Bio News – December, 2019

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

10/30　中国の肥満有病率が 10 年間で 3 倍以上上昇

2013-2014 年の中国の成人肥満（BMI 28 以上）有病率は 14%であり、その 10 年前に比べて 3 倍以上上昇。地域ごとの有病率では、例えば海南島（海南省）の肥満有病率が僅かに 4.4%なのに対して、北京は 4 人に 1 人以上の 26.6%だった。

10/30　重度肥満小児の手術治療を米国小児科学会が推奨

10/31　FDA が調べたベビーパウダーを J&J 側が再検査したところアスベストは検出されず：どちらが本当なのか?

10/31　がんゲノム医療、見えてきた課題

https://business.nikkei.com/atcl/gen/19/00002/102900810/

https://headlines.yahoo.co.jp/article?a=20191031-66092421-business-sctch

11/1　大日本住友製薬、Roivant の語尾が”vant”の子会社 5 つの株式を取得の合意が成立

11/1　はしか感染で免疫システム「リセット」、ハーバード大などの研究で明らかに

https://headlines.yahoo.co.jp/hl?a=20191101-00000023-jij_afp-int

11/2　トランプ大統領がテキサス州の医師 Stephen Hahn 氏を FDA 長官に指名

トランプ大統領は現在の暫定 FDA 長官ではなくテキサス州ヒューストンの病院 MD Anderson Cancer Center の医師 Stephen Hahn 氏を FDA 正式長官に指名すると大統領官邸が発表した。Hahn 氏の FDA 長官就任を議会上院が認めれば、Scott Gottlieb 氏が 4 月に辞任してからの暫定長官 Norman Sharpless 氏は古巣の National Cancer Institute (NCI) に戻る。

11/4　中国で Green Valley のアルツハイマー病薬 Oligomannate (GV-971) が承認された

軽～中程度アルツハイマー病患者の有意な認知機能改善がプラセボ対照 Ph3 試験で認められた事を受け、Shanghai Green Valley Pharmaceuticals のアルツハイマー病薬 Oligomannate (GV-971) が中国 National Medical Products Administration (NMPA) に承認された。
プラセボとの ADAS-Cog12 点数の差は 2.54（p< 0.0001）で、効果は早くも治療 4 週時点に認められ、9 か月間の治療完了まで維持された。
Green Valley によると全世界で承認されたアルツハイマー病薬は 2003 年以来。Oligomannate は今年中に中国で利用可能になる。

11/5　第一三共が米国の痛み治療市場から撤退～癌や鉄注射剤事業に専念

11/6　アルツハイマーを早期診断＝血液中で減るたんぱくで―名古屋市立大

https://headlines.yahoo.co.jp/hl?a=20191106-00000010-jij-sctch

11/6　脳梗塞後の神経細胞“再生”期待　岡山大大学院教授ら、実験成功

https://headlines.yahoo.co.jp/hl?a=20191106-00010000-sanyo-sctch

11/6　開発品の革新性と層の厚さで製薬会社を順位付け～AstraZeneca が第一位

IDEA Pharma が毎年発表するその順位付け Pharmaceutical Invention Index によると、今年の開発品の革新性と層の厚さで製薬会社を順位付けすると AstraZeneca が第一位、第二位以下は以下の通り。

1 位：AstraZeneca
2 位：Celgene
3 位：Eli Lilly
4 位：Novartis
5 位：AbbVie、Vertex
6 位：Bristol-Myers Squibb（BMS）
7 位：Regeneron Pharmaceuticals
8 位：第一三共（Daiichi Sankyo）
9 位：GlaxoSmithKline（GSK）
10 位：Biogen

11/7　Biogen が Samsung Bioepis に 1 億ドルを払ってバイオシミラーを手に入れる

11/7　暗闇で目が慣れるメカニズムを解明　阪大研究チーム、関係分子を特定

https://headlines.yahoo.co.jp/hl?a=20191107-00000052-mai-sctch

11/7　1 滴足らずの血液でアルツハイマー病を早期診断 名古屋市立大研究グループが診断マーカー発見

https://headlines.yahoo.co.jp/hl?a=20191107-00010000-sportal-sctch

11/8　HIV の新種サブタイプを特定 19 年ぶり -Abbott の研究者らが発見

https://headlines.yahoo.co.jp/hl?a=20191108-00000008-jij_afp-sctch

11/11　Novartis のジェネリック事業 Sandoz が Aspen の日本事業を取得

11/11　皮膚病薬の 2 社・Foamix Pharmaceuticals と Menlo Therapeutics が合併

11/12　NEC と VAXIMM 社、ネオアンチゲンによる個別化がんワクチンの共同開発に合意

https://jpn.nec.com/press/201911/20191112_01.html

11/12　Juul（本社：サンフランシスコ）がミント風味電子タバコの販売を中止

https://newsroom.juul.com/juul-labs-stops-the-sale-of-mint-juulpods-in-the-united-states/

11/12　インドの Lupin が日本の子会社・共和薬品を投資会社に売却

インドの Lupin Limited が日本の子会社・共和薬品工業の所有分を日本の医療分野投資会社 Unison Capital Partners に 5 億 2,600 万ドル（574 億円）で売却する。

11/12　Kaiser Permanente（本拠地：カリフォルニア州オークランド）の CEO/会長 Bernard J. Tyson 氏が死亡

11/12　伝染性のがん、世界各地のムール貝で見つかる、研究

https://headlines.yahoo.co.jp/article?a=20191112-00010001-nknatiogeo-sctch

11/13　Merck がフランスの研究所を閉鎖、製造を縮小～200 職超が消失

11/13　佐賀大、バイオ 3D 血管を作製　透析患者の臨床研究へ

https://headlines.yahoo.co.jp/hl?a=20191113-00000003-jij-sctch

11/14　Pfizer の Upjohn 事業と Mylan の統合後の社名は Viatris

11/14　脳疾患治療を目指す米 3 大学（UC サンフランシスコ、UC バークレー、ワシントン州立大学）連携 Weill Neurohub が 1 億ドル超の寄附を受けて発足

11/14　武田薬品が Finch Therapeutics から細菌薬を調達

11/14　Abbott の CEO・Miles White 氏が来年辞任～後任は現 COO の Robert Ford 氏

11/15　Allergan が Exicure と組んで男性型脱毛症薬の開発を目指す

11/16　富士フィルムが遺伝子治療生産工程開発拠点をテキサス州工場近くに新設予定

11/16　BMS の Celgene 買収を米国連邦取引委員会が許可～20 日に成立予定

11/16　塩野義製薬の複雑尿路感染症治療抗生剤が米国 FDA に承認された

11/16　水に沈まない金属構造を開発中 –ロチェスター大学

https://headlines.yahoo.co.jp/hl?a=20191116-00000004-giz-sctch

11/17　異常をきたすと癌を生じやすくするらしい遺伝子

The Cancer Genome Atlas（TCGA）の 8,500 を超える腫瘍情報を新たな数学理論 iEDGE（integration of Epi–DNA and Gene Expression）で解析し、異常をきたすと癌を生じやすくするらしい遺伝子一揃いが同定され、結果がボストン大学のウェブサイトで公開されている。
montilab.bu.edu/iEDGE
今回の解析で、3 受容体陰性乳癌（TNBC）で増幅するスプライシング因子 RBM17 や腫瘍抑制因子 RBM17 を含む乳癌を助長しうる遺伝子が幾つか見つかった。また、TRIP13, ORAOV1, TPX2 等の癌全般を助長しうる遺伝子も見つかっている。TRIP13 はかつての研究で大腸癌の増殖を促すことや予後不良の前立腺癌と関連することが把握されており、ORAOV1 は多くの固形癌で過剰発現する遺伝子。TPX2 も多くの癌で増幅する強力な発がん遺伝子であり、有望な治療標的。

11/19　薬価引き下げのルール拡大を検討　医療費抑制が狙い　厚労省

https://headlines.yahoo.co.jp/hl?a=20191119-00000074-mai-soci

11/19　京大iPS細胞備蓄事業、国支援打ち切りか

https://headlines.yahoo.co.jp/hl?a=20191119-00000007-asahi-soci

11/19　AbbVie の Humira の Pfizer 製バイオシミラーABRILADA を米国 FDA が承認

11/20　Novartis が Medicines を買収か？

11/21　Eli Lilly が 4 億ドルで本拠地インディアナポリスの工場を拡大～新規 100 人雇用

11/21　BMS の Celgene 買収が完了

11/22　世界の 81% の思春期若者の運動量は必要量に達していない

11/22　110 歳以上の人に特殊な免疫細胞　長寿の仕組み解明に期待

https://headlines.yahoo.co.jp/hl?a=20191122-00000517-san-sctch

11/25　超長寿者、免疫細胞に特徴　特殊な「T 細胞」多い　理研と慶大

https://headlines.yahoo.co.jp/hl?a=20191125-00000021-jij-sctch

11/25　血液 1 滴でがん 13 種 99%検出　東芝、20 年から実証試験

https://headlines.yahoo.co.jp/hl?a=20191125-00000001-kyodonews-soci

11/25　The Medicines を Novartis が約 97 億ドルで買収合意

11/26　iPS 細胞利用心不全治療を開発する東京拠点の Heartseed が 2,600 万ドル調達

11/26　英国首相 Boris Johnson 氏が認知症研究への投資を倍増すると約束

11/26　腎移植薬を売る Veloxis Pharmaceuticals を旭化成が約 13 億 1,000 万ドルで買収合意

https://www.nikkei.com/article/DGXMZO52572680V21C19A1X93000/

11/26　Roche のゾフルーザを効き難くするインフルエンザ変異が日本の患者から見つかった

https://www.fiercepharma.com/pharma/roche-s-flu-med-xofluza-drives-drug-resistance-and-may-be-a-bad-choice-for-kids-study-says

https://headlines.yahoo.co.jp/hl?a=20191126-00000002-asahi-soci

11/27　米国の癌患者の半数近くが診断から 2 年以内に破産

11/27　iPS で軟骨 臨床研究を申請 -京大

https://news.yahoo.co.jp/pickup/6343688

11/28　11 の製薬会社が 2018 年以降 20 億ドルを遺伝子治療製造に投資

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. 血圧上昇の一要因

2. イヌの乳腺腫瘍に対するエストロゲンの反対の効果

3. 幹細胞移植で完全に機能する肺がマウスで成長

4. マウスの性格をマッピングする

5. 黄色ブドウ球菌感染から守る新しいワクチン –マウス実験

6. 新しい細胞療法で外傷性脳損傷後の記憶改善と発作停止

7. 腸内微生物が老化プロセスを変える可能性

8. あまり知られていないタンパク質が、肥満と代謝疾患において重要な役割を果たすようだ

9. Mount Sinai の研究者らがパーキンソン病の分子ドライバーを発見

10. CAGE が脂肪を閉じ込めて肥満を治療する

1. 血圧上昇の一要因

血圧を制御するメカニズム、特に高血圧については、多くの疑問が残っている。血管の挙動調節に関与する因子の中で、アペリン受容体（APJ）は血管の収縮に重要な役割を果たすと推定されているが、これまでに生体内で検証されていなかった。
今回 *Journal of Biochemistry* 誌で発表された筑波大学らの新しい研究で、研究チームは、血管や心臓などの心臓血管組織で一般的に発現する膜受容体である APJ の活性を調査したところ、APJ が、実験用マウスの血管平滑筋細胞への影響を通して、高血圧と密接に関連していることを発見した。以前の実験では、APJ が低血圧に関連している可能性があることが示されたが、これらの実験では APJ を発現する主要な細胞である血管平滑筋細胞は使用されていなかった。今回、研究者らは血管平滑筋細胞で、そのレベルが生理学的に正常なマウスよりもはるかに高くなるように APJ を過剰発現させた。これによってこれらのマウスの血管平滑筋細胞で APJ を活性化する効果を具体的に評価することにつながった。
また、血管平滑筋細胞で APJ を過剰発現させたトランスジェニックマウスは、アペリン注射による APJ の活性化により、一過性かつ激しい血圧上昇を示したため、これらのマウスからα1A アドレナリン受容体を除去することで血管収縮が減少するかどうかを試験した。その場合に、高レベルの活性化 APJ にもかかわらず、血管収縮はα1A アドレナリン受容体の喪失により大幅に減少することが分かった。
更に研究者らは、APJ とα1A アドレナリン受容体が細胞内で物理的に相互作用することを示し、この相互作用がマウスで観察される血管収縮の原因である可能性を示唆している。この研究の結果は、血圧を制御し、血管狭窄や血管痙攣などの症状に対する治療法の開発をサポートするメカニズムを理解するのに役立つ可能性がある、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/11/191101100148.htm

Here's something that will raise your blood pressure

Date:

November 1, 2019

Source:

University of Tsukuba

Summary:

The apelin receptor (APJ) has been presumed to play an important role in the contraction of blood vessels involved in blood pressure regulation. A research team found that APJ was

closely associated with hypertension through effects on vascular smooth muscle cells in laboratory mice.

FULL STORY

Many questions remain about the mechanisms that control blood pressure, particularly in relation to hypertension. Among the factors involved in regulation of blood vessel behavior, the apelin receptor (APJ) has been presumed to play an important role in the contraction of blood vessels; however, this was not verified in vivo until now.

In a new study published in the *Journal of Biochemistry*, a research team led by experts from the University of Tsukuba investigated the activity of APJ, a membrane receptor that is commonly expressed in cardiovascular tissue, such as blood vessels and the heart, and found that APJ was closely associated with hypertension (increased blood pressure) through effects on vascular smooth muscle cells in laboratory mice.

Although prior experiments indicated that APJ might be related to hypotension (lower blood pressure), those experiments did not use vascular smooth muscle cells, which are the primary cells that express APJ. In this study, the researchers overexpressed APJ in vascular smooth muscle cells, so that its levels were much higher than in physiologically normal mice. This allowed the researchers to specifically assess the effects of activating APJ in the vascular smooth muscle cells of those mice.

"Transgenic mice that overexpressed APJ in vascular smooth muscle cells showed transient and intense elevation of blood pressure due to APJ activation through apelin injection," says Akiyoshi Fukamizu, corresponding author on the study. "This was consistent with the vasoconstriction -- blood vessel contraction -- present in some types of endothelial dysfunction."

In the study, the researchers found that activation of APJ in the presence of noradrenaline or phenylephrine, known mediators of vasoconstriction, led to further vasoconstriction. This suggested a potential synergistic effect with the target of noradrenaline and phenylephrine, the α1A-adrenergic receptor.

"Our analyses revealed that vasoconstriction was prominent in transgenic mice with activated APJ, so we tested whether vasoconstriction would be reduced by the removal of α1A-adrenergic receptor from those mice," says Junji Ishida, author on the study. "We found that vasoconstriction was greatly reduced by the loss of α1A-adrenergic receptor, despite the high levels of activated APJ in those mice."

Furthermore, the researchers showed that APJ and α1A-adrenergic receptor physically interacted within cells in laboratory assays, which suggested that this direct interaction may be responsible for the vasoconstriction observed in the mice. The results of this study may help to understand the mechanisms that control blood pressure and support the development of therapies for conditions such as vascular stenosis and vasospasm.

Story Source:

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

Journal Reference:

1. Katsumasa Nagano, Chulwon Kwon, Junji Ishida, Tatsuo Hashimoto, Jun-Dal Kim, Nana Kishikawa, Mei Murao, Kenjiro Kimura, Yoshitoshi Kasuya, Sadao Kimura, Yi-Ching Chen, Hirotsugu Tsuchimochi, Mikiyasu Shirai, James T Pearson, Akiyoshi Fukamizu. **Cooperative action of APJ and α1A-adrenergic receptor in vascular smooth muscle cells induces vasoconstriction**. *The Journal of Biochemistry*, 2019; 166 (5): 383 DOI: 10.1093/jb/mvz071

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- Chicago

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2. イヌの乳腺腫瘍に対するエストロゲンの反対の効果

若い年齢で去勢されたイヌは、乳癌を発症するリスクが低くなる。早期の避妊は、エストロゲン産生レベルを低下させるため、多くの獣医や科学者が乳癌のことになるとエストロゲンに対して否定的な見方をする。
今回 *Plos One* 誌で公開された Penn の獣医学部の研究者らが率いる新しい研究によると、「エストロゲンは乳癌の発症を促進しているようにみえるが、転移の進行に関してエストロゲンが行うことは、もっと複雑である」としている。つまり、エストロゲンと乳腺腫瘍の発生リスクの増加との関連性はあるとしても、血清エストロゲン値が高い時、イヌが病気の最も危険な側面を回避することができるようだ、というのである。血清エストロゲンが高いエストロゲン受容体陽性腫瘍の患者は、転移性疾患の発症に時間が掛かり、血清エストロゲンレベルの低いイヌよりも長く生存した。また、エストロゲンの保護的役割は、エストロゲン受容体陰性の乳腺腫瘍のイヌにおいても驚くほど顕著で、高い血清エストロゲンが転移の遅延や転移しないことに関連していた。又、血清エストロゲンが低いイヌは、乳腺腫瘍手術後のフォローアップ中に血管肉腫などの他の非乳腺侵襲性致死腫瘍を発症するリスクが大幅に増加した。
研究者らは、エストロゲンが何をしているのか、どの遺伝子や免疫細胞と相互作用しているのかを正確に分析すれば、エストロゲンの力を利用して治療戦略をより賢くすることができるかもしれない、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.sciencedaily.com/releases/2019/11/191101183437.htm

Estrogen's opposing effects on mammary tumors in dogs

Date:

November 1, 2019

Source:

University of Pennsylvania

Summary:

Estrogen's role in canine mammary cancer is more complex than previously understood, according to new research. The nuanced findings may help explain why dogs spayed at a young age are more likely to develop more aggressive cancers, the team says.

FULL STORY

Dogs that are spayed at a young age have a reduced risk of developing mammary tumors, the canine equivalent of breast cancer. Early spaying reduces levels of estrogen production, leading many veterinarians and scientists to cast estrogen in a negative light when it comes to mammary cancer.

But the effects of estrogen on cancer risk in dogs aren't straightforward, according to a new study led by researchers from Penn's School of Veterinary Medicine. While it's clear that spaying dogs greatly minimizes their risk of developing mammary cancer, the findings suggest that the practice may increase the risk of more aggressive cancers. And in spayed animals with mammary tumors, the team found that higher serum estrogen levels were actually protective, associated with longer times to metastasis and improved survival times.

"Dogs that remain intact and have their ovaries develop many more mammary tumors than dogs that were spayed, so removing that source of estrogen does have a protective effect," says Karin U. Sorenmo, a veterinary oncologist at Penn Vet and senior author on the study, published in *PLOS ONE*. "Estrogen does seem to drive mammary cancer development. But what it does for progression to metastasis -- that I think is more complicated."

Sorenmo and colleagues have been studying mammary tumors in dogs as a way of improving care and treatment for pets but also to make insights into human breast cancer biology.

"Much of the research we do in veterinary medicine looks at what is done in people and then adapts it," she says. "But dogs are such a great, comprehensive model for cancer. Yes, there are differences in biology between dogs and people, but here those differences may allow us to ask very probing questions about what estrogen is doing in both dogs with mammary cancer and women with breast cancer."

The research used data from two prospective studies, including one involving dogs in the Penn Vet Shelter Canine Mammary Tumor Program, through which shelter dogs with mammary tumors receive treatment, are studied by researchers like Sorenmo, and then find foster or permanent homes.

The team evaluated 159 dogs with mammary cancer, 130 that were spayed as part of the study and 29 that remain intact. In addition to surgically removing the dogs' measurable tumors, the team collected information on serum estrogen levels, tumor type, disease grade and stage, time to metastasis, and survival time.

Despite estrogen's link with an increased risk of developing mammary tumors, the researchers found that higher serum estrogen levels also seemed to help dogs avoid some of the riskiest aspects of their disease. Unexpectedly, when dogs were spayed at the same time their tumors were removed, those with estrogen receptor-positive tumors that had higher serum estrogen took longer to develop metastatic disease and survived longer than dogs with lower estrogen levels, confirming that these tumors depended on estrogen for progression.

Sorenmo speculates that, in these cases, estrogen's action may be nuanced. "It drives the cancer, but it also seems to control or modulate it, reining it in," she says, because most dogs with high serum estrogen levels had lower-grade and estrogen receptor-positive tumors, rendering them susceptible to hormonal deprivation by spaying.

The protective role of estrogen was also surprisingly pronounced in dogs with estrogen-receptor negative mammary tumors. In these higher-risk cancers, high serum estrogen was associated with delayed or absent metastasis. Complementing these findings and supporting a potential broader, tumor receptor-independent anti-cancer effect driven by estrogen, dogs with low serum estrogen had a significantly increased risk for developing other non-mammary aggressive fatal tumors, such as hemangiosarcoma, during their follow-up after mammary tumor surgery.

Some of the findings contradict what has been found in women with breast cancer. For example, higher serum estrogen levels in women following breast cancer therapy have been associated with higher rates of recurrence. But Sorenmo also notes that many cases of breast cancer in women arise just after menopause, when estrogen levels tumble. So there may be a more complex role for estrogen in people's cancer risk as well.

The work points to new possibilities for examining the role of estrogen in cancer initiation and progression. Already, Sorenmo and colleagues, including Penn Vet's Susan Volk and Ellen Puré, are pursuing investigations of how the hormone affects the tumor microenvironment, cells that aren't themselves cancerous but may either stem or encourage a tumor's growth and spread.

"I think this study opens some really complicated questions," Sorenmo says. "If we start dissecting exactly what estrogen is doing, what genes or immune cells it's interacting with, maybe we could harness the power of estrogen to be more clever in our treatment strategies."

Story Source:

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

Journal Reference:

1. Karin U. Sorenmo, Amy C. Durham, Enrico Radaelli, Veronica Kristiansen, Laura Peña, Michael H. Goldschmidt, Darko Stefanovski. **The estrogen effect; clinical and histopathological evidence of dichotomous influences in dogs with spontaneous mammary carcinomas**. *PLOS ONE*, 2019; 14 (10): e0224504 DOI: 10.1371/journal.pone.0224504

Cite This Page:

- MLA
- APA
- Chicago

University of Pennsylvania. "Estrogen's opposing effects on mammary tumors in dogs." ScienceDaily. ScienceDaily, 1 November 2019. <www.sciencedaily.com/releases/2019/11/191101183437.htm>.

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3. 幹細胞移植で完全に機能する肺がマウスで成長

コロンビア大学アービン医療センターの研究者らは、移植された幹細胞を使って、マウス胚で完全に機能する胚を成長させることに成功した。この研究成果は、移植を必要とする患者の為に人間の肺を動物内で成長させる技術を使って、新しい肺治療研究をすることが最終的に可能になるかもしれないことを示唆するものだとして、*Nature Medicine* 誌のオンライン版に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/11/191107160640.htm

Stem cell transplants used to grow fully functional lungs in mice

Date:

November 7, 2019

Source:

Columbia University Irving Medical Center

Summary:

Researchers have used transplanted stem cells to grow lungs in mice. Findings could lead to new options for lung transplant patients.

FULL STORY

Researchers at Columbia University were able to grow fully functional lungs in mouse embryos using transplanted stem cells. The findings suggest that it may be ultimately possible to use the technique to grow human lungs in animals for patients who need transplants and to study new lung treatments.

The paper was published online in the journal *Nature Medicine*.

"Millions of people worldwide who suffer from incurable lung diseases die without treatment due to the limited supply of donor lungs for transplantation," said co-senior author Wellington V. Cardoso, MD, PhD, professor of medicine and of genetics & development at Columbia University Vagelos College of Physicians and Surgeons. "Our study shows that it may eventually be possible to develop new strategies for generating human lungs in animals for transplantation as an alternative to waiting for donor lungs."

Researchers have dedicated major efforts to bioengineer lungs by growing stem cells on synthetic scaffolds or in lungs that have been stripped of their original cells. Though substantial progress has been made, researchers have been unable to generate a fully functional lung capable of maintaining survival in animal models??? Or capable of keeping an animal alive?.

"We thought it might be simpler to grow new lungs in a developing animal, so that we could take advantage of the animal's natural signals for lung development," says first author Munemasa Mori, MD, PhD, instructor of medicine at Columbia University Vagelos College of Physicians and Surgeons.

The researchers' first challenge was to create tissue culture conditions that would allow the donor stem cells to expand proliferate and maintain their ability to transform into many different cell types.

Next, the researchers implanted these stem cells in two types of engineered mouse embryos. One type lacked the stem cells that develop into mature lung cells and another could not produce enough of the cells to make a lung. This procedure created a "chimeric" embryo that was a mix of donor and host cells.

The implanted stem cells outcompeted the host cells for growth-promoting molecules present in the embryo, leading to the formation of functional lungs that allowed the mice to live well into adulthood. A variety of lung function tests confirmed that the "chimeric" lungs worked as well as normal mouse lungs, with no signs of rejection.

"The stem cells were implanted before the embryos' immunological system was turned on, which may explain why the organs were not rejected," says Mori, who will later test his approach in larger animals and in interspecies organ transplants.

"Many of the signals for lung development are conserved across species, from frogs to mice to humans, so the idea of using animals to grow human lungs is not out of the question," Cardoso says.

Story Source:

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

Journal Reference:

1. Munemasa Mori, Kazuhiro Furuhashi, Jennifer A. Danielsson, Yuichi Hirata, Miwako Kakiuchi, Chyuan-Sheng Lin, Mayu Ohta, Paul Riccio, Yusuke Takahashi, Xinjing Xu, Charles W. Emala, Chao Lu, Hiromitsu Nakauchi, Wellington V. Cardoso. **Generation of functional lungs via conditional blastocyst complementation using pluripotent stem cells**. *Nature Medicine*, 2019; DOI: 10.1038/s41591-019-0635-8

- Chicago

Columbia University Irving Medical Center. "Stem cell transplants used to grow fully functional lungs in mice." ScienceDaily. ScienceDaily, 7 November 2019. <www.sciencedaily.com/releases/2019/11/191107160640.htm>.

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4. マウスの性格をマッピングする

ドイツのミュンヘンにあるマックスプランク精神医学研究所およびイスラエルのワイツマン科学研究所の科学者らは、半自然のグループ環境に住んでいるマウスの性格を客観的に測定するための計算方法を開発した。
人間と同じように、すべてのマウスは異なっている。すぐに新しい環境を探索するものもいれば、巣の快適さの中にとどまることを好むものもいる。ケージメイトの近くにいることを好むものもいれば、一人でいるのを好むものもいる。これらの個々のユニークな特性は、生涯を通じてかなり安定しており、その人格（マウス格？）を定義する。人間では、多肢選択式アンケートを使用して性格スコアを導き出すことができるが、動物の性格をどのように測定できるか？
研究者らは、マウスのグループから撮影したビデオ映像を分析して膨大な量のデータを収集。各マウスの毛皮を異なる色に染め、研究者がマウスのグループを追跡できるようにした。各ビデオについては、60 の行動のレパートリーについて分析。
彼らは、行動の違いに基づいて個々を識別することができる安定した特性を求める数学的アルゴリズムを開発。この方法は、人間のパーソナリティーテストと同じように機能する。人間のパーソナリティーテストでは、5 つの次元で評価されることがよくあり、長期間にわたって一貫性のある特性を具体的に検索する。マウスでは、アルゴリズムにより、マウスの行動をキャプチャして説明できる 4 つの形質のような次元が特定された。これらの特性が安定していることをテストするために、研究者らは、グループを混同することによって行動の一部は変化したが、マウスの性格は安定していることを発見した。高度な RNA シーケンスツールと遺伝子組み換えマウス系統を使用して、これらの特性で捕捉された個々差がマウス脳の遺伝子発現のさまざまな差に対応し、異なる遺伝子構造を持つマウスを特定できることも示すことができた、としている。
この論文は、*Nature Neuroscience* 誌に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.weizmann-usa.org/news-media/in-the-news/scientists-map-mouse-personality

Improving Health & Medicine

Scientists Map Mouse Personality

November 07, 2019・
Phys.org・Max Planck Society・
TAGS: Neuroscience, Genetics, Evolution

Some mice are curious and explore every new hiding place. Others are more anxious and prefer to stay in their nest.
©MPI f. *Molecular Genetics*

Scientists at the Max Planck Institute of Psychiatry in Munich, Germany, together with colleagues at the Weizmann Institute of Science in Israel have developed a computational method to objectively measure the personality of mice living in a semi-natural, group environment.

Just like humans, every mouse is different. Some are quick to explore a new environment while others prefer to stay within the comfort of their nest. Some prefer to stay close to their cagemates, while others prefer to be alone. These unique characteristics of an individual remain fairly stable through life and define their personality. In humans, personality can be measured using multiple-choice questionnaires to derive personality scores, but how can one measure personality in animals?

Oren Forkosh and Stoyo Karamihalev, together with other colleagues collected huge amounts of data by analyzing video footage taken of groups of mice. To do this, they dyed the fur of each mouse a different color, allowing the researchers to track the groups of mice undisturbed. Each video was analyzed for a repertoire of 60 behaviors, such as how close a mouse stays to other mice, if they chase one another or run away, or the time spent in the nest or eating.

Stable personalities

The scientists developed a mathematical algorithm that sought stable traits that were able to discriminate individuals based on differences in behavior. This method works somewhat in the same way as personality tests in humans, in which people are often assessed on five dimensions. However, it specifically searches for traits that are consistent over time. In mice, the algorithm identified four trait-like dimensions that could capture and describe the behavior of mice. To test that these traits were stable, the researchers mixed up the groups and found that, while some of the behaviors had changed, the personalities of the mice were still stable. Using advanced RNA-sequencing tools and genetically modified mouse strains, the researchers were also able to show that individual differences captured in these traits corresponded to a variety of differences in gene expression in the mouse brain and could identify mice with different genetic makeup.

"This method has the potential to greatly advance our knowledge beyond what is possible using the current simplified methods for assessing behavior and toward stable and consistent differences in personality. It opens up the possibility to study how personality is affected by genes, drugs, aging, etc., how it is represented and maintained by the brain, and how it contributes to mental health and disease," explains Karamihalev, together with Oren Forkosh, one of the first authors of the study. "This is a good first step in the direction of better preclinical methods for assessing individual differences in behavior and physiology," says Alon Chen, the principal investigator for this study. "Our hope is that such approaches will aid in the effort toward a more personalized psychiatry."

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5. 黄色ブドウ球菌感染から守る新しいワクチン –マウス実験

黄色ブドウ球菌感染は、米国で毎年 3 万人以上の院内感染による死亡を引き起こしており、ヘルスケアシステムの費用は 100 億ドルにも上る。
今回新しく開発された実験用ワクチンは、黄色ブドウ球菌感染のマウスおよびウサギモデルでテストされた。免疫マウスの 80 パーセント以上が生存し、3 分の 2 が感染を除去、また、免疫ウサギでは、ほぼ 3 分の 2 が感染を除去した（ウサギは通常、黄色ブドウ球菌感染には強い）。この研究は、今週、米国微生物学会の *Infection and Immunity* 誌に掲載された。

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/2019/11/191111133326.htm

New vaccine protects from widespread, costly infection, mice study shows

Date:

November 11, 2019

Source:

American Society for Microbiology

Summary:

A newly developed experimental vaccine was more than eighty percent effective in protecting mice from succumbing to Staphylococcus aureus infection. S. aureus causes more than 30,000 deaths from hospital-acquired infections annually in the US, costing the healthcare system $10 billion.

FULL STORY

A newly developed experimental vaccine was more than eighty percent effective in protecting mice from succumbing to *Staphylococcus aureus* infection. *S. aureus* causes more than 30,000 deaths from hospital-acquired infections annually in the US, costing the healthcare system $10 billion. The research is published this week in *Infection and Immunity*, a journal of the American Society for Microbiology.

S. aureus is associated with a wide range of acute and chronic diseases such as bacteremia, sepsis, skin and soft tissue infections, pneumonia endocarditis, and osteomyelitis (bone infection), and has a high rate of mortality, estimated at 20-30 percent in bacteremia (blood infection) patients.

In the study, the investigators tested the vaccine in mouse and rabbit models of *S. aureus* infection. More than 80 percent of immunized mice survived, and two thirds of them cleared the infection, versus less than 10 percent of controls. On the 21st day post infection, the surviving animals -- both those immunized, and controls -- showed no signs of ill health, such as ruffled fur, or other abnormalities of appearance, and all had regained pre-infection weight.

In the rabbit experiments, the researchers injected the pathogen into the tibial bone marrow. Twenty-four days post infection, nearly two thirds of the immunized rabbits had cleared the infection; none of the controls had done so. Additionally, while control rabbits had hole-like lesions within the bone, immunized rabbits had smaller lesions or no lesions at all. (Rabbits do not typically succumb to *S. aureus* infection.)

Effective vaccination "would have enormous therapeutic utility in patients undergoing surgery, especially orthopedic and cardiovascular procedures where medical structures or devices are implanted, and in cases of traumatic injury," said Janette M. Harro, PhD, Research Assistant Professor, University of Maryland, Baltimore. Surgical site infections represent 20 percent of hospital acquired infections, and *S. aureus* is the major causative agent.

The diversity of disease caused by *S. aureus* results from differential expression of more than 70 virulence factors. Virulence factors initiate colonization and growth, mediate damage to the host, and hinder immune response.

Biofilm formation is a powerful virulence factor. *S. aureus* is difficult to eradicate largely because it so readily forms biofilms.

Biofilms are communities of bacteria that adhere powerfully to surfaces, in the manner of dental plaque. They are notably resistant to host immune response, and to antibiotics, because they are hard to penetrate, and because microbes in biofilms have low metabolism, which further reduces the potential to gain entry into bacterial cells.

Biofilms frequently form on medical implants such as artificial knees, hips, and cardiac devices. They can form anywhere there's a surface, moisture, and a nutrient source.

The vaccine the investigators developed recognizes five different *S. aureus* proteins. Four of these proteins are specific to *S. aureus* biofilms, and one is specific to *S. aureus* in the planktonic state.

"We identified vaccine candidates by screening *S. aureus* proteins with antibodies elicited during chronic *S. aureus* infections in animal models," said Dr. Harro. "This method permitted us to select protein targets for vaccination that were both expressed during an infection and were capable of being recognized by the immune response."

Story Source:

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

Journal Reference:

1. Janette M. Harro, Yvonne Achermann, Jeffrey A. Freiberg, Devon L. Allison, Kristen J. Brao, Dimitrius P. Marinos, Salar Sanjari, Jeff G. Leid, Mark E. Shirtliff. **Clearance of Staphylococcus aureus from In**

Vivo Models of Chronic Infection by Immunization Requires Both Planktonic and Biofilm Antigens. *Infection and Immunity*, 2019; DOI: 10.1128/IAI.00586-19

Cite This Page:

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American Society for Microbiology. "New vaccine protects from widespread, costly infection, mice study shows." ScienceDaily. ScienceDaily, 11 November 2019. <www.sciencedaily.com/releases/2019/11/191111133326.htm>.

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6. 新しい細胞療法で外傷性脳損傷後の記憶改善と発作停止

カリフォルニア州立大学アーバイン校（UCI）の研究者らは、マウスの外傷性脳損傷後の記憶を改善し、発作を防ぐ画期的な細胞療法を開発した。この研究は「移植された介在ニューロンが外傷性脳損傷後の記憶精度を改善」というタイトルで、*Nature Communications* 誌で本日公開された。
外傷性脳損傷は毎年 200 万人のアメリカ人に影響を及ぼし、脳の細胞死と炎症を引き起こす。頭部外傷を経験する人々は、しばしば生涯の記憶喪失に苦しみ、てんかんを発症する可能性もある。
この研究で、UCI チームは、脳回路の活動を制御する特定の種類の神経細胞である抑制性介在ニューロンを生成できる胚性前駆細胞を、外傷性脳損傷マウスの脳に移植した。彼らは、移植されたニューロンが損傷部に移動し、損傷した脳細胞と新しいつながりを形成し、長期的に機能することを発見した。治療後 1 か月以内に、マウスは、不快な体験をしたボックスとそうでないボックスを区別できるなど、記憶改善の兆候を示した。また、脳に損傷を受けたことのないマウスでも同様であった。また、細胞移植は、新しい介在ニューロンで治療されなかったマウスの半数以上に影響を与えたてんかんの発症からマウスを保護した。
現在、頭部外傷を負った人に対する治療法はないが、マウスでの結果をヒトで再現できる場合、患者に多大な影響を与える可能性がある。研究者らは、次のステップはヒト幹細胞から介在ニューロンを作成することだ、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/11/191115101102.htm

New cell therapy improves memory and stops seizures following TBI

Transplanting new inhibitory neurons may repair damaged brain circuits

Date:

November 15, 2019

Source:

University of California - Irvine

Summary:

Researchers have developed a breakthrough cell therapy to improve memory and prevent seizures in mice following traumatic brain injury.

Researchers from the University of California, Irvine developed a breakthrough cell therapy to improve memory and prevent seizures in mice following traumatic brain injury. The study, titled "Transplanted interneurons improve memory precision after traumatic brain injury," was published today in *Nature Communications*.

Traumatic brain injuries affect 2 million Americans each year and cause cell death and inflammation in the brain. People who experience a head injury often suffer from lifelong memory loss and can develop epilepsy.

In the study, the UCI team transplanted embryonic progenitor cells capable of generating inhibitory interneurons, a specific type of nerve cell that controls the activity of brain circuits, into the brains of mice with traumatic brain injury. They targeted the hippocampus, a brain region responsible for learning and memory.

The researchers discovered that the transplanted neurons migrated into the injury where they formed new connections with the injured brain cells and thrived long term. Within a month after treatment, the mice showed signs of memory improvement, such as being able to tell the difference between a box where they had an unpleasant experience from one where they did not. They were able to do this just as well as mice that never had a brain injury. The cell transplants also prevented the mice from developing epilepsy, which affected more than half of the mice who were not treated with new interneurons.

"Inhibitory neurons are critically involved in many aspects of memory, and they are extremely vulnerable to dying after a brain injury," said Robert Hunt, PhD, assistant professor of anatomy and neurobiology at UCI School of Medicine who led the study. "While we cannot stop interneurons from dying, it was exciting to find that we can replace them and rebuild their circuits."

This is not the first time Hunt and his team has used interneuron transplantation therapy to restore memory in mice. In 2018, the UCI team used a similar approach, delivered the same way but to newborn mice, to improve memory of mice with a genetic disorder.

Still, this was an exciting advance for the researchers. "The idea to regrow neurons that die off after a brain injury is something that neuroscientists have been trying to do for a long time," Hunt said. "But often, the transplanted cells don't survive, or they aren't able to migrate or develop into functional neurons."

To further test their observations, Hunt and his team silenced the transplanted neurons with a drug, which caused the memory problems to return.

"It was exciting to see the animals' memory problems come back after we silenced the transplanted cells, because it showed that the new neurons really were the reason for the memory improvement," said Bingyao Zhu, a junior specialist and first author of the study.

Currently, there are no treatments for people who experience a head injury. If the results in mice can be replicated in humans, it could have a tremendous impact for patients. The next step is to create interneurons from human stem cells.

"So far, nobody has been able to convincingly create the same types of interneurons from human pluripotent stem cells," Hunt said. "But I think we're close to being able to do this."

Jisu Eom, an undergraduate researcher, also contributed to this study. Funding was provided by the National Institutes of Health.

Story Source:

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

Journal Reference:

1. Bingyao Zhu, Jisu Eom, Robert F. Hunt. **Transplanted interneurons improve memory precision after traumatic brain injury**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-13170-w

Cite This Page:

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- Chicago

University of California - Irvine. "New cell therapy improves memory and stops seizures following TBI: Transplanting new inhibitory neurons may repair damaged brain circuits." ScienceDaily. ScienceDaily, 15 November 2019. <www.sciencedaily.com/releases/2019/11/191115101102.htm>.

7. 腸内微生物が老化プロセスを変える可能性

シンガポールのナンヤン工科大学（NTU シンガポール）が率いる国際研究チームは、腸内に生息する微生物が老化プロセスを変える可能性があることを発見した。
人間を含むすべての生物は、無数の微生物種と共存し、過去 20 年間に行われた研究によって、栄養、生理学、代謝、および行動における重要な役割が確立されている。
NTU 医学部が率いる研究チームは、老齢マウス（24 ヶ月）の腸内微生物を若い無菌マウス（6 週齢）に移植したところ、8 週間後、若いマウスは腸の成長と神経新生として知られる脳内のニューロンの生産を増加させた。
チームは、神経新生の増加が、酪酸と呼ばれる特定の短鎖脂肪酸を生成する腸内微生物の濃縮によるものであることを示した。酪酸は、下部腸管で食物繊維の微生物発酵によって生成され、FGF21 と呼ばれる長寿ホルモンの生成を刺激する。FGF21 は、体のエネルギーと代謝の調節に重要な役割を果たす。また、通常年をとるにつれて、酪酸塩の生産は減少する。
その後、研究者たちは、若い無菌マウスに酪酸を単独で与えると、同じ成体の神経発生効果があることを示した。この研究は昨日（11 月 13 日）、*Science Translational Medicine* 誌に掲載された。
研究者らは、「老齢マウスから採取した微生物が、若いマウスの神経成長をサポートする能力がある、これは驚くべき、非常に興味深い観察である。これらの結果は、酪酸が脳卒中、脊髄損傷のような状況での修復と再構築をサポートするかどうかを探求し、老化加速と認知機能低下を緩和することにつながるのではないか」としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/11/191114103128.htm

Bacteria in the gut may alter aging process

Date:

November 14, 2019

Source:

Nanyang Technological University

Summary:

Microorganisms living in the gut may alter the aging process, which could lead to the development of food-based treatment to slow it down.

FULL STORY

An international research team led by Nanyang Technological University, Singapore (NTU Singapore) has found that microorganisms living in the gut may alter the ageing process, which could lead to the development of food-based treatment to slow it down.

All living organisms, including human beings, coexist with a myriad of microbial species living in and on them, and research conducted over the last 20 years has established their important role in nutrition, physiology, metabolism and behaviour.

Using mice, the team led by Professor Sven Pettersson from the NTU Lee Kong Chian School of Medicine, transplanted gut microbes from old mice (24 months old) into young, germ-free mice (6 weeks old). After eight weeks, the young mice had increased intestinal growth and production of neurons in the brain, known as neurogenesis.

The team showed that the increased neurogenesis was due to an enrichment of gut microbes that produce a specific short chain fatty acid, called butyrate.

Butyrate is produced through microbial fermentation of dietary fibres in the lower intestinal tract and stimulates production of a pro-longevity hormone called FGF21, which plays an important role in regulating the body's energy and metabolism. As we age, butyrate production is reduced.

The researchers then showed that giving butyrate on its own to the young germ-free mice had the same adult neurogenesis effects.

The study was published in *Science Translational Medicine* yesterday (13 November), and was undertaken by researchers from Singapore, UK, and Australia.

"We've found that microbes collected from an old mouse have the capacity to support neural growth in a younger mouse," said Prof Pettersson. "This is a surprising and very interesting observation, especially since we can mimic the neuro-stimulatory effect by using butyrate alone."

"These results will lead us to explore whether butyrate might support repair and rebuilding in situations like stroke, spinal damage and to attenuate accelerated ageing and cognitive decline."

How gut microbes impact the digestive system

The team also explored the effects of gut microbe transplants from old to young mice on the functions of the digestive system.

With age, the viability of small intestinal cells is reduced, and this is associated with reduced mucus production that make intestinal cells more vulnerable to damage and cell death.

However, the addition of butyrate helps to better regulate the intestinal barrier function and reduce the risk of inflammation.

The team found that mice receiving microbes from the old donor gained increases in length and width of the intestinal villi -- the wall of the small intestine. In addition, both the small intestine and colon were longer in the old mice than the young germ-free mice.

The discovery shows that gut microbes can compensate and support an ageing body through positive stimulation.

This points to a new potential method for tackling the negative effects of ageing by imitating the enrichment and activation of butyrate.

"We can conceive of future human studies where we would test the ability of food products with butyrate to support healthy ageing and adult neurogenesis," said Prof Pettersson.

"In Singapore, with its strong food culture, exploring the use of food to 'heal' ourselves, would be an intriguing next step, and the results could be important in Singapore's quest to support healthy ageing for their silver generation."

Group leader Dr Dario Riccardo Valenzano at the Max Planck Institute for Biology of Ageing in Germany, who was not involved in the study, said the discovery is a milestone in research on microbiome.

"These results are exciting and raise several new open questions for both biology of aging and microbiome research, including whether there is an active acquisition of butyrate producing microbes during mice life and whether extreme aging leads to a loss of this fundamental microbial community, which may be eventually responsible for dysbiosis and age-related dysfunctions," he added.

Professor Brian Kennedy, Director of the Centre for Healthy Ageing at the National University of Singapore, who provided an independent view, said, "It is intriguing that the microbiome of an aged animal can promote youthful phenotypes in a young recipient. This suggests that the microbiota with aging have been modified to compensate for the accumulating deficits of the host and leads to the question of whether the microbiome from a young animal would have greater or less effects on a young host. The findings move forward our understanding of the relationship between the microbiome and its host during ageing and set the stage for the development of microbiome-related interventions to promote healthy longevity."

The study builds on Prof Pettersson's earlier studies on how transplantation of gut microbes from healthy mice can restore muscle growth and function in germ-free mice with muscle atrophy, which is the loss of skeletal muscle mass.

Story Source:

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

Journal Reference:

1. Parag Kundu, Hae Ung Lee, Isabel Garcia-Perez, Emmy Xue Yun Tay, Hyejin Kim, Llanto Elma Faylon, Katherine A. Martin, Rikky Purbojati, Daniela I. Drautz-Moses, Sujoy Ghosh, Jeremy K. Nicholson, Stephan Schuster, Elaine Holmes, Sven Pettersson. **Neurogenesis and prolongevity signaling in young germ-free mice transplanted with the gut microbiota of old mice**. *Science Translational Medicine*, 2019; 11 (518): eaau4760 DOI: 10.1126/scitranslmed.aau4760

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Nanyang Technological University. "Bacteria in the gut may alter aging process." ScienceDaily. ScienceDaily, 14 November 2019. <www.sciencedaily.com/releases/2019/11/191114103128.htm>.

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8. あまり知られていないタンパク質が、肥満と代謝疾患において重要な役割を果たすようだ

Scripps Research の科学者らは、脂肪組織で高度に発現されるタンパク質に関する予期しない発見によって、肥満と代謝に関する重要な新しい理解への扉を開いた。*Nature* 誌に 11 月 20 日に掲載された彼らの発見は、肥満や他の多くの病気に対処するための新しいアプローチにつながる可能性がある。
PGRMC2 として知られるシグナル伝達タンパク質は、これまであまり広く研究されてこなかった。「プロゲステロン受容体膜成分 2」の略で、子宮、肝臓、および身体のいくつかの領域で検出されていた。しかし、今回 Enrique Saez 博士の研究室は、PGRMC2 が脂肪組織、特に食物を熱に変えて体温を維持する褐色脂肪内で最も豊富であることを知り、そこでの機能に興味を持った。
チームは、PGRMC2 がヘムと呼ばれる必須分子に結合してヘムを放出するという最近の発見に基づいて、遊離状態では細胞を害しうる蛋白質ヘムのミトコンドリアから核への細胞内輸送を PGRMC2 が担っていると分かり、その低分子活性化剤は肥満かつ糖尿病マウスの糖尿病病態を改善することを示した。また、PGRMC2 を豊富に宿す褐色脂肪組織は食べた物を熱に変えて体温を維持する働きがあり、PGRMC2 を欠くマウスは寒いところで体温を維持することができなかった、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.eurekalert.org/pub_releases/2019-11/sri-lpa112019.php

NEWS RELEASE 20-NOV-2019

Little-known protein appears to play important role in obesity and metabolic disease

The recently discovered protein is normally abundant in fat; without it, the body struggles to manage glucose and insulin

SCRIPPS RESEARCH INSTITUTE

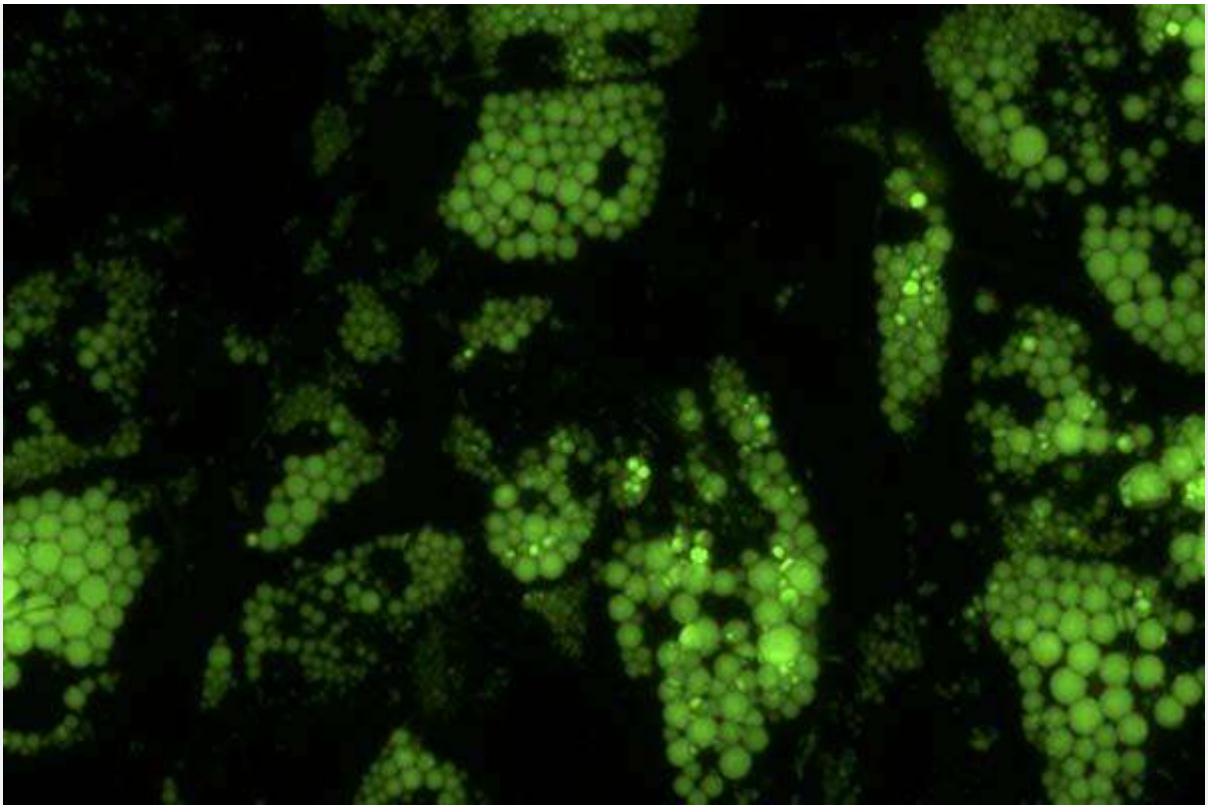

IMAGE: Healthy brown fat cells (shown in green) require ample amounts of a molecule called heme, which enables the body to metabolize food properly. The Saez laboratory at Scripps Research has... **view more**

Credit: Scripps Research

LA JOLLA, CA - With unexpected findings about a protein that's highly expressed in fat tissue, scientists at Scripps Research have opened the door to critical new understandings about obesity and metabolism. Their discovery, which appears Nov. 20 in the journal *Nature*, could lead to new approaches for addressing obesity and potentially many other diseases.

The signaling protein, known as PGRMC2, had not been extensively studied in the past. Short for "progesterone receptor membrane component 2," it had been detected in the uterus, liver and several areas of the body. But the lab of Enrique Saez, PhD, saw that it was most abundant in fat tissue--particularly in brown fat, which turns food into heat to maintain body temperature--and became interested in its function there.

An important role: heme's travel guide

The team built on their recent discovery that PGRMC2 binds to and releases an essential molecule called heme. Recently in the spotlight for its role in providing flavor to the plant-based Impossible Burger, heme holds a much more significant role in the body. The iron-containing molecule travels within cells to enable crucial life processes such as cellular respiration, cell proliferation, cell death and circadian rhythms.

Using biochemical techniques and advanced assays in cells, Saez and his team found that PGRMC2 is a "chaperone" of heme, encapsulating the molecule and transporting it from the cell's mitochondria, where heme is created, to the nucleus, where it helps carry out important functions. Without a protective chaperone, heme would react with--and destroy--everything in its path.

"Heme's significance to many cellular processes has been known for a long time," says Saez, associate professor in the Department of Molecular Medicine. "But we also knew that heme is toxic to the cellular materials around it and would need some sort of shuttling pathway. Until now, there were many hypotheses, but the proteins that traffic heme had not been identified."

An innovative approach for obesity?

Through studies involving mice, the scientists established PGRMC2 as the first intracellular heme chaperone to be described in mammals. However, they didn't stop there; they sought to find out what happens in the body if this protein doesn't exist to transport heme.

And that's how they made their next big discovery: Without PGRMC2 present in their fat tissues, mice that were fed a high-fat diet became intolerant to glucose and insensitive to insulin--hallmark symptoms of diabetes and other metabolic diseases. By contrast, obese-diabetic mice that were treated with a drug to activate PGRMC2 function showed a substantial improvement of symptoms associated with diabetes.

"We saw the mice get better, becoming more glucose tolerant and less resistant to insulin," Saez says. "Our findings suggest that modulating PGRMC2 activity in fat tissue may be a useful pharmacological approach for reverting some of the serious health effects of obesity."

The team also evaluated how the protein changes other functions of brown and white fat, says the study's lead author, Andrea Galmozzi, PhD. "The first surprise finding was that the brown fat looked white," he says.

Brown fat, which is normally the highest in heme content, is often considered the "good fat." One of its key roles is to generate heat to maintain body temperature. Among mice that were unable to produce PGRMC2 in their fat tissues, temperatures dropped quickly when placed in a cold environment.

"Even though their brain was sending the right signals to turn on the heat, the mice were unable to defend their body temperature," Galmozzi says. "Without heme, you get mitochondrial dysfunction and the cell has no means to burn energy to generate heat."

Saez believes it's possible that activating the heme chaperone in other organs--including the liver, where a large amount of heme is made--could help mitigate the effects of other metabolic disorders such as non-alcoholic steatohepatitis (NASH), which is a major cause of liver transplantation today.

"We're curious to know whether this protein performs the same role in other tissues where we see defects in heme that result in disease" Saez says.

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Authors of the study, "PGRMC2 is an intracellular heme chaperone critical for adipocyte function," include Andrea Galmozzi, Bernard P. Kok, Arthur S. Kim, J. Rafael Montenegro-Burke, Jae Y. Lee, Roberto Spreafico, Sarah Mosure, Verena Albert, Rigo Cintron-Colon, Cristina Godio, William R. Webb, Bruno Conti1, Laura A. Solt, Douglas Kojetin, Christopher G. Parker, John J. Peluso, James K. Pru, Gary Siuzdak, Benjamin F. Cravatt and Enrique Saez.

The work was supported by National Institutes of Health grants (DK099810, DK114785, DK121196, S10OD016357, OD016564). Two of the researchers, Kok and Albert, also were supported by fellowships from the American Heart Association.

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9. Mount Sinai の研究者らがパーキンソン病の分子ドライバーを発見

アイカーン医科大学（Icahn School of Medicine at Mount Sinai –ニューヨーク市）の科学者らは、マルチスケール遺伝子ネットワーク解析（MGNA）と呼ばれる高度な統計手法を使用して、パーキンソン病の新しい分子ドライバーを発見した。また、チームは、これらの分子ドライバーが疾患に関与する遺伝子の機能にどのように影響するかを決定することにも成功した。新しい治療法の可能性を示唆する結果が本日の *Nature Communications* 誌で発表されている。
パーキンソン病のいくつかの症例は、遺伝子変異によって直接引き起こされるが、これらの症例はまれで、その約 80%は原因が不明であり、個人の疾患発症リスクをわずかに増加させる可能性のある遺伝子もあるが、これらの遺伝子の生物学的影響は不明のままである。今回、元々アルツハイマー病の分子機構を調べるのに開発された統計手法 MGNA を用いた解析で、パーキンソン病転写網主軸遺伝子 STMN2 が見付かり、マウス脳の STMN2 を抑制するとパーキンソン病様の病態・ドーパミン神経変性、リン酸化 α シヌクレイン増加、運動障害が発現した。
解析では、STMN2 はシナプス輸送に携わると推定され、マウスのドーパミン神経の STMN2 抑制でその推定の正しさが確認された。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.eurekalert.org/pub_releases/2019-11/tmsh-msr111519.php

NEWS RELEASE 20-NOV-2019

Mount Sinai researchers uncover new molecular drivers of Parkinson's disease

New approach will lead to a better understanding of most cases

THE MOUNT SINAI HOSPITAL / MOUNT SINAI SCHOOL OF MEDICINE

Scientists at the Icahn School of Medicine at Mount Sinai have uncovered new molecular drivers of Parkinson's disease using a sophisticated statistical technique called multiscale gene network analysis (MGNA). The team was also able to determine how these molecular drivers impact the functions of genes involved in the disease. The results, which may point to potential new treatments, were published today in *Nature Communications*.

Some cases of Parkinson's are directly caused by genetic mutations, but these cases are rare. Approximately 80 percent of cases have no known cause, and though there are some genes that may

slightly increase an individual's risk of developing the disease, the biological impacts of these genes remain unclear.

"This study offers a novel approach to understanding the majority of cases of Parkinson's," said Bin Zhang, PhD, Professor of Genetics and Genomic Sciences at the Icahn Institute for Data Science and Genomic Technology and Director of the Mount Sinai Center for Transformative Disease Modeling at the Icahn School of Medicine at Mount Sinai. "The strategy not only reveals new drivers, but it also elucidates the functional context of the known Parkinson's disease risk factor genes."

Dr. Zhang and his team originally developed the MGNA method to research the molecular mechanisms of Alzheimer's disease. Since that study was published about six years ago, they have significantly improved the technique through funding from the National Institutes of Health (NIH)/National Institute on Aging (NIA) Accelerating Medicines Partnership - Alzheimer's Disease (https://www.nia.nih.gov/research/amp-ad) (AMP-AD) program and have applied it to a variety of complex diseases from Alzheimer's to cancer. The strategy takes into account genetic, epigenetic, transcriptomic, pathological, and clinical data from a large pool of tissue samples and identifies links between them.

"This multiscale network analysis approach is a powerful way to dissect the molecular mechanisms of complex diseases like Alzheimer's," said Suzana Petanceska, PhD, program director of the AMP-AD Target Discovery program at the NIA, which co-funded the study. "It is exciting to see that AMP-AD can provide new mechanistic insights to Parkinson's disease that could lead to new therapeutic opportunities."

Unfortunately, there are no gene expression data sets based on a sufficiently large number of informative brain samples from Parkinson's patients for the powerful MGNA to be effective. Instead, the researchers combined data from eight different studies that included postmortem analyses of the substantia nigra--the part of the brain most affected by Parkinson's disease. This gave the team a larger dataset from a total of 83 patients, which they then compared to 70 controls who did not have Parkinson's.

Applying MGNA to the combined data set, the scientists identified a number of key regulators of the gene networks that had never before been associated with the disease.

Next, they teamed up with Zhenyu Yue, PhD, Professor of Neurology and Neuroscience at the Icahn School of Medicine and the Director of Basic and Translational Research in Movement Disorders, whose work is supported by NIH Udall Centers of Excellence for Parkinson's Disease Research, to experimentally validate the findings in mice. They chose to test the effects of STMN2, a gene that the analysis identified as a key regulator of the Parkinson's molecular network. The gene is normally expressed in neurons that produce dopamine, a neurotransmitter that is depleted in the substantia nigra of Parkinson's patients.

To test its influence on Parkinson's disease, Dr. Yue and his team knocked down the STMN2 gene in the substantia nigra of the mice. RNA sequencing showed that reduction of STMN2 led to upregulation of nine genes that had previously been associated with the disease. The mice developed Parkinson's-like pathologies such as degeneration of dopaminergic neurons in the substantia nigra and an increase in the concentration of the toxic, modified α-synuclein protein, both of which are considered hallmarks of the disease. Additionally, the mice struggled with motor tasks such as maintaining balance on a rod, indicative of the disruption of their motor function control.

Despite the fact that the team was able to create a large enough sample size to apply the multiscale network analysis, the researchers emphasized that 83 patients is still a relatively small number and the results should be validated in larger studies. Still, "The work opens up a new avenue for studying the disease," said Dr. Yue. "The new genes we identified suggest that new pathways should be considered as potential targets for drug development, particularly for idiopathic Parkinson's cases."

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This study was supported in part by NIH grants U01AG046170, RF1AG057440, R01NS060809 and P50NS094733.

About the Mount Sinai Health System

The Mount Sinai Health System is New York City's largest integrated delivery system, encompassing eight hospitals, a leading medical school, and a vast network of ambulatory practices throughout the greater New York region. Mount Sinai's vision is to produce the safest care, the highest quality, the highest satisfaction, the best access and the best value of any health system in the nation. The Health System includes approximately 7,480 primary and specialty care physicians; 11 joint-venture ambulatory surgery centers; more than 410 ambulatory practices throughout the five boroughs of New York City, Westchester, Long Island, and Florida; and 31 affiliated community health centers. The Icahn School of Medicine is one of three medical schools that have earned distinction by multiple indicators: ranked in the top 20 by U.S. News & World Report's "Best Medical Schools", aligned with a U.S. News & World Report's "Honor Roll" Hospital, No. 12 in the nation for National Institutes of Health funding, and among the top 10 most innovative research institutions as ranked by the journal Nature in its Nature Innovation Index. This reflects a special level of excellence in education, clinical practice, and research. The Mount Sinai Hospital is ranked No. 14 on U.S. News & World Report's "Honor Roll" of top U.S. hospitals; it is one of the nation's top 20 hospitals in Cardiology/Heart Surgery, Diabetes/Endocrinology, Gastroenterology/GI Surgery, Geriatrics, Gynecology, Nephrology, Neurology/Neurosurgery, and Orthopedics in the 2019-2020 "Best Hospitals" issue. Mount Sinai's Kravis Children's Hospital also is ranked nationally in five out of ten pediatric specialties by U.S. News & World Report. The New York Eye and Ear Infirmary of Mount Sinai is ranked 12th nationally for Ophthalmology and the South Nassau Communities Hospital is ranked 35th nationally for Urology. Mount Sinai Beth Israel, Mount Sinai St. Luke's, Mount Sinai West, and South Nassau

Communities Hospital are ranked regionally. For more information, visit https://www.mountsinai.org or find Mount Sinai on Facebook, Twitter and YouTube.

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10. CAGE が脂肪を閉じ込めて肥満を治療する

ハーバード大学の Wyss Institute for Biologically Inspired Engineering と John A. Paulson School for Engineering and Applied Science (SEAS) による新しい研究によると、新しい液体(経口投与)が副作用を引き起こすことなく高脂肪食を与えられたラットの体重を減らし、これが今後可能な肥満治療法を指摘するものだ、としている。
FDA は過去数十年間で体重を約 10%減らすいくつかの薬を承認したが、それらの薬には頭痛、下痢、重度の肝障害、先天異常、睡眠時無呼吸、膵炎、自殺念慮などの重大な副作用がある。
Wyss Institute と SEAS によって作成されたコリンとゼラネート、または CAGE と呼ばれる経口投与された液体塩は、ラットで認識できる副作用なしに、食物からの脂肪の吸収を物理的に制限し、総体重を約 12 パーセント減らす。この研究は PNAS(米国科学アカデミー紀要)で報告されている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://news.harvard.edu/gazette/story/2019/11/liquid-salt-can-reduce-fat-absorption-and-weight-in-rats/

Health & Medicine

CAGEs lock up fats to treat obesity

CAGE can physically limit the absorption of fats from food with no discernable side effects in rats, and reduce total body weight by about 12 percent.

Sonsedska/iStock

Orally administered liquid salt helps prevent fat absorption, slow weight gain in rats

BY Lindsay Brownell Wyss Institute Communications
DATE November 25, 2019

A new, orally administered liquid reduces weight in rats fed high-fat diets without causing side effects, pointing to a possible therapy for obesity, according to a new study from Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School for Engineering and Applied Sciences (SEAS)

Although the FDA has approved several drugs that reduce weight by about 10 percent over the last few decades, those drugs have come with significant side effects, including headaches, diarrhea, severe liver injury, birth defects, sleep apnea, pancreatitis, and suicidal thoughts.

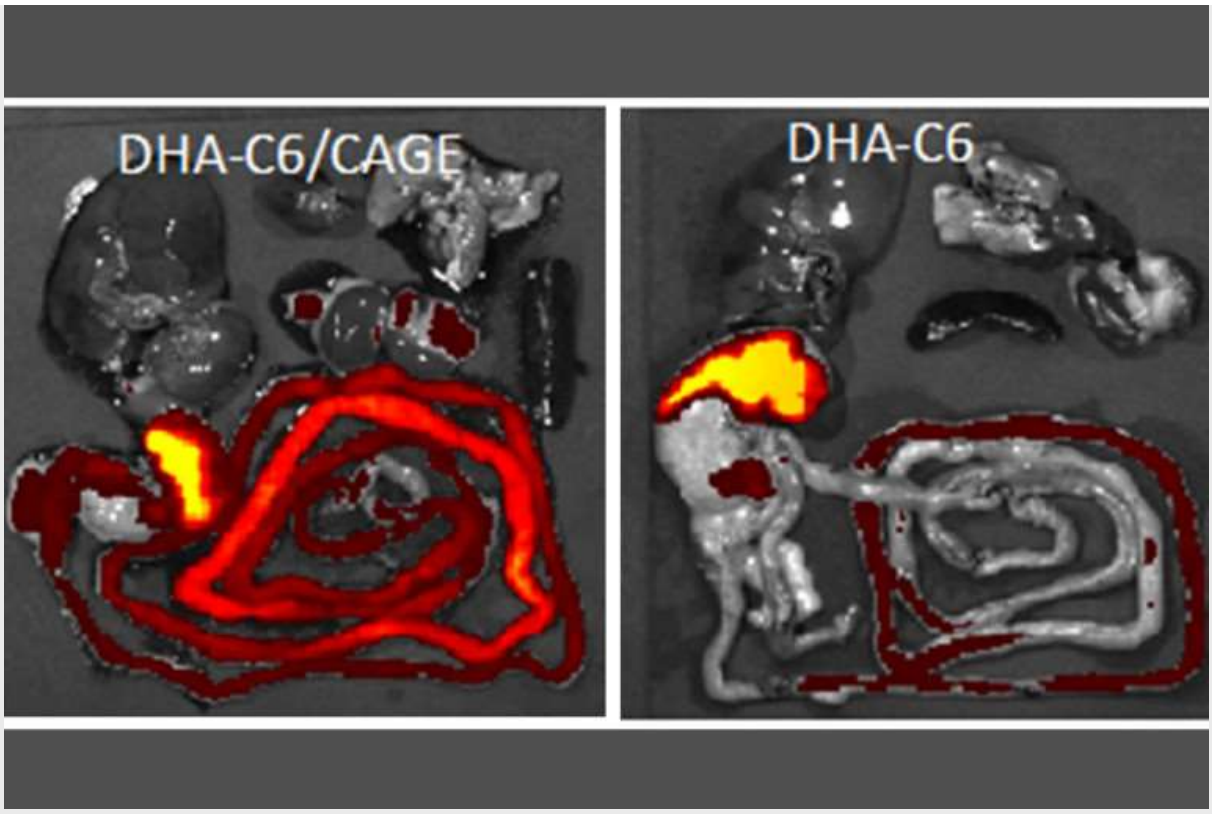
The orally administered liquid salt created by the Wyss Institute and SEAS, called choline and geranate, or CAGE, can physically limit the absorption of fats from food with no discernable side effects in rats, and reduce total body weight by about 12 percent. The research is reported in PNAS.

"A reduction in body weight of 12 percent is like getting a human from 200 pounds down to 176, which is a significant change," said first author Md Nurunnabi, a former postdoctoral fellow at the Wyss Institute and SEAS who is now an assistant professor of pharmaceutical sciences at the University of Texas, El Paso. "Our goal is to translate this work into a product that can help people maintain a healthier weight, and this study marks the very beginning of that journey."

TURNING A BUG INTO A FEATURE

CAGE, which is a salt in its liquid state, was created a few years ago by Wyss core faculty member Samir Mitragotri as part of an effort to improve the body's absorption of medicines. Last year, his lab published

a paper describing CAGE's ability to enhance the uptake of insulin when given orally. However, in their study of CAGE's properties, they found that one small hydrophobic molecule was not helped by the liquid. Mitragotri's team had a hunch that CAGE was somehow binding to this molecule and preventing it from being absorbed.



When the fat DHA is given to rats alone (right), it concentrates in their livers. The addition of the CAGE liquid causes much more of the DHA to remain in the stomach and intestine (left), suggesting that CAGE helps prevent the absorption of fats by the body.

Credit: Wyss Institute at Harvard University

"That observation led us to wonder if there were any contexts in which we would want to prevent the uptake of this type of molecule. We realized that fats are small and hydrophobic, and that CAGE could potentially be of interest as a medical treatment for obesity," said Mitragotri, who is also the Hiller Professor of Bioengineering and Hansjörg Wyss Professor of Biologically Inspired Engineering at SEAS.

The researchers got to work evaluating CAGE's interactions with fats by mixing the liquid with an omega-3 fat called DHA and water. They saw that the DHA formed large particles about 3–4 microns in length, about the size of a cell's nucleus. DHA molecules mixed with water alone

formed much smaller particles, in the range of 50–400 nanometers, suggesting that there is some interaction between the CAGE and DHA molecules that causes them to aggregate into larger particles.

The team then added the DHA-CAGE mixture to healthy rat intestines *ex vivo*. Compared with intestines that were injected with DHA only, the inclusion of CAGE significantly reduced the permeation of DHA into the intestinal tissue over the course of six hours.

HELPING RATS RESIST OBESITY

To evaluate the performance of CAGE in living organisms, the researchers prepared capsules with a mixture of DHA and CAGE and gave them orally to rats. After six hours, the amount of DHA absorbed into their blood from the mixture was about half the amount that was absorbed when they were given DHA alone. Biodistribution studies showed that giving CAGE along with the DHA increased its concentration in the rats' stomachs and intestines twofold and reduced its presence in their livers, suggesting that CAGE prevents DHA from leaving the gastrointestinal tract.

They then studied the effect of CAGE on fat uptake in rats fed a high-fat diet, which has 20 percent more fat than a regular diet, for 30 days. A daily, 10-microliter dose of CAGE caused rats to gain 12 percent less weight than rats that received either a 5-microliter dose or no CAGE. The untreated rats usually ate about 10 grams of food every day, whereas the high-dose CAGE cohort ate about 8 grams of food, suggesting that CAGE might also have an effect on enzymes that regulate digestion, and/or increase the feeling of fullness after a meal.

> "A reduction in [a rat's] body weight of 12 percent is like getting a human from 200 pounds down to 176, which is a significant change."
>
> — Md Nurunnabi

Importantly, over the 30-day time period, no side effects were observed in the rats treated with CAGE, and there were no signs of inflammation or differences in the animals' organ structure or function. There was also no trace of CAGE's components in the body following treatment.

"This is the first proof of concept that orally administered ionic liquids can help reduce fat uptake and body mass, and this approach has significant clinical potential given that it is simple, fast, and much less invasive than liposuction or bariatric surgery and, because its mechanism of action is physical rather than chemical, it lacks the side effects observed with other drugs," said Mitragotri.

The team is now pursuing answers to the more mechanistic questions about CAGE, including exactly how CAGE binds to fats, how long its effects last, what its potential interactions with the obesity-associated leptin signaling pathway are, and where the unabsorbed fat goes.

"This study is a perfect example of the potentially transformative innovations that can come from looking at an unexpected result in the lab as a solution rather than a problem. We love simple solutions here at the Wyss Institute," said Wyss Founding Director Donald Ingber, who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, as well as professor of bioengineering at SEAS.

Additional authors of the study are Kelly Ibsen, a former postdoctoral fellow in the Mitragotri lab, and Eden Tanner, a current postdoctoral fellow.

The research was supported by Harvard SEAS.
