Bio News – August, 2020

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

6/30　査読前 COVID-19 報告から重要成果を AI で探す取り組みが発足

正確さの検討・査読がまだの新型コロナウイルス感染（COVID-19）研究報告（プレプリント）をまず人工知能（AI）にかけ、次いで無償のヘルパー1,600 人の人海戦術で校閲して査読に進めるべき最重要報告を選別後、その検討結果を公表する取り組み Rapid Reviews: COVID-19 を米国マサチューセッツ工科大学（MIT）とカリフォルニア大学バークレー校が立ち上げた。
COVID-19 研究のプレプリントは medRxiv と bioRxiv に現時点で 6,000 報近く登録されている。
今回発足した Rapid Reviews: COVID-19 は莫大な数の COVID-19 研究プレプリントの山から無意味な成果を排除して有意義な成果を拾い上げることを目指す。
Rapid Reviews: COVID-19 による最初の校閲結果は来月中に発表される予定。

6/30　中国で新型豚インフルを確認、パンデミックの可能性も

7/1　日本初のコロナワクチンの治験を開始 -創薬ベンチャーの「アンジェス」

https://www.jiji.com/jc/article?k=20200629005l5&g=eco

7/1　靴下の悪臭＋バニラ＝チョコ？　におい調和の仕組み、九大などが解明

https://www.nishinippon.co.jp/item/n/621832/

7/1　受精卵が成体になる課程で重要なたんぱく質　近大グループ確認

7/1　組織工学でウサギの子宮を修復、ヒトへの応用にも期待 -米 Wake Forest University など

7/1　欧州や米国の新型コロナウイルスに備わる感染力増強変異が見つかった

7/2　膵臓がんになりやすい遺伝子変異を発見　日本人の 1 割に -愛知県がんセンターなど

7/3　iPS から骨格筋幹細胞　筋ジス治療に可能性　京大

https://www.jiji.com/jc/article?k=20200703005l5&g=soc

7/4　iPS 細胞使い筋ジスを治療　京大など、筋肉再生に成功

https://www.asahi.com/articles/ASN735HSVN71PLBJ00C.html

7/6　アビガンとフサン併用、重症患者に有効か　東大が発表

7/6　COVID-19 ワクチン接種予定の米国人は僅か 2 人に 1 人

https://www.sciencemag.org/news/2020/06/just-50-americans-plan-get-covid-19-vaccine-here-s-how-win-over-rest

7/7　米、コロナワクチン開発で Novavax に 16 億ドル提供

新型コロナウイルスワクチンを巡り、米政府がバイオ医薬の Novavax に対して16億ドルの資金を提供することに。ワクチンの臨床試験（治験）や実用化、製造を支援するもので、来年1月までに1億人分のワクチン供給を目指す。
今回の支援は、3月のジョンソン・エンド・ジョンソン（J&J）（4億5600万ドル）、4月のモデルナ（4億8

600万ドル）、5月の英アストラゼネカとオックスフォード大（最大12億ドル）などに続くもので、コロナワクチン開発に向けた「ワープ・スピード作戦」の下で最大規模となる。

7/7　iPS 治験の詳細公表　京大など再生医療の規格化めざす

7/7　スペインの新型コロナウイルス(SARS-CoV-2)抗体保有 5%～集団免疫には程遠い

欧州で最も新型コロナウイルス感染（COVID-19）が蔓延した国の 1 つスペインのおよそ 6 万人（61,075 人）を 4 月 27 日から 5 月 11 日に調べたところ抗体保有率は 5%で、感染経験率は依然として低いと予想され、感染者増加を防ぐのに必要な集団免疫には程遠いと示唆された。

7/8　新型コロナウイルスの空気感染に対する WHO や各国の対処を世界の科学者が要請

新型コロナウイルス（SARS-CoV-2）感染者の呼吸、発声、咳で生じる空中を浮遊するほど小さな飛沫（microdroplet）に含まれるウイルスが感染者から 1～2 メートル以上離れたところまでふりかかることはほぼ間違いなく、世界保健機関（WHO）や各国はその感染（COVID-19）が空気を介して広まりうることを認識すべきとの要望を世界 32 カ国の科学者 239 人が発表。

7/9　フランスの Osivax、万能インフルエンザワクチンの開発資金 800 万ユーロ調達

7/9　アトピー性皮膚炎のかゆみ抑える薬　京大など治験で効果

7/10　武田薬品が Twist のファージディスプレイライブラリーを頼りに抗体を探す

武田薬品工業と米 Twist Bioscience 社は、2020 年 7 月 8 日、Twist 専有のファージディスプレイライブラリーを用いた抗体医薬の共同開発契約を締結したと発表。武田薬品のがん、希少疾患の他、神経科学分野、および消化器分野の抗体開発パイプラインの拡充に活用。

7/10　ヒト受精卵にゲノム編集　基礎研究の指針案了承　厚労・文科省

https://mainichi.jp/articles/20200710/k00/00m/040/250000c

7/10　ごみからつくった国産消毒液でコロナと闘う、イスラエルの科学者ら

7/12　日本での無作為化試験で COVID-19 へのアビガンの有意効果示せず

7/13　新型コロナウイルス感染患者の 9 割近くが発症から 2 か月後も症状あり

7/13　接触確認アプリ、iOS 用修正版を配布　厚労省

7/14　中国 BeiGene の売り出し株式 21 億ドルの 2 割を 4 億 2,100 万ドルで Amgen が取得

7/14　Moderna の COVID-19 ワクチン早期承認の公算はかなり高いとアナリストが予想

7/14　抗体にコロナ感染防ぐ能力を確認　3 都府県の疫学調査、厚労省

https://www.nikkei.com/article/DGXMZO61499750U0A710C2CR8000/

7/15　新型コロナ「後遺症」の原因を究明へ 厚労省が 2 千人対象に調査

7/15　カナダの Medicago の植物から作る新型コロナウイルス(SARS-CoV-2)ワクチン Ph1 開始

7/16　紙ベースの COVID-19 抗原検査を 3M が MIT と協力して開発

https://www.businesswire.com/news/home/20200714005522/en/

7/17　J&J の COVID-19 ワクチンの臨床試験が予定より早く今月中に開始

9 月開始予定だった Johnson & Johnson 新型コロナウイルス感染（COVID-19）ワクチン Ad26.COV2-S の Ph1/2a 試験が前倒しで 7 月中に始まる。
米国とベルギーの健康な成人 1,045 人を募り、安全性や免疫反応などが調べられる。

7/17　英語の L と R、聞き分け能力は瞳孔反応で分かる

https://scienceportal.jst.go.jp/news/newsflash_review/newsflash/2020/07/20200717_01.html

7/19　Sanofi が Principia（South San Francisco）や他の米国バイオテックを買う検討をしている

7/20　大学病院の赤字、4・5 月で計 313 億円　コロナが影響

https://www.asahi.com/articles/ASN7N6QSDN7NULBJ00L.html

7/20　PTSD 患者脳内で恐怖のオン・オフ繰り返す仕組み明らかに　民間研究機関 ATR

7/20　新型コロナウイルスは蚊から人には移らない～蚊の体内で増えないことが判明 -カンザス州立大学

7/20　2～3 月に米国で死亡した COVID-19 患者の剖検～主だった病変はびまん性肺胞障害

7/21　国内 2 例目の新型コロナ治療薬認定

新型コロナウイルス感染症の治療薬として、抗炎症薬「デキサメタゾン」が厚生労働省の診療の手引きに追加掲載されたことが 21 日、分かった。効果が検証され、国内で使用が認められた治療薬は、5 月に特例承認された「レムデシビル」に続いて 2 例目。

7/21　AstraZeneca とオックスフォード由来のコロナワクチン、開発順調　英、初期治験で好結果

7/21　認知症予防で全国初の共同研究　高齢者200人に18カ月健康指導　神戸大と兵庫・丹波市

7/21　COVID-19 ワクチン開発のドイツの CureVac が 6 億 4,000 万ドル調達

7/21　Pfizer/BioNTech の COVID-19 ワクチンで殆どの被験者が良好な T 細胞反応を示した

7/22　金属を食す細菌がようやく見つかった

7/22　米国での実際の新型コロナウイルス感染者数は報告数より 6～24 倍多い

3 月 23 日から 5 月 12 日に米国の 10 地域の 16,025 人から採取された血清検体の抗体を調べた結果、それら地域での実際の新型コロナウイルス（SARS-CoV-2）感染者数は報告数を 6-24 倍上回ると推定された。
とはいえ SARS-CoV-2 スパイク蛋白質への抗体保有率は最も高いニューヨーク市でもせいぜい 7%、サンフランシスコでは僅か 1%で、その程度の感染率では SARS-CoV-2 流行継続の歯止めに何の足しにもならないと著者は言っている。

https://www.nytimes.com/2020/07/21/health/coronavirus-infections-us.html

7/23　Pfizer/BioNTech の COVID-19 ワクチンを米国政府が少なくとも 1 億回投与分予約

7/23　軽～中等度 COVID-19 へのアビガンの無作為化試験で主要転帰は有意改善せず

7/23　Novavax（米メリーランド州）の CEO 含む 4 人には COVID-19 ワクチンが失敗しても大金が舞い込みうる

7/23　WHO専門家「新型コロナワクチン接種は来年前半になる」

7/23　コロナ感染、世界 1,500 万人超　再び過去最悪ペースで増加

7/24　阪大などの研究チーム　切らずに“光”でがんを迅速診断

7/24　米国政府が COVID-19 ワクチンの値段をインフルエンザワクチン相当と見積もり

Pfizer/BioNTech が開発中の新型コロナウイルス感染（COVID-19）予防ワクチン BNT162 が承認されたら、米国政府が 1 億回投与分を 19 億 5,000 万ドルで買い取る合意が発表されたことを受けて、他の COVID-19 ワクチン開発会社も同様の値段にすることを恐らく強いられるだろうとアナリスト等が Reuters に話している。
BNT162 は恐らく 1 人に 2 回投与されるとして米国政府は 5,000 万人分を 19 億 5,000 万ドルで買い取ることになり、1 人当たりの値段は 39 ドル（1 回投与分は 19.5 ドル）の計算だ。この額は毎年のインフルエンザワクチンの値段とだいたい同じ。

7/25　COVID-19 に伴う嗅覚消失は神経ではなくその取り巻き細胞への感染が原因らしい

7/27　CureVac が 1 億ドルの IPO 調達開始

新型コロナウイルス感染（COVID-19）ワクチン開発勢の一角 CureVac が 1 億ドルの IPO 調達目論見書をアメリカ証券取引委員会（SEC）に提出。

7/28　Moderna が予定通り COVID-19 ワクチンの第 3 相試験開始

7/28　Boehringer Ingelheim がベルギーの動物治療バイオテック Global Stem cell Technology（GST）を取得

7/29　Moderna のワクチンがサルの新型コロナウイルス感染阻止

7/29　抗体陽性率、犬 3%、猫 4%　新型コロナで大規模調査　伊

7/29　ヒト iPS から腎組織の一部作製　遺伝性の病気再現の可能性　京大グループ発表

7/29　白亜紀の細菌、いまも増殖能力　約 1 億年前の地層で発見 -海洋研究開発機構などの研究チーム

https://www.asahi.com/articles/ASN7X6418N7WULBJooW.html

7/29　コロナから回復した人の抗体を大規模調査　横浜市大が国内初

7/29　Roche の新型コロナ薬候補「アクテムラ」 欧米で有効性確認されず

7/30　Sanofi が第一三共との小児ワクチン開発提携を打ち切り

7/30　英国 RECOVERY 試験でのアクテムラの検討は続く～より重症の COVID-19 が対象

7/30　「究極の長寿」に関連の分子　高齢者 1,400 人調査で発見　慶大など

慶応大などの研究チームは、110 歳以上の超長寿者 36 人を含む高齢者の追跡調査から、心疾患に関連する分子の血中濃度が低いほど、110 歳以上に到達する可能性が高いことを見いだした。超長寿者は心臓の老化が遅いことを示しているといい、高齢者の心疾患予防や新たな治療法開発の糸口になると期待される。論文は 30 日、英科学誌 *Nature Communications* 電子版に掲載された。

7/31　幼児が新型コロナ媒介か 上気道に年長者の最大 100 倍の遺伝物質 米研究

https://www.afpbb.com/articles/-/3296698

7/31　Moderna が開発中の COVID-19 ワクチン、2 回投与分 50-60 ドルに対して、Pfizer/BioNTech のワクチンは 1 回投与で約 19.5 ドル

7/31　Genentech がサウスサンフランシスコ従業員 500 人近くを解雇

7/31　J&J の COVID-19 ワクチンの Ph1/2a 試験開始～サルへの投与実験を *Nature* 誌掲載

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. 生体内の老化細胞を除去する新規治療ワクチン
   ～糖尿病モデルマウスで治療効果を確認～

2. 動脈が老化する理由：腸内細菌および食事との関係

3. 加齢に関連する障害、マウスで回復に成功

4. ナトリウムがマウスの体内時計を調節

5. 皮膚が老化すると「幹細胞の顔」が変わる
   ～加齢に伴う皮膚幹細胞の糖鎖変化の解析に成功～

6. 抗生物質がマウスの「社会脳」の発達を混乱させる

7. COVID-19 が嗅覚喪失を引き起こす理由

8. 発達障害関連の DNA ピンポイント領域上の化学マークマップ
   発達障害をよりよく理解するために、マウスの DNA メチル化が時間とともにどのように変化するかをマッピング

9. 頭足類で初の遺伝子ノックアウトを達成

1. 生体内の老化細胞を除去する新規治療ワクチン ～糖尿病モデルマウスで治療効果を確認～

日付：2020 年 6 月 30 日
ソース：大阪大学
概要：

http://www.med.osaka-u.ac.jp/activities/results/2020year/n-y-ra-m-22052020

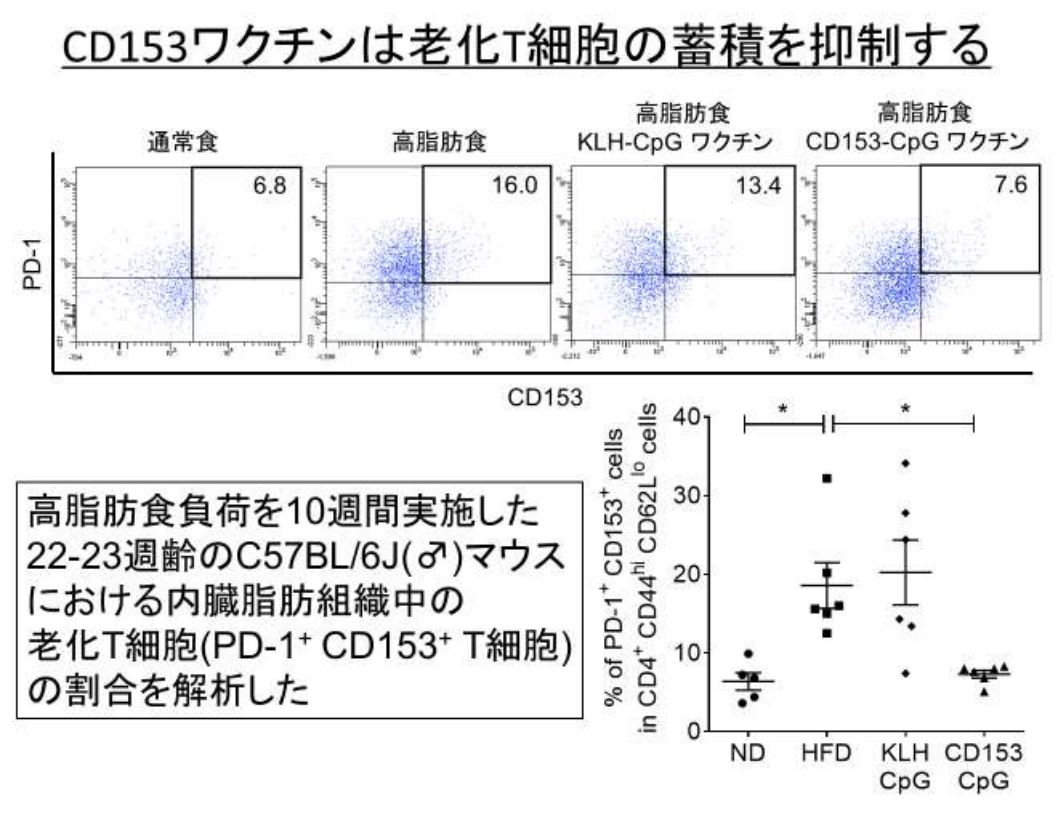

図１．FACS を用いたマウス内臓脂肪に存在する老化 T 細胞の解析

老化細胞は PD-1 陽性・CD153 陽性です。通常食で飼育したマウスの内臓脂肪と比べ、高脂肪食で飼育したマウスの内臓脂肪での老化 T 細胞は 6.8%から 16.0%に増加した。高脂肪食で飼育したマウスに CD153 ワクチンを投与しておくと、7.6%まで増加が抑えられた。

クリックで拡大表示します

研究成果のポイント

- 老化細胞を生体から除去する治療ワクチンの開発に成功
- マウスの脂肪組織の老化 T 細胞を減らすことで、糖尿病マウスの高血糖が改善

- ワクチンと一緒に投与するアジュバントの使い分けで、細胞除去ワクチンの作製が可能となった

概要

大阪大学 大学院医学系研究科の中神啓徳 寄附講座教授（健康発達医学）、吉田翔太 医員(老年・総合内科学)、楽木宏実 教授(老年・総合内科学)、森下竜一 寄附講座教授（臨床遺伝子治療学）らの研究グループは、老化 T 細胞除去を目的とした治療ワクチンを作製し、糖尿病モデルマウスに投与した結果、老化 T 細胞を減らすことによる病態の改善効果が得られたことを明らかにしました。
老化 T 細胞は加齢とともに増加して、いろいろな病気の進展に関与することが分かっています。下図に示すように、マウスに高脂肪食を負荷して肥満にさせると内臓脂肪で老化 T 細胞（PD-1 陽性/CD153 陽性細胞）が増えてきます。このマウスに CD153 を標的としたペプチドワクチンを投与したところ、老化 T 細胞の増加が抑えられることが分かりました。同時にこの老化 T 細胞数を減少させたマウスは糖尿病が改善していることが分かりました。
老化細胞は加齢に伴ういろいろな病気の原因となっていることが報告されていますが、本研究はワクチンによって老化細胞数を減らすことに成功した世界初の報告となります
本研究成果は、5 月 19 日に Nature Communication に掲載されました。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2020-06/ou-avt063020.php

NEWS RELEASE 30-JUN-2020

A VACCINE TARGETING AGED CELLS MITIGATES METABOLIC DISORDERS IN OBESE MICE

Researchers from Osaka University develop a novel vaccine that removes senescent immune cells from the body to improve obesity-induced metabolic disorders

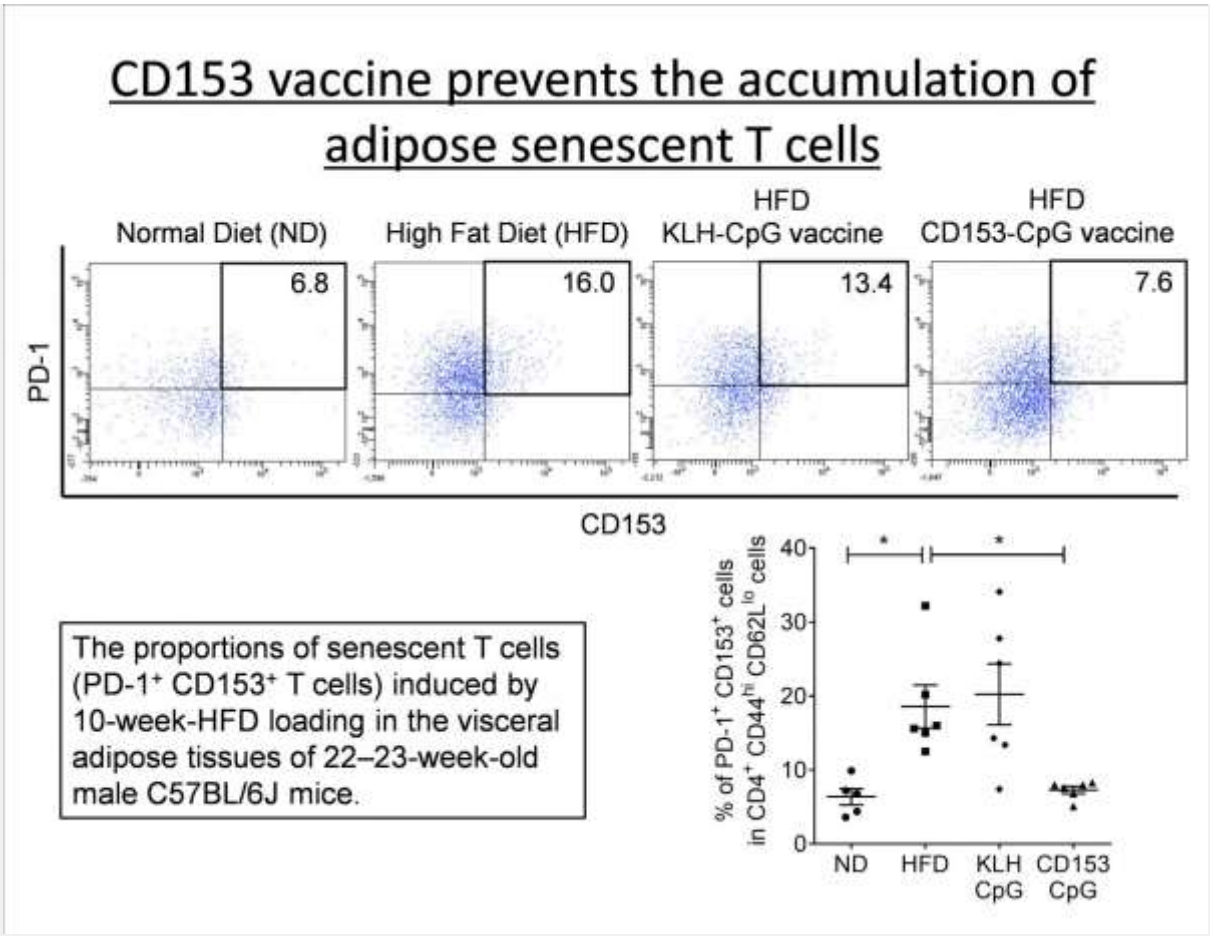

IMAGE: UPPER: SENESCENT T CELLS WERE DEFINED AS PD-1⁺ CD153⁺ CELLS IN CD4⁺ T CELLS. THE PROPORTION OF SENESCENT T CELLS IN VISCERAL ADIPOSE TISSUES (VAT) OF THE HIGH FAT DIET... **view more**

CREDIT: OSAKA UNIVERSITY

Osaka, Japan - Aging is a multifaceted process that affects our bodies in many ways. In a new study, researchers from Osaka University developed a novel vaccine that removes aged immune cells and then demonstrated an improvement of diabetes-associated metabolic derangements by vaccinating obese mice.

Aged, or senescent, cells are known to harm their surrounding younger cells by creating an inflammatory environment. A specific type of immune cell, called T cell, can accumulate in fat tissues in obese individuals in senescence, causing chronic inflammation, metabolic disorders and heart disease. To reduce the negative effects of senescent cells on the body, senotherapy was developed to target and eliminate these rogue cells. However, as this approach does not discriminate between different types of senescent cells, it has remained unknown whether specific depletion of senescent T cells can improve their adverse effects on organ physiology.

"The idea that eliminating senescent cells improves the organ dysfunction that we experience during aging is fairly new," says corresponding author of the study Hironori Nakagami. "Because senescent T cells can facilitate metabolic derangements similar to diabetes, we wanted to come up with a new approach to reduce the number of senescent T cells to then reverse the negative effects they have on glucose metabolism."

To achieve their goal, the researchers developed a novel vaccine targeting the surface protein CD153 that is present on senescent T cells populating fat tissues, thereby ensuring that normal T cells are not affected. To test the effects of their vaccine, the researchers fed mice with a high-fat diet to make them obese and ultimately to mimic the metabolic changes seen in diabetes. These include insulin resistance and an improperly functioning glucose metabolism, both of which can facilitate a deterioration of the eyes, kidneys, nerves and the heart. When they vaccinated these mice against CD153, the researchers observed a sharp decline of senescent T cells in the fat tissues of the mice, demonstrating the success of their approach.

But did it improve glucose metabolism in the obese mice? To investigate this, the researchers turned to a test that is widely used in clinically diagnosing diabetic patients and performed an oral glucose tolerance test in the mice, in which blood glucose levels were measured for up to 2 hours after giving the animals a known amount of glucose to drink. Vaccination against CD153 was able to restore glucose tolerance in obese mice. Unvaccinated obese mice, however, continued to have difficulties metabolizing glucose after intake and took a much longer time to reach similar blood levels as the vaccinated animals. The researchers also measured the extent of insulin resistance, which is a cornerstone of the metabolic changes seen in obesity and diabetes. Vaccinated mice showed significant improvements in insulin resistance as compared with the unvaccinated animals, demonstrating that the hormone that the body produces to lower blood glucose levels functioned properly.

"These are striking results that show how reducing senescent T cells in adipose tissues improves glucose metabolism of obese mice," says Nakagami. "Our findings provide new insights into removing specific senescent cells using specific vaccines and could potentially be used as a novel therapeutic tool for controlling glucose metabolism in obese individuals."

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The article, "The CD153 vaccine is a senotherapeutic option for preventing the accumulation of senescent T cells in mice," was published in *Nature Communications* at
DOI: https://doi.org/10.1038/s41467-020-16347-w

About Osaka University

Osaka University was founded in 1931 as one of the seven imperial universities of Japan and is now one of Japan's leading comprehensive universities with a broad disciplinary spectrum. This

strength is coupled with a singular drive for innovation that extends throughout the scientific process, from fundamental research to the creation of applied technology with positive economic impacts. Its commitment to innovation has been recognized in Japan and around the world, being named Japan's most innovative university in 2015 (Reuters 2015 Top 100) and one of the most innovative institutions in the world in 2017 (Innovative Universities and the Nature Index Innovation 2017). Now, Osaka University is leveraging its role as a Designated National University Corporation selected by the Ministry of Education, Culture, Sports, Science and Technology to contribute to innovation for human welfare, sustainable development of society, and social transformation.

Website: https://resou.osaka-u.ac.jp/en/top

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2. 動脈が老化する理由：腸内細菌および食事との関係

日付：2020 年 7 月 1 日
ソース：コロラド大学ボルダー校
概要：

例えばステーキやスクランブルエッグを食べると、常在する腸内細菌がすぐに働いてそれらを分解する。腸内細菌は、アミノ酸 L-カルニチンとコリンを代謝するとき、トリメチルアミンと呼ばれる代謝副産物を作り出し、その副産物は肝臓がトリメチルアミン-N-オキシド（TMAO）に変換して、血流を介して送り出す。
以前の研究では、TMAO の血中濃度が高い人は、心臓発作や脳卒中を発症する可能性が 2 倍以上高く、早死する傾向があることが示されている。しかし、これまでのところ、その理由は完全には理解されていなかった。
そこで、コロラド大学ボルダー校の研究者らは、マウスとヒトの実験に基づいて、TMAO が血管系に損傷を与えるのではないか？もしそうならどのようにして？そして加齢と共に心血管の健康が悪化する理由はこれではないか？という3つの疑問に向き合った。
先ず、ヒトを対象として、TMAO レベルは年齢と共に上昇することを発見。これは以前のマウス研究での結果と一致しており、腸内細菌のコレクションが年齢と共に変化し、TMAO の生成に役立つより多くの細菌が繁殖していることを示している。また、TMAO の血中濃度が高いヒトは、動脈機能が著しく悪化し、血管の内層に酸化ストレスや組織損傷のより大きな徴候が見られた。
TMAO を直接若いマウスに与えたところ、マウスの血管が急速に老化した。又、予備データとして、TMAO レベルがより高いマウスは、学習と記憶の減少を示し、この化合物が加齢に伴う認知機能低下にも一役買っている可能性を示している。
反対に、ジメチルブタノールと呼ばれる化合物を食した老齢のマウスは、血管の機能障害を逆転させた。研究者らは、この化合物が TMAO の生成を妨げるのでは、としている。
研究者らは、若いビーガンを含む全ての人が TMAO を生成しているが、加齢や多くの動物性食品摂取が大きい原因となっている可能性があるとしている。
研究チームは現在、加齢に伴う血管の衰退を防ぐために TMAO の生成を阻害する可能性のある化合物を調査している。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/07/200701100019.htm

WHY DO ARTERIES AGE? STUDY EXPLORES LINK TO GUT BACTERIA, DIET

Date:

July 1, 2020

Source:

University of Colorado at Boulder

Summary:

Eat a slab of steak and your resident gut bacteria get to work immediately to break it down. But new research shows that a metabolic byproduct, called TMAO, produced in the process can be harmful to the lining of arteries, making them age faster.

FULL STORY

A compound produced in the gut when we eat red meat damages our arteries and may play a key role in boosting risk of heart disease as we get older, according to new University of Colorado Boulder research.

The study, published this month in the American Heart Association journal *Hypertension*, also suggests that people may be able to prevent or even reverse such age-related decline via dietary changes and targeted therapies, like novel nutritional supplements.

"Our work shows for the first time that not only is this compound directly impairing artery function, it may also help explain the damage to the cardiovascular system that naturally occurs with age," said first author Vienna Brunt, a postdoctoral researcher in the Department of Integrative Physiology.

Eat a slab of steak or a plate of scrambled eggs, and your resident gut bacteria get to work immediately to break it down. As they metabolize the amino acids L-carnitine and choline, they churn out a metabolic byproduct called trimethylamine, which the liver converts to trimethylamine-N-Oxide (TMAO) and sends coursing through your bloodstream.

Previous studies have shown that people with higher blood levels of TMAO are more than twice as likely to have a heart attack or stroke and tend to die earlier.

But to date, scientists haven't completely understood why.

Drawing on animal and human experiments, Brunt and her team set out to answer three questions: Does TMAO somehow damage our vascular system? If so, how? And could it be one reason why cardiovascular health gets worse -- even among people who exercise and don't smoke -- as we get older?

The researchers measured the blood and arterial health of 101 older adults and 22 young adults and found that TMAO levels significantly rise with age. (This falls in line with a previous study in mice, showing the gut microbiome -- or your collection of intestinal bacteria -- changes with age, breeding more bacteria that help produce TMAO).

Adults with higher blood levels of TMAO had significantly worse artery function, the new study found, and showed greater signs of oxidative stress, or tissue damage, in the lining of their blood vessels.

When the researchers fed TMAO directly to young mice, their blood vessels swiftly aged.

"Just putting it in their diet made them look like old mice," said Brunt. She noted that 12-month-old mice (the equivalent of humans about 35 years old) looked more like 27-month-old mice (age 80 in people) after eating TMAO for several months.

Preliminary data also show that mice with higher levels of TMAO exhibit decreases in learning and memory, suggesting the compound could also play a role in age-related cognitive decline.

On the flip side, old mice that ate a compound called dimethyl butanol, (found in trace amounts in olive oil, vinegar and red wine) saw their vascular dysfunction reverse. Scientists believe that this compound prevents the production of TMAO.

Brunt notes that everyone -- even a young vegan -- produces some TMAO. But over time, eating a lot of animal products may take a toll.

"The more red meat you eat, the more you are feeding those bacteria that produce it," she said.

Senior author Doug Seals, director of the Integrative Physiology of Aging Laboratory, said the study is an important breakthrough because it sheds light on why our arteries erode with age, even in the healthiest people.

"Aging is the single greatest risk factor for cardiovascular disease, primarily as a result of oxidative stress to our arteries," said Seals. "But what causes oxidative stress to develop in our arteries as we age? That has been the big unkown. This study identifies what could be a very important driver."

The research team is now further exploring compounds that might block production of TMAO to prevent age-related vascular decline.

For now, they said, a plant-based diet may also keep levels in check.

Story Source:

Materials provided by **University of Colorado at Boulder**. Original written by Lisa Marshall. *Note: Content may be edited for style and length.*

Journal Reference:

1. Vienna E. Brunt, Rachel A. Gioscia-Ryan, Abigail G. Casso, Nicholas S. VanDongen, Brian P. Ziemba, Zachary J. Sapinsley, James J. Richey, Melanie C. Zigler, Andrew P. Neilson, Kevin P. Davy, Douglas R. Seals. **Trimethylamine-N-Oxide Promotes Age-Related Vascular Oxidative Stress and Endothelial Dysfunction in Mice and Healthy Humans**. *Hypertension*, 2020; 76 (1): 101 DOI: 10.1161/HYPERTENSIONAHA.120.14759

Cite This Page:

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3. 加齢に関連する障害、マウスで回復に成功

日付：2020 年 7 月 6 日
ソース：ベルン大学
概要：

虚弱と免疫低下は老年期における 2 つの主な特徴的症状である。ベルン大学とベルン大学病院の研究者たちは、動物モデルで、これら 2 つの加齢に関連する障害を停止し、新しい細胞ベースの治療アプローチを使用して部分的に回復することに成功した。
高齢者は、加齢とともに免疫系の機能が低下し続けるため、感染症にかかりやすくなる。高齢者におけるワクチン接種の有効性も大幅に低下するため、この年齢層は感染性病原体に対して特に脆弱となり、しばしば高死亡率を示す。
長年にわたり、科学者らは慢性的軽度炎症が老化プロセスと加齢性障害の発症を促進すると考えていたが、今回チームは、腹部脂肪として知られる内臓脂肪組織が慢性的軽度炎症の発症に対して決定的に寄与していることを明らかにした。
研究チームは、主に血液循環に見られる好酸球と呼ばれる特定の種類の免疫細胞が、ヒトとマウスの両方の腹部脂肪にも存在することを発見。この腹部脂肪にある好酸球は、免疫恒常性を維持する役割をしているが、加齢と共に減少する。
そこで、若いマウスの好酸球を老齢マウスに移植したところ、局所的な炎症だけでなく全身の軽度炎症も解消することができた、としている。このアプローチで、老化したマウスが体力の大幅な改善を示しただけでなく、ワクチン接種反応の改善を示す免疫システムに若返り効果をもたらした、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/2020/07/200706140905.htm

AGE-RELATED IMPAIRMENTS REVERSED IN ANIMAL MODEL

Date:

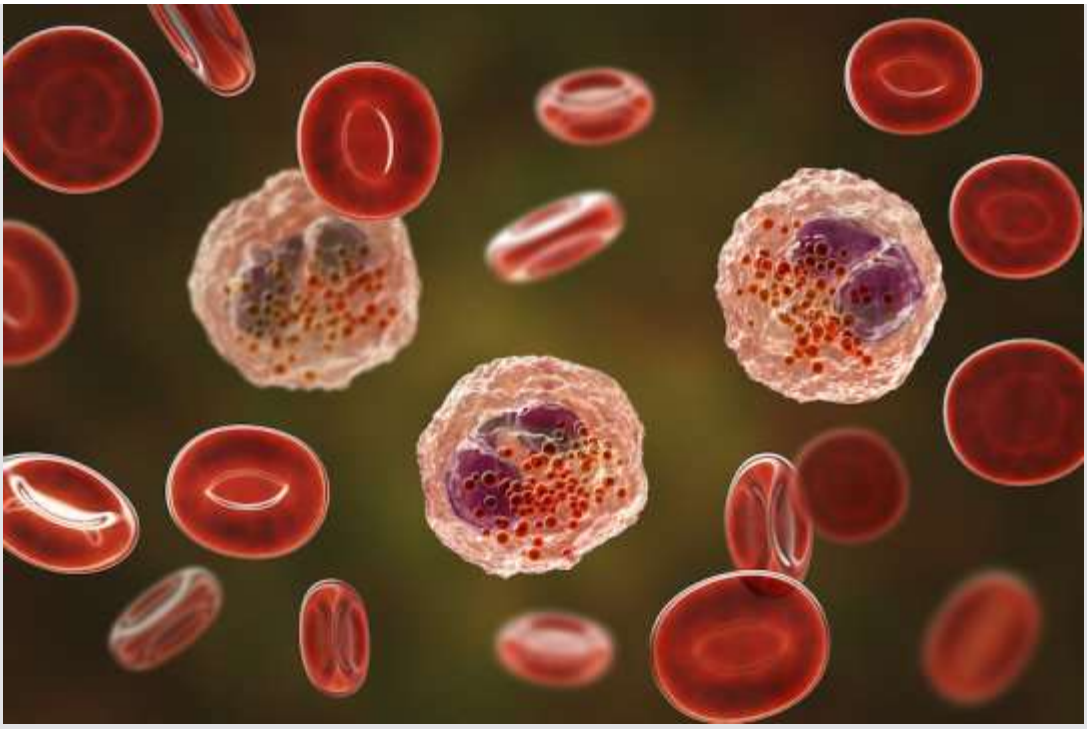
July 6, 2020

Source:

University of Bern

Summary:

Researchers demonstrate in an animal model that age-related frailty and immune decline can be halted and even partially reversed using a novel cell-based therapeutic approach.



Eosinophils surrounded by red blood cells (stock image).

Credit: © Kateryna_Kon / stock.adobe.com

Frailty and immune decline are two main features of old age. Researchers from the University of Bern and the University Hospital Bern now demonstrate in an animal model that these two age-related impairments can be halted and even partially reversed using a novel cell-based therapeutic approach.

Elderly people are more prone to infectious diseases as the function of their immune system continuously declines with progression of age. This becomes especially apparent during seasonal influenza outbreaks or the occurrence of other viral diseases such as COVID-19. As the efficacy of vaccination in the elderly is strongly reduced, this age group is particularly vulnerable to such infectious pathogens and often shows the highest mortality rate. In addition to the age-related immune decline aged individuals are commonly affected by frailty that negatively impacts quality-of-life. Even though the average life-expectancy for humans continuous to rise, living longer is often associated with age-related health issues.

Important role of belly fat in aging processes identified

Researchers from the Department for BioMedical Reserarch (DBMR) and the Institute of Pathology at the University of Bern as well as the University Hospital Bern (Inselspital) have set out to identify new approaches to improve health-span in a fast-growing aging population. For many years scientists speculated that chronic low-grade inflammation accelerates aging processes and the development of age-related disorders. An international team of researchers under Bernese guidance has now demonstrated that visceral adipose tissue, known as belly fat, crucially contributes to the development of chronic low-grade inflammation. Scientist around Dr.

Mario Noti, formerly at the Institute of Pathology of the University of Bern and Dr. Alexander Eggel from the Department for BioMedical Research (DBMR) of the Universität of Bern reported that certain immune cells in the belly fat play and an essential role in regulating chronic low-grade inflammation and downstream aging processes. They could show, that these immune cells may be used to reverse such processes. The findings of this study have been published in the scientific journal *Nature Metabolism* and were further highlighted by a News and Views editorial article.

Belly fat as a source of chronic inflammation

The team around Dr. Noti and Dr. Eggel could demonstrated that a certain kind of immune cells, known as eosinophils, which are predominantly found in the blood circulation, are also present in belly fat of both humans and mice. Although classically known to provide protection from parasite infection and to promote allergic airway disease, eosinophils located in belly fat are responsible to maintain local immune homeostasis. With increasing age the frequency of eosinophils in belly fat declines, while the number of pro-inflammatory macrophages increases. Owing to this immune cell dysbalance, belly fat turns into a source of pro-inflammatory mediators accumulating systemically in old age.

Eosinophil cell therapy promotes rejuvenation

In a next step, the researchers investigated the possibility to reverse age-related impairments by restoring the immune cell balance in visceral adipose tissue. "In different experimental approaches, we were able to show that transfers of eosinophils from young mice into aged recipients resolved not only local but also systemic low-grade inflammation," says Dr. Eggel. "In these experiments, we observed that transferred eosinophils were selectively homing into adipose tissue," adds Dr. Noti. This approach had a rejuvenating effect on the aged organism. As a consequence, aged animals showed significant improvements in physical fitness as assessed by endurance and grip strength tests. Moreover, the therapy had a rejuvenating effect on the immune system manifesting in improved vaccination responses of aged mice.

Translating findings into clinics

"Our results indicate that the biological processes of aging and the associated functional impairments are more plastic than previously assumed," states Dr. Noti. Importantly, the observed age-related changes in adipose immune cell distribution in mice were also confirmed in humans. "A future direction of our research will be to now leverage the gained knowledge for the establishment of targeted therapeutic approaches to promote and sustain healthy aging in humans," says Dr. Eggel.

This study has been supported by the VELUX STIFTUNG, the FONDATION ACTERIA, and funds of the FreeNovation and medical-biological science research programs of Novartis.

Story Source:

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

Journal References:

1. Daniel Brigger, Carsten Riether, Robin van Brummelen, Kira I. Mosher, Alicia Shiu, Zhaoqing Ding, Noemi Zbären, Pascal Gasser, Pascal Guntern, Hanadie Yousef, Joseph M. Castellano, Federico Storni, Neill Graff-Radford, Markus Britschgi, Denis Grandgirard, Magdalena Hinterbrandner, Mark Siegrist, Norman Moullan, Willy Hofstetter, Stephen L. Leib, Peter M. Villiger, Johan Auwerx, Saul A. Villeda, Tony Wyss-Coray, Mario Noti, Alexander Eggel. **Eosinophils regulate adipose tissue inflammation and sustain physical and immunological fitness in old age**. *Nature Metabolism*, 2020; DOI: 10.1038/s42255-020-0228-3

2. Chih-Hao Lee. **Young eosinophils rejuvenate ageing adipose tissues**. *Nature Metabolism*, 2020; DOI: 10.1038/s42255-020-0230-9

Cite This Page:

- MLA
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- Chicago

University of Bern. "Age-related impairments reversed in animal model." ScienceDaily. ScienceDaily, 6 July 2020. <www.sciencedaily.com/releases/2020/07/200706140905.htm>.

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4. ナトリウムがマウスの体内時計を調節

日付：2020 年 7 月 9 日
ソース：マギル大学
概要：

Nature 誌で発表されたマギル大学の新しい研究は、血中ナトリウムの増加がマウスの体内時計に影響を与える可能性があることを示しており、長距離移動やシフト作業に関連する悪影響を治療するための新しい道を開いている。
光が我々の体内時計を調節する主な要因であることは充分に証明されているが、生理学的要因が視交叉上核（suprachiasmatic nucleus – SCN）を調節できるのかどうか、またはどのように調節できるのかは不明であった。
この研究によると、食塩水をマウスに注射すると脳の主要概日時計– SCN に関連したニューロンの活性化につながる、としている。
研究者らは現在、食事による血中ナトリウム濃度の自然な増加が同じ効果を持っているのかどうか、そしてこれらがヒトでも起こるのかどうかを確立したい、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2020-07/mu-sft070920.php

NEWS RELEASE 9-JUL-2020

SODIUM FOUND TO REGULATE THE BIOLOGICAL CLOCK OF MICE

New study by McGill researchers first to establish physiological signals influence circadian rhythms

MCGILL UNIVERSITY

A new study from McGill University shows that increases in the concentrations of blood sodium can have an influence on the biological clock of mice, opening new research avenues for potentially treating the negative effects associated with long distance travel or shift work.

The findings, published in *Nature* by former McGill PhD student Claire Gizowski and Charles Bourque, a professor in McGill's Department of Neurology-Neurosurgery, are the first to show that injecting mice with a salt solution leads to the activation of neurons associated with the brain's master circadian clock - the suprachiasmatic nucleus (SCN).

Our biological clock - or circadian rhythm - adapts our body's cells and organs to changing requirements at different times of day. Prolonged disruption of these rhythms because of jetlag or shift work can lead to adverse health effects.

Though it is well established that light is the primary factor regulating our body's biological clock, it was unknown if or how physiological factors could regulate the SCN.

"Our study is the first to show that the SCN is listening to physiological signals and that such signals can in fact regulate clock time," says Bourque.

Gizowski and Bourque were able to show that salt-sensitive neurons found in a specific region of the brain - the organum vasculosum of the lamina terminalis - are capable of activating the brain's master circadian clock at a time of day when it is normally silent.

"This suggests that there could be ways by which we could speed up the clock, which could be useful to adapt more quickly to the time change associated with long distance travel, or when our work schedule is shifted by several hours," explains Gizowski.

The researchers now hope to establish if natural increases in blood sodium levels - through eating - have the same effect and whether or not these also occur in humans.

"One concern is that although ingestion of small amounts of salt is pleasant and not dangerous, it can be toxic when consumed in large amounts," Bourque adds. "Much more work is needed to examine if this finding is applicable to humans in a safe and practical way."

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About this study

"Sodium regulates clock time and output via an excitatory GABAergic pathway," by Claire Gizowski and Charles W. Bourque was published in *Nature*.

This work received financial support from the Canadian Institutes of Health Research.

About McGill University

Founded in Montreal, Quebec, in 1821, McGill is a leading Canadian post-secondary institution. It has two campuses, 11 faculties, 13 professional schools, 300 programs of study and over 40,000 students, including more than 10,200 graduate students. McGill attracts students from over 150 countries around the world, its 12,800 international students making up 31% per cent of the student body. Over half of McGill students claim a first language other than English, including approximately 19% of our students who say French is their mother tongue.

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5. 皮膚が老化すると「幹細胞の顔」が変わる
～加齢に伴う皮膚幹細胞の糖鎖変化の解析に成功～

日付：2020 年 7 月 21 日
ソース：筑波大学
概要：

http://www.tsukuba.ac.jp/attention-research/p202007211400.html

国立大学法人筑波大学 生存ダイナミクス研究センターの佐田亜衣子助教（研究当時、現 国立大学法人熊本大学 国際先端医学研究機構特任准教授）、柳沢裕美教授、国立研究開発法人産業技術総合研究所 細胞分子工学研究部門の舘野浩章研究グループ長らの研究グループは、糖鎖プロファイリング技術を用いて、老化皮膚において、幹細胞表面の糖鎖構造（糖鎖修飾パターン）が変化することを見出しました。

細胞表面に存在する糖鎖は、「細胞の顔」とも呼ばれるように、細胞の種類や状態によって構造が劇的に変化することが知られています。血液型や腫瘍マーカーをはじめ、糖鎖の違いは優れたバイオマーカーとしても幅広く利用されてきました。しかし、細胞の中でも、分化細胞を生み出す組織幹細胞注１は、成体組織の全細胞の１パーセント以下に過ぎず、微量のサンプルしか得られないため、糖鎖解析を行うことは困難でした。本研究は、「レクチンアレイ法」という新しい技術を使うことで、糖鎖構造を高感度かつ迅速に検出し、加齢に伴って起こる皮膚幹細胞の糖鎖変化を捉えることに成功しました。本成果は、幹細胞の糖鎖を標的とした新たな老化対策やバイオマーカーの創出へとつながることが期待されます。

図　レクチンアレイ法を用いた幹細胞の糖鎖プロファイリング
若齢・加齢マウスよりセルソーターを用いて皮膚幹細胞を単離し、レクチンアレイ

法を用いた糖鎖解析を行う。糖結合タンパク質であるレクチンをスライドガラス上に固定化し、細胞から抽出、蛍光標識した膜タンパク質をガラス上のレクチンと相互作用させることで、細胞表面に存在する糖鎖構造を高感度かつ迅速に検出することができる。この技術により加齢した皮膚幹細胞で有意に結合が変化するレクチンを同定した。

PDF 資料

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/07/200721102209.htm

SKIN STEM CELLS SHUFFLE SUGARS AS THEY AGE

Date:

July 21, 2020

Source:

University of Tsukuba

Summary:

Researchers have shown by in vitro experimentation that changes of glycans in mouse epidermal stem cells may serve as a biomarker of aging. Further, by overexpression of specific glycogenes in mouse keratinocytes, they replicated the glycome profile of aging cells as well as their decreased proliferation ability. These findings hold promise for stem cell research into skin disorders, specifically senile degeneration, wound healing and skin cancer.

FULL STORY

Age shows nowhere better than on the skin. The ravages of time on skin and the epidermal stem cells that differentiate to replenish its outer layer have been hypothesized, but there has been no method to evaluate their aging at the molecular level. Now, researchers at the University of Tsukuba and the National Institute of Advanced Industrial Science and Technology

(AIST) have revealed that changes in the complex sugars called glycans that coat the surface of epidermal stem cells can serve as a potential biological marker of aging.

Skin is the largest human organ and a vital barrier against infection and fluid loss. Aging impairs environmental defenses and wound healing, while increasing hair loss and cancer risk. A key process underlying epidermal function in health and disease is cellular glycosylation that mediates cell-cell interactions and cell-matrix adhesions. Glycosylation involves attaching glycans to proteins; the profile of all glycans on and in a cell -- collectively 'the cell glycome' -- could reflect its functional scope and serve as an index of its age.

The researchers first isolated epidermal stem cells from the skin of young and old laboratory mice, including both hair follicle cells and interfollicular epidermal cells. These cells underwent glycan profiling using the lectin microarray platform; this technique uses lectins -- proteins that bind specific glycans -- and enables glycome analysis even for cells sparsely dispersed in tissues.

"Our results clearly showed that high mannose-type N-glycans are replaced by a2-3/6 sialylated complex type N-glycans in older epidermal stem cells," senior author, Professor Hiromi Yanagisawa, explains. "We followed this with gene expression analysis; this revealed up-regulation of a glycosylation-related mannosidase and two sialyltransferase genes, suggesting that this 'glycome shift' may be mediated by age-modulated glycosyltransferase and glycosidase expression."

Finally, to check whether the glycan changes were the cause or merely the result of aging, the research team overexpressed the up-regulated glycogenes in primary epidermal mouse keratinocytes *in vitro.* The keratinocytes showed decreased mannose and increased Sia modifications, replicating the *in vivo* glycosylation pattern of aging epidermal stem cells. In addition, their decreased ability to proliferate suggested that these alterations may reflect the waning ability of aging epidermal stem cells to proliferate.

Professor Aiko Sada, currently Principal Investigator at Kumamoto University, and Professor Hiroaki Tateno at AIST, co-corresponding authors, explain the implications of their results. "Our work is broadly targeted at investigating stem cell dysfunction specifically in aging skin. Future advances may help manage skin disorders at the stem cell level, including age-related degenerative changes, impaired wound healing and cancer."

Story Source:

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

Journal Reference:

1. Lalhaba Oinam, Gopakumar Changarathil, Erna Raja, Yen Xuan Ngo, Hiroaki Tateno, Aiko Sada, Hiromi Yanagisawa. **Glycome profiling by lectin microarray reveals dynamic glycan alterations during epidermal stem cell aging**. *Aging Cell*, 2020; DOI: 10.1111/acel.13190

Cite This Page:

- MLA
- APA
- Chicago

University of Tsukuba. "Skin stem cells shuffle sugars as they age." ScienceDaily. ScienceDaily, 21 July 2020. <www.sciencedaily.com/releases/2020/07/200721102209.htm>.

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6. 抗生物質がマウスの「社会脳」の発達を混乱させる

日付：2020 年 6 月 22 日
ソース：オックスフォード大学
概要：

今日 *BMC Neuroscience* 誌に掲載されたオックスフォード大学による新しい研究によると、マウスの幼少期の抗生物質治療は、社会的行動や痛みの調節で機能する脳のシグナル伝達経路を妨げる、としている。
微生物叢の破壊によるマウスの脳に対する影響を研究していた科学者らは、以前から無菌マウス（微生物を欠いている）や抗生物質で処理されたマウス（微生物が著しく枯渇している）など、微生物を失ったマウスが社会的行動を害していることが分かった。
この研究は、微生物叢が脳のエンドルフィン系（エンドルフィンがオピオイド受容体を活性化するシステム）に影響を与えるかどうかを調査した最初の研究であり、これらの所見には臨床的関連性がある可能性がある、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/2020/07/200722134929.htm

ANTIBIOTICS DISRUPT DEVELOPMENT OF THE 'SOCIAL BRAIN' IN MICE

Date:

July 22, 2020

Source:

University of Oxford

Summary:

Antibiotic treatment in early life impedes brain signalling pathways that function in social behavior and pain regulation in mice, a new study has found.

FULL STORY

Antibiotic treatment in early life impedes brain signalling pathways that function in social behaviour and pain regulation in mice, a new study by Dr

Katerina Johnson and Dr Philip Burnet has found. It was published today in *BMC Neuroscience*.

Katerina Johnson, from the University's Departments of Psychiatry and Experimental Psychology, was researching the effects of disrupting the microbiome on the brain in mice. 'We know from previous research that animals missing microbes, such as germ-free animals (which are devoid of microbes) or antibiotic-treated animals (whose microbes are severely depleted), have impaired social behaviour,' she explains. 'I was therefore particularly interested in the effects of the microbiome on endorphin, oxytocin and vasopressin signalling since these neuropeptides play an important role in social and emotional behaviour.'

The most striking finding was in young animals treated with antibiotics. This resulted in reduced expression of the receptors which mediate endorphin, oxytocin and vasopressin signalling in the frontal cortex. Dr Johnson commented, 'If these signalling pathways are less active, this may help explain the behavioural deficits seen in antibiotic-treated animals. Whilst this study was in animals given a potent antibiotic cocktail, this finding highlights the potential detrimental effects that antibiotic exposure may have on the brain when it's still developing.'

Dr Burnet added, 'Our research underlines the growing consensus that disturbing the microbiome during development can have significant impacts on physiology, including the brain.'

The study was conducted using a relatively small number of animals with high doses of antibiotics and further research should follow up this finding given society's reliance on antibiotics, though of course they still play a vital role in medicine to fight bacterial infections.

This was also the first study to investigate whether the microbiome affects the brain's endorphin system (where endorphin activates opioid receptors) and so these findings may have clinical relevance. Dr Johnson said, 'The adverse effect of antibiotics on the endorphin system may have implications not only for social behaviour but also for pain regulation. In fact we know that the gut microbiome affects the pain response so this might be one of the ways in which it does so.'

'A somewhat surprising observation from our research was the contrast in results for germ-free and antibiotic-treated mice, since the neurogenetic changes were generally in the opposite direction. This is a pertinent finding as the use of antibiotics to deplete the microbiome is often seen as a more accessible alternative to germ-free animals. However, we highlight the need to consider these two treatments as distinct models of microbiome manipulation when investigating the effects of microbes on the brain and behaviour.'

Story Source:

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

Journal Reference:

1. Katerina V. A. Johnson, Philip W. J. Burnet. **Opposing effects of antibiotics and germ-free status on neuropeptide systems involved in social behaviour and pain regulation**. *BMC Neuroscience*, 2020; 21 (1) DOI: 10.1186/s12868-020-00583-3

Cite This Page:

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- APA
- Chicago

University of Oxford. "Antibiotics disrupt development of the 'social brain' in mice." ScienceDaily. ScienceDaily, 22 July 2020. <www.sciencedaily.com/releases/2020/07/200722134929.htm>.

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7. COVID-19 が嗅覚喪失を引き起こす理由

日付：2020 年 7 月 24 日
ソース：ハーバード医科大学
概要：

最近の報告によると、完全無嗅覚症または嗅覚の部分的喪失が SARS-CoV-2 感染の初期マーカーであることが示されているが、COVID-19 患者の臭いが失われる根本的なメカニズムは不明である。
一部の研究では、COVID-19 の無嗅覚症は、他のウイルス感染によって引き起こされる無嗅覚症とは異なる。例えば、COVID-19 患者は通常、数週間かけて嗅覚を回復。これは、嗅覚ニューロンに直接損傷を与えることが知られているウイルス感染のサブセットによって引き起こされる無嗅覚症から回復するのにかかる時間よりもはるかに短い。更に、多くのウイルスは、鼻づまりなどの上気道の問題を引き起こすことにより、一時的に臭いを失うのに対して、COVID-19 患者の一部は、鼻づまりなしで無嗅覚症を経験する。
今回、ハーバード医科大学の神経科学者らが率いる国際的研究チームが COVID-19 を引き起こすウイルスである SARS-CoV-2 による感染に対して最も脆弱な嗅覚細胞タイプを特定、臭いの感覚を検出して脳に伝達する感覚ニューロンは、脆弱な細胞タイプの中にはないとして、7 月 24 日に *Science Advances* 誌で報告した。
この研究は、鼻と前脳の非ニューロン支持細胞の感染が COVID-19 の患者の臭い喪失の原因である可能性がある、としている。また、嗅覚感覚ニューロンは、ウイルスがヒト細胞に侵入するために使用する主要なタンパク質である ACE2 を発現しないため、SARS-CoV-2 感染に対して脆弱ではないことが判明した。
この研究は、COVID-19 関連の臭いの喪失をよりよく理解するための貴重な取り組みである。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/07/200724141027.htm

HOW COVID-19 CAUSES SMELL LOSS

OLFACTORY SUPPORT CELLS, NOT NEURONS, ARE VULNERABLE TO NOVEL CORONAVIRUS INFECTION

Date:

July 24, 2020

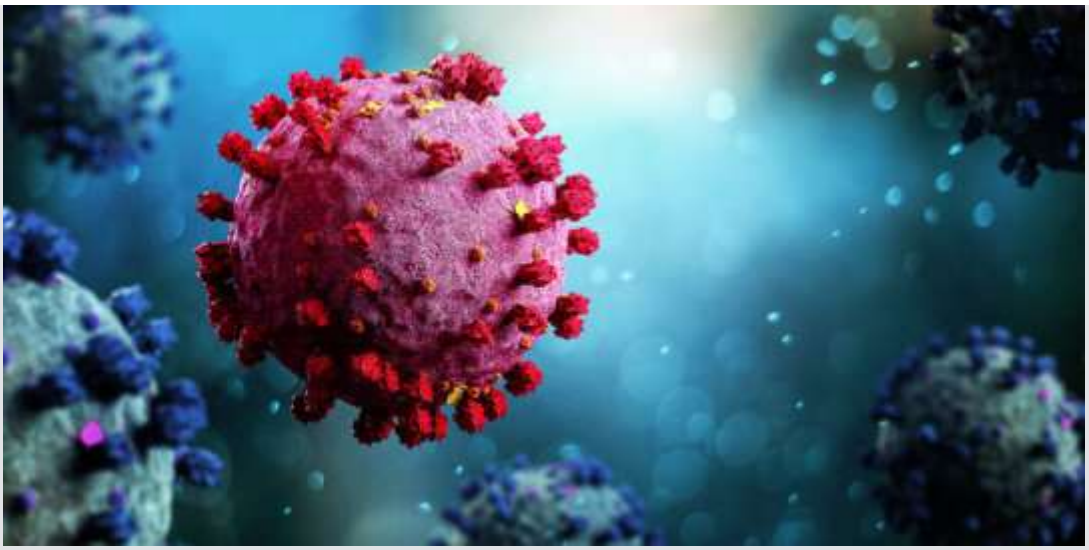
Source:

Harvard Medical School

Summary:

Loss of smell, or anosmia, is one of the earliest and most commonly reported symptoms of COVID-19. A new study identifies the olfactory cell types most vulnerable to infection by the novel coronavirus. Surprisingly, sensory neurons involved in smell are not among the vulnerable cell types.

FULL STORY



Coronavirus illustration (stock image).

Credit: © Production Perig / stock.adobe.com

Temporary loss of smell, or anosmia, is the main neurological symptom and one of the earliest and most commonly reported indicators of COVID-19. Studies suggest it better predicts the disease than other well-known symptoms such as fever and cough, but the underlying mechanisms for loss of smell in patients with COVID-19 have been unclear.

Now, an international team of researchers led by neuroscientists at Harvard Medical School has identified the olfactory cell types most vulnerable to infection by SARS-CoV-2, the virus that causes COVID-19.

Surprisingly, sensory neurons that detect and transmit the sense of smell to the brain are not among the vulnerable cell types.

Reporting in *Science Advances* on July 24, the research team found that olfactory sensory neurons do not express the gene that encodes the ACE2 receptor protein, which SARS-CoV-2 uses to enter human cells. Instead, ACE2 is expressed in cells that provide metabolic and

structural support to olfactory sensory neurons, as well as certain populations of stem cells and blood vessel cells.

The findings suggest that infection of nonneuronal cell types may be responsible for anosmia in COVID-19 patients and help inform efforts to better understand the progression of the disease.

"Our findings indicate that the novel coronavirus changes the sense of smell in patients not by directly infecting neurons but by affecting the function of supporting cells," said senior study author Sandeep Robert Datta, associate professor of neurobiology in the Blavatnik Institute at HMS.

This implies that in most cases, SARS-CoV-2 infection is unlikely to permanently damage olfactory neural circuits and lead to persistent anosmia, Datta added, a condition that is associated with a variety of mental and social health issues, particularly depression and anxiety.

"I think it's good news, because once the infection clears, olfactory neurons don't appear to need to be replaced or rebuilt from scratch," he said. "But we need more data and a better understanding of the underlying mechanisms to confirm this conclusion."

A majority of COVID-19 patients experience some level of anosmia, most often temporary, according to emerging data. Analyses of electronic health records indicate that COVID-19 patients are 27 times more likely to have smell loss but are only around 2.2 to 2.6 times more likely to have fever, cough or respiratory difficulty, compared to patients without COVID-19.

Some studies have hinted that anosmia in COVID-19 differs from anosmia caused by other viral infections, including by other coronaviruses.

For example, COVID-19 patients typically recover their sense of smell over the course of weeks -- much faster than the months it can take to recover from anosmia caused by a subset of viral infections known to directly damage olfactory sensory neurons. In addition, many viruses cause temporary loss of smell by triggering upper respiratory issues such as stuffy nose. Some COVID-19 patients, however, experience anosmia without any nasal obstruction.

Pinpointing vulnerability

In the current study, Datta and colleagues set out to better understand how sense of smell is altered in COVID-19 patients by pinpointing cell types most vulnerable to SARS-CoV-2 infection.

They began by analyzing existing single-cell sequencing datasets that in total catalogued the genes expressed by hundreds of thousands of individual cells in the upper nasal cavities of humans, mice and nonhuman primates.

The team focused on the gene ACE2, widely found in cells of the human respiratory tract, which encodes the main receptor protein that SARS-CoV-2 targets to gain entry into human cells. They also looked at another gene, TMPRSS2, which encodes an enzyme thought to be important for SARS-CoV-2 entry into the cell.

The analyses revealed that both ACE2 and TMPRSS2 are expressed by cells in the olfactory epithelium -- a specialized tissue in the roof of the nasal cavity responsible for odor detection that houses olfactory sensory neurons and a variety of supporting cells.

Neither gene, however, was expressed by olfactory sensory neurons. By contrast, these neurons did express genes associated with the ability of other coronaviruses to enter cells.

The researchers found that two specific cell types in the olfactory epithelium expressed ACE2 at similar levels to what has been observed in cells of the lower respiratory tract, the most common targets of SARS-CoV-2, suggesting a vulnerability to infection.

These included sustentacular cells, which wrap around sensory neurons and are thought to provide structural and metabolic support, and basal cells, which act as stem cells that regenerate the olfactory epithelium after damage. The presence of proteins encoded by both genes in these cells was confirmed by immunostaining.

In additional experiments, the researchers found that olfactory epithelium stem cells expressed ACE2 protein at higher levels after artificially induced damage, compared with resting stem cells. This may suggest additional SARS-CoV-2 vulnerability, but it remains unclear whether or how this is important to the clinical course of anosmia in patients with COVID-19, the authors said.

Datta and colleagues also analyzed gene expression in nearly 50,000 individual cells in the mouse olfactory bulb, the structure in the forebrain that receives signals from olfactory sensory neurons and is responsible for initial odor processing.

Neurons in the olfactory bulb did not express ACE2. The gene and associated protein were present only in blood vessel cells, particularly pericytes, which are involved in blood pressure regulation, blood-brain barrier maintenance and inflammatory responses. No cell types in the olfactory bulb expressed the TMPRSS2 gene.

Smell loss clue

Together, these data suggest that COVID-19-related anosmia may arise from a temporary loss of function of supporting cells in the olfactory epithelium, which indirectly causes changes to olfactory sensory neurons, the authors said.

"We don't fully understand what those changes are yet, however," Datta said. "Sustentacular cells have largely been ignored, and it looks like we need to pay attention to them, similar to how we have a growing appreciation of the critical role that glial cells play in the brain."

The findings also offer intriguing clues into COVID-19-associated neurological issues. The observations are consistent with hypotheses that SARS-CoV-2 does not directly infect neurons but may instead interfere with brain function by affecting vascular cells in the nervous system, the authors said. This requires further investigation to verify, they added.

The study results now help accelerate efforts to better understand smell loss in patients with COVID-19, which could in turn lead to treatments for anosmia and the development of improved smell-based diagnostics for the disease.

"Anosmia seems like a curious phenomenon, but it can be devastating for the small fraction of people in whom it's persistent," Datta said. "It can have serious psychological consequences and could be a major public health problem if we have a growing population with permanent loss of smell."

The team also hope the data can help pave inroads for questions on disease progression such as whether the nose acts as a reservoir for SARS-CoV-2. Such efforts will require studies in facilities that allow experiments with live coronavirus and analyses of human autopsy data, the authors said, which are still difficult to come by. However, the collaborative spirit of pandemic-era scientific research calls for optimism.

"We initiated this work because my lab had a couple of datasets ready to analyze when the pandemic hit, and we published an initial preprint," Datta said. "What happened after that was amazing, researchers across the globe offered to share and merge their data with us in a kind of impromptu global consortium. This was a real collaborative achievement."

Co-first authors on the study are David Brann, Tatsuya Tsukahara and Caleb Weinreb. Additional authors include Marcela Lipovsek, Koen Van den Berge, Boying Gong, Rebecca Chance, Iain Macaulay, Hsin-jung Chou, Russell Fletcher, Diya Das, Kelly Street, Hector Roux de Bezieux, Yoon-Gi Choi, Davide Risso, Sandrine Dudoit, Elizabeth Purdom, Jonathan Mill, Ralph Abi Hachem, Hiroaki Matsunami, Darren Logan, Bradley Goldstein, Matthew Grubb and John Ngai.

The study was supported by grants from the National Institutes of Health (grants RO11DC016222 and U19 NS112953) and the Simons Collaboration on the Global Brain. Additional funding information can be found in the full text of the paper.

Story Source:

Materials provided by **Harvard Medical School**. Original written by Kevin Jiang. *Note: Content may be edited for style and length.*

Journal Reference:

1. David H. Brann, Tatsuya Tsukahara, Caleb Weinreb, Marcela Lipovsek, Koen Van den Berge, Boying Gong, Rebecca Chance, Iain C. Macaulay, Hsin-Jung Chou, Russell B. Fletcher, Diya Das, Kelly Street, Hector Roux de Bezieux, Yoon-Gi Choi, Davide Risso, Sandrine Dudoit, Elizabeth Purdom, Jonathan Mill, Ralph Abi Hachem, Hiroaki Matsunami, Darren W. Logan, Bradley J. Goldstein, Matthew S. Grubb, John Ngai, Sandeep Robert Datta. **Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia**. *Science Advances*, July 24, 2020; DOI: 10.1126/sciadv.abc5801

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Harvard Medical School. "How COVID-19 causes smell loss: Olfactory support cells, not neurons, are vulnerable to novel coronavirus infection." ScienceDaily. ScienceDaily, 24 July 2020. <www.sciencedaily.com/releases/2020/07/200724141027.htm>.

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8. 発達障害関連の DNA ピンポイント領域上の化学マークマップ

発達障害をよりよく理解するために、マウスの DNA メチル化が時間とともにどのように変化するかをマッピング

日付：2020 年 7 月 29 日
ソース：ソーク研究所
概要：

人間の発達障害の原因を明らかにすることを目的とした研究で、ソークの科学者らは、発達中のマウスの DNA 鎖にメチルマークと呼ばれる 168 の新しい化学マークマップを生成した。データは、統合失調症やレット症候群などの疾患に関与するヒトゲノムの領域を絞り込むのに役立つ、としている。
これらのデータは、7 月 29 日に、ENCODE プロジェクト（ヒトおよびマウスのゲノムのすべての機能要素を特定することを目的とした公的研究）に特化した *Nature* の特別版で公開された。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/07/200729114746.htm

NEW MAPS OF CHEMICAL MARKS ON DNA PINPOINT REGIONS RELEVANT TO MANY DEVELOPMENTAL DISEASES

RESEARCHERS MAPPED HOW DNA METHYLATION CHANGES OVER TIME IN MICE TO BETTER UNDERSTAND DEVELOPMENTAL DISORDERS

Date:

July 29, 2020

Source:

Salk Institute

Summary:

In research that aims to illuminate the causes of human developmental disorders, scientists have generated 168 new maps of chemical marks on strands of DNA -- called methylation -- in developing mice. The data can help narrow down regions of the human genome that play roles in diseases such as schizophrenia and Rett Syndrome.

FULL STORY

In research that aims to illuminate the causes of human developmental disorders, Salk scientists have generated 168 new maps of chemical marks on strands of DNA -- called methylation -- in developing mice.

The data, published July 29, 2020, in a special edition of *Nature* devoted to the ENCODE Project (a public research effort aimed at identifying all functional elements in the human and mouse genomes), can help narrow down regions of the human genome that play roles in diseases such as schizophrenia and Rett Syndrome. The paper's authors are also on two additional papers in the special edition.

"This is the only available dataset that looks at the methylation in a developing mouse over time, tissue by tissue," says senior author and Howard Hughes Medical Institute Investigator Joseph Ecker, a professor in Salk's Genomic Analysis Laboratory. "It's going to be a valuable resource to help in narrowing down the causal tissues of human developmental diseases."

While the sequence of DNA contained in every cell of your body is virtually identical, chemical marks on those strands of DNA give the cells their unique identities. The patterns of methylation on adult brain cells, for instance, are different than those on adult liver cells. That's in part because of short stretches in the genome called enhancers. When transcription factor proteins bind to these enhancer regions, a target gene is much more likely to be expressed. When an enhancer is methylated, however, transcription factors generally can't bind and the associated gene is less likely to be activated; these methyl marks are akin to applying the hand brake after parking a car.

Researchers know that mutations in these enhancer regions -- by affecting the expression levels of a corresponding gene -- can cause disease. But there are hundreds of thousands of enhancers and they can be located far from the gene they help regulate. So narrowing down which enhancer mutations may play a role in a developmental disease has been a challenge.

In the new work, Ecker and collaborators used experimental technologies and computational algorithms that they previously developed to study the DNA methylation patterns of cells in samples of a dozen types of tissues from mice over eight developmental stages.

"The breadth of samples that we applied this technology to is what's really key," says first author Yupeng He, who was previously a Salk postdoctoral research fellow and is now a senior bioinformatics scientist at Guardant Health.

They discovered more than 1.8 million regions of the mouse genome that had variations in methylation based on tissue, developmental stage or both. Early in development, those changes were mostly the loss of methylation on DNA -- akin to removing the brake on gene expression and allowing developmental genes to turn on. After birth, however, most sites became highly methylated again, putting the brakes on gene expression as the mouse approaches birth.

"We think that the removal of methylation makes the whole genome more open to dynamic regulation during development," says He. "After birth, genes critical for early development need to be more stably silenced because we don't want them turned on in mature tissue, so that's when methylation comes in and helps shut down the early developmental enhancers."

In the past, many researchers have studied methylation by homing in on areas of the genome near genes called CpG islands -- sections of DNA that have a lot of cytosine and guanine base pairs in them, since typical methylation occurs when a methyl is added to a cytosine that's

followed by a guanine. However, in the new work, He and Ecker showed that 91.5 percent of the methylation variations they found during development far away from CpG islands.

"If you only look at those CpG island regions near genes, as many people do, you'll miss a lot of the meaningful DNA changes that could be directly related to your research questions," says He.

To show the utility of their new data set, the researchers looked at genetic variations that had been linked to 27 human diseases and disorders in previous genome-wide association studies (GWAS). They found associations between some human disease mutations and tissue-specific methylation patterns in corresponding regions of the mouse genome. For instance, mutations associated with schizophrenia were more likely to be found in suspected gene control regions in the mouse genome that undergo methylation changes in an area of the brain called the forebrain during development. Such patterns could help other researchers narrow down which mutations found in a GWAS they should focus on.

Story Source:

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

Journal Reference:

1. Yupeng He, Manoj Hariharan, David U. Gorkin, Diane E. Dickel, Chongyuan Luo, Rosa G. Castanon, Joseph R. Nery, Ah Young Lee, Yuan Zhao, Hui Huang, Brian A. Williams, Diane Trout, Henry Amrhein, Rongxin Fang, Huaming Chen, Bin Li, Axel Visel, Len A. Pennacchio, Bing Ren, Joseph R. Ecker. **Spatiotemporal DNA methylome dynamics of the developing mouse fetus**. *Nature*, 2020; 583 (7818): 752 DOI: 10.1038/s41586-020-2119-x

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Cite This Page:

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Salk Institute. "New maps of chemical marks on DNA pinpoint regions relevant to many developmental diseases: Researchers mapped how DNA methylation changes over time in mice to better understand developmental disorders." ScienceDaily. ScienceDaily, 29 July 2020. <www.sciencedaily.com/releases/2020/07/200729114746.htm>.

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9. 頭足類で初の遺伝子ノックアウトを達成

日付：2020 年 7 月 30 日
ソース：海洋生物学研究所（MBL）
概要：

海洋生物学研究所（MBL）のチームは、約 1 世紀にわたって生物学において非常に重要な研究生物であるイカ Doryteuthis pealeii を使用して、頭足類で最初の遺伝子ノックアウトを達成した。この画期的な研究は、*Current Biology* 誌の 7 月 30 日号で報告されている。
チームは CRISPR-Cas9 ゲノム編集を使用して、イカの胚の色素形成遺伝子をノックアウトした。これにより、目と皮膚細胞（色素胞）の色素沈着が高効率で排除された、としている。
現在、ショウジョウバエ、ゼブラフィッシュ、マウスなどが遺伝的に扱いやすい生物として遺伝子研究を支配しているが、これら少数の種を増やす上でも、遺伝子をノックアウトしてその機能をテストすることは、頭足類の開発においてとても重要なステップだとしている。

研究関連/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2020-07/mbl-fgk072420.php

NEWS RELEASE 30-JUL-2020

FIRSTGENE KNOCKOUT IN A CEPHALOPOD IS ACHIEVED AT MARINE BIOLOGICAL LABORATORY

MARINE BIOLOGICAL LABORATORY

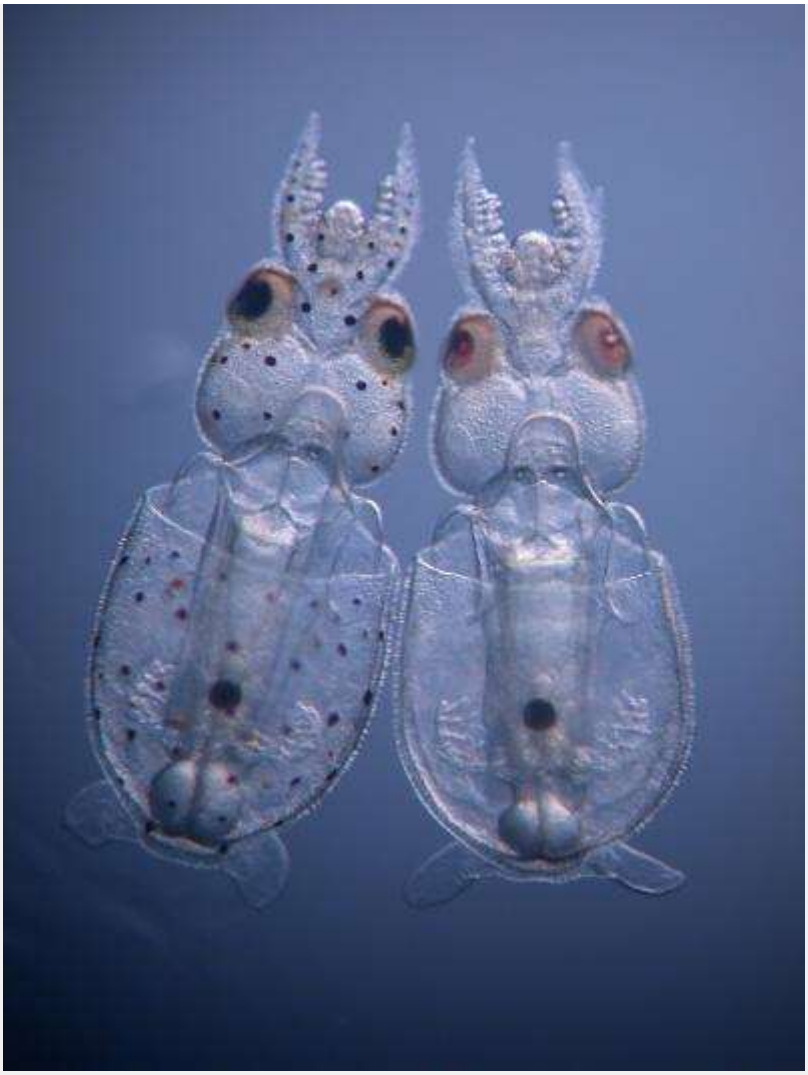

IMAGE: LONGFIN INSHORE SQUID (DORYTEUTHIS PEALEII) HATCHLINGS. ON THE LEFT IS A CONTROL HATCHLING; NOTE THE BLACK AND REDDISH BROWN CHROMATOPHORES EVENLY PLACED ACROSS ITS MANTLE, HEAD AND TENTACLES. IN CONTRAST,... **view more**

CREDIT: KAREN CRAWFORD

WOODS HOLE, Mass. --A team at the Marine Biological Laboratory (MBL) has achieved the first gene knockout in a cephalopod using the squid *Doryteuthis pealeii*, an exceptionally important research organism in biology for nearly a century. The milestone study, led by MBL Senior Scientist Joshua Rosenthal and MBL Whitman Scientist Karen Crawford, is reported in the July 30 issue of *Current Biology*.

The team used CRISPR-Cas9 genome editing to knock out a pigmentation gene in squid embryos, which eliminated pigmentation in the eye and in skin cells (chromatophores) with high efficiency.

"This is a critical first step toward the ability to knock out -- and knock in -- genes in cephalopods to address a host of biological questions," Rosenthal says.

Cephalopods (squid, octopus and cuttlefish) have the largest brain of all invertebrates, a distributed nervous system capable of instantaneous camouflage and sophisticated behaviors, a unique body plan, and the ability to extensively recode their own genetic information within messenger RNA, along with other distinctive features. These open many avenues for study and have applications in a wide range of fields, from evolution and development, to medicine, robotics, materials science, and artificial intelligence.

The ability to knock out a gene to test its function is an important step in developing cephalopods as genetically tractable organisms for biological research, augmenting the handful of species that currently dominate genetic studies, such as fruit flies, zebrafish, and mice.

It is also a necessary step toward having the capacity to knock in genes that facilitate research, such as genes that encode fluorescent proteins that can be imaged to track neural activity or other dynamic processes.

"CRISPR-Cas9 worked really well in *Doryteuthis*; it was surprisingly efficient," Rosenthal says. Much more challenging was delivering the CRISPR-Cas system into the one-celled squid embryo, which is surrounded by an exceedingly tough outer layer, and then raising the embryo through hatching. The team developed micro-scissors to clip the egg's surface and a beveled quartz needle to deliver the CRISPR-Cas9 reagents through the clip.

Studies with *Doryteuthis pealeii* have led to foundational advances in neurobiology, beginning with description of the action potential (nerve impulse) in the 1950s, a discovery for which Alan Hodgkin and Andrew Huxley became Nobel Prize laureates in 1963. For decades *D. pealeii* has drawn neurobiologists from all over the world to the MBL, which collects the squid from local waters.

Recently, Rosenthal and colleagues discovered extensive recoding of mRNA in the nervous system of *Doryteuthis* and other cephalopods. This research is under development for potential biomedical applications, such as pain management therapy.

D. pealeii is not, however, an ideal species to develop as a genetic research organism. It's big and takes up a lot of tank space plus, more importantly, no one has been able to culture it through multiple generations in the lab.

For these reasons, the MBL Cephalopod Program's next goal is to transfer the new knockout technology to a smaller cephalopod species, Euprymna berryi (the hummingbird bobtail squid), which is relatively easy to culture to make genetic strains.

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The MBL Cephalopod Program is part of the MBL's New Research Organisms Initiative, which is widening the palette of genetically tractable organisms available for research - and thus expanding the universe of biological questions that can be asked.

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The Marine Biological Laboratory (MBL) is dedicated to scientific discovery - exploring fundamental biology, understanding marine biodiversity and the environment, and informing the human condition through research and education. Founded in Woods Hole, Massachusetts in 1888, the MBL is a private, nonprofit institution and an affiliate of the University of Chicago.
