Bio News – May, 2019

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

3/27　Celgene がもたもたしている間に Novartis が早々と多発性硬化症薬の FDA 承認獲得

3/27　大麻成分入り食品と関連する救急科行きが予想以上に多い～米国コロラド州

マリファナ（大麻）を楽しむことが 2014 年に合法となった米国コロラド州のデータによると、その年を挟む 2012-2016 年に大麻と関連する救急科（ED）受診が 3 倍以上増え、大麻成分入り食品（Edible Cannabis）関連の ED 受診数はその販売量からの推定を大きく上回っている。

3/27　AbbVie の年間売り上げ 10 億ドル超えが予想される乾癬薬 SKYRIZI （risankizumab） が日本でまず承認された

3/28　Sana Biotechnology、免疫拒絶なしで移植しうる幹細胞作成技術をハーバード大学から取得

3/28　Eli Lilly が、J&J、Sanofi、Roche に倣って、ImmuNext と組んで自己免疫疾患薬を開発

3/28　iPS で色素細胞のもと作製＝皮膚がん研究に活用期待 -神戸大

3/29　週 1 本のワインの発癌性は週 5-10 本の喫煙量に相当 -英研究

3/29　AstraZeneca、第一三共に 13 億 5,000 万ドルを払って Ph3 段階乳癌薬を共同販売

3/29　AbbVie が Rova-T の Ph3 失敗で、買収した Stemcentrx の従業員 178 人を解雇

4/1　Novartis が IFM Therapeutics の子会社 IFM Tre を 3 億 1,000 万ドルで買収

4/1　抗菌薬セファゾリン供給停止 手術に影響、病院悲鳴

セファゾリンは、世界保健機関（WHO）が必要不可欠な医薬品に挙げる薬の一つ。国内シェア約 6 割を占める日医工（富山市）によると、昨年末からイタリアの会社で製造する原薬に異物が混入したものが増えて製造できなくなり３月上旬に在庫がなくなったという。

4/3　AbbVie、オランダでは Humira の大幅値下げでバイオシミラーを封じ込めている

4/3　英国ケンブリッジ生まれの投資会社 Cambridge Innovation Capital (CIC) が 1 億 5,000 万ポンド (1 億 9,600 万ドル) 調達

4/3　米国の今年の麻疹患者数は昨年を既に上回っている

4/4　米国 FDA が若者のタバコ依存を減らす取り組みを進める

主に電子タバコ使用が 10 代青少年に増えていることを背景に、FDA が若者のタバコ依存とその断ち切りについて 5 月 15 日に公開討論。

4/5　Amgen が Novartis に片頭痛薬 Aimovig 提携の解消を通知～Novartis は Amgen を告訴

Amgen が Novartis に Amgen 生まれの片頭痛薬 Aimovig（erenumab）の提携解消を通知し、2015 年の提携から少なくとも 8 億 7,000 万ドルを同剤につぎ込んだという Novartis はその通知に納得がいかず Amgen に提携解消の権利はないとの判断を求める訴訟を起こした。
Novartis は Aimovig のライバル薬となりうる Alder の片頭痛薬を受託製造する約束を交わしており、

Amgen によると、Novartis に解決を求めたものの聞き入れず更なる製造合意に踏み切った。Aimovig は昨年欧米で承認され、米国では Novartis と Amgen が共同販売、日本を除くそれ以外の地域では Novartis、日本では Amgen が独占販売する取り決めとなっている。

4/5　ゲノム編集の Editas Medicine と iPS 細胞の BlueRock が組んで患者毎作製不要の細胞治療を開発

4/5　第一三共、白血病薬 quizartinib の米国審査延長～アステラスの Xospata と対照的

4/5　Cytovant Sciences（新たな語尾"vant"企業）誕生～アジアの患者を救う細胞治療開発

Vivek Ramaswamy 氏の Roivant Sciences とその中国向け新薬開発子会社 Sinovant Sciences が協力して新たな語尾"vant"企業 Cytovant Sciences が設立され、Medigene から手に入れた技術を使って中国・韓国・日本の患者を救う NY-ESO-1 癌抗原標的 T 細胞製品の開発に取り組む。

4/6　Merck & Co と提携する脂肪肝治療会社 NGM Biopharmaceuticals が 1 億 700 万ドル IPO 調達達成

4/6　Humira 等の抗炎症薬市場は飽和状態ではなくまだまだ成長の余地あり/アナリスト

Credit Suisse のアナリストによると、年間売上 200 億ドル近い Humira（adalimumab）を初めとして大成功薬が幾つかある抗炎症薬市場は飽和状態かといえばそうでもなく、新しい作用機序の新薬や経口薬、さらには生物薬後発品にさえも支えられてまだまだ拡大しうる。

4/8　昨年 2018 年の売り上げ上位 15 の製薬会社の顔ぶれは 2017 年と変わらず

製薬会社大手の 2018 年決算が大方出揃い、製薬ニュース FiercePharma が去年の売り上げ上位 15 社を発表した。

https://www.fiercepharma.com/special-report/top-15-pharma-companies-by-2018-revenue

4/8　厚労省 B 型肝炎ワクチン不足恐れ　10 月以降供給停止 -Merck & Co.の原液製造工程に問題

4/9　Alnylam が Sanofi を離れ、入れ替わりで Regeneron と提携

4/9　日本の 18～39 歳の男女のおよそ 4 人に 1 人は異性との性交の経験なし、これに対して、米国の男性の 8%もが 13 歳までに性交を経験

https://headlines.yahoo.co.jp/hl?a=20190408-00000025-jij-soci

4/9　がん10年生存率、56.3%に　早期の乳がんは 9 割超　-国立がん研究センター

4/10　Novartis の眼科医療機器事業 Alcon が正式に独立

4/10　寄生虫でダイエット効果　世界初証明　群馬大など

https://this.kiji.is/488454163811271777

https://headlines.yahoo.co.jp/hl?a=20190423-00000033-asahi-soci

4/11　塩野義製薬、オピオイドによる便秘薬の欧米販売を Novartis（欧州　-ドイツ、英国、オランダ）と BioDelivery（米）に任せる

4/11　Sanofi が6月から米国の糖尿病患者にインスリンを一律 99 ドルの月極で安く提供

4/12　アメリカンフットボール元プロ選手脳のタウ蛋白質量増加が示された

4/12　ヒト受精卵の遺伝子改変、臨床応用防止へ法規制　−政府検討

4/12　トリカブトの根から神経障害性疼痛抑える成分発見　治療薬に期待 −名古屋市立大

4/13　サルの脳に人間の遺伝子、中国の研究者が移植実験　批判も

4/13　日本人特有の光線過敏症を発見　富山大学

4/15　Bristol-Myers Squibb の株主が Celgene の買収を承認

Bristol-Myers Squibb（BMS）が 740 億ドル（$74 billion）で Celgene を買収するのを BMS の株主が許可。Celgene の株主も BMS による Celgene 買収を許可している。買収は今年 3Q に完了見込み。

4/15　Catalent が遺伝子治療開発受託会社 Paragon を 12 億ドルで買収

4/16　バイオテック 4 社がナスダック IPO 調達を予定

バイオテック 4 社、NextCure、Cortexyme、Applied Therapeutics、Milestone Pharmaceuticals がいずれも最大 8,625 万ドルのナスダック IPO 調達を目指している。

4/16　Gelesis の胃の水を吸って膨らんで体重減少を助けるカプセル剤販売を FDA が許可

4/18　死後 4 時間後の豚から取り出した脳の機能を回復させることに成功　−エール大学

https://news.yahoo.co.jp/pickup/6320732

4/18　iPS網膜移植、治療実用化へ「7合目まできた」　世界初臨床研究で移植の 5 人、経過良好 −理化学研究所生命機能科学研究センター

4/18　痛みや痒みの神経細胞のみを黙らす薬を開発する Nocion、2,700 万ドル調達

4/19　親から引き継いだ肥満傾向を言い当てる遺伝子検査が開発された

4/23　世界一の癌研究センターMD Anderson Cancer Center が中国人科学者 3 人を解雇

米国での研究成果を中国が盗もうとしているとの懸念を受け、テキサス州ヒューストンの世界一有名な癌研究センターMD Anderson Cancer Center が中国人科学者 3 人を解雇。地元情報サイト Houston Chronicle によると、それら 3 人を含む MD Anderson のアジア人教授 5 人が利害の対立や米国外からの未申告の報酬があるとの米国立衛生研究所（NIH）からの指摘を受け解雇が決定。

4/23　Alvogen、箱への用量誤記載でフェンタニル貼り薬を回収

4/23　Gladstone Institutes と AstraZeneca が CRISPR ゲノム編集の余計な作用を隈なく検出する方法を開発

4/23　皮膚の細胞から 3D プリンターで人工血管　透析患者への移植を申請　−佐賀大

4/23　腎臓病の危険示す目印を発見　−東北大

4/24　Sanofi がマサチューセッツ州のバイオテク集積地である Kendall Square 事務所を bluebird bio に又貸し

4/24　米国では若者も成人も 10 年前に比べて毎日 1 時間長く座っている

4/25　ヒト胚の遺伝子編集を全世界で停止すべきとの手紙を専門家が米国政府に送付

中国の研究者 He Jiankui 氏がやがて出産まで至るヒト胚を所属大学に無断で遺伝子編集したことを受け、米国の遺伝子/細胞治療学会・American Society of Gene & Cell Therapy (ASGCT) の経営陣や元リーダー等 62 人がヒト生殖細胞の遺伝子編集を全世界で停止するように協力すべきとの手紙を米国政府に送付。

4/25　2018 年までの 10 年間の承認アルツハイマー病薬は 1 つのみ　～86 の開発が潰えた

IQVIA のまとめによると、2018 年までの 10 年間に承認されたアルツハイマー病薬は Namzaric の 1 つだけで、86 の開発品が中止された。しかも Namzaric は新有効成分ではなく、2 つの承認薬・memantine（メマンチン）と donepezil（ドネペジル）の合剤。今年に入ってもアルツハイマー病の開発は失敗続きで、1 月には Roche が Crenezumab の第 3 相試験 2 つを中止し、3 月には Biogen が aducanumab の Ph3 試験失敗を発表している。aducanumab と Crenezumab はどちらも Aβ 標的薬であり、Aβ 標的無効の証明が一段と増している。

4/25　GSK、帯状疱疹ワクチン Shingrix のモンタナ州ハミルトンの製造拠点を拡張

4/26　世界一売れている AbbVie の薬 Humira、全世界での売り上げ初めて減少

4/26　米国妊婦の 9 人に 1 人が飲酒

4/26　今年の米国麻疹患者数が 2000 年の撲滅宣言以降最多の 695 人に達した

4/28　ブタ体内で人の膵臓、iPS 利用　東大が年度内にも実施、国内初

4/28　食品の防腐剤・プロピオン酸が糖尿病を生じ易くする可能性

4/29　2050 年の米国 1 人あたりの医療費は 15,000 ドルを超える

4/30　先天性疾患を子宮内で遺伝子治療　米チーム、マウスをゲノム編集

https://headlines.yahoo.co.jp/hl?a=20190430-00000554-san-sctch

企業関連ニュース/他のトップページに戻る

今月の研究関連ニュース/他

1. 新しい遺伝子変異を持つほとんど痛み知らずの女性

British Journal of Anaesthesia 誌に掲載された研究記事によると、今まで同定されていなかった遺伝子変異によって、ほとんど痛みのない生活を送っている女性がスコットランドに存在。彼女は不安や恐怖もほとんど経験したことがないという。例えば、65 歳の時、彼女は股関節に問題があり治療を求めたが、痛みがないにもかかわらず、重度の間接変性を伴うことが判明。66 歳の時に受けた手術では、通常は相当な痛みを伴うのだが、手術後の痛みは報告されていないという。また、歯科手術などの後にも鎮痛剤を使用したことがない、と研究者に伝えている。ロンドン大学とオックスフォード大学の疼痛遺伝学者に紹介された彼女の遺伝分析から、2 つの注目すべき突然変異が発見された。1 つは、偽遺伝子の微小欠失で、これは FAAH-OUT と名付けられた。もう 1 つは、FAAH 酵素を制御する隣接遺伝子の突然変異である。FAAH 遺伝子は、痛みの感覚、気分および記憶の中心となる内在性カンナビノイドシグナル伝達に関与しているため、痛みの研究者にはよく知られているが、FAAH-OUT と呼ばれる遺伝子は、以前は機能的ではない「ジャンク」遺伝子であると考えられていた。実際に、FAAH 遺伝子を持たないマウスでは、疼痛知覚が低下し、創傷治癒が促進され、恐怖消去の記憶が増強され不安が減少した。研究者らは、この女性が 60 代までこの状態に気付いていなかったことを考えると、同じ突然変異を持つ人がもっといる可能性があるとしている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/03/190327203450.htm

WOMAN WITH NOVEL GENE MUTATION LIVES ALMOST PAIN-FREE

Date:

March 27, 2019

Source:

University College London

Summary:

A woman in Scotland can feel virtually no pain due to a mutation in a previously-unidentified gene, according to a research article. She also experiences very little anxiety and fear, and may have enhanced wound healing due to the mutation, which the researchers say could help guide new treatments for a range of conditions.

FULL STORY

A woman with a novel gene mutation lives a virtually pain-free life.

Credit: © gustavofrazao / Fotolia

A woman in Scotland can feel virtually no pain due to a mutation in a previously-unidentified gene, according to a research paper co-led by UCL.

She also experiences very little anxiety and fear, and may have enhanced wound healing due to the mutation, which the researchers say could help guide new treatments for a range of conditions, they report in the *British Journal of Anaesthesia*.

"We found this woman has a particular genotype that reduces activity of a gene already considered to be a possible target for pain and anxiety treatments," said one of the study's lead researchers, Dr James Cox (UCL Medicine).

"Now that we are uncovering how this newly-identified gene works, we hope to make further progress on new treatment targets."

At age 65, the woman sought treatment for an issue with her hip, which turned out to involve severe joint degeneration despite her experiencing no pain. At age 66, she underwent surgery on her hand, which is normally very painful, and yet she reported no pain after the surgery. Her pain insensitivity was diagnosed by Dr Devjit Srivastava, Consultant in Anaesthesia and Pain Medicine at an NHS hospital in the north of Scotland and co-lead author of the paper.

The woman tells researchers she has never needed painkillers after surgery such as dental procedures.

She was referred to pain geneticists at UCL and the University of Oxford, who conducted genetic analyses and found two notable mutations. One was a microdeletion in a pseudogene, previously only briefly annotated in medical literature, which the researchers have described for the first time and dubbed FAAH-OUT. She also had a mutation in the neighbouring gene that controls the FAAH enzyme.

Further tests by collaborators at the University of Calgary, Canada, revealed elevated blood levels of neurotransmitters that are normally degraded by FAAH, further evidence for a loss of FAAH function.

The FAAH gene is well-known to pain researchers, as it is involved in endocannabinoid signalling central to pain sensation, mood and memory. The gene now called FAAH-OUT was previously assumed to be a 'junk' gene that was not functional. The researchers found there was more to it than previously believed, as it likely mediates FAAH expression.

Mice that do not have the FAAH gene have reduced pain sensation, accelerated wound healing, enhanced fear-extinction memory and reduced anxiety.

The woman in Scotland experiences similar traits. She notes that in her lifelong history of cuts and burns (sometimes unnoticed until she can smell burning flesh), the injuries tend to heal very quickly. She is an optimist who was given the lowest score on a common anxiety scale, and reports never panicking even in dangerous situations such as a recent traffic incident. She also reports memory lapses throughout life such as forgetting words or keys, which has previously been associated with enhanced endocannabinoid signalling.

The researchers say that it's possible there are more people with the same mutation, given that this woman was unaware of her condition until her 60s.

"People with rare insensitivity to pain can be valuable to medical research as we learn how their genetic mutations impact how they experience pain, so we would encourage anyone who does not experience pain to come forward," said Dr Cox.

The research team is continuing to work with the woman in Scotland, and are conducting further tests in cell samples, in order to better understand the novel pseudogene.

"We hope that with time, our findings might contribute to clinical research for post-operative pain and anxiety, and potentially chronic pain, PTSD and wound healing, perhaps involving gene therapy techniques," said Dr Cox.

"The implications for these findings are immense," said Dr Srivastava.

"One out of two patients after surgery today still experiences moderate to severe pain, despite all advances in pain killer medications and techniques since the use of ether in 1846 to first 'annul' the pain of surgery. There have already been unsuccessful clinical trials targeting the FAAH protein -- while we hope the FAAH-OUT gene could change things particularly for post-surgical pain, it remains to be seen if any new treatments could be developed based on our findings."

"The findings point towards a novel pain killer discovery that could potentially offer post-surgical pain relief and also accelerate wound healing. We hope this could help the 330 million patients who undergo surgery globally every year," Dr Srivastava said.

"I would be elated if any research into my own genetics could help other people who are suffering," the woman in Scotland commented.

"I had no idea until a few years ago that there was anything that unusual about how little pain I feel -- I just thought it was normal. Learning about it now fascinates me as much as it does anyone else."

Lead funding for the study came from the Medical Research Council and Wellcome.

Story Source:

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

Journal Reference:

1. Abdella M. Habib, Andrei L. Okorokov, Matthew N. Hill, Jose T. Bras, Man-Cheung Lee, Shengnan Li, Samuel J. Gossage, Marie van Drimmelen, Maria Morena, Henry Houlden, Juan D. Ramirez, David L.H. Bennett, Devjit Srivastava, James J. Cox. **Microdeletion in a pseudogene identified in a patient with high anandamide concentrations and pain insensitivity**. *British Journal of Anaesthesia*, 2019; DOI: 10.1016/j.bja.2019.02.019

Cite This Page:

- MLA
- APA
- Chicago

University College London. "Woman with novel gene mutation lives almost pain-free." ScienceDaily. ScienceDaily, 27 March 2019. <www.sciencedaily.com/releases/2019/03/190327203450.htm>.

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2. 鬱、肥満、慢性痛は同一タンパク質を標的にして治療できる

鬱、肥満、慢性痛は全て「FK506 結合タンパク質 51」または「FKBP51」と呼ばれる同一のタンパク質の影響を受ける。これまで、この標的を阻害するための努力は、類似したタンパク質には影響を及ぼさないというハードルが非常に高いために、報われないでいた。
今回、ドイツのダルムシュタット工科大学を始めとする研究グループは、マウスの FKBP51 を効果的にブロックし、慢性痛を軽減し、食餌性肥満や鬱にも良い効果をもたらすことのできる化合物の開発に成功した。この SAFit2 と呼ばれる新しい化合物は、アルコール依存症や脳腫瘍にも応用できる、としている。
研究者らは、今日、American Chemical Society (ACS) の 2019 年春季全国大会＆博覧会でこの研究結果を発表する。

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/2019/04/190401075208.htm

DEPRESSION, OBESITY, CHRONIC PAIN COULD BE TREATED BY TARGETING THE SAME KEY PROTEIN

Date:

April 1, 2019

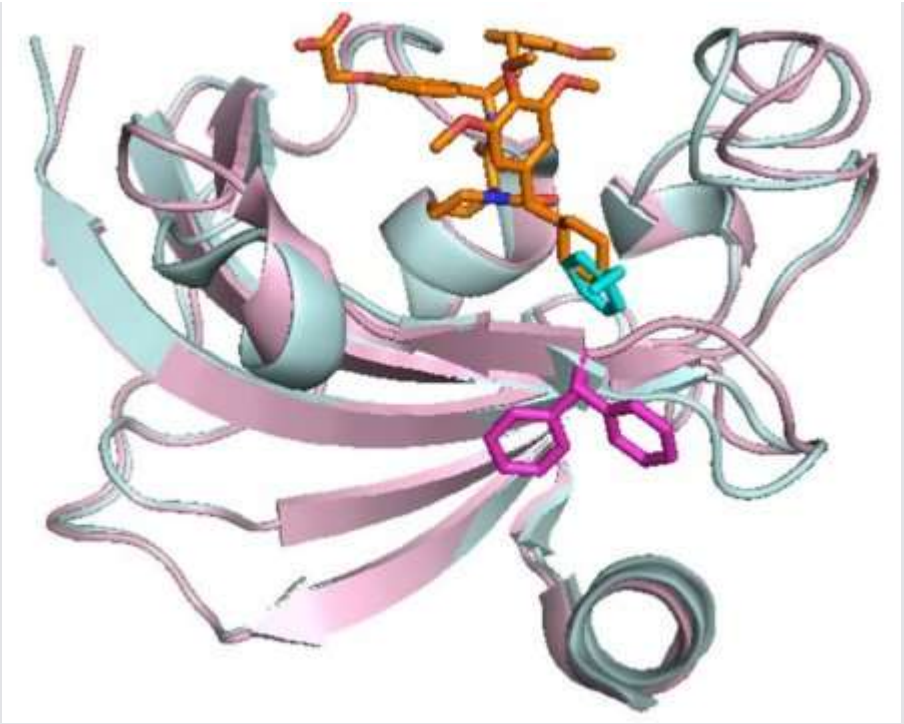
Source:

American Chemical Society

Summary:

Major depression, obesity and chronic pain are all linked to the effects of one protein, called FKBP51. Researchers have now developed a highly selective compound that can effectively block FKBP51 in mice, relieving chronic pain and having positive effects on diet-induced obesity and mood. The new compound also could have applications in alcoholism and brain cancer.

FULL STORY



A new inhibitor (orange) is selective for FKBP51, which is involved in depression, chronic pain and obesity.

Credit: Felix Hausch

Major depression, obesity and chronic pain are all linked to the effects of one protein, called "FK506-binding protein 51," or FKBP51. Until now, efforts to inhibit this target have been hampered by the difficulty of finding something specific enough to do the job and not affect similar proteins. Now a research group has developed a highly selective compound that can effectively block FKBP51 in mice, relieving chronic pain and having positive effects on diet-induced obesity and mood. The new compound also could have applications in alcoholism and brain cancer.

The researchers will present their results today at the American Chemical Society (ACS) Spring 2019 National Meeting & Exposition.

"The FKBP51 protein plays an important role in depression, obesity, diabetes and chronic pain states," says Felix Hausch, Ph.D., the project's principal investigator. "We developed the first highly potent, highly selective FKBP51 inhibitor, called SAFit2, which is now being tested in mice. Inhibition of FKBP51 could thus be a new therapeutic option to treat all of these conditions."

Hausch, who is at the Technical University of Darmstadt, started the project when studies were published linking the protein to depression. "I was intrigued by the peculiar regulatory role it seemed to play in cells," he says. "And there was a known natural product that could serve as a starting point. Collectively, this looked like an interesting protein to work on."

FKBP51 is expressed in multiple places throughout the body, such as the brain, skeletal muscle tissue and fat. It also has multiple effects. For example, the protein can restrict the uptake of glucose

and the browning of fat, so that the body stores fat instead of burning it. It also affects stress responses. So, Hausch and his colleagues figured that blocking this protein could be the key to developing drugs to treat a variety of conditions.

But FKBP51 looks a lot like its closest protein cousin, FKBP52. "These two proteins are very similar in structure, but they are doing opposing things in cells," Hausch says. "We have this yin-yang situation. Selectivity between these two proteins is thought to be crucial, but this is hard to achieve since the two proteins are so similar. We discovered that FKBP51 can change its shape in a way that FKBP52 can't, and this allowed the development of highly selective inhibitors."

The researchers have now used nuclear magnetic resonance techniques to detect a previously hidden binding site in FKBP51. The approach could help other researchers identify similar "cryptic" binding sites in challenging drug targets in the future, Hausch says.

His team is now testing SAFit2, the lead FKBP51 inhibitor they developed from these studies, in animals. "It indeed helps mice cope better in stressful situations," Hausch says. In mice, SAFit2 reduced stress hormone levels, promoted more active stress coping, was synergistic with antidepressants, protected against weight gain, helped normalize glucose levels and reduced pain in three animal models.

According to Hausch, much more needs to be done to get FKBP1 inhibitors to the point where they could be used as a drug molecule in human testing. In the meantime, the team is also exploring FKBP51 inhibitors in other applications. So far, the group has conducted a number of mouse studies on the involvement of FKBP51 in alcoholism, but results are still preliminary. In addition, Hausch points out that certain types of glioblastoma tumors overexpress FKBP51. He hopes that this result indicates FKBP51 inhibitors could be used in cancer treatment, when patients' tumors mutate beyond current drugs' capacity to treat them. "We may be able to resensitize them to different types of chemotherapy using these specific inhibitors," he says.

Story Source:

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

Cite This Page:

- MLA
- APA
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American Chemical Society. "Depression, obesity, chronic pain could be treated by targeting the same key protein." ScienceDaily. ScienceDaily, 1 April 2019. <www.sciencedaily.com/releases/2019/04/190401075208.htm>.

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3. あるタンパク質の活性を遮断することで、老齢マウスの認知が回復

スタンフォード大学医学部の研究者らは、抗体であるタンパク質の活性をブロックすることで、老齢マウスの認知行動を改善することに成功した。この研究成果は、4 月 3 日の *Nature* オンライン版で公開されている。
この研究の上級著者である神経学および神経科学の教授である Tony Wyss-Coray 博士の研究の焦点の一つは、ミクログリアと呼ばれる脳細胞であり、それは脳の免疫細胞としての機能とゴミ収集員としての機能がある。一般的に、ミクログリアのごみ収集性能は老化した脳において減少するが、なぜこれが起きるのか、そしてこのごみ収集の欠陥がどの程度認知障害の原因になるのか、不明であった。
研究者らは、彼らが薬物によって標的とされる可能性があると判断し、すでに薬物開発の焦点となっているタンパク質をコードする約 3,000 の遺伝子を選択。一度に 1 つずつ、タンパク質をコードする各遺伝子の能力をブロックした。目標は、各ブロックがマウスの培養ミクログリアの蛍光標識ラテックス小粒子摂取能力にどのように影響するかを学ぶことだった（ミクログリア細胞が明るく輝くほど、ゴミを食べやすくなる）。
並行実験において、研究者らは、老齢マウスと対比して若いマウスの海馬からのミクログリアにおいてこれらの約 3,000 の遺伝子のどれが活性であるかを決定した（海馬は、脳の両側に 1 つずつある脳の構造で、学習と記憶には不可欠）。
驚くべきことに、両方の実験の結果を比較したとき、彼らはミクログリアの食作用に影響を及ぼし、ミクログリアにおけるその活性が加齢と共に実質的に増加するただつ 1 の遺伝子を見出した。年配のミクログリアはこの遺伝子のコピーをはるかに多く生産し、その機能をノックアウトすることでミクログリアのゴミの食作用を大いに改善した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/04/190403135103.htm

BLOCKING PROTEIN'S ACTIVITY RESTORES COGNITION IN OLD MICE

Date:

April 3, 2019

Source:

Stanford Medicine

Summary:

By blocking a protein's activity with antibodies, investigators were able to improve cognitive behavior in aging mice.

Mouse. (stock image)

Credit: © Nady / Fotolia

By blocking a protein's activity with antibodies, Stanford University School of Medicine investigators were able to improve cognitive behavior in aging mice.

A paper describing the finding will be published online April 3 in *Nature*. Tony Wyss-Coray, PhD, professor of neurology and neurological sciences, is the senior author. The lead author is MD-PhD student John Pluvinage.

Wyss-Coray has been working for several years on the question of what causes the brain to lose its acuity with advancing age. One focus of his research has been a class of brain cells called microglia, which serve both as the brain's immune cells and its garbage crew. Among the many different things microglia do to keep the brain healthy is scarfing up bits of cellular debris and protein deposits that build up in the course of normal metabolic activity.

On average, the garbage-collecting performance of microglia diminishes in aging brains. Why this happens, and the extent to which the faulty garbage service is actually responsible for age-related cognitive losses, are unclear. But it's a decent bet that one way or another, microglial malperformance plays a role in neurodegeneration, said Wyss-Coray, the D. H. Chen Professor II and a senior research career scientist at the Veterans Affairs Palo Alto Health Care System.

"Many of the genes whose high-risk variants have recently been linked to Alzheimer's disease are known to be active in the brain only in microglia," he said. "Microglial genes' activation patterns are abnormal in Alzheimer's patients, and in other neurodegenerative disorders including Parkinson's disease and amyotrophic lateral sclerosis.

"We think we may have discovered a way to get these cells back on track and make them work the way they used to when we were young."

The ingest-then-digest procedure employed by microglia and other immune-cell types in the body is called phagocytosis. The study used laboratory techniques to identify mouse genes whose activity either impairs or enhances microglial phagocytosis and whose activity levels either increase or decrease substantially with age.

Blocking genes' functionality

The investigators picked about 3,000 genes encoding proteins that they judged could be targeted by drugs or that had already been the focus of drug development. One at a time, they blocked each gene's ability to encode a protein. The goal was to learn how each blockade affected the ability of cultured microglia from mice to ingest small particles of fluorescently labeled latex. (The brighter a microglial cell glowed, the better a refuse eater it was.)

"It was like examining the books of the garbage-hauling company," Wyss-Coray said. "We wanted to know: 'Is it the garbage truck's faulty wheels? The rusty containers? An unanticipated garbage overflow? Lazy or poorly trained staff? Or is the street in bad shape?'"

In a parallel experiment, the investigators determined which of those approximately 3,000 genes are more or less active in microglia from the hippocampi of young mice versus old mice. (The hippocampus is a brain structure, one on each side of the brain, that's essential to learning and memory.)

Surprisingly, when the scientists compared the results of both experiments, they found just one gene that affected microglial phagocytosis and whose activity in microglia substantially increased with advancing age. Older microglia produced far more copies of this gene -- a proxy for upregulated production of the protein for which the gene is a blueprint -- than younger ones did, and knocking out its function greatly improved microglial phagocytosis.

"Now we had a tentative suspect, a gene that had never before been implicated in microglial garbage removal," Wyss-Coray said. So they zeroed in on this gene, called CD22, which is found in both mice and humans.

In a follow-on experiment, the CD22 protein turned up three times as often on the surface of older mice's microglia as on those of younger mice's microglia, confirming the gene-activity finding. These proteins could be blocked by antibodies, molecules that bind to a specific protein and can be generated in the lab. Antibodies are bulky and don't easily penetrate cells, but they're excellent for targeting cell-surface proteins.

Injecting antibodies

Wyss-Coray's team injected antibodies to the CD22 protein into the hippocampus on one side of mice's brains. They also injected similar antibodies that were incapable of binding to CD22 into the hippocampus on the opposite side.

Along with the antibodies, the scientists administered fluorescence-labeled bits of myelin. This substance coats numerous nerve cells, for which it provides insulation. But myelin debris accumulates in aging brains and has been shown to overwhelm microglia's ability to clear it away.

Wyss-Coray and his associates found that, 48 hours later, the myelin bits they'd injected into the mice's hippocampi were far less prevalent on the side where they had administered CD22-blocking antibodies rather than "dummy" antibodies.

"Microglia are the only cells in mice's brain that actually express the CD22 protein, so this difference is likely due to the CD22-blocking antibodies' effect on microglia," Pluvinage said.

The investigators conducted analogous experiments, substituting a protein called beta-amyloid, whose buildup in the brain is a hallmark of Alzheimer's disease, and alpha-synuclein, another protein similarly associated with Parkinson's disease. In both cases, microglia exposed to CD22-

blocking antibodies outperformed their peers on the opposite side of the brain in ingesting the neurodegeneration-linked substances.

Then, the researchers lengthened the period of exposure from 48 hours to a full month. They reconfigured their injection technique to provide continuous CD22-blocking antibody infusion on both sides of the brain over this period. Along with a host of findings consistent with their earlier ones, Wyss-Coray's team observed that old mice receiving these infusions outperformed control mice of the same age on two different tests of learning and memory that are commonly used to assess mice's cognitive ability.

"The mice became smarter," Wyss-Coray said. "Blocking CD22 on their microglia restored their cognitive function to the level of younger mice. CD22 is a new target we think can be exploited for treatment of neurodegenerative diseases."

Story Source:

Materials provided by **Stanford Medicine**. Original written by Bruce Goldman. *Note: Content may be edited for style and length.*

Journal Reference:

1. John V. Pluvinage, Michael S. Haney, Benjamin A. H. Smith, Jerry Sun, Tal Iram, Liana Bonanno, Lulin Li, Davis P. Lee, David W. Morgens, Andrew C. Yang, Steven R. Shuken, David Gate, Madeleine Scott, Purvesh Khatri, Jian Luo, Carolyn R. Bertozzi, Michael C. Bassik, Tony Wyss-Coray. **CD22 blockade restores homeostatic microglial phagocytosis in ageing brains**. *Nature*, 2019; DOI: 10.1038/s41586-019-1088-4

Cite This Page:

- MLA
- APA
- Chicago

Stanford Medicine. "Blocking protein's activity restores cognition in old mice." ScienceDaily. ScienceDaily, 3 April 2019. <www.sciencedaily.com/releases/2019/04/190403135103.htm>.

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4. 2018 年の収入によるトップ 15 の製薬会社

製薬業界は常に流動的だが、有名企業は常に年間売上高ではトップ近くを占める。2018 年までのビッグファーマ企業のトップ5は、Johnson＆Johnson、Roche、Pfizer、Novartis、Merck＆Co。
実際、上位 15 社の名前は前年度のランキングと同じだが、順序には若干の変化が見られる。昨年の第 5 位の Sanofi は、売上高が前年同期比でほぼ 2%減少し第 7 位に転落。Gilead Sciences は、長年にわたり C 型肝炎の価格圧力を受け、2018 年には更に下落し、ポジションを 3 つ落とし第 13 位に。
反対に、Bristol-Myers Squibb は第 15 位から第 12 位へと上昇。Celgene の大量買収がスコアに含まれると、来年は更に高くなる見込み。 Celgene の 2018 年の売上高 150 億ドルを追加すると、BMS の年間売上高は約 380 億ドルになり、年間売上高でトップ 10 にランクインすることになる。
そして来年のランキングでは、少なくとも武田という全く新しい参入者が見られるはずだ。日本のバイオファーマは最近 Shire を買収したが、それをランキングに適格に反映するための合同財務を 2018 年分では発表していない。
このリストに載っている多くの企業は、近年大きな特許の喪失に直面している。Amgen と Johnson＆Johnson は、昨年貧血治療薬 Procrit と Epogen の最初の模倣品競争があり、Amgen は、Neulasta バイオシミラーとも対決しなければならなかった。
これらのトップ企業のいくつかは、今後の大ヒット商品の発売にも取り組んでいる。市場監視者は、世界のトップ医薬品である Humira を販売している AbbVie が今年、リウマチ性関節炎薬 upadacitinib の承認を獲得するだろうとしている。Novartis、AstraZeneca および他の製薬会社も 2019 年にヒット商品発売を予定している。
Boehringer Ingelheim はこのリストに入るのに十分な売上を生み出したかもしれないが、会社は 4 月 17 日まで報告しないので、Boehringer が 2018 の結果を発表した後にレポートを更新する。
FDA によると、全体として、業界は昨年 59 の新薬承認を獲得し、記録を樹立した。その中には、製薬業界で最初のカンナビノイド由来薬である GW Pharma の Epidiolex、およびいくつかの新しい CGRP 片頭痛予防薬があった。 Amgen と Novartis、Teva と Eli Lilly は、この新しいクラスの構築に取り組んでいる。
2019 年は、製薬会社が大きな疑問符に直面している。民主党員がアメリカの議会を管理している中で、議員は既に最高経営責任者らを呼んで薬の価格設定を説明している。
そしておそらくもっと重要なのは、FDA の Scott Gottlieb（MD）コミッショナーが手綱を引き渡すこと。トランプ政権がこの機関の運営を誰に託すか、そしてその新首長がどれほど活発に活動するか、まだ不透明だ。

THE TOP 15 PHARMA COMPANIES BY 2018 REVENUE

1. Johnson & Johnson
2. Roche
3. Pfizer
4. Novartis
5. Merck & Co.
6. GlaxoSmithKline

7. Sanofi
8. AbbVie
9. Bayer
10. Eli Lilly
11. Amgen
12. Bristol-Myers Squibb
13. Gilead Sciences
14. AstraZeneca
15. Teva Pharmaceutical Industries

研究関連ニュース/他のトップページに戻る

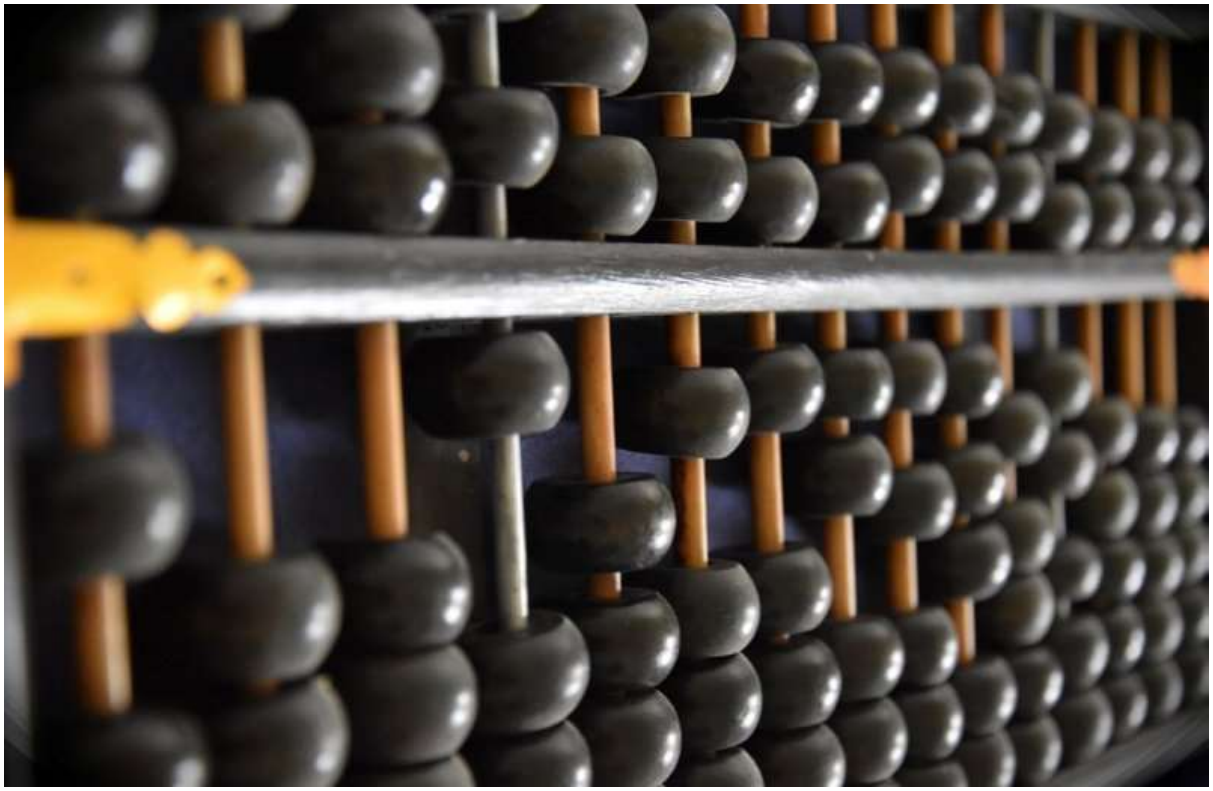
＜英文＞https://www.fiercepharma.com/special-report/top-15-pharma-companies-by-2018-revenue

PHARMA

THE TOP 15 PHARMA COMPANIES BY 2018 REVENUE

by Eric Sagonowsky |

Apr 8, 2019 12:00pm



Together, the top 15 drugmakers by 2018 revenue generated $560 billion in 2018. (Pixabay)

The pharma industry is always in flux, but the big names always turn up near the top of yearly sales rankings. This year is no different, with Johnson & Johnson, Roche, Pfizer, Novartis and Merck & Co. taking the top 5 spots in Big Pharma companies by 2018 sales.

In fact, the top 15 names are the same against prior year rankings, but the order has shifted. Last year's No. 5, Sanofi, slipped to No. 7 as its sales sank almost 2% year over year. Gilead Sciences, famously under hepatitis C pricing pressure for years, sank even farther in 2018, slipping three positions to No. 13.

On the flip side, Bristol-Myers Squibb climbed from No. 15 to No. 12. And if the company scores its massive Celgene buyout, it'll be even higher next year. Adding Celgene's $15 billion in 2018 revenue would have given BMS nearly $38 billion in annual sales, ranking it among the top 10 pharma companies by annual sales

And next year's ranking will see at least one entirely new entrant in Takeda. The Japanese biopharma recently scooped up Shire but hasn't released its combined financials for 2018 to make it eligible for the rankings.

Many companies on this list have faced big patent losses in recent years, while some have big launches coming up, too. Amgen and Johnson & Johnson saw their first copycat competition for anemia drugs Procrit and Epogen last year, while Amgen also had to face off against Neulasta biosims.

Looking ahead, several of these top companies will be working on blockbuster launches. Market watchers believe AbbVie, which markets the world's top drug, Humira, will win approval for rheumatoid arthritis drug upadacitinib this year. Analysts predict the drug will generate $2.24 billion by 2024, a much-needed boost as megablockbuster Humira starts facing biosims in 2023. Novartis, AstraZeneca and other drugmakers have blockbuster launches slated for 2019 as well.

RELATED: **From AbbVie's upadacitinib to new gene therapies: Pharma's 2019 blockbuster launches, ranked**

For these rankings and company profiles, FiercePharma consulted company earnings reports, securities filings, earnings transcripts and analyst reports, plus our own archives. We segregated Bayer's crop sciences unit as too far removed from human or animal health but included healthcare businesses at other top drugmakers, such as J&J's medical devices and Roche's diagnostics divisions.

We converted 2018 results to U.S. dollars using average exchange rates for the year provided by drugmakers. Average conversion rates for the year were 1 Swiss franc to $0.98 USD, £1 to $1.33 and €1 to $1.18.

Pharma revenues by year

Boehringer Ingelheim might have generated enough sales last year to make the list, but the company doesn't report until April 17. We'll update the report after Boehringer releases 2018 results.

Beyond their individual challenges, these top-ranked companies saw plenty of shared changes and setbacks last year. The Trump administration rolled out numerous drug pricing measures and proposals, some favored by the industry and others hated. In one big setback, last year Congress boosted their share of responsibility in Medicare Part D's "doughnut hole." The change could cost some companies hundreds of millions of dollars, or even billions, each year. But drugmakers support the administration's proposal to shake up rebates in Medicare and Medicaid.

RELATED: **FDA chief Scott Gottlieb steps down, leaving pet projects behind**

Overall, the industry garnered approvals for 59 novel drugs last year, setting a record, according to the FDA. Among them were the pharma industry's first cannabinoid-derived drug, Epidiolex from GW Pharma, and several new CGRP migraine prevention drugs. Amgen and Novartis, Teva and Eli Lilly are working to build that new class.

Drugmakers face some big question marks in 2019. With Democrats in control of the U.S. House, lawmakers have already called top CEOs on the carpet to explain their drug pricing, and numerous bills aimed at cutting drug costs are in the offing.

And perhaps more importantly, FDA Commissioner Scott Gottlieb, M.D., will be handing over the reins. It remains to be seen who the Trump administration will tap to run the agency and just how active that new chief might be. During his time at the

FDA, Gottlieb garnered an industry-friendly reputation, instituted new programs and guidelines across the board, and worked hard to fight high drug costs.

If you'd like to check out previous rankings, you'll find our top pharmas by 2017 revenues report **here**, and our 2016 edition **here**. As always, let us know if you have questions, comments or suggestions.

The top 15 pharma companies by 2018 revenue

- 1. Johnson & Johnson
- 2. Roche
- 3. Pfizer
- 4. Novartis
- 5. Merck & Co.
- 6. GlaxoSmithKline
- 7. Sanofi
- 8. AbbVie
- 9. Bayer
- 10. Eli Lilly
- 11. Amgen
- 12. Bristol-Myers Squibb
- 13. Gilead Sciences
- 14. AstraZeneca
- 15. Teva Pharmaceutical Industries

5. マウスが明らかにする 難聴に関与する 38 の新遺伝子

難聴に関与する複数の新しい遺伝子が、イギリスの Wellcome Sanger Institute および King's College London の研究者らによるマウス突然変異体の大規模研究で明らかにされている。同定された新たな遺伝子は、聴覚に関与する代謝経路および調節過程を明らかにする、としている。
本日（4 月 11 日）オープンアクセスジャーナル *PLOS Biology* 誌に発表されたこの研究は、聴覚障害の根底にある生物学を理解するのに役立ち、また聴覚回復のための豊富な治療標的を提供する。
加齢に伴う進行性難聴は極めて一般的であり、言語理解における困難、社会的孤立の増加、および関連するうつ病をもたらす、とされる。それはしばしば受け継がれるが、ほとんどの難聴につながる分子経路については知られていないため、治療法の開発にも繋がっていない。
難聴に関与する新しい分子を同定するために、研究者らは遺伝的アプローチを取り、1,211 の新しいマウス変異体を作り出した。彼らは敏感な電気生理学的テスト、聴覚脳幹反応を使ってこれらのマウスのそれぞれをスクリーニングし、彼らの聴力がどれほど良いかを調べた。
標的化マウス変異体のこの大規模スクリーニングは、これまで聴覚に関与していると疑われていなかった、マウスにおける難聴に関与する 38 個の遺伝子を同定。研究者らはまた、マウスで発見されたこれらの 38 個の遺伝子のいずれかがヒト成人発症型難聴と関連しているかどうかを調べるためにヒト DNA データを分析。彼らは、これらの 38 個の遺伝子のうちの 11 個が英国の集団の聴力と有意に関連していることを発見した。さらに 1 つの遺伝子、SPNS2 は、小児難聴と関連していた。

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/2019/04/190411145136.htm

MICE REVEAL 38 NEW GENES INVOLVED IN HEARING LOSS

MOLECULAR PATHWAYS REVEALED COULD IDENTIFY POTENTIAL DRUG TARGETS FOR RESTORING HEARING

Date:

April 11, 2019

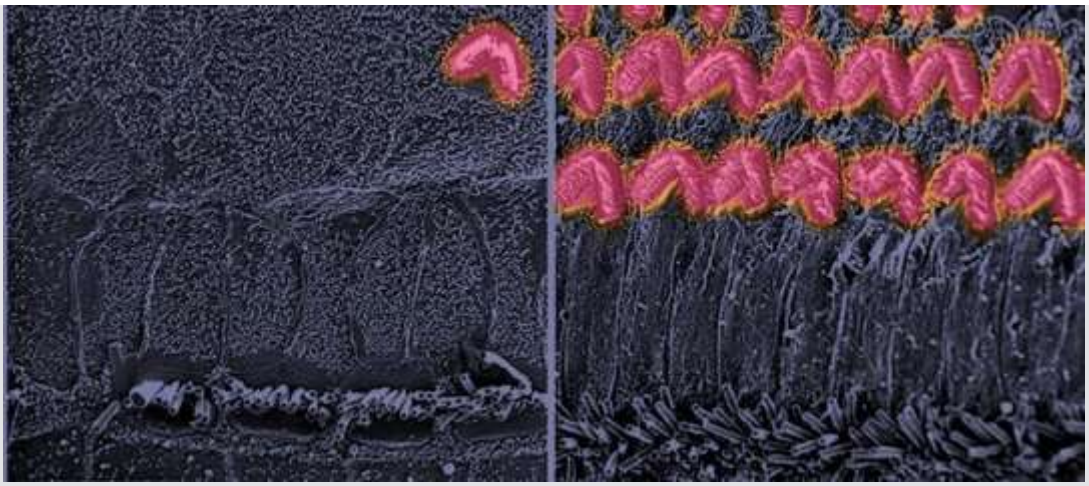
Source:

Wellcome Trust Sanger Institute

Summary:

Multiple new genes involved in hearing loss have been revealed in a large study of mouse mutants. The new genes reveal the metabolic pathways and regulatory processes involved in hearing.

FULL STORY



Extensive loss of outer hair cell (OHC) hair bundles (colored pink) revealed by scanning electron microscope (on the left), resulting in impaired hearing.

Credit: Ingham et al. (2019) PLOS Biology DOI: 10.1371/journal.pbio.3000194

Multiple new genes involved in hearing loss have been revealed in a large study of mouse mutants by researchers from the Wellcome Sanger Institute and King's College London, and colleagues. The new genes identified reveal the metabolic pathways and regulatory processes involved in hearing.

The study, published today (April 11) in the open-access journal *PLOS Biology*, helps to understand the underlying biology of deafness, and also provides a rich source of therapeutic targets for the restoration of hearing.

Progressive hearing loss with age is extremely common in the population, leading to difficulties in understanding speech, increased social isolation and associated depression. It can often be inherited, but so far very little is known about the molecular pathways leading to hearing loss, hampering the development of treatments.

To identify new molecules involved in hearing loss, the researchers took a genetic approach and created 1,211 new mouse mutants. They screened each of these mice using a sensitive electrophysiological test, the auditory brainstem response, to find out how good their hearing was.

This large-scale screen of targeted mouse mutants identified 38 genes involved in hearing loss in the mice, that had not been previously suspected to be involved in hearing.

The researchers also analysed human DNA data to ask if any of these 38 genes discovered in mice were associated with human adult-onset hearing loss. They found eleven of these 38 genes were significantly associated with hearing ability in the UK population. Furthermore one gene, SPNS2, was associated with childhood deafness.

Some of these genes revealed molecular pathways that may be useful targets for drug development.

Dr Chris Lelliott, an author from the Wellcome Sanger Institute, said: "This is the first time that a study of this scale has looked at levels of hearing and different types of hearing loss in mouse mutants and shows the power of large genetic screens. Only a handful of genes have previously been linked specifically to age-related hearing loss in adults, now our study adds many more potential new genes to follow up."

Further analysis of the genes identified, and the many different mechanisms within the ear that were revealed by the mutations, suggested that hearing loss is an extremely varied disorder and may involve as many as 1,000 genes.

Dr Selina Pearson, from the Wellcome Sanger Institute said: "This study is giving a huge insight into the complicated biology of hearing loss, and shows that because of all the different genes and pathways found, there won't be a single 'magic bullet' to stop all age-related deafness. This emphasises the value of mouse studies for identifying genes and mechanisms underlying complex processes such as hearing."

The study findings suggest that therapies may need to be directed at common molecular pathways involved in deafness rather than individual genes or mutations.

Prof Karen Steel, senior author on the paper from the Wellcome Sanger Institute and King's College London, said: "Several of these new mouse mutant lines showed normal development of hearing followed by later deterioration, suggesting the genes involved are good candidates for human age-related hearing loss. Our next step is to find out if we can influence the molecular pathways involved to slow down or stop the progression of hearing loss."

Story Source:

Materials provided by **Wellcome Trust Sanger Institute**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Neil J. Ingham, Selina A. Pearson, Valerie E. Vancollie, Victoria Rook, Morag A. Lewis, Jing Chen, Annalisa Buniello, Elisa Martelletti, Lorenzo Preite, Chi Chung Lam, Felix D. Weiss, Zöe Powis, Pim Suwannarat, Christopher J. Lelliott, Sally J. Dawson, Jacqueline K. White, Karen P. Steel. **Mouse screen reveals multiple new genes underlying mouse and human hearing loss**. *PLOS Biology*, 2019; 17 (4): e3000194 DOI: 10.1371/journal.pbio.3000194

Cite This Page:

- MLA
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Wellcome Trust Sanger Institute. "Mice reveal 38 new genes involved in hearing loss: Molecular pathways revealed could identify potential drug targets for restoring hearing." ScienceDaily. ScienceDaily, 11 April 2019. <www.sciencedaily.com/releases/2019/04/190411145136.htm>.

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6. マイクロ RNA で損傷した心臓を保護

心臓が完全に形成されると、心筋細胞は自己再生能力が非常に限られたものになる。心臓発作後、心筋細胞は死亡して、新しいものを作ることはできない。その代わりに心臓は瘢痕組織を作り、時間と共に心不全の素地を作る。
4 月 17 日に *Nature Communications* 誌で発表された新しい研究は、遺伝子機能を調節し、心臓の発達に豊富な小分子であるマイクロ RNA を使用して心臓の再生能力を復活させる可能性を高めている。
2013 年に、ボストン小児病院の心臓病研究者でハーバード大学医学部の小児科教授でもある Da-Zhi Wang 博士は、心筋細胞の増殖を調節する miR-17-92 と呼ばれるマイクロ RNA ファミリーを同定した。今回発表された新しい研究で、彼のチームは心臓発作を治療するために特に強力で潜在的にも良い候補であると思われる 2 つのファミリー構成員である miR-19a と miR-19b を示している。
心臓発作の後、直接心臓に投与するか全身投与するかのいずれかでマウスに注射した miR-19a/b は、即時的および長期的な防御を提供した。心臓発作後最初の 10 日の初期段階では、マイクロ RNA は急性細胞死を減少させ、心臓の損傷を悪化させる炎症性免疫応答を抑制した。試験は、これらのマイクロRNAがこれらの過程に関与する複数の遺伝子を阻害することを示した。また、長期的には、心エコー検査において左心室の短縮率が増加することによって証明されるように、治療された心臓はより健康な組織、より少ない死亡または瘢痕化した組織、および改善された収縮性を有した。拡張型心筋症 － 心筋を伸ばして薄くすることで最終的に心臓を衰弱させる － も減少した。

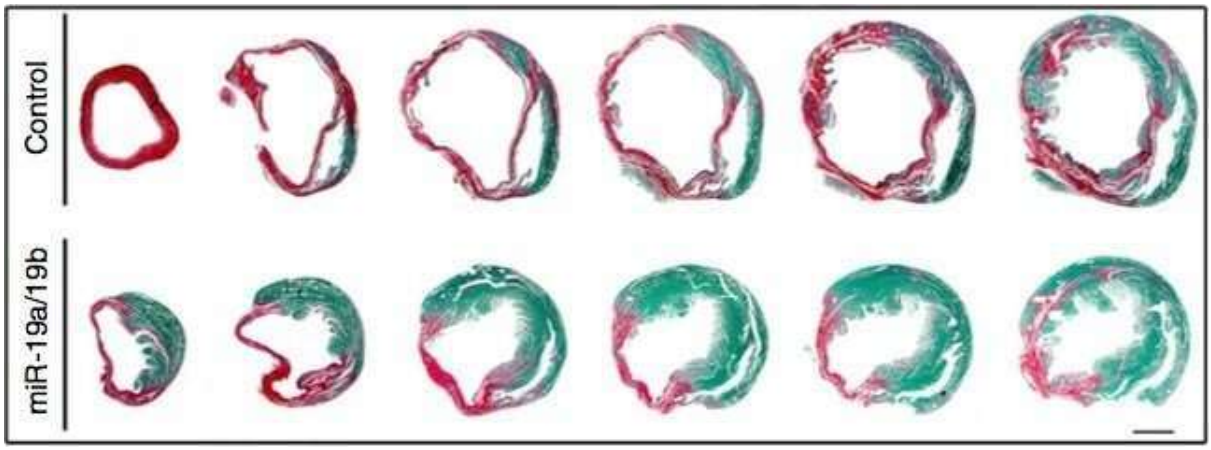
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-04-hearts-micrornas.html

APRIL 22, 2019

PROTECTING DAMAGED HEARTS WITH MICRORNAS

by Children's Hospital Boston



Cross sections of the heart two months after treatment. Mice receiving miR-19a/b have more heart muscle (in green) relative to scar tissue (red). Credit: Wang Lab/Boston Children's Hospital and *Nature Communications* (DOI 10.1038/s41467-019-09530-1)

Once the heart is fully formed, the cells that make up heart muscle, known as cardiomyocytes, have very limited ability to reproduce themselves. After a heart attack, cardiomyocytes die off; unable to make new ones, the heart instead forms scar tissue. Over time, this can set people up for heart failure.

New work published April 17th in *Nature Communications* advances the possibility of reviving the heart's regenerative capacities using microRNAs—small molecules that regulate gene function and are abundant in developing hearts.

In 2013, Da-Zhi Wang, Ph.D., a cardiology researcher at Boston Children's Hospital and a professor of pediatrics of Harvard Medical School, identified a family of microRNAs called miR-17-92 that regulates proliferation of cardiomyocytes. In new work, his team shows two family members, miR-19a and miR-19b, to be particularly potent and potentially good candidates for treating heart attack.

Short- and long-term protection

Wang and colleagues tested the microRNAs delivered two different ways. One method gave them to mice directly, coated with lipids to help them slip inside cells. The other method put the microRNAs into a gene therapy vector designed to target the heart.

Injected into mice after a heart attack—either directly into the heart or systemically—miR-19a/b provided both immediate and long-term protection. In the early phase, the first 10 days after heart attack, the microRNAs reduced the acute cell death and suppressed the inflammatory immune response that exacerbates cardiac damage. Tests showed that these microRNAs inhibited multiple genes involved in these processes.

Longer-term, the treated hearts had more healthy tissue, less dead or scarred tissue and improved contractility, as evidenced by increased left-ventricular fractional shortening on echocardiography. Dilated cardiomyopathy—a stretching and thinning of the heart muscle that ultimately weakens the heart—was also reduced.

"The initial purpose is to rescue and protect the heart from long-term damage," says Wang. "In the second phase, we believe the microRNAs help with cardiomyocyte proliferation."

One and done?

Aside from regulating multiple genetic targets, microRNAs have another advantage as a therapy: unlike gene therapy, they don't linger in the heart.

"They go in very fast and do not last long, but they have a lasting effect in repairing damaged hearts," says Jinghai Chen, Ph.D., a former member of the Wang lab and co-corresponding author on the paper with Wang. (Chen is now on the faculty at the Institute of Translational Medicine, Zhejiang University, Hangzhou, China.) "We gave mice only one shot when the heart needed the most help, then so we kept checking expression level of miRNA19a/b post-injection. After one week, expression decreased to a normal level, but the protection lasted for more than one year."

Even when given systemically, the microRNAs tended to go to the site of heart damage. But Wang would like to optimize the specificity of the treatment, since the miRNAs can also affect other tissue and organs. The next step would be to test that treatment in a larger animal before advancing to studies in humans.

All of us make miR-19a/b to some degree, so the treatment would be boosting something we already have. "MicroRNAs hold tremendous promise to become powerful tools to battle cardiovascular disease," the researchers write.

Explore further

[How the heart sends an SOS signal to bone marrow cells after a heart attack]

More information: Feng Gao et al, Therapeutic role of miR-19a/19b in cardiac regeneration and protection from myocardial infarction, *Nature Communications* (2019). DOI: 10.1038/s41467-019-09530-1

Journal information: Nature Communications

Provided by Children's Hospital Boston

7. 湿疹と食物アレルギーの関係を明らかにするマウス研究

マウスで行われた研究によると、皮膚をひっかくと小腸内で活性化肥満細胞（アレルギー反応に関与する免疫細胞）の数が増加する結果となる一連の免疫反応が引き起こされる、ことが発見された。この新しく同定された皮膚－腸のコミュニケーションは食物アレルギーとアトピー性皮膚炎（湿疹の一種で、乾燥したかゆみのある皮膚を特徴とする疾患）の関係を明らかにするのに役立つ。
この研究は、国立衛生研究所の一部である国立アレルギー感染症研究所（NIAID）によって支援され、ボストン小児病院の研究者らによって主導された。
アトピー性皮膚炎は食物アレルギーを発症するための強力な危険因子であるが、2 つの間の正確な関係は不明のままであった。かゆみはアトピー性皮膚炎の主な症状で、この疾患を持つ人、特に乳児は皮膚を傷付ける。
研究者らは、マウスの皮膚にテープの小片を張り付けたり取り除いたりして皮膚の一部の細胞が血流に入る IL-33 という細胞シグナル伝達タンパク質を産生して反応することを発見。IL-33 が腸に到達すると、腸内の細胞から分泌されるタンパク質である IL-25 と共に作用し、2 型先天性リンパ球細胞（ILC2）を活性化。活性化された ILC2 が、2 つの細胞シグナル伝達タンパク質 IL-13 と IL-14 を作り、これらが腸肥満細胞の増殖に関与することが分かった。また、肥満細胞が増殖するにつれて、腸の内層がより透過性になり、アレルゲンが組織に入りやすくなることも発見した。
ヒトによる研究においても、アトピー性皮膚炎の 4 人の子供からの腸生研材料は、症状のない子供からのものよりも多くの肥満細胞を含んでいた、としている。
この研究により、かゆみを制限する介入がアトピー性皮膚炎患者の食物アレルギーの重症度を低下させる可能性がある、と研究者らは示唆している。

研究関連ニュース/他のトップページに戻る

＜英文＞
https://www.sciencedaily.com/releases/2019/04/190423133803.htm?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+sciencedaily%2Fhealth_medicine%2Fcolitis+%28Colitis+News+--+ScienceDaily%29

SCRATCHING THE SKIN PRIMES THE GUT FOR ALLERGIC REACTIONS TO FOOD, MOUSE STUDY SUGGESTS

RESEARCH ILLUMINATES RELATIONSHIP BETWEEN ECZEMA AND FOOD ALLERGY

Date:

April 23, 2019

Source:

NIH/National Institute of Allergy and Infectious Diseases

Summary:

Scratching the skin triggers a series of immune responses culminating in an increased number of activated mast cells -- immune cells involved in allergic reactions -- in the small intestine, according to research conducted in mice. This newly identified skin-gut communication helps illuminate the relationship between food allergy and atopic dermatitis (a type of eczema), a disease characterized by dry, itchy skin.

FULL STORY

Scratching the skin triggers a series of immune responses culminating in an increased number of activated mast cells -- immune cells involved in allergic reactions -- in the small intestine, according to research conducted in mice. This newly identified skin-gut communication helps illuminate the relationship between food allergy and atopic dermatitis (a type of eczema), a disease characterized by dry, itchy skin. The study was supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and led by researchers at Boston Children's Hospital.

Atopic dermatitis is a strong risk factor for developing food allergy, but the precise relationship between the two conditions remains unclear. As itching is a major symptom of atopic dermatitis, people with the disease, particularly babies, often scratch their skin. The current study proposes that scratching the skin instigates mast-cell expansion in the intestine.

The researchers found that some cells in the skin respond to scratching -- simulated by applying and removing small strips of tape on the skin of mice -- by producing a cell-signaling protein called IL-33, which enters the bloodstream. When IL-33 reaches the gut, it works in concert with IL-25, a protein secreted by cells in the lining of the intestine, to activate type 2 innate lymphoid cells (ILC2s). Activated ILC2s make two additional cell-signaling proteins, IL-13 and IL-4, which were found to be responsible for the expansion of intestinal mast cells.

The researchers also found that as mast cells expanded, the intestinal lining became more permeable, making it easier for allergens to enter the tissues. Notably, mice that underwent tape stripping had more severe reactions to food allergen than mice that did not. Finally, the researchers found that intestinal biopsies from four children with atopic dermatitis contained more mast cells than those from four children without the condition.

Although additional work is needed to determine the relevance of the findings to humans, the researchers suggest that interventions to limit itching potentially could lessen the severity of food allergy among people with atopic dermatitis.

Story Source:

Materials provided by **NIH/National Institute of Allergy and Infectious Diseases**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Juan-Manuel Leyva-Castillo, Claire Galand, Christy Kam, Oliver Burton, Michael Gurish, Melissa A. Musser, Jeffrey D. Goldsmith, Elizabeth Hait, Samuel Nurko, Frank Brombacher, Chen Dong, Fred D. Finkelman, Richard T. Lee, Steven Ziegler, Isaac Chiu, K. Frank Austen, Raif S. Geha. **Mechanical Skin Injury Promotes Food Anaphylaxis by Driving Intestinal Mast Cell Expansion**. *Immunity*, 2019; DOI: 10.1016/j.immuni.2019.03.023

Cite This Page:

- MLA
- APA
- Chicago

NIH/National Institute of Allergy and Infectious Diseases. "Scratching the skin primes the gut for allergic reactions to food, mouse study suggests: Research illuminates relationship between eczema and food allergy." ScienceDaily. ScienceDaily, 23 April 2019. <www.sciencedaily.com/releases/2019/04/190423133803.htm>.

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8. マウスの飼い方研究

ブリティッシュコロンビア大学による新しい研究によると、マウスは自分の廃棄物（糞尿）からは離れて巣作りすることを強く望んでいるらしい。
この研究では 3 つの相互接続されたケージに収容されたマウスについて、ネスティングと廃棄物のために別々のケージを使用した、としている。通常実験室ではマウスは廃棄物とごく近くに収容するが、これがマウスの福祉を危うくし、研究データにも悪影響を及ぼす可能性があることを示唆している。
4 月 16 日に *Scientific Reports* 誌に発表されたこの研究結果によると、他のどの動物よりも生物医学的研究のために使用されているマウスに対して、彼らの福祉を確実にするために、いわゆる「専用のトイレ」スペースを提供すべきである、と言っている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/04/190423133719.htm

GOOD MOUSEKEEPING: EN SUITE BATHROOM MAKES FOR HAPPIER MICE

Date:

April 23, 2019

Source:

University of British Columbia

Summary:

Mice have a strong preference to nest away from their own waste, new research has found. The study showed that mice who were housed in a system of three interconnected cages used separate cages for nesting and eliminating waste. Typically, laboratories house mice in close proximity with their excrement. The study suggests this compromises their welfare and may also negatively affect research data.

FULL STORY

Mice have a strong preference to nest away from their own waste and should be housed in a system of cages that allows them to create a toilet area, according to work led by researchers at the University of British Columbia.

The study, published April 16 in *Scientific Reports*, showed that mice who were housed in a system of three interconnected cages used separate cages for nesting and eliminating waste.

The findings suggest that mice -- used in more biomedical research than any other animal -- should be provided with a so-called "en suite bathroom" space to ensure their welfare. Standard housing for these laboratory animals consists of simple cages with a single, small, open space.

"This finding is important, because housing mice in constant contact with their excrement is common practice in laboratories," said Joanna Makowska, adjunct professor in the UBC faculty of land and food systems' animal welfare program. "Housing animals in an environment they are motivated to avoid compromises their welfare, and may also negatively affect research data."

Scientists believe that the segregation of space into clean and dirty areas is a behaviour that has evolved among many species as protection against disease. The UBC researchers were the first to directly test whether mice do it as well. They began by housing 60 mice, divided into small groups between standard single-compartment cages, and complex "triad" caging systems that featured three separate compartments connected by external tunnels.

During 15 weeks of observation, mice nested and urinated in the same location only two per cent of the time. Even the mice in single compartments made an effort to keep their nesting and waste areas separate within their cage, while the mice in triads used separate compartments for each.

The researchers also discovered that mice moved bedding and nesting material between the cages, showing that they were willing to work to maintain a comfortable place to rest, well away from the dirty compartment.

"In humans, the most common elicitors of disgust are feces and urine. This finding opens avenues for exciting new research, such as whether disgust is a reaction that has evolved across species in much the same way that pleasure and pain have," said Makowska.

"Our ultimate goal, however, was to give mice more autonomy in designing their own space and thereby enhance our appreciation for their capabilities and preferences," said co-author Becca Franks, a former postdoctoral fellow in the animal welfare program who is now visiting assistant professor at New York University.

Story Source:

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

Journal Reference:

1. I. Joanna Makowska, Becca Franks, Cathy El-Hinn, Tina Jorgensen, Daniel M. Weary. **Standard laboratory housing for mice restricts their ability to segregate space into clean and dirty areas**. *Scientific Reports*, 2019; 9 (1) DOI: 10.1038/s41598-019-42512-3

Cite This Page:

- MLA

- APA
- Chicago

University of British Columbia. "Good mousekeeping: En suite bathroom makes for happier mice." ScienceDaily. ScienceDaily, 23 April 2019. <www.sciencedaily.com/releases/2019/04/190423133719.htm>.

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9. 毛包からの幹細胞で損傷を受けたマウスの神経細胞を修復

VA メリーランドヘルスケアシステムとメリーランド大学医学部の研究者らが *PLOS Genetics* 誌の 4 月 24 日号で報告した新しい研究によると、毛包の幹細胞のサブセットは、マウスの神経細胞を隔離するコーティングを再形成する可能性があり、この研究が特定の神経変性疾患においてその治療の選択肢を探す際の新たな方向性を提供する。
髪や肌は、メラノサイトと呼ばれる細胞によって作り出される顔料によって、赤、茶色、黒、黄色といった色合いを持つようになる。メラノサイトは又、ニューロンおよびそのニューロンをサポートするグリア細胞を生じさせることができる神経堤細胞と呼ばれる細胞から胚性的にできる。研究者らは以前、成熟した毛包内のメラニン細胞を作る幹細胞の異なる 2 つのポケットを同定したが、今回の研究では、メラニン細胞の幹細胞のこの 2 つのグループが、CD34 と呼ばれる糖たんぱく質（血液幹細胞を含む他の種類の細胞に存在する表面分子）でコーティングされているかどうかに基づいて識別分離されることを示した。
研究者らは、マウスの毛包からメラノサイト幹細胞の 2 つのグループを分離して培養。
CD34 を有する細胞がグリア細胞に変わることを発見した。
さらに、CD34 陽性幹細胞は、細胞培養でも遺伝的に欠陥のあるマウスに注入した場合でも、ニューロンのミエリンを再生成できることを発見した。

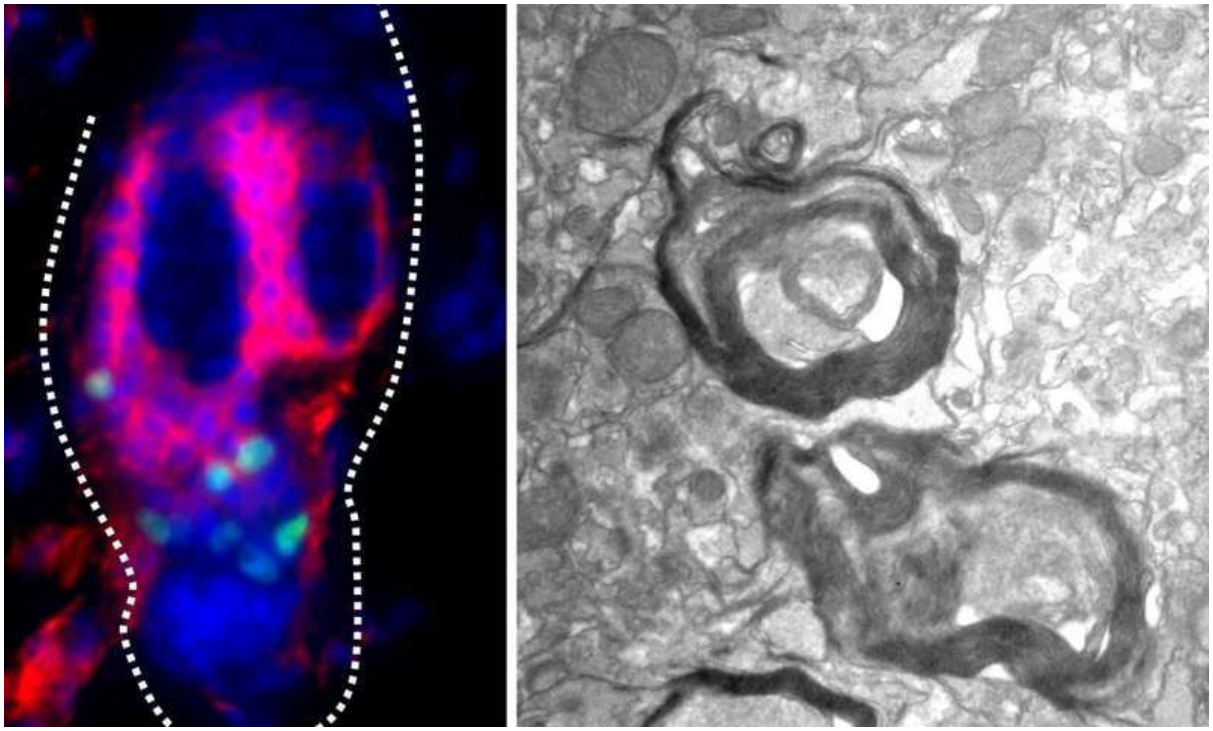
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-04-stem-cells-hair-follicles-potential.html

APRIL 24, 2019

STEM CELLS FROM HAIR FOLLICLES HAVE POTENTIAL TO REPAIR DAMAGED NEURONS IN MICE

by Public Library of Science



Melanocyte stem cells from the telogen, or resting, phase of the mouse hair follicle (green, left panel) within the CD34-positive bulge region (red, left panel) differentiate and form dense myelin sheaths (right panel) in the brain of myelin-deficient mice. Credit: Sandeep Joshi, University of Maryland School of Medicine

A subset of the stem cells in hair follicles have the potential to regenerate the coating that insulates neurons in mice, reports Thomas Hornyak of the VA Maryland Health Care System and the University of Maryland School of Medicine and colleagues, in a new study published 24th April in *PLOS Genetics*. The study offers a new direction for finding therapeutic options for certain neurodegenerative diseases.

Hair and skin take on varying shades of red, brown, black and yellow due to the pigments produced by cells called melanocytes. Melanocytes originate embryonically from cells called neural crest cells, which are cells that can also give rise to neurons and their supporting glial cells. Previously, Hornyak and colleagues identified two different pockets of stem cells that create melanocytes inside mature hair follicles. In the current study, they show that the two

groups of the melanocyte stem cells can be identified and separated based on whether they are coated in a glycoprotein called CD34, a surface molecule which is present on other types of stem cells, including stem cells of the blood.

Using hair follicles from mice, the researchers isolated the two populations of melanocyte stem cells and grew them in culture. They were surprised to find that the cells carrying CD34 turn into glial cells. In the nervous system, glial cells coat neurons with a fatty insulation called myelin, which increases the speed that nerve impulses can travel. Furthermore, the researchers discovered that the CD34-positive stem cells could regenerate myelin on neurons, both in cell cultures and when injected into mice carrying a genetic defect that prevents them from forming myelin sheaths.

The new findings suggest that the pocket of CD34-positive melanocyte stem cells in the hair follicle retain some of their earlier abilities. If similar populations exist in human hair follicles, they potentially could be tapped to develop new treatments for nerve injuries and for demyelinating diseases, such as multiple sclerosis. "In the future, we plan to continue our research in this area by determining whether these cells can enhance functional recovery from neuronal injury," said author Dr. Thomas Hornyak, "and leverage genome-wide information we have described in the current study to identify similar cells in human skin."

Explore further

New research provides clues on why hair turns gray

More information: Joshi SS, Tandukar B, Pan L, Huang JM, Livak F, Smith BJ, et al. (2019) CD34 defines melanocyte stem cell subpopulations with distinct regenerative properties. *PLoS Genet* 15(4): e1008034. doi.org/10.1371/journal.pgen.1008034

Journal information: PLoS Genetics

Provided by Public Library of Science

10.　マウス研究によって乳癌腫瘍再発の未知の経路が明らかに

デューク大学医療センターの研究者らは、乳癌の治療抵抗性癌細胞の小さな貯蔵庫が休眠から目覚め、成長し、そして広がるのを可能にしている一連の出来事を追跡し、このプロセスを停止させる可能性のある戦略について *eLife* 誌オンライン版で発表している。
研究者らは、約 20%の女性を苦しめている再発性の HER2 陽性乳癌を再現するマウスモデルを使用したマウス実験によって、これら残存する治療抵抗性の腫瘍細胞が急速に増殖する元の癌細胞とは異なることを発見した。その代わりに、身を潜めて周囲の細胞、特に免疫系の細胞と複雑な相互作用を開始、時間の経過と共に免疫細胞との重要な伝達物質であるサイトカインと呼ばれるシグナル伝達タンパク質の群れにスイッチを入れる、としている。
研究者らはまた、ある特定の種類のサイトカインである CCL5 が腫瘍の再発を加速させるため、それをブロックするとプロセスを遅らせるか停止させる可能性があることを示した。
これらの実験は現在マウスで行われており、うまくいけば、抗 HER2 治療と組み合わせてこれらの薬をテストする臨床試験への移行を試みることができる、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/04/190425122351.htm

STUDY IN MICE UNCOVERS AN UNKNOWN PATHWAY FOR BREAST CANCER TUMORS TO RECUR

THE FINDING SUGGESTS IMMUNE CELLS COULD BE TARGETED USING EXISTING THERAPIES

Date:

April 25, 2019

Source:

Duke University Medical Center

Summary:

Experimenting in mice, the researchers tracked a series of events that enable a small reservoir of treatment-resistant cancer cells to awake from dormancy, grow and spread.

FULL STORY

For many women who thought they had beaten breast cancer, the news that it has roared back years later comes as an especially cruel diagnosis with no clear answers for why or how it recurs.

Now a team of Duke Cancer Institute researchers has filled in some critically unknown details that could lead to potential strategies to halt the process.

Experimenting in mice, the researchers tracked a series of events that enable a small reservoir of treatment-resistant cancer cells to awake from dormancy, grow and spread. The findings appear online in *eLife*.

"These are the cells that are left over following therapy, and we haven't known much about them because we can't see them. There are too few of them to show up in mammography or PET scans," said senior author James V. Alvarez, Ph.D., assistant professor in Duke's Department of Pharmacology & Cancer Biology.

"But using mouse models that replicate recurrent HER2-positive breast cancers, which afflict about 20 percent of women, we were able to locate the residual cancer cells that survive after treatment and study them," he said.

Alvarez and colleagues, including lead author Andrea Walens, found that these residual, treatment-resistant tumor cells aren't like the original cancer cells, which grow and proliferate rapidly.

Instead, they lay low and begin an intricate interaction with surrounding cells, especially those of the immune system. Over time, they switch on a horde of small signaling proteins called cytokines that are vital communicators with immune cells.

Responding to the cytokines, immune cells come rushing to the tumor sites. Among the most abundant of these responding immune cells are macrophages, a type of white blood cells that digest cellular debris and deposit a form of collagen, which has been shown to be important for dormant cells to wake up and grow again.

In mapping this route to recurrence, Alvarez, Walens and their colleagues noted that the macrophages might be targetable by current drugs. They showed that one particular type of cytokine -- CCL5 -- is able to accelerate tumor recurrence, and blocking it might delay or halt the process.

"There are drugs already approved or under development that inhibit macrophages in general or specifically CCL5 function," Walens said. "Our next step is to test these macrophage inhibitors to see whether they can delay or prevent recurrence in mice and if can kill the residual, dormant tumor cells.

"We are doing those experiments now in mice and if those work, we could begin trying to move to a clinical trial that would test these drugs in conjunction with anti-HER2 therapies," Walens said.

In addition to Walens, study authors include Ashley V. DiMarco, Ryan Lupo, Benjamin R. Kroger and Jeffrey S. Damrauer.

Story Source:

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

Journal Reference:

1. Andrea Walens, Ashley V DiMarco, Ryan Lupo, Benjamin R Kroger, Jeffrey S Damrauer, James V Alvarez. **CCL5 promotes breast cancer recurrence through macrophage recruitment in residual tumors**. *eLife*, 2019; 8 DOI: 10.7554/eLife.43653

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- APA
- Chicago

Duke University Medical Center. "Study in mice uncovers an unknown pathway for breast cancer tumors to recur: The finding suggests immune cells could be targeted using existing therapies." ScienceDaily. ScienceDaily, 25 April 2019. <www.sciencedaily.com/releases/2019/04/190425122351.htm>.
