記事：
https://www.sciencedaily.com/releases/2019/02/190214084646.htm

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Healthy fats improve nerve function in obese mice

Data support further investigation of diets rich in monounsaturated fats as potential treatment for common diabetes complication

Date:

March 18, 2019

Source:

Society for Neuroscience

Summary:

Swapping dietary saturated fats for monounsaturated fats reverses nerve damage and restores nerve function in male mice, finds new preclinical research. These data support

further investigation of diets rich in healthy fats as a potential treatment for the nerve damage that occurs with diabetes, known as diabetic neuropathy.

FULL STORY

Swapping dietary saturated fats for monounsaturated fats reverses nerve damage and restores nerve function in male mice, finds new preclinical research published in *JNeurosci*. These data support further investigation of diets rich in healthy fats as a potential treatment for the nerve damage that occurs with diabetes, known as diabetic neuropathy.

Type 2 diabetes is associated with high-fat diets characterized by large amounts of saturated fats. In contrast, monounsaturated fatty acid-rich diets have been shown to have health benefits. Professor Eva Feldman and colleagues at the University of Michigan investigated how these two types of fats affect the progression of diabetic neuropathy, the most common complication of diabetes.

The researchers found switching mice from a saturated fat-based diet to a diet rich in monounsaturated fats derived from sunflower oil restored and protected nerve function in obese mice. Studying the beneficial effects of monounsaturated fats in sensory dorsal root ganglion neurons showed the intervention helped the cells maintain normal energy production.

These results suggest that interventions targeting dietary fats may provide a new therapeutic avenue for the treatment of diabetic neuropathy.

Story Source:

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

Journal Reference:

1. Amy E. Rumora, Giovanni LoGrasso, John M. Hayes, Faye E. Mendelson, Maegan A. Tabbey, Julia A. Haidar, Stephen I. Lentz, Eva L. Feldman. **The divergent roles of dietary saturated and monounsaturated fatty acids on nerve function in murine models of obesity**. *The Journal of Neuroscience*, 2019; 3173-18 DOI: 10.1523/JNEUROSCI.3173-18.2019

目次に戻る

7. 高齢者の骨の治癒力喪失の原因は「老化炎症 (Inflamm-aging)」

2019 年 3 月 18 日

3 月 18 日の米国科学アカデミー紀要に発表されたニューヨーク大学医学部のマウスおよびヒトにおける研究発表では、負傷した骨が年齢と共に治癒し難くなる原因は、年齢そのものではなく、慢性炎症の増加である、としている。
この研究は、骨髄内の幹細胞数が加齢と共に劇的に減少し、それによって骨折治癒により長い時間が掛かるというヒト患者における経験に基づき、マウスモデルに移動してその関連メカニズムを探ったものである。
研究者らは、若いマウスの幹細胞を老齢マウスの血清にさらすと、幹細胞が分裂して増殖する可能性が 4 倍少なくなることを発見。これは老化と呼ばれる不可逆的な状態であるが、具体的には、若いマウスからの幹細胞が老齢マウスの血清にさらされることによって、間接的に重要な免疫関連のタンパク質である NFkB (NFkB は DNA と相互作用して炎症誘導性遺伝子を作動させる) を活性化することを発見した。そして、このタンパク質のシグナルが骨格幹細胞の増殖を停止させることを明らかにした。更にアスピリンの成分であるサリチル酸ナトリウムを用いた経時的な治療は、NFkB シグナルおよび関連する加齢誘発性慢性炎症を抑制し骨格幹細胞の数を増大させることも発見した。

英文記事：
https://medicalxpress.com/news/2019-03-inflamm-aging-loss-bone-ability-elderly.html

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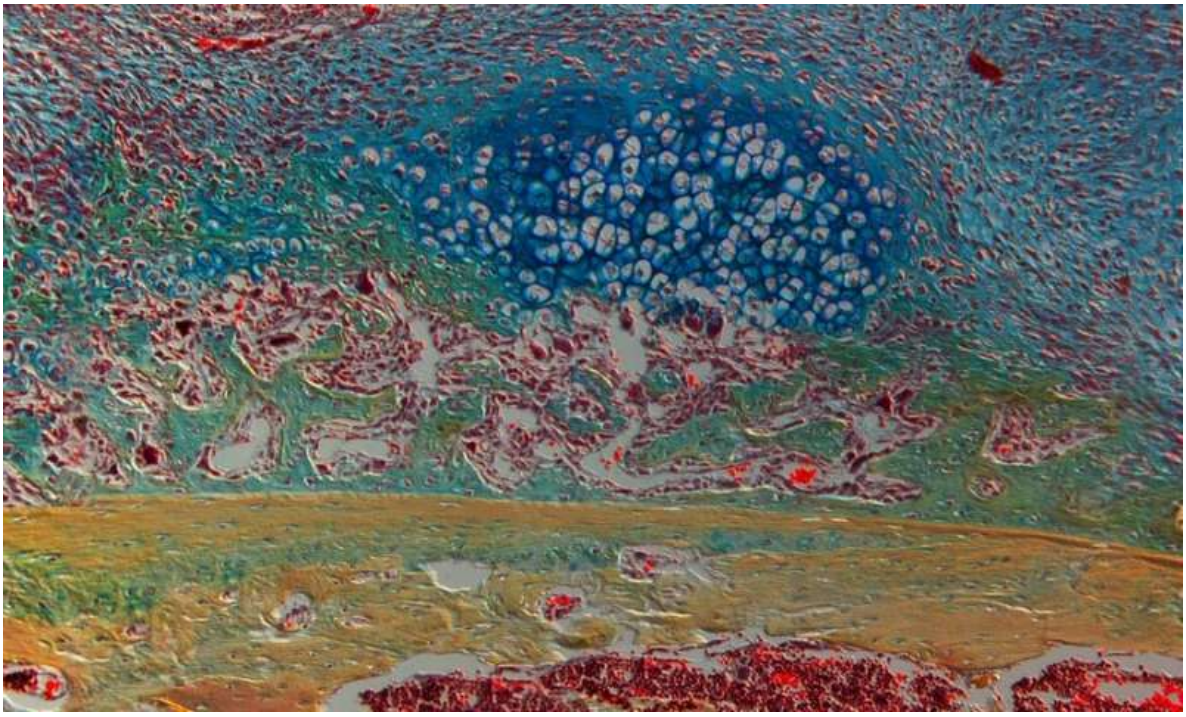
MARCH 18, 2019

'Inflamm-aging' causes loss of bone healing ability in the elderly

by NYU Langone Health



Pictured is bone near a fracture, with marrow full of red blood cells at the bottom, healthy bone on top of that (tan), and new bone (green) and cartilage (dark blue) in the upper layer. Credit: NYU School of Medicine

Increases in chronic inflammation—not the passage of time—is the main reason why injured bones do not heal as well with age. This is the finding of a study in mice and humans published March 18 in the *Proceedings of the National Academy of Sciences* (*PNAS*).

The results revolve around the known breakdown, due to wear and tear, of the protein machines and large molecules necessary for the life of human cells, the remnants of which trigger the immune system. First studied in its role in destroying invading microbes, this system also can react to the body's own proteins to cause inflammation, a response that fights infection at the site of injury and transitions into the healing process.

The current study explains how this age-driven increase in immune signals diminishes the ability of stem cells—essential ingredients in bone repair—to multiply. This results in a smaller number of stem cells in the aged skeleton, say the study authors, and compromises their ability to help make new bone after a fracture. The research team also restored skeletal stem cell number and function by treating aging mice with an anti-inflammatory component of aspirin.

"Our results argue that age-associated inflammation—called 'inflamm-aging' – is the culprit in the decline in the number and function of the skeletal stem cells that enable bones to heal," says senior study author Philipp Leucht, MD, assistant professor in the departments of Orthopedic Surgery and Cell Biology at NYU School of Medicine.

Diseases that weaken the skeleton are among the most common impairments in the United States, with one report estimating that more than three of every five injuries are to the musculoskeletal system. While seldom fatal, bone fractures greatly diminish quality

of life, say researchers—and more so with advanced age, when some fractures never heal.

It's Not the Years

The current study is based on the observation in human patients that stem cell number in the bone marrow significantly declines with increasing age, and that fractures take longer to heal as the stem cell number drops. The research team then moved to mouse models to explore the related mechanisms.

The researchers found that exposing stem cells from young mice to the blood serum of the older mice made their stem cells four times less likely to divide and multiply, an irreversible state called senescence. Past studies had also shown that senescent stem cells send signals that encourage inflammation in a vicious circle.

Specifically, the team found that exposing stem cells from young mice to blood serum of older mice indirectly activated the key immune-related protein, NFκB. As a known centerpiece of the immune response, NFκB interacts with DNA to turn on several pro-inflammatory genes. Experiments revealed that this protein's signals cause skeletal stem cells to stop multiplying.

Furthermore, treatment over time with sodium salicylate, an ingredient in aspirin, repressed NFκB signals and related aged-induced chronic inflammation, increasing the number and bone-

healing contribution of skeletal stem cells. Further experiments revealed that anti-inflammatory treatment changed the action of thousands of genes in the stem cells, restoring them to a genetic profile seen in young skeletal stem cells.

“These results suggest that it is inflammation, not chronological age, that hinders bone healing in the elderly,” says first study author Anne Marie Josephson, a graduate student at NYU School of Medicine. She says an obstacle to the translation of the findings into future treatments is that rejuvenating bone stem cells with anti-inflammatory drugs just after a bone fracture would also block the acute inflammation that is necessary for successful bone healing.

This suggests, she says, that a more immediate application may be to use anti-inflammatory drugs to build up stem cell pools, not after bone breaks, but during the weeks before elective orthopedic surgeries like hip or knee replacements. In these cases, anti-inflammatory drugs would be used leading up to a surgery, but then be cut off just before to make way for the acute inflammation necessary to normal healing.

In addition, the genetic results suggest signaling pathways that might be targeted by future drug treatments to lessen age-related, chronic inflammation on stem cells without compromising the type of inflammation that quickly follows bone injury.

E

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nflammation signals induce dormancy in aging brain stem cells

More information: Anne Marie Josephson el al., "A“e-related inflammation triggers skeletal stem/progenitor cell dysfunction," *”NAS* (2019).

www.pnas.org/cgi/doi/10.1073/pnas.1810692116

目次に戻る

8. 抗結核薬は結核再感染リスクを高める

治療によって腸内細菌が変化し免疫力が低下

2019 年 3 月 22 日

現在の結核治療は、結核菌によって引き起こされる TB 感染を制御するのに非常に有効である。しかしながら、その治療が常に再感染を予防するわけではない。なぜ結核に対する永久的な免疫を生み出すことができないのかは、結核研究における長年の疑問の一つであったが、今回マギル大学の科学者チームがその答えを腸内に見つけ出した可能性がある。
Mucosal Immunology 誌に発表されたこの研究では、抗結核薬が腸内細菌叢に変化をもたらし Mtb 感染に対する感受性を高めたことを示している。
Mtb 感染に対する宿主の脆弱性が腸内細菌叢の妥協によるものであることを確認するために、研究者らはマウスの糞便を調べた。抗結核薬（具体的にはイソニアジドとピラジナミド）で処理したマウスから感染前に未処理マウスに糞便を移植することによって、彼らは初めて糞便移植が Mtb に対する免疫性を危うくするのに充分であることを示すことができた、としている。

英文記事：
https://www.sciencedaily.com/releases/2019/03/190322163334.htm

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Anti-TB drugs can increase risk of TB re-infection

Treatment leads to changes in gut bacteria, compromising immunity

Date:

March 22, 2019

Source:

McGill University

Summary:

Current treatments for tuberculosis (TB) are very effective in controlling TB infection caused by Mycobacterium tuberculosis (Mtb). They don't, however, always prevent reinfection. Why this happens is one of the long-standing questions in TB research. A team of scientists may have found the answer... in the gut.

FULL STORY

Current treatments for tuberculosis (TB) are very effective in controlling TB infection caused by Mycobacterium tuberculosis (Mtb). They don't, however, always prevent reinfection. Why this happens is one of the long-standing questions in TB research.

So why are our bodies unable to generate permanent immunity to TB, -- the leading infectious disease killer worldwide? A team of scientists at the Research Institute of the McGill University Health Centre (RI-MUHC) and McGill University may have found the answer... in the gut. In a study published recently in *Mucosal Immunology*, they showed that anti-TB drugs caused changes to gut microbiota -- the diverse community of microbes living our intestines -- and increased susceptibility to Mtb infection.

Gut microbiota are critical to keeping us healthy; they help to digest food, combat pathogenic microbes and reinforce our immune system. Recent research has shown that chronic use of antibiotic leads to disruption of this community, which can in turn lead to dysregulation of the immune system. It remains unclear, however, whether changes in the composition of the microbes living in our gut have an influence on TB infection.

Impact of anti-TB drugs on microbiome

To find out, Drs. Irah King and Maziar Divangahi from the Meakins-Christie Laboratories at the RI-MUHC, with colleagues from McGill's Macdonald Campus, treated mice with the most commonly

used anti-TB drugs -- isoniazid, rifampicin and pyrazinamide -- for a period of eight weeks. They found that while all three drugs significantly altered the composition of the mice's gut microbiome, only mice treated with isoniazid combined with pyrazinamide showed an increase in susceptibility to Mtb infection.

To make sure the vulnerability of the host to Mtb infection was due to a compromised gut microbiota, the researchers looked at... feces. By transplanting feces from mice that had been treated with anti-TB drugs (specifically isoniazid and pyrazinamide) into untreated mice prior to infection, they were able to show for the first time that fecal transplant was sufficient to compromise immunity to Mtb.

Relationship between the gut microbiome and the lungs

King and his colleagues also wanted to better understand the gut-lung axis -- a bidirectional communication system between microorganisms residing in the gastrointestinal tract and the lungs -- in order to how this might be involved in Mtb infection and immunity.

To do so, they evaluated a number of lung cell types known to be important for resistance to Mtb infection. Following anti-TB treatment, alveolar macrophages, a type of immune cell located in the airways of mice and humans and the first cell to encounter Mtb upon infection, were compromised in their ability to kill Mtb.

"We need to do more research in order to understand how the microbiome affects alveolar macrophages because these cells are critical for controlling early TB infection. We also need to identify the molecular pathways involved in the gut-lung axis,'' explains King.

"Anti-TB therapies have been incredibly efficient in controlling the TB epidemic by decreasing morbidity and mortality associated with Mtb,'' says King. "Now, this work provides a basis for novel therapeutic strategies exploiting the gut-lung axis in Mtb infection.''

Researchers are already thinking of monitoring patients who are being treated with these drugs to see how their gut microbiota changes over time and once treatment has stopped. The idea will be to control changes to the microbiome in combination with drugs that are effective at killing Mtb.

Story Source:

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

Journal Reference:

1. Nargis Khan, Laura Mendonca, Achal Dhariwal, Ghislaine Fontes, Dick Menzies, Jianguo Xia, Maziar Divangahi, Irah L. King. **Intestinal dysbiosis compromises alveolar macrophage immunity to Mycobacterium tuberculosis**. *Mucosal Immunology*, 2019; DOI: 10.1038/s41385-019-0147-3

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Salk Institute. "CRISPR/Cas9 therapy can suppress aging, enhance health and extend life span in mice." ScienceDaily. ScienceDaily, 19 February 2019. <www.sciencedaily.com/releases/2019/02/190219111747.htm>.

目次に戻る

9. 有力とされた「アルツハイマー病治療薬」の失敗 苦戦が続く認知症薬の開発、今後の見通しは

2019 年 3 月 24 日

https://news.yahoo.co.jp/byline/mamoruichikawa/20190324-00119171/

3 月 21 日、大手製薬企業「バイオジェン」と「エーザイ」は、開発中の**アルツハイマー病治療薬「アデュカヌマブ」の臨床試験を中止する**と発表しました。（プレスリリース）
認知症の最大の原因となっているアルツハイマー病には、現在のところ、病気の進行そのものを抑える「根本治療薬」は開発されていません。
アデュカヌマブは「こんどこそ第 1 号になる」と世界中で注目されていたものでした。
というのも、世界で最も権威のある専門誌のひとつ「Nature」に、効果を期待できるデータが報告されていたからです。
アルツハイマー病の原因として疑われているのがアミロイドベータ（Aβ）という物質です。この物質が脳にたまると、神経が傷つき、脳の働きを衰えさせるのではないか？と考えられています**（アミロイドベータ仮説）**。
2016 年に Nature に報告された研究では、アデュカヌマブを使うと、脳にたまったアミロイドベータが減り、しかも、薬の量を増やせば増やすほど減り方が大きいことが示されました。
さらに投与を受けた人の中には、アルツハイマー病によるものと思われる症状（認知機能テストの点数の低下など）の進行が抑えられた人がいました。
この結果を受けてバイオジェン社は、治療薬としての承認を目指し、多くの人に使って効果を検証する試験を行っていたのですが、そのデータは予想に反して「十分な効果は見込めそうにない」ことを示しており、試験の中止を決めたのです。

検査イメージ　画像：Pixabay

「アミロイドベータ仮説」は誤りなのか？深まる疑い

実はここ 5 年ほど、アルツハイマー病治療薬の開発を目指した試みは「連戦連敗」を続けています。

世界の大手製薬企業が巨額の予算をかけて薬剤を開発し、動物や少人数の試験で期待できるような結果が表れ、「こんどこそ」とチャレンジした臨床試験で「効果なし」という結果に終わる。そんなことが相次いでいるのです。

今回のアデュカヌマブの試験中止は「もうひとつ敗戦が加わっただけ」ともいえるかもしれません。しかし、製薬業界に与えるショックは大きいものがあるだろうと想像できます。

これまで繰り返された失敗に関しては、様々な理由が提唱されています。有力なものとして「薬は早めに投与しなければ効果が出ないのでは？」というものがあります。

そこでアデュカヌマブの臨床試験は、早期の人や、まだアルツハイマー病とは診断されていないMCI（軽度認知障害）の人を対象として選んでおり、効果を示しやすいと考えられていました。
さらに 2017 年には、日本に本社を置く製薬企業「エーザイ」が、開発費用をバイオジェン社と分担することを発表していました。エーザイといえば世界初の抗認知症薬「アリセプト」を開発し、現在もアルツハイマー病の根本治療薬の研究を積極的に進めていることで知られます。
そのエーザイが、わざわざ開発費を分担するリスクをとったわけですから、これは成功を確信するようなデータをつかんだのではないか？と期待が高まっていました。実際、エーザイの内藤晴夫CEO は 2017 年のプレスリリースの中で「Aβ 仮説に基づく創薬への確信を深めています」と自信を示していました。
成功を期待できる状況が積み重なっていたなかでの「失敗」のニュース。驚きと失望の思いが広がり、開発を進めていたバイオジェンとエーザイの株価は大幅に下落しました。

認知症の根本治療薬　今後の開発の見込みは

実はエーザイは、アデュカヌマブの試験中止の発表の翌日、「BAN2401」という別のアルツハイマー病薬の臨床試験の開始を発表しており、積極的な開発を続ける方針を明確にしています。アデュカヌマブの試験中止は、もっと有望な薬候補に予算を集中するためなのかもしれません。
しかしここ 5 年ほどだけを見ても、ファイザーやメルク、イーライリリーなど世界の名だたる製薬企業が、根本治療薬の臨床試験に失敗しています。今度こそ、今度こそと繰り返される臨床試験が失敗するたびに、「有望株」の数が減ってきています。
アミロイドベータがアルツハイマー病の原因であるとする「アミロイドベータ仮説」が提唱されたのは、2000 年代初頭のことです。そこから 20 年近く、この仮説に基づいて根本治療薬を開発しようとする試みは世界各国で行われ、そして残念なことに、ことごとく失敗に終わってきました。
いま世界中で、「アミロイドベータ仮説」が間違っていたのではないか？という疑いが広がりつつあります。そもそもアミロイドベータが「主要な原因ではなかった」とすれば、薬の失敗が相次ぐことの説明がつくからです。
しかしアミロイドベータ仮説の否定は、長年の研究の蓄積を根底から覆すものになりかねず、簡単に議論できるものではありません。現在もアミロイドベータ仮説に基づく研究は世界中で行われ、多額の研究費が投じられています。

いわば「なかなか先の見えない森の中を、もはや引き返すに引き返せず、ただ前に向かって進むしかない」状況といえるかもしれません。

画像：Pixabay

「認知症」にどう向き合うか　変わり続けるパラダイム

認知症を抱える人の増加が問題化して以来、世界中で「根本治療薬」を求める切実な声があげられ続けています。それに応えようと、多くの研究者たちがいまも真摯な努力を続けています。アミロイドベータ仮説以外のメカニズムをもつ薬の開発も始まっています。

個人的には将来、そうした努力が実を結び、アルツハイマー病を中心とした認知症の人を減らせる治療法が出てくると考えています。

ただ、近年報告される研究成果を見ると、もし薬の開発が成功したとしても、その効果には「限界」があると予測されます。根本治療薬と言った場合に通常イメージされる「すっかり治す」というようなものではなく、「病気の進行を、何割かゆるやかにできる」というものになりそうです。

つまり、もし「根本治療薬」ができたとしても、それさえあれば認知症はすっかり解決！とはいかない状況が見えてきたということです。
今回の開発中止のニュースを目にして、私は 15 年ほど前に、ある医療関係者と交わした会話を思い出しました。
当時、アミロイドベータ仮説に基づく研究が進み、次々と根本治療薬の候補が開発され、いくつもの臨床試験が世界中で始められつつありました。
「アミロイドベータ仮説が出てくるまで、老年期のアルツハイマー病は、病気というより『老化現象の一種』だと思っていた。治療するなんて『老化を食い止める』みたいな、ありえないことだという気持ちだったよ。でも、時代は変わった。認知症は老化現象ではなく病気、しかも『完治できる病気』になっていくんだ。」
私は大きくうなずき、医学の進歩のすばらしさに胸を躍らせたのを覚えています。
以前は「痴呆（ちほう）」とも呼ばれていた認知症。いちど発症すれば手立てはなく、絶望だけが待っていると恐れられていました。アミロイドベータ仮説の登場により、認知症のイメージは「撲滅しうる病」に変わり、希望が生まれたといえるかもしれません。
しかしそれから 15 年、当時多くの関係者が夢見た未来予想図は、いまだに実現していません。
その一方で認知症を抱える当事者からは、認知症を予防や治療によって「撲滅しうる病」とする考え方が強まりすぎると、当事者を社会から「見えない存在」として排除する空気が生まれかねない、という危惧が指摘されるようになっています。

認知症は「病気」ではない　当事者から上げられた声

では、どうしていけば良いのか。
いま世界的に進んでいるのは、認知症の「撲滅」を目指すのではなく、どうしたら「認知症になってからも安心して暮らせる社会」を作れるのか？について考えようとする取り組みです。

アルツハイマー病治療薬・フランスで医療保険から外れる　変わる認知症治療の潮流とは

介護の方法や支援のやり方を工夫し、認知症によって起きる様々な状態の変化に対応できる環境を作ることで、本人や支える人の生活の質を維持しつつ、社会として持続可能な仕組みを整えようとする取り組みが国内海外を問わず進められつつあります。
将来的に開発されるだろう「根本治療薬」も、「認知症に対応できる社会」を作るための手段のひとつとして、必要な人に必要なタイミングで使われる、というものになっていくのかもしれません。

「対応不能な絶望」から「撲滅しうる病」へ、そして「対応可能な状態の変化」へと、認知症へのイメージは、この 20 年ほどでも目まぐるしく変わっています。
それは、医療の進歩による「長命化」を達成した人類が、それゆえに直面することになった「認知症」という状態への本質的な理解を深め、受け入れようとする過程そのものなのかもしれません。

市川衛 医療の「翻訳家」

（いちかわ・まもる）医療の「翻訳家」／医療ジャーナリスト／メディカルジャーナリズム勉強会代表／京都大学医学部非常勤講師。00 年東京大学医学部卒業後、NHK入局。医療・福祉・健康分野をメインに世界各地で取材を行う。16 年スタンフォード大学客員研究員。【主な作品】（テレビ）NHKスペシャル「腰痛 治療革命」「医療ビッグデータ」ためしてガッテン「認知症！介護の新技」など。（書籍）「脳がよみがえる・脳卒中リハビリ革命（主婦と生活社）」「誤解だらけの認知症（技術評論社）」など。※記事は個人としての発信であり、いかなる組織の意見も代表するものではありません

英文記事：
https://www.statnews.com/2019/03/21/alzheimers-amyloid-time-to-do-something-else/?utm_source=STAT+Newsletters&utm_campaign=84110d0127-MR_COPY_01&utm_medium=email&utm_term=0_8cab1d7961-84110d0127-150065641

アルツハイマー病とアミロイド：何か別のことをするべき時が来た

Roche は 1 月に抗アミロイド抗体 crenezumab を中止にしたし、Merk は 2017 年に有害なアミロイドの産生を停止させた verubecstat を取り下げた。Eli Lilly は 2016 年にその抗アミロイド solanezumab が軽度のアルツハイマー病患者に有益性を示さなかったと発表。今回 Biogen とそのパートナーである Eisai による木曜日の発表では、抗アミロイド aducanumab の２つの臨床試験を中止した。

ボストンの Brigham and Women's Hospital の Dennis Selkoe 博士は、1980 年代からずっとアミロイド仮説開発に尽力しており、脳神経細胞の周りのこれらのタンパク質の蓄積が病気の原因であると同時にそれを治療するための鍵でもあるという考えだ。ただ、Aducanumab はアミロイド斑を除去するようだが、それは治験患者には役立たなかった。考えられる理由の中で、Selkoe 博士は、ほとんどが逆転するには「進行し過ぎだった」ということを示唆した。言い換えれば、アミロイド仮説は正しいが、一度タンパク質が脳に現れたら、それはすでに非常に多くのニューロンを死滅させ、非常に多くのシナプスを破壊している、と。

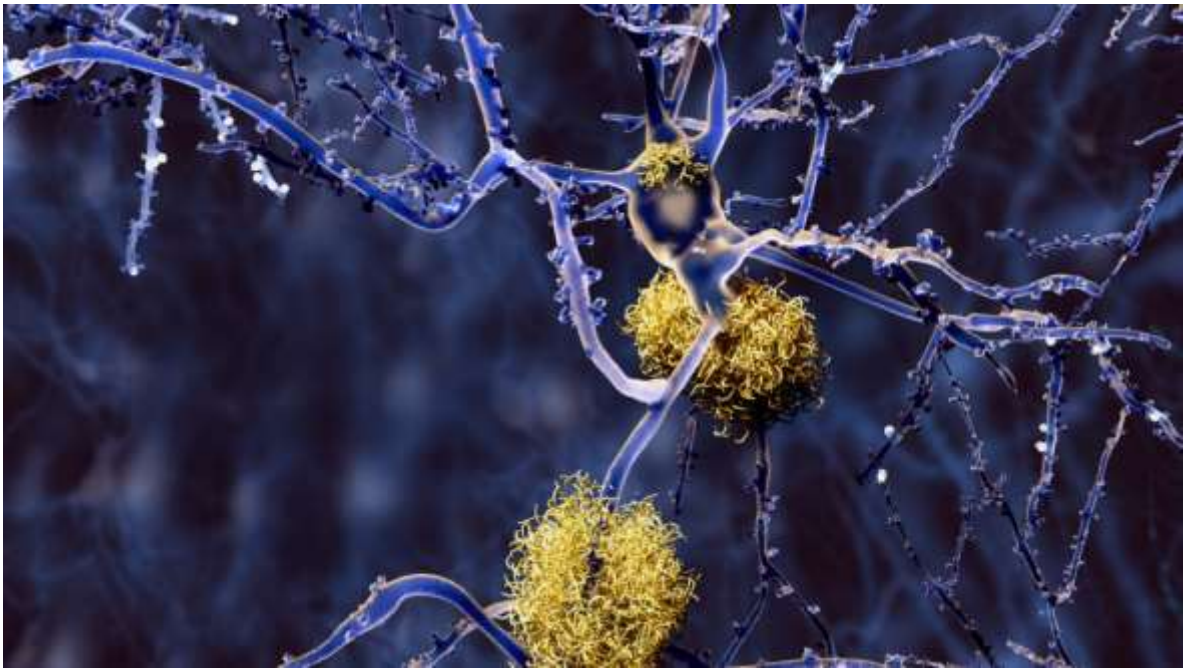
また、実験的アルツハイマー病化合物のフェーズ 2 試験を実施している Neurotrope の最高科学責任者の Daniel Alkon 氏は、次のように述べている。認知障害を伴わずに死亡する何人かの高齢者がそれにもかかわらずアミロイドでいっぱいの脳を持っていることがある。従って、アルツハイマー病を治療するための新戦略の一つは、いくつかのアミロイドが詰まった脳を健康に保つ自然なメカニズムを模倣すること。例えば、Neurotrope の化合物は、アミロイドをターゲットにしつつ、シナプスを回復させる生化学的経路も強化する。ニューロンが近くに新しいシナプスを作り出すことによって、あるいは既存のものが応答することのできる回路を形成させることによってシナプスの喪失に反応する「代償性再生」の脳の能力を利用することだ、としている。

アルツハイマーの治療法に対して、戦略を見直すべき時が来たのだろうか？

Alzheimer's and amyloid: 'It's time to do something else'

By SHARON BEGLEY @sxbegle

MARCH 21, 2019



Amyloid plaques in an Alzheimer's brain ADOBE

If there is anything more certain than the failure of experimental Alzheimer's drugs — nearly 300, at last count — it is the immediate reaction of many diehard supporters of the amyloid hypothesis: They insist that idea, which served as the basis for most of those compounds, is still sound.

Roche pulls the plug on its anti-amyloid antibody crenezumab in January, after it has no chance of showing any benefit? Not enough to kill the amyloid hypothesis. Merck bails on verubecstat, which shut down production of toxic amyloid, in 2017? Still not enough. Eli Lilly announces in 2016 that its anti-amyloid solanezumab failed to show benefit in people with mild Alzheimer's? Nope, not dead yet.

The same chorus was heard after Thursday's terse announcement by Biogen and its partner Eisai that they were halting two clinical trials of the anti-amyloid aducanumab because it had basically no chance of showing effectiveness.

"I do not think it means that the known amyloid accumulation over decades prior to symptoms has nothing to do with the clinical features of the disease," said Dr. Dennis Selkoe of Boston's Brigham and Women's Hospital. Since the 1980s, he has helped develop the amyloid hypothesis, the idea that the accumulation of these proteins around brain neurons is both the cause of the disease and the key to treating it.

It's starting to feel like a very sad real-world version of the old Monty Python sketch, where no matter how many limbs the dark knight has lopped off by his sword-wielding foe, he declares it's only a flesh wound.

If there is a silver lining, it's that the failures of anti-amyloid compounds and antibodies usually teach us more about Alzheimer's. The aducanumab debacle, for instance, reinforces the realization that removing amyloid plaques, as antibody after antibody has done, "is simply too late for symptomatic patients," said longtime Alzheimer's researcher Dr. Rudy Tanzi of Massachusetts General Hospital. And it points to another lesson: Amyloid is likely just one piece of a more complicated puzzle.

"We know that amyloid deposition starts a decade or so before [Alzheimer's] symptoms appear," Tanzi said. (The patients in the Biogen-Eisai trial had mild or very mild Alzheimer's.) He therefore likens an anti-amyloid strategy to blowing out a match (amyloid plaques) after the forest (the brain) is already burning (suffering the death of neurons and destruction of synapses). Although amyloid plays an important role in Alzheimer's, he said, it isn't the right therapeutic target once someone has cognitive symptoms. By then, neurons have started dying off and synapses are vanishing.

Aducanumab seems to clear amyloid plaques, but that didn't help the trial patients. Among the possible reasons, Selkoe suggested, are that most had disease that was "too advanced" to be reversed. In other words, the amyloid hypothesis is sound, but once the protein shows up in the brain, it has already killed so many neurons and destroyed so many synapses there's no turning back — or at least, no turning back by eliminating amyloid.

Related:
Listen: Another big Alzheimer's failure, postpartum progress, and Long Island shores

At the risk of oversimplifying, Alzheimer's disease likely begins with an infectious agent or head trauma. (The rare inherited forms, which strike people in their 50s, are caused by mutations.) In response, the brain ramps up production of amyloid, which forms sticky plaques between neurons. That triggers inflammation as well as production of the "other" Alzheimer's protein, called tau, which accumulates within neurons; both inflammation and tau are toxic to neurons.

In this model, amyloid is likely necessary for Alzheimer's but not sufficient. "I don't think anyone can say that amyloid is not related to this disease, but it's not enough," said Daniel Alkon, chief science officer of Neurotrope, which is running a phase 2 trial of an experimental Alzheimer's compound.

For one thing, study after study shows that some elderly people who die with no cognitive impairment nonetheless have brains full of amyloid. "If you're not demented despite amyloid, that shows that something else was going on, such as neuroprotective or even neuroregenerative mechanisms," Alkon said.

One emerging strategy to treat Alzheimer's is therefore to emulate the natural mechanisms that let some amyloid-packed brains remain healthy. Neurotrope's compound, for instance, targets amyloid (remove the match that started the forest

fire) and also boosts a biochemical pathway that restores synapses (like replanting trees after the inferno).

Related:
Alzheimer's drug failure leaves Biogen in a precarious place

The hope is to tap into the brain's capacity for "compensatory regeneration," in which neurons respond to the loss of synapses by creating new ones nearby or causing existing ones to form circuits able to replace those lost to synaptic death. "Nearby synapses can step in," Tanzi said. Ideally, compensatory regeneration would mimic the function of the lost synapses closely enough to maintain or regain the cognitive capacity and memories that are otherwise lost.

Another strategy is to damp down inflammation. Among the many companies trying this are AZTherapies, where Tanzi chairs the scientific advisory board. "If you want to help patients, you have to hit neuroinflammation," he said.

An even newer idea is to treat seriously the growing body of evidence that Alzheimer's can start with the arrival of viruses or other pathogens in the brain. In response, argue Tanzi and his Mass. General colleague Robert Moir, the brain churns out amyloid, an antimicrobial peptide but also one that, in large quantities, is toxic to synapses. That implies that interventions as simple as treating herpes infections might reduce the risk of Alzheimer's, as a 2018 study found, or that eliminating from the brain the bacteria that cause gum disease (and can reach the gray matter) might treat Alzheimer's, as a 2019 study in mice suggests.

Links between heart health and the risk of Alzheimer's suggest that increasing blood flow to the brain might at least slow down the disease, said Heather Snyder, the senior director of medical and scientific operations at the Alzheimer's Association. Similarly, changes in the immune system (processes related to inflammation as well as distinct ones) occur in Alzheimer's brains, she said.

Related:

After the blowup of the biggest hope for Alzheimer's, what's next in the pipeline?

In an indication of how much about Alzheimer's remains mysterious, however, scientists don't even know if a component of the immune system that they're pretty sure is involved in the disease — cells called microglia — are killers or saviors. On the one hand, there is evidence that microglia protect against Alzheimer's: When they're impaired (for genetic reasons, say), it raises the risk of the disease. But evidence just as strong shows that overactive microglia can harm neurons. They can surround synapses and protect them from amyloid, but they can also worsen the neuron-killing tendencies of tau.

"We are still struggling to understand the basic biology of the brain as well as the basic biology of Alzheimer's," Snyder said.

Even those who insist that the amyloid hypothesis is alive and well recognize that removing amyloid from the brains of Alzheimer's patient has almost no chance of reversing the disease. At minimum, an anti-amyloid strategy will have to be paired with others.

"Something is wrong with the way we're thinking about Alzheimer's and amyloid," said chemist Derek Lowe, a longtime pharma industry scientist who blogs at In the Pipeline. "It's been wrong for a long time and that's been clear for a long time. It's time to do something else."

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目次に戻る

10. 遺伝子組み換え食品は安全である、日本のパネルが結論

2019 年 3 月 19 日

遺伝子組み換え食品、日本でも夏以降流通か、というニュース、早速アメリカでも取りあげられているので、それを簡単に紹介する。
昨日、諮問委員会で合意された勧告が厚生労働省によって採用された場合、関連する技術が特定の基準を満たす限り、日本は安全性評価なしで遺伝子編集食品を消費者に販売することを許可する。これは、日本国内でヒトが消費することが前提の動植物への CRISPR や他の技術使用の扉を開くであろう。
遺伝子組み換え食品を規制する方法は国際的にも熱く議論されている。1 年前に米国農務省は、遺伝子組み換え食品の多くは規制を必要としない、と結論付けている。逆に EU の裁判所は、2018 年 7 月に遺伝子組み換え作物は伝統的なトランスジェニック植物と同じ長い承認プロセスを経なければならない、と判断した。
今回、日本はアメリカの例に従うように設定されたようだ。
今現在日本は、表示されているものに限り、安全性試験に合格した遺伝子組み換え食品の販売が承認されている。しかし、ほとんどの日本農家は遺伝子組み換え作物を避けている、が、一方で大量の GM 加工食品や家畜飼料を輸入している。

英文記事：
https://www.sciencemag.org/news/2019/03/gene-edited-foods-are-safe-japanese-panel-concludes?utm_campaign=news_daily_2019-03-20&et_rid=375979900&et_cid=2725816

In Japan, genetically modified products have to be labeled; an advisory panel did not say whether that should apply to gene-edited food as well.

SHIHO FUKADA/BLOOMBERG/GETTY IMAGES

Gene-edited foods are safe, Japanese panel concludes

By **Dennis Normile** Mar. 19, 2019 , 1:15 PM

Japan will allow gene-edited foodstuffs to be sold to consumers without safety evaluations as long as the techniques involved meet certain criteria, if recommendations agreed on by an advisory panel yesterday are adopted by the Ministry of Health, Labour and Welfare. This would open the door to using CRISPR and other techniques on plants and animals intended for human consumption in the country.

"There is little difference between traditional breeding methods and gene editing in terms of safety," Hirohito Sone, an endocrinologist at Niigata University who chaired the expert panel, told NHK, Japan's national public broadcaster.

How to regulate gene-edited food is a hotly debated issue internationally. Scientists and regulators have recognized a difference between genetic modification, which typically involves transferring a gene from one organism to another, and gene editing, in which certain genes within an organism are disabled or altered using new techniques such as CRISPR. That's why a year ago, the U.S.Department of Agriculture concluded that most gene-edited foods would not need regulation. But the European Union's Court of Justice ruled in July 2018 that gene-edited crops must go through the same lengthy approval process as traditional transgenic plants.

Now, Japan appears set to follow the U.S. example. The final report, approved yesterday, was not immediately available, but an earlier draft was posted on the ministry website. The report says no safety screening should be required provided the techniques used do not leave foreign genes or parts of genes in the target organism. In light of that objective, the panel concluded it would be reasonable to require information on the editing technique, the genes targeted for modification, and other details from developers or users that would be made public while respecting proprietary information.

The recommendations leave open the possibility of requiring safety evaluations if there are insufficient details on the editing technique. The draft report does not directly tackle the issue of whether such foods should be labeled. The ministry is expected to largely follow the recommendations in finalizing a policy on gene-edited foods later this year.

Consumer groups had voiced opposition to the draft recommendations, which were released for public comment in December 2018. Using the slogan "No need for genetically modified food!" the Consumers Union of Japan joined other groups circulating a petition calling for regulating the cultivation of all gene-edited crops, and safety reviews and labeling of all gene-edited foods.

Whether consumers will embrace the new technology remains to be seen. Japan has approved the sale of genetically modified (GM) foods that have passed safety tests as long as they are labeled. But public wariness has limited consumption and has led most Japanese farmers to shun GM crops. The country does import sizable volumes of GM processed food and livestock feed, however. Japanese researchers are reportedly

working on gene-edited potatoes, tomatoes, rice, chicken, and fish. "Thorough explanations [of the new technologies] are needed to ease public concerns," Sone said.

Correction, 22 March, 3:25 p.m.: *This story has been updated to note that the U.S. Department of Agriculture, not the U.S. Food and Drug Administration, decided not to regulate gene-edited foods.*

Posted in:

- Asia/Pacific
- Plants & Animals

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Dennis Normile