Bio News – July, 2020

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

6/1　新型コロナウイルスはまず鼻から気道を下っていくらしい

新型コロナウイルス（SARS-CoV-2）はその受容体 ACE2 発現の勾配と同じく気道の近くから遠くへ行くほど感染し難く、鼻腔の細胞には最も容易に感染して肺の奥深くには最も感染し難いことが示された。

6/1　米国 NY 市での COVID-19 流行は主に欧州や米国の他の地域からのウイルスが起源

6/1　COVID-19 で入院した糖尿病患者の約 10 人のうち 1 人(10.6%)が 7 日内に死亡～フランス

6/2　人工の「けん」作製技術開発　治療への応用期待　医科歯科大など

6/2　関節リウマチ治療薬「アクテムラ」の治験開始　コロナ薬候補　中外製薬

6/3　コロナの遺伝子ワクチン候補、最初の臨床試験をクリア、年内に最終段階の可能性も -米 Moderna

6/3　Gilead がスタンフォード大学の研究者を炎症疾患臨床開発リーダーに迎えた

6/4　「バイオ3Dプリンター」活用して薬剤の副作用評価　佐大研究グループが新手法

6/4　コロナワクチン、2021 年前半の接種開始目標…厚労省

6/4　iPS 細胞使い効果確認　アルツハイマー病の薬を治験へ -京都大と三重大

6/4　新型コロナ感染を最短 40 分で判定 東大、ゲノム編集による迅速診断法を開発

https://scienceportal.jst.go.jp/news/newsflash_review/newsflash/2020/06/20200604_01.html

6/4　Gilead の COVID-19 薬 Remdesivir は米国定価を 5,000 ドルと著名アナリストが予想

6/5　男性が新型コロナウイルスに弱いのは男性ホルモンのせいかもしれない

イタリアの前立腺癌男性を調べたところ、テストステロンを減らす抗アンドロゲン（ADT）薬使用と新型コロナウイルス（SARS-CoV-2）感染率低下が関連した。

6/6　ユトレヒト大学等が見つけた抗 COVID-19 抗体を AbbVie が共同開発

オランダのユトレヒト大学、Erasmus Medical Center（EMC）、Harbour BioMed の 3 者が見つけて先月初めに Nature Communications に報告した新型コロナウイルス（SARS-CoV-2）中和抗体 47D11 の前臨床開発を支援し、その後の臨床開発や販売を独占的に担う選択権利を AbbVie が取得。

6/6　シンガポールが国民全員に COVID-19 追跡ウェアラブル装置を配布する予定

6/6　年内の COVID-19 ワクチン供給を目指す米国政府取り組みが支援する 5 社

安全で有効な新型コロナウイルス感染（COVID-19）ワクチンを今年中に米国人に十分量届けることを目指す米国政府の取り組み Operation Warp Speed（OWS）が 5 社の支援を決めた。その 5 社は、Moderna、AstraZeneca、Johnson & Johnson（J&J）、Merck & Co、Pfizer だと The New York Times が報じている。

6/6　ウシが作る新型コロナウイルス中和抗体の臨床試験が初夏には始まる見込み

ヒトの抗体作製 DNA を備えたウシが作る新型コロナウイルス（SARS-CoV-2）への抗体 SAB-185 の細胞感染阻止力が回復者血漿を 4 倍上回った。
SAB-185 はサウスダコタ州の SAB Biotherapeutics が CSL Behring と協力して開発しており、この初夏には臨床試験が始まる見込み。
小動物に比べて血液が多いことに加えてヒトよりも血液中の抗体濃度が高いことからウシは抗体の製造に適していると SAB の CEO・Eddie Sullivan 氏は言っている。

6/7　AstraZeneca が Gilead に合併を打診/Bloomberg

時価総額 1400 億ドルの英国最大の製薬会社 AstraZeneca が金曜日時点で 960 億ドル相当の Gilead Sciences に合併を先月打診したと事情通が Bloomberg に話している。

6/7　Lancet と NEJM の COVID-19 論文撤回でデータ監視の在り方が問題視されている

抗マラリア薬ヒドロキシクロロキンと COVID-19 患者死亡率上昇の関連を示した注目の Lancet 報告が報告されてから 2 週間後の 6 月 4 日、米国企業 Surgisphere が解析したとされるその情報源が確認不可能であるとして 1 人を除く 3 人の著者がその報告を取り下げた。

（参考）：一流医学誌で論文撤回～新型コロナウイルスの研究に何が起こっているのか

https://news.yahoo.co.jp/byline/enokieisuke/20200606-00182065/

6/8　Melinta が AcelRx との Tetraphase 買収戦に勝利

AcelRx は Tetraphase を 1,440 万ドル相当で買うことで合意していたが、その合意破棄により Tetraphase は手切れ金約 178 万ドルを支払った。Melinta はその Tetraphase 買収に 3,900 万ドル支払った、ということで得をしたのはどの会社か。

6/9　上海の Junshi が Lilly と組んで開発している COVID-19 治療抗体の中国での Ph1 試験開始

6/10　新型コロナウイルス感染サルの肺疾患を Gilead のレムデシビルが防いだ

6/10　生命科学データ解析を簡単にするソフトウェア会社 DNAnexus（カリフォルニア州マウンテンビュー市）が 1 億ドル調達

6/11　アビガンと成分を同じくする COVID-19 薬 Avifavir のロシアでの出荷が始まった

6/11　iPS で「網膜色素変性症」治療　神戸の病院の計画を厚労省が了承

6/11　脳神経刺激してマウスの「人工冬眠」に成功　救急医療や宇宙旅行へ応用期待　筑波大など

https://www.nikkei.com/article/DGXMZO60243470R10C20A6100000/

神経ペプチド QRFP を発現する視床下部神経（Q 神経）の活性化でマウスが数時間の休眠とは違って何日も続く冬眠に似た低体温/低代謝状態になると分かった。
別の研究チームも独自に視床下部の休眠誘導神経を見つけており、その作用を下垂体アデニル酸シクラーゼ活性化ポリペプチド（PACAP）発現神経が担うことを見出している。
QRFP 発現 Q 神経が冬眠様の状態を誘導することを見出した理研/筑波大学のチームは Q 神経の一部が PACAP を発現することを把握しているが、PACAP 神経の多くは QRFP を発現しないことから、Q 神経は PACAP 神経の一部のようだ、としている。

理研/筑波大学のチームの PACAP 神経の砂川玄志郎氏や櫻井武氏はヒトを含む冬眠しない哺乳類にも必要に応じて低体温/低代謝を誘導しうると考えている。
この研究は 6 月 5 日、筑波大学・国際統合睡眠医科学研究機構（WPI-IIIS）と理化学研究所が、「冬眠状態を促す神経回路を発見した」と発表。6 月 11 日、イギリスの科学誌 *Nature*（オンライン版）に掲載された。

今月の研究関連ニュース 4 参照

6/13　Moderna の COVID-19 ワクチンがマウスの感染を阻止

6/15　AstraZeneca が COVID-19 ワクチン最大 4 億回投与分を欧州の連盟に無償提供する

AstraZeneca が開発しているオックスフォード大学由来の新型コロナウイルス感染（COVID-19）ワクチン AZD1222 が欧州 4 か国・ドイツ、フランス、イタリア、オランダの連盟 Inclusive Vaccines Alliance (IVA) に最大 4 億回投与分無償提供される。

6/16　特定遺伝子持つ細菌を狙い撃ちする殺菌技術開発　検査に応用も　自治医大グループ

6/16　新型コロナウイルスへの抗マラリア薬使用承認を米国 FDA が撤回

新型コロナウイルス感染入院患者への抗マラリア薬・ヒドロキシクロロキンやクロロキン使用許可を米国 FDA が取り消した。

6/17　AstraZeneca の COVID-19 ワクチンの効果は接種後約 1 年で消失と同社 CEO が予想

6/17　ノルウェーが新型コロナウイルス感染（COVID-19）追跡アプリの使用を停止

6/17　新型コロナ感染症、20 歳未満はリスク半分程度

https://www.afpbb.com/articles/-/3288754

6/17　新型コロナ、全国初のワクチン治験を開始へ　大阪大など

6/17　ステロイド剤、重症のコロナ患者治療に効果か　オックスフォード大発表

6/18　血液型 A 型だと重症 COVID-19 になり易く、O 型だとなり難いことを示した試験が NEJM に掲載された

6/18　スウェーデンの小都市 Gallivare で COVID-19 が大流行で制御不可能に

欧州の多くの国と違って完全なロックダウンなしで新型コロナウイルス感染流行をやり過ごそうとしているスウェーデンの人口約 18,000 人の街 Gallivare でその蔓延が手に負えなくなり、公共施設の閉鎖が始まった。

6/19　新型コロナウイルスにつきまとってその細胞侵入を防ぐ分子スポンジができた

https://www.eurekalert.org/pub_releases/2020-06/bu-nrs061820.php

6/19　若者の血を輸血するのではなく「血液を希釈」することで若返り効果が得られるかもしれない−マウス研究

老いたマウスに若いマウスの血が入ると若返ることが示されているが、そうしなくても単に血を薄めるだけで同様の効果が得られると分かった。

老いたマウスの血漿の半分をそれらに含まれるアルブミン相当量添加（アルブミン 5%）生理食塩水で置き換えて血漿中の蛋白質を薄めたところ脳、肝臓、筋肉が若い血を入れたときと同程度かそれ以上に若返った。
血漿成分を変える瀉血が自己免疫疾患の治療として米国 FDA にすでに承認されている。研究者は少し手を加えた瀉血で高齢者の体調を改善できるかどうかや、筋肉減少・神経変性・2 型糖尿病・免疫不全などの老化疾患を治療できるかどうかを調べる試験の準備をしている。

https://news.livedoor.com/article/detail/18439465/

6/20　新型コロナ感染、米州中心に加速　WHOが警告

世界保健機関（WHO）は 21 日、世界全体の新型コロナウイルス感染者数が 24 時間で 18 万 3,020 人増加し、これまでで最多を記録したと発表した。
増加数が最も多かったのは北米と中南米で、11 万 6,000 人を超えた。世界の感染者数は累計で 870 万人超、死者は 46 万 1,000 人超となった。1 日当たりの感染者数は 6 月 18 日に記録した 18 万 1,232 人がこれまでの最多だった。

6/20　ブラジル感染 100 万人超　米に次ぎ 2 カ国目

6/20　永久凍土から太古のバクテリア発見、プラごみ分解に期待 -スイス

https://www.swissinfo.ch/eng/swiss-researchers-identify-new-bacteria-in-permafrost/45849866

6/22　鹿児島大、コロナ治療薬候補の化合物確認「増殖を抑制」

https://www.asahi.com/articles/ASN6Q6SNXN6QTLTB008.html

6/23　新型コロナウイルス感染力をほぼ 100%失わせるマスク繊維が間もなく出来上がる

イスラエルのマスク製造会社 Sonovia が開発している抗菌繊維に新型コロナウイルス（SARS-CoV-2）をかけたところ 90%超が感染能を失った。繊維は細菌、真菌、ウイルスを破壊する酸化亜鉛ナノ粒子で被覆されており、洗って繰り返し使う事が可能。

6/23　新型コロナ患者に「再生医療」 ロート製薬が8月から治験へ

https://www.nikkei.com/article/DGXMZO60686760T20C20A6000000/

6/23　Gilead、吸入型レムデシビルの治験開始へ－使用拡大目指す

6/24　適切な手洗い実行を助ける Apple Watch 機能追加が発表された

6/24　オックスフォード由来の AstraZeneca の COVID-19 ワクチンでブタへの 2 回接種がより強力な抗体反応を誘導

6/24　ユニクロ柳井氏、京大に 100 億円寄付　がん研究を支援

6/25　インドの Hetero が Gilead の COVID-19 薬 Remdesivir 後発品を 71 ドルで販売

6/25　La Jolla が Tetraphase を買収

6/26　欧州オーストリアの COVID-19 大流行地住民の抗体保有率が最も高い 42%を記録

新型コロナウイルスの大規模クラスター（感染者集団）が発生したオーストリアのスキーリゾート、イシュグルで住民の抗体検査を実施したところ、参加者の約42%が抗体を保有していたことが分かった。抗体保有率はこれまで分かった中で最高水準。
調査は、インスブルック医科大学ウイルス学研究所のドローテ・フォン・ラエル所長らが実施。所長は声明で、「参加者の抗体保有率は42．4%だった。イシュグルは、これまでの研究で最高の保有率となった」とした。
そのうえで、「この保有率でも集団免疫が獲得されたと推定することはできない」とした。
オーストリア最大規模となったイシュグルのクラスターは、国内の感染拡大初期に発生。アフタースキーのバーで感染が拡大して数千人が感染した。

6/26　コンゴ共和国での約 2 年前からのエボラ流行終息宣言

6/26　Sanofi が数百人規模の従業員削減に取り掛かっている/Reuters

6/27　カイコのまま「食べるコロナワクチン」視野　候補のタンパク質、九大など開発

https://www.nishinippon.co.jp/item/n/620746/

6/27　肝臓毛細血管をコーティング　遺伝子治療効率向上　川崎市財団・東大

https://www.jiji.com/jc/article?k=20200627003478&g=soc

6/27　米でまた新規感染者最多更新　テキサス、フロリダでバー再規制

6/27　コロナワクチン開発、アストラゼネカとモデルナが先行＝WHO

6/27　AstraZeneca の COVID-19 ワクチンの日本供給のための話し合いを第一三共が開始

AstraZeneca が開発中の新型コロナウイルス感染（COVID-19）ワクチン AZD1222 を日本に供給するための話し合いを第一三共が始めている。AstraZeneca から原液を調達して第一三共の国内工場で製剤化される予定。
第一三共は手持ちの COVID-19 ワクチン開発も進めることを今月中旬に発表。

6/28　WHO 評価で「最も開発が進んでいる」ワクチン -AstraZeneca 製、ブラジルが1億回分確保

6/29　iPS 免疫細胞でがん治療　千葉大など世界初の治験開始

6/29　新型コロナ、最悪ペースで拡大 世界の感染者 1,000 万人、死者は 50 万人に

6/29　世界中で唯一感染者いない南極…コロナ持ち込まないため次期隊員半減

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. 免疫細胞はマウスの出生時に肺で増殖多様化

2. 「脂肪燃焼」分子が肥満治療に影響 -マウス研究

3. ヒヒモデルがアルツハイマー病の介入を支援できる可能性を示唆した研究

4. 冬眠様状態を誘導する新規神経回路の発見
   ー人工冬眠の実現へ大きな前進ー

5. エネルギーを燃焼する脂肪細胞の熱をオンにする新アプローチ

6. COVID-19 のマウスモデル作成のための既製ツール

7. 血液脳関門を透過する大豆由来のジペプチドの摂取は急性アルツハイマー病マウスの記憶障害改善に有効

8. 受容体がマウスを強くてスリムにする
   2 つの老化現象を調節する分子を特定

9. 人工免疫細胞が、ヒトおよびマウスの固形腫瘍の癌細胞を認識して攻撃する

1. 免疫細胞はマウスの出生時に肺で増殖多様化

日付：2020 年 6 月 2 日
ソース：eLife スタンフォード大学
概要：

eLife 誌で本日発表されたスタンフォード大学の新しい研究成果によると、マウスの肺の免疫細胞は、出生直前から生後数週間の間にその数と種類において劇的に増加することを示しており、これが呼吸に順応し、感染から保護するのに役立っている可能性がある、としている。
研究チームは、出生直前にマクロファージと呼ばれる免疫細胞がマウスの肺の小血管を取り囲んでおり、おそらくそれらを成長させるように刺激しているのだろう、としている。また、出生後、血管の成長、肺の発達、および感染症との戦いに必要なものを含む、多種類の免疫細胞が出現する、ともしている。
これらの発見は、感染症、過剰な酸素レベル、またはステロイド薬によって引き起こされる人生の早い段階での免疫系の混乱が、生涯にわたる肺の問題につながる可能性がある理由を説明するのに役立つ。更に肺の発達の重要な要素は妊娠後期と出生後の最初の数年間に発生するため、未熟な肺への損傷は生涯にわたって重大な結果をもたらす可能性がある、と報告している。

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/2020-06/e-icm060220.php

NEWS RELEASE 2-JUN-2020

IMMUNE CELLS MULTIPLY AND DIVERSIFY IN MOUSE LUNGS AT BIRTH

A rapid increase in the number and types of immune cells in the lungs of mice after birth may aid development and help protect against infections

ELIFE

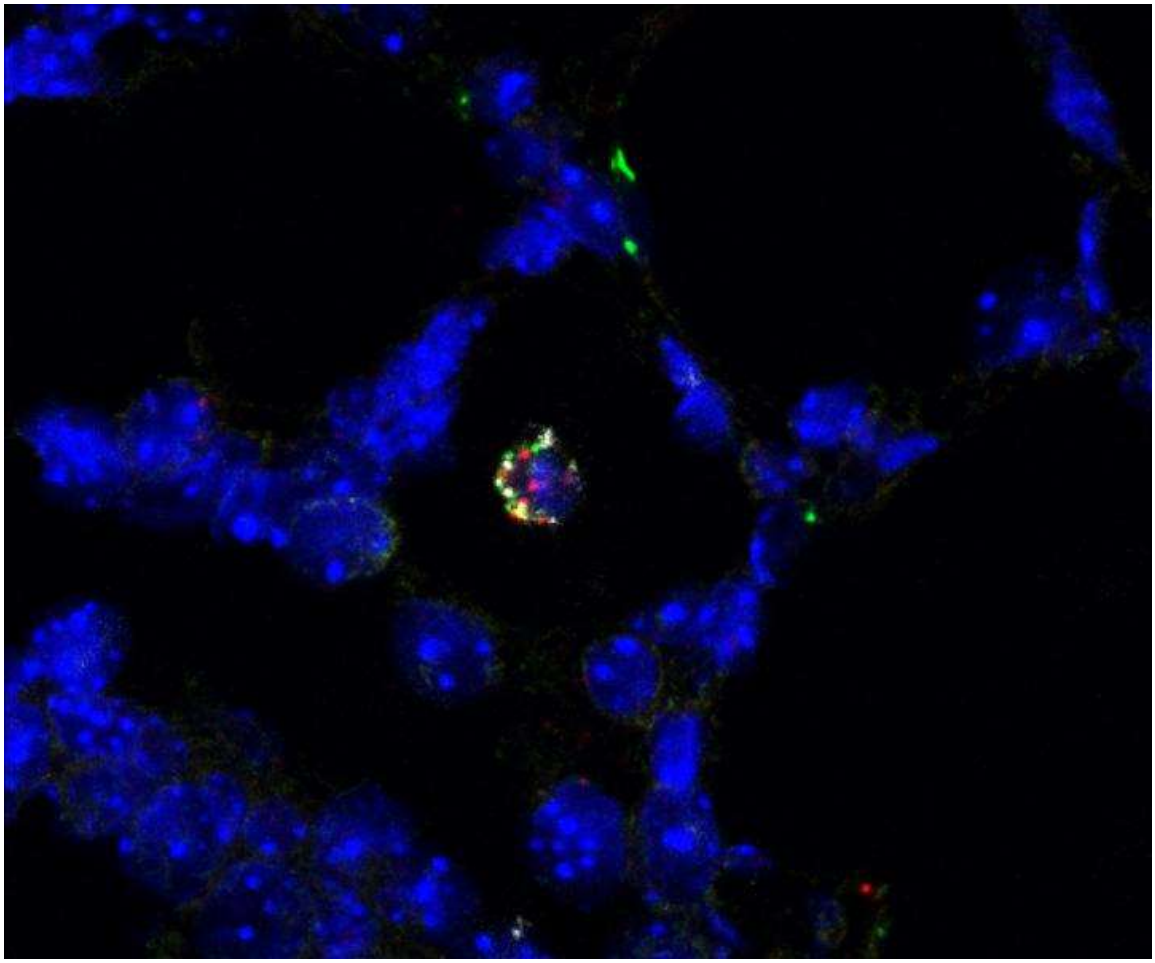

IMAGE: THIS IMAGE SHOWS A MACROPHAGE IN THE DEVELOPING MOUSE LUNG EXPRESSING A COMBINATION OF DISTINGUISHING GENES, WHICH ARE HIGHLIGHTED HERE IN RED, WHITE AND GREEN. **view more**

CREDIT: DOMINGO-GONZALEZ ET AL. (CC BY 4.0)

An explosion in the number and types of immune cells in the lungs of newborn mice likely helps them adapt to breathing and protects them from infection, says a new study published today in *eLife*.

The findings, from Stanford University and Stanford School of Medicine, US, provide detailed information about dramatic shifts in the immune cells in the lungs of mice from just before birth through the first weeks of life. This insight may help scientists learn more about how problems in early development can lead to breathing problems such as asthma later in life.

"At birth, the lung undergoes marked physiological changes as it changes from a fluid-filled, low-oxygen environment to an air-filled, oxygen-rich environment," says co-lead author Racquel Domingo-Gonzalez, who was a postdoctoral researcher at the Department of Pediatrics, Stanford University School of Medicine, when the study was carried out. "How these changes affect immune cell populations during this transition and the ensuing rapid lung growth after birth is unclear."

To learn more, Domingo-Gonzalez and her collaborators used a technique called single-cell transcriptomics to track gene expression in individual immune cells in the lungs of mice just before birth and through the first three weeks of life. This allowed them to create an atlas of all the immune cells in the mouse lung during early life.

The team found that, just before birth, immune cells called macrophages encircle the small blood vessels in the lungs, likely stimulating them to grow. After birth, a large number of many different types of immune cells appear, including those needed for blood-vessel growth, lung development and to fight off infections.

These discoveries may help explain why disruptions to the immune system early in life caused by infections, excessive levels of oxygen, or steroid drugs may lead to life-long lung problems. "Injuries to the immature lung can have profound, life-long consequences since a significant component of lung development occurs during late pregnancy and the first few years of postnatal life," explains co-lead author Fabio Zanini, who was a postdoctoral fellow in Stephen Quake's lab at Stanford University when the study was initiated and has since transitioned to Senior Researcher at UNSW Sydney, Australia.

"Our work lays the foundation for further studies on the diversity of immune cells and their roles during this important window of lung development," adds senior author Cristina Alvira, Associate Professor of Pediatrics at Stanford University School of Medicine. "This could ultimately lead to new therapies to preserve or enhance lung development in infants and young children."

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Reference

The paper 'Diverse homeostatic and immunomodulatory roles of immune cells in the developing mouse lung at single cell resolution' can freely accessed online at https://doi.org/10.7554/eLife.56890.

This study was a collaborative effort between Racquel Domingo-Gonzalez, Fabio Zanini and Cristina Alvira, as well as Stephen Quake - the Lee Otterson Professor of Bioengineering and Professor of Applied Physics at Stanford University, and Co-President of the Chan Zuckerberg Biohub - and David Cornfield, the Anne T. and Robert M. Bass Professor in Pediatric Pulmonary Medicine at Stanford University.

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2. 「脂肪燃焼」分子が肥満治療に影響 –マウス研究

日付：2020 年 6 月 8 日
ソース：バージニア工科大学
概要：

米国の成人の 40%以上、そして世界人口の約 13%が肥満とされている。バージニア工科大学の研究者らは最近、BAM15 という名前の小さなミトコンドリア脱共役剤を特定した。これは、摂食量と筋肉量に影響を与えたり、体温を上げたりすることなく、マウスの体脂肪量を減少させる。さらに、この分子はインスリン抵抗性を低下させ、酸化ストレスと炎症に有益な効果をももたらす。5 月 14 日に *Nature Communications* 誌で発表された調査結果によると、肥満、糖尿病、特に非アルコール性脂肪性肝炎（NASH）–肝臓での炎症と脂肪蓄積を特徴とする脂肪性肝疾患の一種– の将来の治療と予防に有望だとしている。
一連のマウス研究を通じて、BAM15 は高用量でも毒性がなく、空腹か満腹かを体に伝える脳の満腹中枢にも影響を与えないことが分かった。以前は、多くの抗脂肪薬が患者の身体に食事をやめるように指示していたが、その結果、治療後にはリバウンドしてより多く食べるようになった。BAM15 マウスの研究では、マウスは対照群と同じ量を食べたにも拘わらず、そ脂肪量を失った。
以前のミトコンドリア脱共役剤の別の副作用は、体温の上昇であったが、今回、研究者らは直腸プローブを使用して、BAM15 を与えられたマウスの体温を測定したが、体温に変化は認められなかった。
しかし、BAM15 の半減期に関して 1 つの問題がある。薬物の有効時間は、マウスモデルで比較的短い。ヒトへの経口投与では、最適な半減期ははるかに長くなければならない。BAM15 はマウスモデルでいくつかの大きな可能性を秘めているものの、この薬は必ずしも人間で成功するとは限らない。研究者らは、少なくともこれと全く同じ分子ではないが、基本的にほぼ同じタイプの分子を探している、と報告している。

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/2020/06/200608132539.htm

'FAT BURNING' MOLECULE HAS IMPLICATIONS FOR TREATMENT OF OBESITY

Date:

June 8, 2020

Source:

Virginia Tech

Summary:

Scientists have recently identified a small mitochondrial uncoupler, named BAM15, that decreases the body fat mass of mice without affecting food intake and muscle mass or increasing body temperature.

FULL STORY

Mouse and cheese (stock image).

Credit: © leli / stock.adobe.com

Obesity affects more than 40 percent of adults in the United States and 13 percent of the global population. With obesity comes a variety of other interconnected diseases including cardiovascular disease, diabetes, and fatty liver disease, which makes the disease one of the most difficult -- and most crucial -- to treat.

"Obesity is the biggest health problem in the United States. But, it is hard for people to lose weight and keep it off; being on a diet can be so difficult. So, a pharmacological approach, or a drug, could help out and would be beneficial for all of society," said Webster Santos, professor of

chemistry and the Cliff and Agnes Lilly Faculty Fellow of Drug Discovery in the College of Science at Virginia Tech.

Santos and his colleagues have recently identified a small mitochondrial uncoupler, named BAM15, that decreases the body fat mass of mice without affecting food intake and muscle mass or increasing body temperature. Additionally, the molecule decreases insulin resistance and has beneficial effects on oxidative stress and inflammation.

The findings, published in *Nature Communications* on May 14, 2020, hold promise for future treatment and prevention of obesity, diabetes, and especially nonalcoholic steatohepatitis (NASH), a type of fatty liver disease that is characterized by inflammation and fat accumulation in the liver. In the next few years, the condition is expected to become the leading cause of liver transplants in the United States.

The mitochondria are commonly referred to as the powerhouses of the cell. The organelle generates ATP, a molecule that serves as the energy currency of the cell, which powers body movement and other biological processes that help our body to function properly.

In order to make ATP, nutrients need to be burned and a proton motive force (PMF) needs to be established within the mitochondria. The PMF is generated from a proton gradient, where there is a higher concentration of protons outside of the inner membrane and a lower concentration of protons in the matrix, or the space within the inner membrane. The cell creates ATP whenever protons pass through an enzyme called ATP synthase, which is embedded in the membrane. Hence, nutrient oxidation, or nutrient burning, is coupled to ATP synthesis.

"So anything that decreases the PMF has the potential to increase respiration. Mitochondrial uncouplers are small molecules that go to the mitochondria to help the cells respire more. Effectively, they change metabolism in the cell so that we burn more calories without doing any exercise," said Santos, an affiliated member of the Fralin Life Sciences Institute and the Virginia Tech Center for Drug Discovery.

Mitochondrial uncouplers transport protons into the matrix by bypassing ATP synthase, which throws off the PMF. To reestablish the gradient, protons must be exported out of the mitochondrial matrix. As a result, the cell begins to burn fuel at higher than necessary levels.

Knowing that these molecules can change a cell's metabolism, researchers wanted to be sure that the drug was reaching its desired targets and that it was, above all, safe. Through a series of mouse studies, the researchers found that BAM15 is neither toxic, even at high doses, nor does it affect the satiety center in the brain, which tells our body if we are hungry or full.

In the past, many anti-fat drugs would tell your body to stop eating. But as a result, patients would rebound and eat more. In the BAM15 mouse studies, animals ate the same amount as the control group -- and they still lost fat mass.

Another side effect of previous mitochondrial uncouplers was increased body temperature. Using a rectal probe, researchers measured the body temperature of mice who were fed BAM15. They found no change in body temperature.

But one issue arises concerning the half-life of BAM15. The half-life, or the length of time that a drug is still effective, is relatively short in the mouse model. For oral dosing in humans, the optimal half-life is much longer.

Even as BAM15 has some serious potential in mouse models, the drug won't necessarily be successful in humans -- at least not this same exact molecule.

"We are essentially looking for roughly the same type of molecule, but it needs to stay in the body for longer to have an effect. We are tweaking the chemical structure of the compound. So far, we have made several hundred molecules related to this," said Santos.

The penultimate goal of the Santos lab is to transition the anti-fat treatment from animal models to a treatment for NASH in humans. The lab has used their better compounds in animal models of NASH, which have been proven to be effective as anti-NASH compounds in mice.

Working alongside Santos is Kyle Hoehn, an assistant professor of pharmacology from the University of Virginia and an associate professor of biotechnology and biomolecular sciences at the University of New South Wales in Australia. Hoehn is a metabolic physiology expert who is in charge of conducting the animal studies. Santos and Hoehn have been collaborating for several years now and they even founded a biotech company together.

Co-founded by Santos and Hoehn in 2017, Continuum Biosciences aims to improve the ways in which our bodies burn fuel and fight back against our bodies ability to store excess nutrients as we age. These promising NASH treatment compounds are licensed by their company and are patented by Virginia Tech.

The company is looking to use mitochondrial uncouplers for more than just obesity and NASH. The molecules also have a unique anti-oxygen effect that can minimize the accumulation of reactive oxygen species, or oxidative stress, in our bodies, which ultimately results in neurodegeneration and aging.

"If you just minimize aging, you could minimize the risk of Alzheimer's disease and Parkinson's disease. All of these reactive oxygen species-related or inflammation-related diseases could benefit from mitochondrial uncouplers. So, we could see this heading that way," said Santos.

Story Source:

Materials provided by **Virginia Tech**. Original written by Kendall Daniels. *Note: Content may be edited for style and length.*

Journal Reference:

1. Stephanie J. Alexopoulos, Sing-Young Chen, Amanda E. Brandon, Joseph M. Salamoun, Frances L. Byrne, Christopher J. Garcia, Martina Beretta, Ellen M. Olzomer, Divya P. Shah, Ashleigh M. Philp, Stefan R. Hargett, Robert T. Lawrence, Brendan Lee, James Sligar, Pascal Carrive, Simon P. Tucker, Andrew Philp, Carolin Lackner, Nigel Turner, Gregory J. Cooney, Webster L. Santos, Kyle L. Hoehn. **Mitochondrial uncoupler BAM15 reverses diet-induced obesity and insulin resistance in mice**. *Nature Communications*, 2020; 11 (1) DOI: 10.1038/s41467-020-16298-2

Cite This Page:

- MLA
- APA
- Chicago

Virginia Tech. "'Fat burning' molecule has implications for treatment of obesity." ScienceDaily. ScienceDaily, 8 June 2020. <www.sciencedaily.com/releases/2020/06/200608132539.htm>.

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3. ヒヒモデルがアルツハイマー病の介入を支援できる可能性を示唆した研究

日付：2020 年 6 月 10 日
ソース：テキサスバイオメディカルリサーチインスティチュート
概要：

テキサスバイオメディカルリサーチインスティテュート（Texas Biomed）サウスウェスト国立霊長類研究センター（SNPRC）の科学者らが最近発表した調査結果は、ヒヒが初期アルツハイマー病や関連認知症などの神経変性疾患の治療法およびその介入をテストするための重要モデルである可能性を示している。
科学者らは、20 歳前後のヒヒで、年齢に関連した急激な認知機能の低下を観察した。これは、60 歳の人間に相当する。Texas Biomed の SNPRC の准教授である Marcel Daadi 博士が率いる科学者チームは、5 月の *Aging* 誌に調査結果を発表した。この研究は、初期アルツハイマー病の適切な動物モデルとしてヒヒを開発する最初のステップだ、と報告している。

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/2020-06/tbri-ssb061020.php

NEWS RELEASE 10-JUN-2020

STUDY SUGGESTS BABOON MODEL COULD AIDE IN ALZHEIMER'S DISEASE INTERVENTIONS

Findings may lead to better understanding of neurodegenerative disease

TEXAS BIOMEDICAL RESEARCH INSTITUTE

San Antonio, Texas (June 8, 2020) - Scientists at Texas Biomedical Research Institute's (Texas Biomed) Southwest National Primate Research Center (SNPRC) recently published findings indicating the baboon could prove to be a relevant model to test therapeutics and interventions for neurodegenerative diseases, such as early stage Alzheimer's and related dementias. The scientists observed a steep age-related cognitive decline in baboons about 20-years-old, which is the equivalent of a 60-year-old human. The team of scientists, led by Dr. Marcel Daadi, Associate Professor at Texas Biomed's SNPRC, published their findings in the May issue

of *Aging* . These studies are a first step in developing the baboon as an appropriate animal model for early stage Alzheimer's disease.

According to the Alzheimer's Association, more than five million Americans are living with Alzheimer's, and one in three seniors die from the disease or related dementias. Dr. Daadi explained that early detection of age-associated cognitive dysfunction is crucial and may provide an understanding of the breakdown of brain systems, leading to better interventions.

"We don't know how Alzheimer's disease starts, and if you are trying to treat a patient already with advanced disease, it is nearly impossible to treat them because of the significant loss in brain cells" said Dr. Daadi. "If we detect early on pathology in the brain then we can target interventions to prevent it from progressing, and we are in a better position to help. This is the first time a naturally-occurring model for early-stage Alzheimer's has been reported. This model could be relevant to test promising drugs, to better understand how and why the disease develops and to study the areas of the brain affected in order to determine how can we impact these pathways."

Aging is currently irreversible and a significant reason for the gradual deterioration of general health and function. Neurodegenerative diseases, in particular, are related to the aging of brain cells and synaptic loss, which is a loss of the lines of communications inside the brain. As noted in the paper, humans and nonhuman primates (NHP) share many similarities, including age-dependent changes in gene expression and a decline in neural and immune functions. Previous studies have pinpointed the prefrontal cortex (PFC) of the brain as one of the regions most affected by age. The PFC plays an important role in working memory function, self-regulatory and goal-directed behaviors, which are all vulnerable to aging. To observe whether these PFC functions are impacted by aging in baboons and determine whether the baboons at varying ages could discern and learn new tasks, Dr. Daadi and his team separated the baboons into two groups based on age (adult group and aged group). Four cognitive tests were performed to observe novel learning, motor function and memory and shape association.

"What we found is that aged baboons lagged significantly in performance among all four tests for attention, learning and memory" Dr. Daadi said. "The delay or inability to collect rewards (response latency) also increased in older baboons, suggesting a decline in motivation and/or motor skills. The team then used a more complex task requiring integration of several cognitive processes and demonstrated that aged subjects actually have deficiencies in attention, learning and memory. Human studies have suggested a precipitous decline in brain systems function and cognition with 60 years as the potential breakpoint. These findings are consistent with our results."

Rodents have been the primary lab model to test therapeutic interventions for neurodegenerative diseases. However, mice do not always reflect human processes, so while this animal model has

been integral to understanding neurodegenerative disease processes, it has not proven as effective in translating promising therapies to the clinic.

"The failure rate in clinical trials of Alzheimer's disease therapeutics is extremely high at about 99.6%, and we need to change that" said Dr. Daadi.

A nonhuman primate, or monkey, which is more similar to humans in terms of genetics, physiology, cognition, emotion and social behavior, could prove to be a more effective model to test therapeutic interventions.

Dr. Daadi and his team are moving forward and plan to submit a National Institutes of Health grant to allow for further research. This published study was funded by the Marmion Family Fund, the Worth Family Fund, The Perry and Ruby Stevens Charitable Foundation and The Robert J., Jr. and Helen C. Kleberg Foundation, The William and Ella Owens Medical Research Foundation, the NIH Primate Center Base grant (Office of Research Infrastructure Programs/OD P51 OD011133), the National Institute on Aging R56 AG059284.

"Our next step is to investigate the neuropathologies behind this cognitive decline and perform imaging to understand what happens to the neural connections and determine where defects may be," he said. "We will also look at biomarkers that can give us an idea of why this steep decline is happening. All this data will enable us to further characterize the baboon as a naturally-occurring model that may prove useful for testing early therapeutic interventions."

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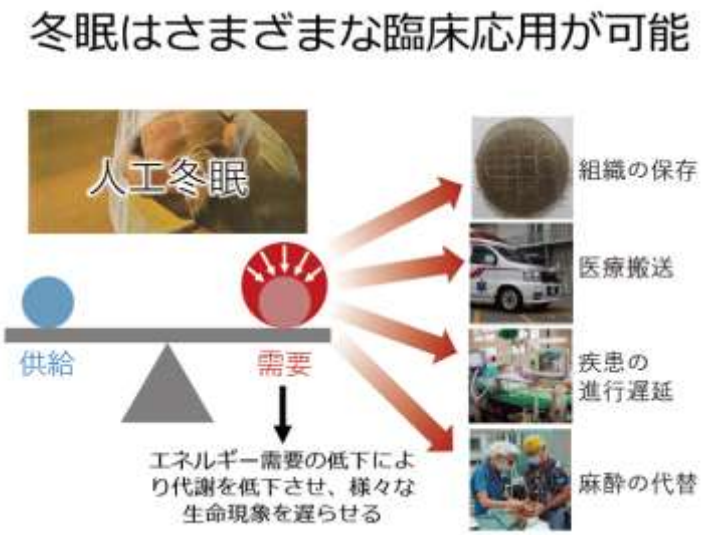
Texas Biomed is one of the world's leading independent biomedical research institutions dedicated to eradicating infection and advancing health worldwide through innovative biomedical research. Texas Biomed partners with researchers and institutions around the world to develop vaccines and therapeutics against viral pathogens causing AIDS, hepatitis, hemorrhagic fever, tuberculosis and parasitic diseases responsible for malaria and schistosomiasis disease. The Institute has programs in host-pathogen interaction, disease intervention and prevention and population health to understand the links between infectious diseases and other diseases such as aging, cardiovascular disease, diabetes and obesity. For more information on Texas Biomed, go to http://www.TxBiomed.org.

4. 冬眠様状態を誘導する新規神経回路の発見
－人工冬眠の実現へ大きな前進－

日付：2020 年 6 月 12 日
ソース：筑波大学、理化学研究所
概要：

http://www.tsukuba.ac.jp/attention-research/p202006111800.html
http://www.tsukuba.ac.jp/wp-content/uploads/202006110000-2.pdf

筑波大学医学医療系/国際統合睡眠医科学研究機構（WPI-IIIS）の櫻井武教授、髙橋徹・大学院生（生命システム医学専攻博士課程２年）らの研究グループは、理化学研究所生命機能科学研究センターの砂川玄志郎・基礎科学特別研究員との共同研究により、マウスを冬眠に似た状態に誘導できる新しい神経回路を同定しました。
冬眠中の動物は正常時と比べて数%まで酸素消費量が低下し、外気温よりも数度高い程度の低体温を呈しますが、何ら組織障害を伴うことなく自発的に元の状態に戻ります。このような“制御された低代謝”は、臨床への応用が期待されています。外傷や疾患によって組織が受けるダメージを回避することができるからです。しかし、冬眠のメカニズムは全く分かっていません。冬眠研究を困難にしている理由の一つが、通常使用される実験動物であるマウスやラットが冬眠をしないことでした。
本研究では、マウスの脳（視床下部）の一部に存在する神経細胞群を興奮させると、マウスの体温・代謝が数日間にわたって著しく低下することを発見しました。この神経細胞群をQ神経（Quiescence-inducing neurons：休眠誘導神経）と名付け、このQ神経を刺激することにより生じる低代謝をQIH（Q neuron-induced hypometabolism）と名付けました。QIH中のマウスは動き・摂食がほぼなくなり、体温セットポイントが低下していました。行動解析・組織学的解析では、QIHの前後で異常が見られず、きわめて冬眠に似た状態であることが分かりました。さらに、休眠しない齧歯類（げっしるい）の一種であるラットのQ神経を興奮させたところ、マウスと同様に長期的かつ可逆的な低代謝が確認されました。
本研究によって、哺乳類に広く保存されているQ神経を選択的に刺激することで、冬眠を通常はしない動物に冬眠様状態を誘導できることが明らかとなり、人間でも冬眠を誘導できる可能性が示唆されました。QIHの発見によって人工冬眠の研究開発が大きく前進したと言えます。



研究関連ニュース/他のトップページに戻る

5. エネルギーを燃焼する脂肪細胞の熱をオンにする新アプローチ

日付：2020 年 6 月 12 日
ソース：ミシガン大学
概要：

ミシガン大学の研究者らは、あるタイプの脂肪細胞が脂肪を熱に変換するように促すために送受信する新しい信号を発見した、として 6 月 12 日の *Developmental Cell* 誌のオンライン版で発表予定である。この研究によると、マウスで発見されたこのシグナル伝達経路は、ヒトにおいて同じタイプの熱生産脂肪を活性化するためのヒントになる、としている。
褐色脂肪と呼ばれる熱生産脂肪細胞は、脂肪として蓄えられたエネルギーを燃焼する能力により、肥満やその他の代謝障害を抑制する可能性があり、近年注目を集めている。この可能性を効果的な治療法に変換するためには、ヒトの褐色脂肪を活性化するという課題が発生するが、アドレナリン作動性シグナル伝達によって調節されるため、血圧や心拍数の調節など、他の重要な生物学的機能も制御されるため、危険な副作用が生じることもある。
この研究チームは、今回、アドレナリン作動性シグナル伝達とは無関係に褐色細胞の熱発生を調節できる経路について、コリン作動性受容体ニコチン性アルファ 2 サブユニット（CHRNA2）と呼ばれる受容体タンパク質を介して作動する経路を発見した。マウスの脂肪細胞でのみ CHRNA2 経路を遮断し、その後、マウスに高脂肪食を与えたところ、CHRNA2 受容体タンパク質がない場合、マウスは通常のマウスよりも体重が増加し、過剰な食物摂取に反応して熱発生を活性化する能力が低下した、としている。この研究は、褐色脂肪の部分集団が、CHRNA2 経路を通じて活性化できることを示している。

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/2020/06/200612111425.htm

NEW APPROACH TO TURNING ON THE HEAT IN ENERGY-BURNING FAT CELLS

Date:

June 12, 2020

Source:

University of Michigan

Summary:

Researchers have discovered a new set of signals that cells send and receive to prompt one type of fat cell to convert fat into heat. The signaling pathway, discovered in mice, has potential implications for activating this same type of thermogenic fat in humans.

FULL STORY

Researchers have discovered a new set of signals that cells send and receive to prompt one type of fat cell to convert fat into heat. The signaling pathway, discovered in mice, has potential implications for activating this same type of thermogenic fat in humans.

Thermogenic fat cells, also called beige fat or beige adipocytes, have gained attention in recent years for their potential to curb obesity and other metabolic disorders, due to their ability to burn energy stored as fat. But scientists have yet to translate this potential into effective therapies.

The challenge of activating beige fat in humans arises, in part, because this process is regulated through so-called adrenergic signaling, which uses the hormone catecholamine to instruct beige fat cells to start burning energy. But adrenergic signaling also controls other important biological functions, including blood pressure and heartbeat regulation, so activating it in humans with agonists has potentially dangerous side effects.

In a new study scheduled for online publication June 12 in the journal *Developmental Cell*, a team of researchers led by the University of Michigan Life Sciences Institute describes a pathway that can regulate beige fat thermogenesis independently of adrenergic signaling. Instead, it operates through a receptor protein called CHRNA2, short for Cholinergic Receptor Nicotinic Alpha 2 Subunit.

"This pathway opens a whole new direction for approaching metabolic disorders," said Jun Wu, an assistant professor at the LSI and the study's senior author. "Of course, this cholinergic pathway also is involved in other important functions, so there is still much work to do to really figure out how this might work in humans. But we are encouraged by these initial findings."

For their study, Wu and her colleagues blocked the CHRNA2 pathway only in adipocytes in mice, and then fed the mice a high-fat diet. Without the CHRNA2 receptor proteins, the mice showed greater weight gain than normal mice, and were less able to activate thermogenesis in response to excess food intake.

Wu believes the findings are particularly exciting in light of another research team's recent discovery of a new type of beige fat that is not regulated by catecholamine. This newest study from the LSI indicates that this subpopulation of beige fat, called glycolytic beige fat (or g-beige fat), can be activated through the CHRNA2 pathway.

"Many patients with metabolic disorders have catecholamine resistance, meaning their cells do not detect or respond to catecholamine," said Wu, who is also an assistant professor of molecular and integrative physiology at the U-M Medical School.

"So even if it could be done safely, activating that adrenergic pathway would not be an effective treatment option for such patients. This new pathway, with this new subtype of beige fat, could be the beginning of a whole new chapter for approaching this challenge."

Story Source:

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

Journal Reference:

1. Heejin Jun, Yingxu Ma, Yong Chen, Jianke Gong, Shanshan Liu, Jine Wang, Alexander J. Knights, Xiaona Qiao, Margo P. Emont, X.Z. Shawn Xu, Shingo Kajimura, Jun Wu. **Adrenergic-Independent Signaling via CHRNA2 Regulates Beige Fat Activation**. *Developmental Cell*, 2020; DOI: 10.1016/j.devcel.2020.05.017

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University of Michigan. "New approach to turning on the heat in energy-burning fat cells." ScienceDaily. ScienceDaily, 12 June 2020. <www.sciencedaily.com/releases/2020/06/200612111425.htm>.

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6. COVID-19 のマウスモデル作成のための既製ツール

日付：2020 年 6 月 17 日
ソース：アイオワ大学ヘルスケア
概要：

COVID-19 のパンデミックは、効果的な治療法やワクチンができるまで、世界中の公衆衛生と経済に重大な脅威であり続ける。COVID-19 に対する新しい抗ウイルス療法やワクチン開発のテストにとって大きなハードルとなっているのは、広く利用可能な優れた動物モデルの欠如である。
中国の広州にあるアイオワ大学カーバー医科大学の研究者らは、そのボトルネックを克服するための簡単なツールを開発、あらゆる実験用マウスを SARS-CoV-2 に感染させ、COVID のような肺疾患を発症するマウスに変換できる遺伝子治療アプローチを作成し、これを無償提供している。
「トリック」は、アデノウイルス遺伝子治療ベクターの使用で、マウスによって吸入されたアデノウイルス遺伝子治療ベクターがヒト ACE2 タンパク質をマウス気道細胞に送達する。これは、SARS-CoV-2 が細胞の感染に使用するタンパク質で、マウスの気道細胞が hACE2 タンパク質を発現すると、マウスは SARS-CoV-2 による感染の影響を受けやすくなり、COVID-19 のような肺症状を発症する。病気はマウスでは致命的ではないが、マウスは病気になり、体重が減り、肺に損傷を与える。重要なことに、ベクターは任意の系統のマウス（および他の実験動物）に容易に適応できる、としており、必要とする研究者に無償で提供される。
Cell 誌に報告された研究成果によると、研究者らは、この遺伝子治療で治療されたマウスを使用して、ワクチンおよびいくつかの潜在的な COVID-19 治療を評価できることを示している。
Ad5-hACE2 ベクターはこちら（University of Iowa Viral Vector Core）から入手できる。

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/2020-06/uoih-otf061620.php

NEWS RELEASE 16-JUN-2020

OFF-THE-SHELF TOOL FOR MAKING MOUSE MODELS OF COVID-19

University of Iowa team makes gene therapy approach freely available for COVID-19 research

UNIVERSITY OF IOWA HEALTH CARE

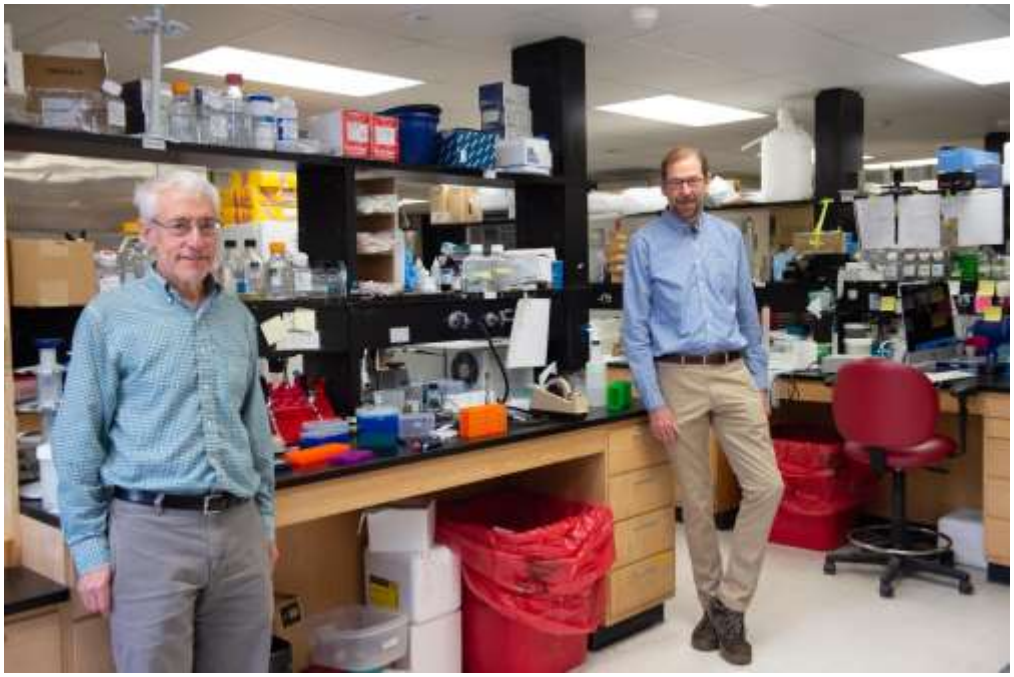

IMAGE: RESEARCHERS LED BY PAUL MCCRAY AND STANLEY PERLMAN AT THE UNIVERSITY OF IOWA HAVE CREATED AN OFF-THE-SHELF TOOL THAT ALLOWS LABS TO CREATE THEIR OWN COVID-19 MOUSE MODEL WITHIN A... **view more**

CREDIT: UNIVERSITY OF IOWA HEALTH CARE

Until there are effective treatments or vaccines, the COVID-19 pandemic will remain a significant threat to public health and economies around the world. A major hurdle to developing and testing new anti-viral therapies and vaccines for COVID-19 is the lack of good, widely available animal models of the disease.

Researchers at the University of Iowa Carver College of Medicine and Medical University, Guangzhou, in China, have developed a simple tool to overcome that bottleneck. The researchers have created a gene therapy approach that can convert any lab mouse into one that can be infected with SARS-CoV-2 and develops COVID-like lung disease. The international team, led by Paul McCray, MD, and Stanley Perlman, PhD, at the UI, and Jincun Zhao, PhD, at Medical University, Guangzhou, have made their gene therapy vector freely available to any researchers who want to use it.

"There is a pressing need to understand this disease and to develop preventions and treatments," says McCray, UI professor of pediatrics, and microbiology and immunology. "We wanted to make it as easy as possible for other researchers to have access to this technology, which allows any lab to be able to immediately start working in this area by using this trick."

The "trick" is the use of an adenovirus gene therapy vector that is inhaled by the mice to deliver the human ACE2 protein into mouse airway cells. This is the protein that SARS-CoV-2 uses to infect cells. Once the mouse airway cells express the hACE2 protein, the mice become

susceptible to infection with SARS-CoV-2 and they develop COVID-19-like lung symptoms. Although the disease is not fatal in the mice, the animals do get sick, losing weight and developing lung damage. Importantly, the vector is readily adaptable to any strain of mice (and other lab animals), which means research teams can rapidly convert mice with specific genetic traits into animals that are susceptible to SARS-Cov-2, allowing them to test whether those traits influence the disease.

Reporting in *Cell*, the researchers showed that mice treated with this gene therapy could be used to evaluate a vaccine and several potential COVID-19 therapies, including a preventative strategy known as poly I:C, which boosts the innate immune response, convalescent plasma from recovered COVID-19 patients, and the anti-viral drug remdesivir. In each case, the therapies prevented weight loss, reduced lung disease, and increased the speed of virus clearance in the mice. The team also showed mice are useful for studying important immune responses involved in clearing the SARS-CoV-2 virus.

Mice are the most commonly used experimental animal for studying human disease in the lab because they are accessible, inexpensive, and easy to use. They are also one of the easier animal models to use in biosafety level three environments, which are needed for work on COVID-19. However, due to differences between the human and mouse ACE2 protein, wild-type mice are not susceptible to the SARS-Cov-2 virus.

The gene therapy vector is essentially an off-the-shelf tool that allows labs to create their own COVID-19 mouse model within a few days. McCray, Zhao, and Perlman developed this approach in 2014, when Zhao was a postdoctoral researcher in Perlman's UI lab, to create mouse models of MERS.

"You can create these mice very quickly. You don't have to breed the strain, which is very time consuming and expensive," McCray explains. "We think this technology will be useful for investigating COVID-19 lung disease and rapidly testing interventions that people think are promising for treating or preventing COVID-19."

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McCray credits the UI's long-standing expertise in gene therapy vector development as a basis for this advance. The vector was made in the University of Iowa Vector Core, which is an outgrowth of the UI Center for Gene Therapy for Cystic Fibrosis funded by the National Institutes of Health. The vector is freely available through the BEI Resources Repository at the National Institute of Allergy and Infectious Diseases (NIAID).

The research was supported by the grants from the NIH (AI060699 and AI129269 and DK-54759), and the Cystic Fibrosis Foundation. Zhao and his team also received funding from

several Chinese governmental organizations. McCray also is supported by the Roy J. Carver Charitable Trust.

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7. 血液脳関門を透過する大豆由来のジペプチドの摂取は急性アルツハイマー病マウスの記憶障害改善に有効

日付：2020 年 6 月 19 日
ソース：九州大学
概要：

九州大学の研究グループは、福岡大学との共同研究により、血液脳関門を透過し脳組織へと到達するジペプチドの摂取が、急性アルツハイマー病のマウスモデルでの記憶障害を改善することを世界で初めて明らかにした。*Nature Partner Journals Science of Food* 誌のオンライン版に掲載されたこの研究成果によると、アミロイド β の注入により誘導した急性記憶障害マウスモデルにジペプチドを毎日投与すると、短期記憶および長期記憶障害が有意に改善された、としている。
今回の知見は、ジペプチドが記憶や学習を司る海馬や大脳皮質に蓄積することを明らかにした同研究グループの報告を動物行動レベルで発展的に実証したものであり、ペプチド摂取が脳認知機能に有効であることを示している。加齢や老化による脳機能低下を食べ物で予防・改善できる可能性を示しており、新たな機能性食品の開発が大いに期待される。

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/2020-06/ku-miio61820.php

NEWS RELEASE 19-JUN-2020

MEMORY IMPAIRMENT IN MICE REDUCED BY SOY DERIVATE THAT CAN ENTER THE BRAIN INTACT

Ingestion of the protein fragment improved working and long-term memory in mice treated to simulate Alzheimer's disease

KYUSHU UNIVERSITY

IMAGE: RESEARCH FROM JAPAN SHOWS THAT A SOY-DERIVED PROTEIN FRAGMENT THAT REACHES THE BRAIN AFTER BEING INGESTED REDUCES MEMORY DEGRADATION IN MICE WITH AN INDUCED COGNITIVE IMPAIRMENT, PROVIDING A NEW LEAD... **view more**

CREDIT: WILLIAM J. POTSCAVAGE JR., KYUSHU UNIVERSITY

In a study that could help one day give a literal meaning to food for thought, researchers from Kyushu University in Japan have reported that a protein fragment that makes its way into the brain after being ingested can reduce memory degradation in mice treated to simulate Alzheimer's disease.

Derived by breaking apart the proteins in soybeans, the memory-effecting molecule is classified as a dipeptide because it contains just two of the protein building blocks known as amino acids. Unique about the dipeptide used in the study is that it is currently the only one known to make the trip from a mouse's stomach to its brain intact despite the odds against it.

"On top of the possibility of being broken down during digestion, peptides then face the challenge of crossing a highly selectively barrier to get from the blood into the brain," says Toshiro Matsui, professor in the Faculty of Agriculture at Kyushu University and leader of the study published in *npj Science of Food*.

"While our previous studies were the first to identify a dipeptide able to make the journey, our new studies now show that it can actually affect memory in mice."

Working in collaboration with researchers at Fukuoka University, the researchers investigated the effects of the dipeptide--named Tyr-Pro because it consists of the amino acids tyrosine and proline--by feeding it to mice for several days before and after injecting them with a chemical that is commonly used to simulate Alzheimer's disease by impairing memory functions.

In tests to evaluate short-term memory by comparing a mouse's tendency to explore different arms of a simple maze, impaired mice that had ingested the dipeptide over the past two weeks fared better than those that had not, though both groups were overall outperformed by mice without induced memory impairment. The same trend was also found in long-term memory tests measuring how long a mouse stays in the lighted area of an enclosure to avoid a mild electrical shock experienced in the dark area after having been trained in the box a day before.

Though there have been other reports suggesting some peptides can reduce the decline of brain functions, this is the first case where evidence also exists that the peptide can enter the brain intact.

"We still need studies to see if these benefits carry over to humans, but we hope that this is a step toward functional foods that could help prevent memory degradation or even improve our memories," comments Matsui.

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For more information about this research, see "Brain-transportable soy dipeptide, Tyr-Pro, attenuates amyloid β peptide$_{25-35}$-induced memory impairment in mice," Mitsuru Tanaka, Hayato Kiyohara, Atsuko Yoshino, Akihiro Nakano, Fuyuko Takata, Shinya Dohgu, Yasufumi Kataoka, and Toshiro Matsui, *npj Science of Food*, https://doi.org/10.1038/s41538-020-0067-3

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8. 受容体がマウスを強くてスリムにする
2 つの老化現象を調節する分子を特定

日付：2020 年 6 月 25 日
ソース：ボン大学
概要：

腹囲の増加と筋肉の減少は一般的な老化現象のうちの 2 つである。ボン大学の研究者らは、マウスでこの 2 つを調節する受容体を発見し、その研究成果が *Cell Metabolism* 誌に掲載されている。
細胞はその表面に、特定のシグナル分子を受け取ることができる多数の異なる「アンテナ」を持っており、これらは「受容体」と呼ばれる。これらのアンテナの 1 つは A2B 受容体である。一部の細胞の表面は、たとえばいわゆる褐色脂肪組織など、事実上その受容体で満たされている。褐色脂肪組織は、白色のものとは異なり、脂肪の貯蔵には使用されず、その代わりに脂肪を燃焼させて熱を発生させる。研究者らは、マウスにおいて、その生成する A2B が多いほど、より多くの熱を生成することを発見した。しかしながら、マウスの体重は、脂肪燃焼が増加している時でも、受容体の少ないマウスに比べてちょっと少ないだけである。受容体の多いマウスはスリムだが、より多くの筋肉を持っているためである。実際に、研究者らは、マウスの筋細胞が A2B 受容体を持っていることを示している。A2B 受容体を活性化する小分子アゴニストを受けた場合、上記 2 つの老化作用は抑制され、更に、4 週間の治療の後では、彼らは若いマウスと同じくらいの筋肉量になる。A2B の活性化は、これらの老化の影響をある程度元に戻すことができる、と言える。
結果が人間にとっても意味があるかどうかを確認するために、研究者らはヒトの細胞培養と組織サンプルを調べた。彼らは、A2B 受容体の数が多い人では、褐色脂肪組織がより高い速度で機能することを発見した。ただ、ヒトでの使用が承認された A2B 活性剤は現在未だ存在しない。これは、そのような治療の副作用についてほとんど知られていないからだ、としている。今後の研究が期待される。

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/2020/06/200625115916.htm

RECEPTOR MAKES MICE STRONG AND SLIM

Molecule that regulates two side effects of aging identified

Date:

June 25, 2020

Source:

University of Bonn

Summary:

Increasing abdominal girth and shrinking muscles are two common side effects of aging. Researchers have discovered a receptor in mice that regulates both effects. Experiments with human cell cultures suggest that the corresponding signaling pathways might also exist in humans.

FULL STORY

Mouse on exercise wheel (stock image).

Credit: © Emilia Stasiak / stock.adobe.com

Increasing abdominal girth and shrinking muscles are two common side effects of aging. Researchers at the University of Bonn have discovered a receptor in mice that regulates both effects. Experiments with human cell cultures suggest that the corresponding signaling pathways might also exist in humans. The study, which also involved researchers from Spain, Finland, Belgium, Denmark and the USA, has now been published in the journal *Cell Metabolism*.

On their surface, cells carry numerous different "antennas," called receptors, which can receive specific signal molecules. These then trigger a specific reaction in the cell. One of these antennas is the A2B receptor. The surfaces of some cells are virtually teeming with it, for example in the so-called brown adipose tissue. Brown adipose tissue, unlike its white-colored counterpart, is not used to store fat. Instead, it burns fat and thereby generates heat.

"In our publication we took a closer look at the A2B receptors in brown adipose tissue," explains Prof. Dr. Alexander Pfeifer from the Institute of Pharmacology and Toxicology at the University Hospital Bonn. "In the course of this we discovered an interesting association: The more A2B a mouse produces, the more heat it generates." Which means the A2B antennas somehow seem to increase the activity of the brown fat cells. But a second observation was even more exciting: Despite their increased fat burning, the animals weigh hardly less than mice with fewer receptors. "They are slimmer, but at the same time have more muscles," explains Pfeifer.

Muscles like a young mouse

In fact, the researchers were able to show that the muscle cells of mice also carry the A2B receptor. When this is stimulated by a small molecule agonist, muscle growth in the rodents is increased. "The receptor regulates both fat burning and muscle development," emphasizes Pfeifer's colleague Dr. Thorsten Gnad, the lead author of the study.

As they age, mice increasingly lose muscle mass -- similar to humans. And just like us, they also tend to gain a lot of fat around the hips over the years. However, if they receive the agonist that activates the A2B receptor, these aging effects are inhibited: Their oxygen consumption (an indicator of energy dissipation) increases by almost half; moreover, after four weeks of treatment they have as much muscle mass as a young animal. "A2B activation can therefore reverse both aging effects to a certain extent," explains Gnad.

In order to see whether the results were also meaningful for humans, the researchers examined human cell cultures and tissue samples. They found that in people with a large number of A2B receptors, the brown adipose tissue works at a higher rate. At the same time, their muscle cells consume more energy, which may indicate that they are also more active and may be more likely to be regenerated.

"Obesity is a growing problem worldwide," emphasizes Prof. Pfeifer. "Every extra pound not only increases the risk of developing diabetes, but also the risk of high blood pressure, vascular damage and therefore heart attacks and strokes. These problems are further exacerbated by muscles that shrink over the years, as they further reduce the body's energy requirements both at rest and in motion." In addition, poor muscle strength has an immense impact on the everyday life of older people, as they are increasingly restricted in their mobility.

The pharmacologists explain that the prospect of having a receptor on hand that might be able to slow down both of these age-related phenomena is therefore highly exciting. However, further research would first have to show to what extent the human mechanisms actually resemble those in mice. Additionally, there is currently no activator of A2B approved for use in humans. This means that little is known about any side effects of such a treatment. "We found no signs of adverse reactions in mice," says Pfeifer. "However, the meaningfulness of the results is, of course, also limited on this matter."

Gnad emphasizes that the success of the study is also the result of good cooperation with numerous international partners: "Nowadays, it is almost impossible to work on complex issues comprehensively without such cooperation."

Story Source:

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

Journal Reference:

1. Thorsten Gnad, Gemma Navarro, Minna Lahesmaa, Laia Reverte-Salisa, Francesca Copperi, Arnau Cordomi, Jennifer Naumann, Aileen Hochhäuser, Saskia Haufs-Brusberg, Daniela Wenzel, Frank Suhr, Naja Zenius Jespersen, Camilla Scheele, Volodymyr Tsvilovskyy, Christian Brinkmann, Joern Rittweger, Christian Dani, Mathias Kranz, Winnie Deuther-Conrad, Holger K. Eltzschig, Tarja Niemi, Markku Taittonen, Peter Brust, Pirjo Nuutila, Leonardo Pardo, Bernd K. Fleischmann, Matthias Blüher, Rafael Franco, Wilhelm Bloch, Kirsi A. Virtanen, Alexander Pfeifer. **Adenosine/A2B Receptor Signaling Ameliorates the Effects of Aging and Counteracts Obesity**. *Cell Metabolism*, 2020; DOI: 10.1016/j.cmet.2020.06.006

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- MLA
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University of Bonn. "Receptor makes mice strong and slim: Molecule that regulates two side effects of aging identified." ScienceDaily. ScienceDaily, 25 June 2020. <www.sciencedaily.com/releases/2020/06/200625115916.htm>.

9. 人工免疫細胞が、ヒトおよびマウスの固形腫瘍の癌細胞を認識して攻撃する

日付：2020 年 6 月 29 日
ソース：イリノイ大学アーバナシャンペーン校、ニュース支局
概要：

CAR-T 療法として知られている方法は、リンパ腫や白血病などの血液の癌患者に対して有効に使用されてきている。この方法では、癌細胞の表面にある独特の特徴を認識する抗体を加えることで、患者自身の T 細胞を改変する。
イリノイ大学アーバナシャンペーン校の研究者らが米国科学アカデミー紀要で報告している新しい研究では、この CAR-T 療法のアプローチの潜在的なターゲットを劇的に拡大、すなわち、彼らの作製した人工 T 細胞が、ヒトやマウスのさまざまな固形腫瘍の癌細胞を攻撃する、としている。
ある種の癌細胞上の異常に短い糖鎖は、これらの糖をたんぱく質に結合させる分子経路を破壊する突然変異が原因である。異常な糖に結合する薬物は、癌細胞を優先的に認識し、健康な細胞を助ける。
研究者らは、固形腫瘍の癌細胞に存在する標的を特定することが困難であるため、受容体として機能する抗体から取り組んだ。この抗体は、マウスの固形腫瘍の癌細胞のたんぱく質に付着した異常に形成された特定の種類の糖と相互作用することが知られている。受容体は癌細胞の表面のたんぱく質と糖の両方に結合するため、短い糖に付着した複数のたんぱく質に結合できるように抗体を変更すれば、様々な種類の癌に広く応用することができる、と報告されている。

研究関連/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2020/06/200629120120.htm

ENGINEERED IMMUNE CELLS RECOGNIZE, ATTACK HUMAN AND MOUSE SOLID-TUMOR CANCER CELLS

Date:

June 29, 2020

Source:

University of Illinois at Urbana-Champaign, News Bureau

Summary:

CAR-T therapy has been used successfully in patients with blood cancers such as lymphoma and leukemia. It modifies a patient's own T-cells by adding a piece of an antibody that recognizes unique features on the surface of cancer cells. In a new study, researchers report that they have dramatically broadened the potential targets of this approach - their engineered T-cells attack a variety of solid-tumor cancer cells from humans and mice.

FULL STORY

A method known as CAR-T therapy has been used successfully in patients with blood cancers such as lymphoma and leukemia. It modifies a patient's own T-cells by adding a piece of an antibody that recognizes unique features on the surface of cancer cells. In a new study, researchers report that they have dramatically broadened the potential targets of this approach -- their engineered T-cells attack a variety of solid-tumor cancer cells from humans and mice.

They report their findings in the *Proceedings of the National Academy of Sciences*.

"Cancer cells express on their surface certain proteins that arise because of different kinds of mutations," said Preeti Sharma, a postdoctoral researcher at the University of Illinois at Urbana-Champaign who led the research with biochemistry professor David Kranz, a member of the Cancer Center at Illinois and an affiliate of the Carl R. Woese Institute for Genomic Biology, also at the U. of I. "In this work, we were looking at protein targets that have short sugar chains attached to them."

The abnormally short sugar chains on some types of cancer cells result from mutations that disrupt the molecular pathway that attaches these sugars to proteins, Sharma said. Drugs that bind to the aberrant sugars preferentially recognize cancer cells and spare healthy cells.

CAR-T therapy is a promising treatment for patients with certain types of blood cancers. But identifying binding sites in solid tumors has been more difficult, Kranz said.

"A major challenge in the field has been to identify targets that exist on cancer cells in solid tumors that are not present on normal tissue," he said.

The team started with a piece of an antibody that could serve as a receptor. The antibody was known to interact with a specific type of abnormally formed sugar attached to a protein on solid-tumor cancer cells in mice.

"We realized that because this receptor binds both to the protein and the sugar on the surface of the cancer cell, there might be room to change the antibody so that it can bind to more than one protein attached to the short sugar," Sharma said. "This could make it broadly reactive to different kinds of cancers."

Study co-author Qi Cai, another postdoctoral researcher in the Kranz lab, tested whether changes in the sequence of amino acids in the vicinity of the abnormal sugar affected the receptor's binding to the site. This allowed the team to determine if the antibody could be slightly changed to accommodate other sugar-linked cancer targets.

They conducted a series of mutation experiments focused on the essential parts of the antibody, Sharma said.

"We generated almost 10 million mutant versions of our receptor, and then we screened those to find the property we wanted," she said. "In this case, we wanted to broaden the specificity of that antibody so that it reacts not only to the mouse target but also to human targets."

Once they found the antibodies with the desirable traits, the researchers engineered them into T-cells and tested them with mouse and human cancer cell lines.

"Our engineered T-cells are showing activity against both human and mouse cancer cell lines," Sharma said. "And the T-cells can now recognize several different proteins that have short sugars attached to them. This is really important because in cancer therapy, most of the time you are going after a single target on a cancer cell. Having multiple targets makes it very difficult for the cancer to evade the treatment."

"Although these engineered cells are early in development, we are particularly excited that we can use the same T-cell product to study efficacy and safety against cancers in mice and humans," Kranz said.

Story Source:

Materials provided by **University of Illinois at Urbana-Champaign, News Bureau**. Original written by Diana Yates. *Note: Content may be edited for style and length.*

Journal Reference:

1. Preeti Sharma, Venkata V. V. R. Marada, Qi Cai, Monika Kizerwetter, Yanran He, Steven P. Wolf, Karin Schreiber, Henrik Clausen, Hans Schreiber, David M. Kranz. **Structure-guided engineering of the affinity and specificity of CARs against Tn-glycopeptides**. *Proceedings of the National Academy of Sciences*, 2020; 201920662 DOI: 10.1073/pnas.1920662117
