Bio News – January, 2021

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

12/2　Pfizer-BioNTech のワクチン、英国が承認－米・EUに先駆け

12/2　「半年後も感染を防ぐ抗体、コロナ感染者の 98%に」海外の研究報告を覆す結果 横浜市立大

横浜市大は 2 月から 5 月に感染した 376 人を対象に、「中和抗体」という感染や重症化を防ぐ抗体が回復後もいつまで体内に残っているかを調査した。その結果、重症や中等症の人は 100%、軽症や無症状は 97%、平均して全体の 98%の人に半年後も「中和抗体」が残っていたということだ。これまで海外からは「抗体は早い段階で消える」などの研究報告があったが、今回の調査結果はこれを覆す形となった。ただ、中和抗体があっても感染する恐れがゼロになる訳ではなく、横浜市大はマスクなどの対策は続ける必要があるとしている。

12/2　米国が新型コロナウイルス感染者の隔離期間の短縮を検討中

12/3　COVID-19 接触者の隔離は検査陰性で無症状なら 7 日間でよいとの方針を米国が発表

新型コロナウイルス感染者と接触した人の隔離期間は検査結果が陰性でずっと無症状なら 7 日間、検査なしでずっと無症状なら 10 日間でよいとの方針を米国が示した。
また、年末の休日を前に国内の旅行については、自分や他人が感染しないように家に居ることが要請されているものの、旅立つならその 1-3 日前と戻ってから 3-5 日に COVID-19 検査を受けることを要求している。
帰宅後は検査で陰性でも 7 日間は後回しにできる活動を慎む必要があり、無検査なら 10 日間はそうしなければならない、としている。

12/3　Merck & Co が Moderna 株式を売却

新型コロナウイルス感染症ワクチン開発とその成功で今年に入って 7 倍ほど上昇している Moderna の株式を Merck & Co が売却。

12/3　感染疑い、喉の血管で把握へ　新型コロナ、検査機器試作　順大

12/4　米国感染症首脳 Fauci 氏が英国の AstraZeneca 製 COVID-19 ワクチン承認を怪しんだことを BBC のインタビューで謝罪

12/4　Moderna の COVID-19 ワクチンへの抗体反応が 1 回目投与から 4 か月時点で持続

12/5　WHO、英国のワクチン承認を歓迎　楽観論にはクギ刺す

新型コロナウイルスのワクチンが英国で承認されたことを受け、世界保健機関（WHO）のテドロス・アダノム事務局長は 4 日の記者会見で「科学の重要な一歩だ」と歓迎した。一方で、「パンデミック（世界的大流行）は終わったとの認識が広がっていることを心配している」とも述べ、楽観論にクギを刺した。

12/6　中国、「ワクチン外交」積極展開　安全性懸念くすぶる

既に 5 種類が臨床試験（治験）の最終段階にあり、一部は年内にも承認される見通し。中国政府は新興国への優先供給を掲げて「ワクチン外交」を積極的に展開するが、承認前から広範な緊急使用に踏み切っており、安全性への懸念もくすぶる。最終段階に差し掛かっているのは、中国医薬集団（シノファーム）や科興控股生物技術（シノバック・バイオテック）などのワクチン。

12/6　ロシア　国産ワクチン「スプートニク V」の大規模接種始まる

12/8　うつ病の脳の特徴、AI で見分ける

うつ病の脳活動の特徴を、国際電気通信基礎技術研究所（ATR、京都府精華町）などの研究チームが人工知能（AI）技術を使って見つけた。脳活動を数値化してうつ病の診断を補助する指標として使えるようにした。米科学誌プロス・バイオロジーに 8 日、発表した。

12/9　AstraZeneca の COVID-19 ワクチンの効果 70%の Ph3 途中解析が論文報告された

12/9　Pfizer/BioNTech の COVID-19 ワクチンは 1 回目投与からすぐに効果を発揮しうる

10 日開催の米国 FDA 諮問委員会に先立って公開された資料によると、Pfizer/BioNTech の 2 回投与の新型コロナウイルス感染症ワクチン BNT162b2 の予防効果は 1 回目投与からすぐに期待できる模様。また、BNT162b2 の効果は年齢や人種/民族を問わず認められ、肥満の人にもそうでない人にも有効であった。

https://www.jwatch.org/fw117305/2020/12/08/covid-19-pfizer-vaccine-astrazeneca-vaccine-healthcare

12/10　インドが AstraZeneca の COVID-19 ワクチン承認を却下/Reuters

12/10　カナダが Pfizer/BioNTech の COVID-19 ワクチンを承認

12/10　アルツハイマー病に関する Biogen と FDA の不適切な関係の調査を消費者保護団体 Public Citizen が要求

12/10　重いアレルギー反応経験者は COVID-19 ワクチンを控えることを英国が要請

12/11　Pfizer/BioNTech のワクチンが COVID-19 発症の 95%を防いだ Ph3 結果論文報告

Pfizer and BioNTech Announce Publication of Results from Landmark Phase 3 Trial of BNT162b2 COVID-19 Vaccine Candidate in –The New England Journal of Medicine

https://www.businesswire.com/news/home/20201210005703/en/

12/11　Pfizer の COVID-19 ワクチンの欧州承認申請資料がサイバー攻撃で引き出された

12/12　ゲノム編集食品 進む実用化

遺伝情報を自在に改変するゲノム編集技術で開発された食品が来年に登場する見通しとなった。第1号として血圧の上昇を抑える「GABA（ギャバ）」という物質を豊富に含むトマトの流通・販売を厚生労働省の調査会が11日、了承した。穀物や魚でも開発が進んでおり、実用化の動きが広がりそうだ。開発中の主なゲノム編集食品は：イネ、ジャガイモ、マダイ、マグロ、など

12/12　FDA が Pfizer 製ワクチンに緊急使用許可　近く接種開始へ　新型コロナ

米食品医薬品局（FDA）は 11 日、米製薬大手ファイザーの新型コロナウイルスワクチンに緊急使用許可を出した。米国でのコロナワクチンの許可は初めて。感染者、死者数ともに世界最多の米国が、コロナ禍の収束に向け大きく前進。ファイザーに続き、米バイオ医薬品企業モデルナのワクチンも、17 日に FDA の諮問委員会が緊急使用の可否を審議する。英アストラゼネカや米ジョンソン・エンド・ジョンソンなども、臨床試験（治験）の最終段階に入っている。

12/12　Sanofi/GSK の蛋白質成分の COVID-19 ワクチンの開発が遅れる

Sanofi/GlaxoSmithKline（GSK）の蛋白質成分の新型コロナウイルス感染症予防ワクチンの第 1/2 相試験で 50 歳以上高齢成人の免疫反応が今ひとつだったため抗原成分の濃度の練り直しが必要となり、開発が遅れる。
濃度を改めた抗原の Ph2b 試験が来年 2 月に始まり、うまくいけば来年 2Q に第 3 相試験が始まり、Ph3 が成功すれば来年後半には認可申請に漕ぎ着け、見通し通り認可申請できたら来年中には使えるようになりうると両社は見込んでいる。

12/14　てんかん性脳症、発症の仕組み解明　九州大助教ら治療薬の研究も検討

12/14　コロナ感染者の 5 人に 1 人が 90 日以内に精神疾患を発症。オックスフォード大学ら、6,900 万人調査結果を発表

12/15　フィンランドの Oura 製の指輪が絶えず測った皮膚温の上昇と COVID-19 が関連

12/15　取り急ぎ認可された COVID-19 ワクチンは接種したくないと米国人の半数超が回答

12/16　AbbVie がオランダのユトレヒト大学が見つけた新型コロナウイルス中和抗体を取得決定

12/16　自宅でできる処方不要の店頭販売 COVID-19 抗原検査を米国 FDA が許可

12/16　Moderna の COVID-19 ワクチンの試験結果詳細を FDA が公表～顔面麻痺が心配

12/16　ミツバチ、動物のふん塗ってスズメバチを撃退 -米研究

アジアに生息するミツバチは、どう猛で大型のスズメバチによる攻撃を阻止するために、鶏や水牛のふんや人間の尿までをも採集して巣の入り口の周りに塗り付けることを、米ウェルズリー大学（Wellesley College）科学者らが発見。この事象に関する論文を 9 日の米科学誌「プロスワン（PLOS ONE）」で発表。

12/17　武田薬品の好酸球性食道炎（EoE）治療薬 Eohilia を FDA が優先審査中

12/17　塩野義製薬が COVID-19 蛋白質ワクチンの国内臨床試験開始

12/17　卵子を作る遺伝子特定　九大研究チーム、短時間で大量作製が可能に

12/18　Novartis が神経精神疾患薬の Cadent Therapeutics (Cambridge, MA) を買収

12/18　Moderna の COVID-19 ワクチンを取り急ぎ認可することを FDA 諮問委員会が支持

12/18　スパイク蛋白質 N501Y 変異新型コロナウイルスが英国で急速に広まっている

12/19　Google と同じ Alphabet を親会社とする Verily が COVID-19 の波に乗って 7 億ドル調達

今年に入って 351 箇所で 200 万人近くに新型コロナウイルス感染（COVID-19）検査を提供した臨床試験被験者登録事業 Baseline や出向かずとも診てもらえる通信医療（virtual clinic）事業 Onduo などの販売を増やすための資金 7 億ドルを Google と同じ Alphabet を親会社とする Verily が調達した。

12/19　新たな新型コロナウイルス変種が感染を増やしているらしいと英国首相が発表

12/19　血液で乳がん発見、臨床試験へ -国立がん研究センター

12/19　米 2 例目の Moderna コロナワクチン許可　数日中に接種

数日中に全米に最初の 590 万回分を発送、接種が始まる。米国で新型コロナワクチンが実用化するのは 2 例目。1 人につき約 1 カ月間隔で 2 回接種する。日本政府は 5 千万回分（2,500 万人分）の供給を受ける契約をモデルナと交わしている。

12/19　大日本住友製薬が大部分を所有する Myovant Sciences (Brisbane, CA) の前立腺癌薬を FDA が承認

12/21　新型コロナウイルス感染から 3 か月も過ぎた患者の半数の小腸からウイルス検出

12/21　南アフリカの 2 回目の COVID-19 流行を後押ししているらしい変異種が同定された

12/21　オランダ Philips がウェアラブル心臓モニターの BioTelemetry (Malvern, PA) を 28 億ドルで買収

12/22　Pfizer/BioNTech の COVID-19 ワクチン COMIRNATY（BNT162b2）を欧州が承認

12/22　Agios (Cambridge, MA) が抗癌剤事業をフランス Servier に 18 億ドルで売却

12/23　南アフリカで広まる新型コロナウイルス N501Y 変異種は英国とは独立して発生

CNN によると Pfizer, BioNTech, Moderna はそれらのワクチンの VUI 202012/01 への効果の検討に着手している。

12/23　武田薬品が中国の非主力医薬品一揃いを 3 億 2,200 万ドルで中国 Hasten Biopharmaceutic に売却

Japan's Takeda Sells Five Prescription Drugs to China's Hasten for $322 Million - Caixin Global

12/23　「英国のコロナ変異株は感染力が最大 7 割増加、監視強化を」国立感染研が見解

12/24　Moderna の COVID-19 ワクチンをカナダが承認～米国では FedEx が出荷開始

12/25　コロナ変異種、英から入国した 5 人が感染　日本国内初確認

12/28　Novavax の COVID-19 ワクチンの米国とメキシコでの第 3 相試験開始

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. COVID-19 ウイルスがどのようにしてマウスに多臓器不全を引き起こすか

2. 肥満は免疫細胞機能を損ない、腫瘍の成長を促進する -マウス実験

3. ある特定のタンパク質をブロックすることで、老齢マウスが体力と持久力を回復

4. ワクチン研究用のマウスを生成するためのワンステップ法

5. マウスの卵子をかたち作る遺伝子群を同定
   ～卵細胞質の大量作製が可能に～

6. COVID-19 ウイルスは脳に侵入する

7. マウスに制御されたマウスで、脳が意図的な制御をどのように表すかを理解

8. 健康な妊娠を確保する上で忘れられた臓器の重要性

9. 造血幹細胞の老化メカニズムの発見 -マウス実験

1. COVID-19 ウイルスがどのようにしてマウスに多臓器不全を引き起こすか

日付：2020 年 12 月 7 日
ソース：カリフォルニア大学ロサンゼルス校ヘルスサイエンス
概要：

研究者らはしばしばマウスを使って人間の病気の基礎を理解するが、人間の健康状態を動物モデルに変換するのは難しい。例えば、SARS-CoV-2 は、ACE2 タンパク質に依存してヒトに感染するが、ウイルスは ACE2 のマウスバージョンを認識しないため、SARS-CoV-2 ウイルスにさらされた健康なマウスはこの病気には感染しない。
他の研究チームによるこれまでの実験において、マウスは、肺に ACE2 のヒトバージョンを含むように遺伝子操作され、その後、鼻から SARS-CoV-2 ウイルスに感染した。これにより、ウイルスがマウスに感染して肺炎を引き起こす可能性はあるが、これらの実験動物は、人間ほど広範囲の症状を示さない。
ヒトの研究は、SARS-CoV-2 が血流を通って循環して複数の臓器に到達できることを示唆しているため、UCLA の研究者らは最初に、心臓やその他の重要な臓器にヒトバージョンの ACE2 を含むようにマウスを設計した。次に、SARS-CoV-2 を血流に注入すると、動物の半分が感染、これらのモデルを使用して、SARS-CoV-2 ウイルスが心臓、腎臓、脾臓、その他の臓器の細胞でエネルギー生成を停止できることを発見した。
調査結果は COVID-19 の治療に直接的な影響はないとしながらも、研究者らは、ウイルスが肺以外の重要な臓器にどのように感染するかについての進行中の研究や、病気を治療する新薬の試験に役立つ、として「JCI Insight」に発表している。

研究関連ニュース/他のトップページに戻る

＜英文＞Scientists discover how COVID-19 virus causes multiple organ failure in mice | EurekAlert! Science News

NEWS RELEASE 7-DEC-2020

SCIENTISTS DISCOVER HOW COVID-19 VIRUS CAUSES MULTIPLE ORGAN FAILURE IN MICE

UCLA researchers study the disease's systemic effects

UNIVERSITY OF CALIFORNIA - LOS ANGELES HEALTH SCIENCES

Research News

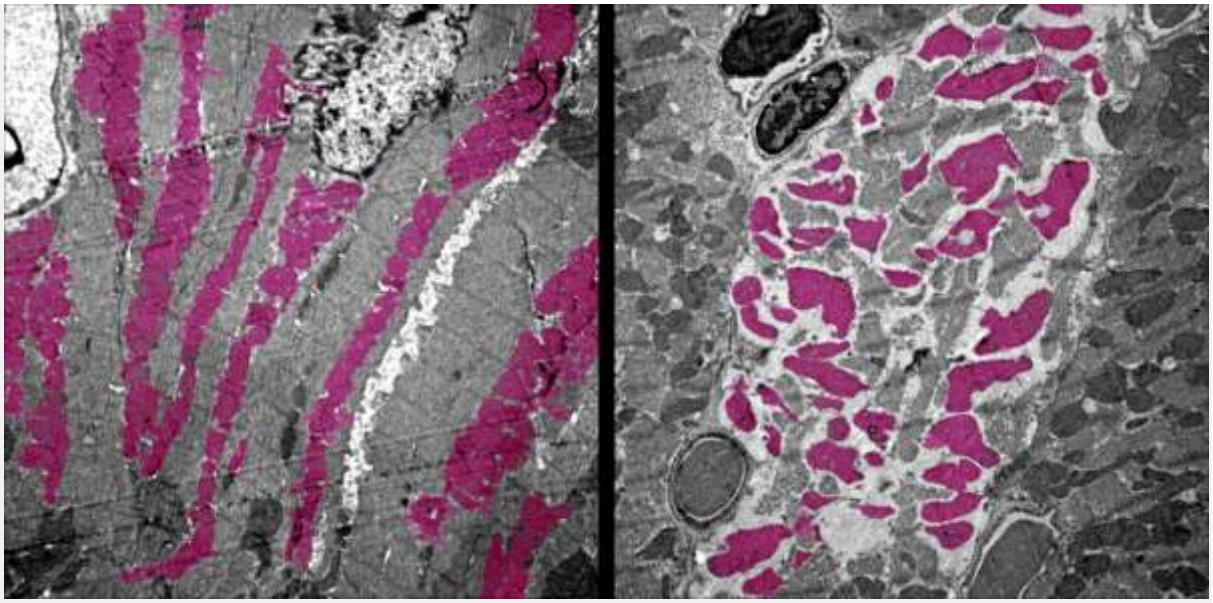

IMAGE: HEART MUSCLE CELLS IN AN UNINFECTED MOUSE (LEFT) AND A MOUSE INFECTED WITH SARS-COV-2 (RIGHT) WITH MITOCHONDRIA SEEN IN PINK. THE DISORGANIZATION OF THE CELLS AND MITOCHONDRIA IN THE IMAGE... **view more**

CREDIT: JCI INSIGHT/UCLA BROAD STEM CELL RESEARCH CENTER

UCLA researchers are the first to create a version of COVID-19 in mice that shows how the disease damages organs other than the lungs. Using their model, the scientists discovered that the SARS-CoV-2 virus can shut down energy production in cells of the heart, kidneys, spleen and other organs.

"This mouse model is a really powerful tool for studying SARS-CoV-2 in a living system," said Dr. Arjun Deb, a co-senior author of a paper about the study and a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. "Understanding how this virus can hijack our cells might eventually lead to new ways to prevent or treat the organ failure that can accompany COVID-19 in humans."

Deb said the same model could also help researchers learn more about other similar viruses that might emerge in the future, and it could be useful for testing eventual treatments.

The paper, published in the journal *JCI Insight*, was co-led by Vaithilingaraja Arumugaswami, an associate professor of molecular and medical pharmacology at the David Geffen School of Medicine at UCLA and a member of the Broad Stem Cell Research Center.

Researchers often study mice to understand the fundamentals of human disease, but translating human health conditions to animal models can be tricky. SARS-CoV-2, for instance, relies on the ACE2 protein to infect humans. But the virus doesn't recognize the mouse version of ACE2, so healthy mice exposed to the SARS-CoV-2 virus don't get sick.

In previous experiments by other research teams around the world, mice have been genetically engineered to have the human version of ACE2 in their lungs and then been infected -- through their noses -- with the SARS-CoV-2 virus. Although that enables the virus to infect the mice and cause pneumonia, animals in those experiments don't get as broad a range of other symptoms as humans do.

"Among COVID-19 patients, those who have organs involved other than the lungs are most at risk of a bad outcome," said Deb, who is also a cardiologist and professor of molecular cell and developmental biology. "So we felt it was really important to understand how the virus affects those other organs."

Research in humans has suggested that SARS-CoV-2 can circulate through the bloodstream to reach multiple organs. So in the UCLA experiment, the researchers first engineered mice to have the human version of ACE2 in the heart and other vital organs. Then, they infected half of the animals by injecting SARS-CoV-2 into their bloodstreams. Over the following days, the researchers tracked the animals' overall health and analyzed how levels of certain genes and proteins in their bodies changed.

Within seven days, all of the mice with COVID-19 had stopped eating and were completely inactive, and had lost, on average, about 20% of their body weight. Animals that had been engineered to carry the human ACE2 protein but had not been infected with the virus, on the other hand, did not lose a significant amount of weight.

Moreover, the COVID-19 infected animals had altered levels of immune cells, swelling of the heart tissue and wasting away of the spleen -- all symptoms that have been observed in people who are critically ill with COVID-19.

Deb's team also looked at which genes were turned on and off in the mice infected with SARS-CoV-2, and they discovered other signs of disease. Common molecular processes that help cells generate energy -- through mechanisms known as the tricarboxylic acid cycle, or TCA cycle, and electron transport chain -- were shut off in the heart, kidney, spleen and lungs.

"If a virus snuffs out the energy-generating pathways in multiple organs of the body, that's going to really wreak havoc," Deb said.

Finally, the study also revealed that some changes were long-lasting throughout the organs in mice with COVID-19. In addition to temporarily altering which genes were turned on and off in some cells, the virus made epigenetic changes -- chemical alterations to the structure of DNA that cause more lasting effects. Deb said that could explain why, in some people with COVID-19, symptoms persist for weeks or months after their bodies are rid of the virus.

Although the findings don't have immediate implications for treating COVID-19, Deb said the mouse model will be useful for ongoing studies on how the virus infects vital organs other than the lungs, and for trials of new drugs to treat the disease.

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The research was supported by the National Institutes of Health, the California Institute for Regenerative Medicine and two UCLA David Geffen School of Medicine-Broad Stem Cell Research Center COVID-19 research awards.

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2. 肥満は免疫細胞機能を損ない、腫瘍の成長を促進する –マウス実験

日付:2020 年 12 月 9 日
ソース:ハーバード大学医学部
概要:

肥満は、12 種類以上の癌のリスク増加、ならびに予後と生存率の低下に関連している。科学者らは何年にもわたって、代謝の変化や慢性炎症など、腫瘍の成長を促進する肥満関連のプロセスを特定してきたものの、肥満と癌の相互作用の詳細な理解ははっきりとできていない。
今回、マウス研究で、ハーバード大学医学部の研究者らは、癌免疫療法に大きな影響を与えるこのパズルの新しい部分を発見した。肥満は、燃料をめぐる戦いで癌細胞が腫瘍を殺す免疫細胞を打ち負かすことを可能にする、としている。
12 月 9 日の「Cell」での報告によると、研究チームは、高脂肪食が癌細胞に代謝を再配線させ、脂肪消費を増加させること、癌細胞は燃料を求めて免疫細胞を打ち負かし、腫瘍内の免疫機能を損なうこと、癌細胞の代謝再配線をブロックすると、抗腫瘍免疫が強化されること、を示している。また、調査結果は、癌の代謝を標的とし、免疫療法を改善するための新しい戦略を示唆するものである、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＞Obesity impairs immune cell function, accelerates tumor growth | EurekAlert! Science News

NEWS RELEASE 9-DEC-2020

OBESITY IMPAIRS IMMUNE CELL FUNCTION, ACCELERATES TUMOR GROWTH

High-fat diet allows cancer cells to outcompete immune cells for fuel

HARVARD MEDICAL SCHOOL

Research News

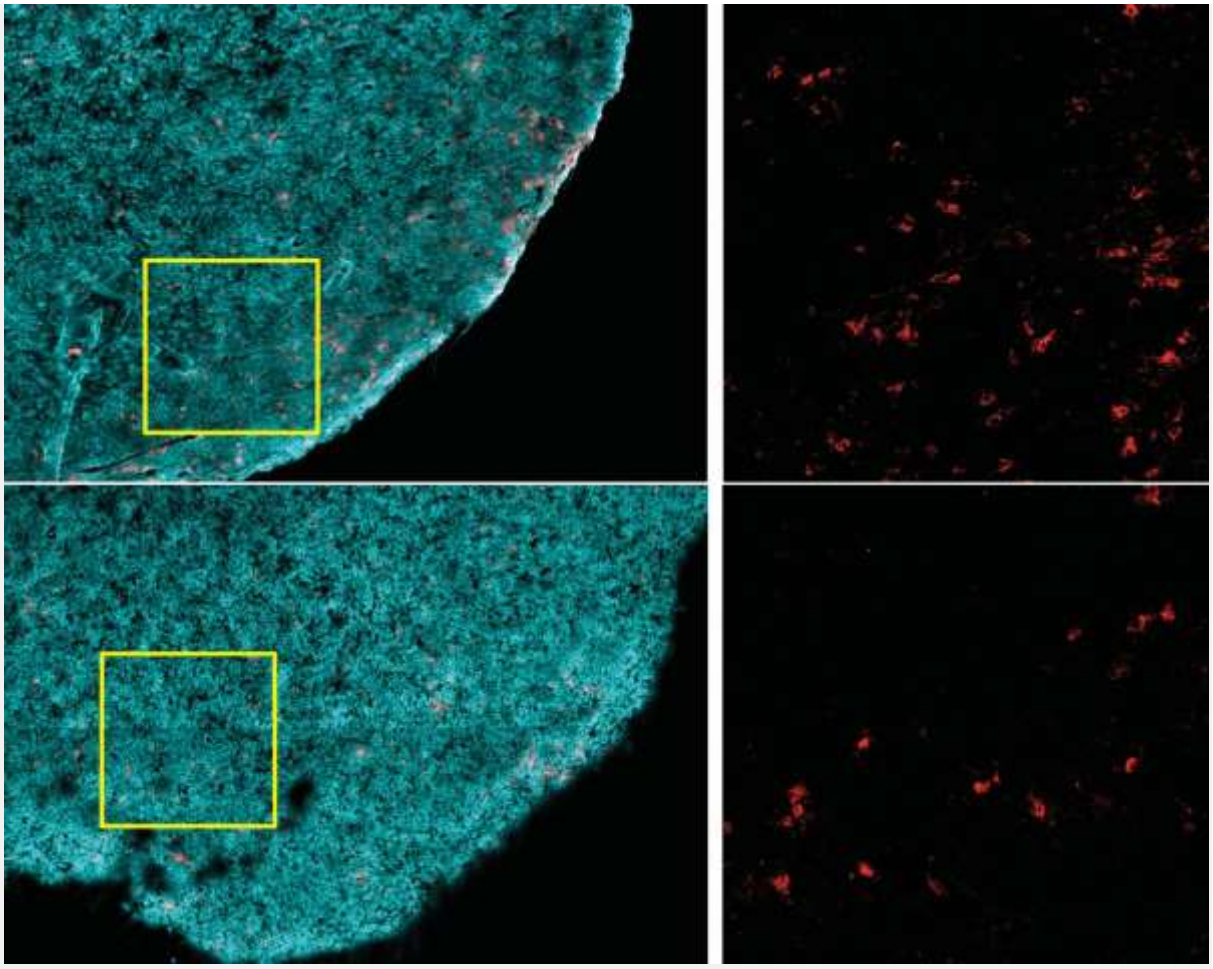

IMAGE: TUMORS FROM A NONOBESE ANIMAL (TOP ROW) CONTAIN MORE CD8+ T CELLS (RED), COMPARED TO THOSE FROM AN OBESE ONE (BOTTOM ROW). TUMOR CELLS ARE HIGHLIGHTED IN CYAN. **view more**

CREDIT: RINGEL ET AL, 2020.

At a glance:

- *High-fat diet causes cancer cells to rewire metabolism, increase fat consumption*
- *Cancer cells outcompete immune cells for fuel, impairing immune function inside tumors*
- *Blocking metabolic rewiring in cancer cells enhances anti-tumor immunity*
- *Findings suggest new strategies to target cancer metabolism, improve immunotherapies*

Obesity has been linked to increased risk for over a dozen different types of cancer, as well as worse prognosis and survival. Over the years, scientists have identified obesity-related processes that drive tumor growth, such as metabolic changes and chronic inflammation, but a detailed understanding of the interplay between obesity and cancer has remained elusive.

Now, in a study in mice, Harvard Medical School researchers have uncovered a new piece of this puzzle, with surprising implications for cancer immunotherapy: Obesity allows cancer cells to outcompete tumor-killing immune cells in a battle for fuel.

Reporting in *Cell* on Dec. 9, the research team shows that a high-fat diet reduces the numbers and antitumor activity of CD8+ T cells, a critical type of immune cell, inside tumors. This occurs because cancer cells reprogram their metabolism in response to increased fat availability to better gobble up energy-rich fat molecules, depriving T cells of fuel and accelerating tumor growth.

"Putting the same tumor in obese and nonobese settings reveals that cancer cells rewire their metabolism in response to a high fat diet," said Marcia Haigis, professor of cell biology in the Blavatnik Institute at HMS and co-senior author of the study. "This finding suggests that a therapy that would potentially work in one setting might not be as effective in another, which needs to be better understood given the obesity epidemic in our society."

The team found that blocking this fat-related metabolic reprogramming significantly reduced tumor volume in mice on high-fat diets. Because CD8+ T cells are the main weapon used by immunotherapies that activate the immune system against cancer, the study results suggest new strategies for improving such therapies.

"Cancer immunotherapies are making an enormous impact on patients' lives, but they do not benefit everyone," said co-senior author Arlene Sharpe, the HMS George Fabyan Professor of Comparative Pathology and chair of the Department of Immunology in the Blavatnik Institute.

"We now know there is a metabolic tug-of-war between T cells and tumor cells that changes with obesity," Sharpe said. "Our study provides a roadmap to explore this interplay, which can help us to start thinking about cancer immunotherapies and combination therapies in new ways."

Haigis, Sharpe and colleagues investigated the effects of obesity on mouse models of different types of cancer, including colorectal, breast, melanoma and lung. Led by study co-first authors Alison Ringel and Jefte Drijvers, the team gave mice normal or high-fat diets, the latter leading to increased body weight and other obesity-related changes. They then looked at different cell types and molecules inside and around tumors, together called the tumor microenvironment.

Fatty paradox

The researchers found that tumors grew much more rapidly in animals on high-fat diets compared to those on normal diets. But this occurred only in cancer types that are immunogenic, which can contain high numbers of immune cells; are more easily recognized by the immune system; and are more likely to provoke an immune response.

Experiments revealed that diet-related differences in tumor growth depended specifically on the activity of CD8+ T cells, immune cells that can target and kill cancer cells. Diet did not affect tumor growth rate if CD8+ T cells were eliminated experimentally in mice.

Strikingly, high-fat diets reduced the presence of CD8+ T cells in the tumor microenvironment, but not elsewhere in the body. Those remaining in the tumor were less robust--they divided more slowly and had markers of decreased activity. But when these cells were isolated and grown in a lab, they had normal activity, suggesting something in the tumor impaired these cells' function.

The team also encountered an apparent paradox. In obese animals, the tumor microenvironment was depleted of key free fatty acids, a major cellular fuel source, even though the rest of the body was enriched in fats, as expected in obesity.

These clues pushed the researchers to craft a comprehensive atlas of the metabolic profiles of different cell types in tumors under normal and high-fat diet conditions.

The analyses revealed that cancer cells adapted in response to changes in fat availability. Under a high-fat diet, cancer cells were able to reprogram their metabolism to increase fat uptake and utilization, while CD8+ T cells did not. This ultimately depleted the tumor microenvironment of certain fatty acids, leaving T cells starved for this essential fuel.

"The paradoxical depletion of fatty acids was one of the most surprising findings of this study. It really blew us away and it was the launch pad for our analyses," said Ringel, a postdoctoral fellow in the Haigis lab. "That obesity and whole-body metabolism can change how different cells in tumors utilize fuel was an exciting discovery, and our metabolic atlas now allows us to dissect and better understand these processes."

Hot and cold

Through several different approaches, including single-cell gene expression analyses, large-scale protein surveys and high-resolution imaging, the team identified numerous diet-related changes to metabolic pathways of both cancer and immune cells in the tumor microenvironment.

Of particular interest was PHD3, a protein that in normal cells has been shown to act as a brake on excessive fat metabolism. Cancer cells in an obese environment had significantly lower expression of PHD3 compared to in a normal environment. When the researchers forced tumor cells to overexpress PHD, they found that this diminished a tumor's ability to take up fat in obese mice. It also restored the availability of key free fatty acids in the tumor microenvironment.

Increased PHD3 expression largely reversed the negative effects of a high-fat diet on immune cell function in tumors. Tumors with high PHD3 grew slower in obese mice compared to tumors with low PHD3. This was a direct result of increased CD8+ T cell activity. In obese mice lacking CD8+ T cells, tumor growth was unaffected by differences in PHD3 expression.

The team also analyzed human tumor databases and found that low PHD3 expression was associated with immunologically "cold" tumors, defined by fewer numbers of immune cells. This

association suggested that tumor fat metabolism plays a role in human disease, and that obesity reduces antitumor immunity in multiple cancer types, the authors said.

"CD8+ T cells are the central focus of many promising precision cancer therapies, including vaccines and cell therapies such as CAR-T," Sharpe said. "These approaches need T cells to have sufficient energy to kill cancer cells, but at the same time we don't want tumors to have fuel to grow. We now have amazingly comprehensive data for studying this dynamic and determining mechanisms that prevent T cells from functioning as they should."

More broadly, the results serve as a foundation for efforts to better understand how obesity affects cancer and the impact of patient metabolism on therapeutic outcomes, the authors said. While it's too early to tell if PHD3 is the best therapeutic target, the findings open the door for new strategies to combat cancer through its metabolic vulnerabilities, they said.

"We're interested in identifying pathways that we could use as potential targets to prevent cancer growth and to increase immune antitumor function," Haigis said. "Our study provides a high-resolution metabolic atlas to mine for insights into obesity, tumor immunity and the crosstalk and competition between immune and tumor cells. There are likely many other cell types involved and many more pathways to be explored."

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Additional authors on the study include Gregory Baker, Alessia Catozzi, Juan García-Cañaveras, Brandon Gassaway, Brian Miller, Vikram Juneja, Thao Nguyen, Shakchhi Joshi, Cong-Hui Yao, Haejin Yoon, Peter Sage, Martin LaFleur, Justin Trombley, Connor Jacobson, Zoltan Maliga, Steven Gygi, Peter Sorger and Joshua Rabinowitz.

This study was supported by the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (grants U54-CA225088, R01CA213062, R01DK103295, P01AI56299, 5F31CA224601 and T32CA207021), the Ludwig Center at Harvard Medical School, the Evergrande Center for Immunologic Disease, the Glenn Foundation for Medical Research and the American Cancer Society.

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3. ある特定のタンパク質をブロックすることで、老齢マウスが体力と持久力を回復

日付：2020 年 12 月 10 日
ソース：スタンフォード大学医学部
概要：

スタンフォード大学医学部の研究者らによる研究によると、老齢マウスの特定の単一タンパク質の活性を 1 か月間ブロックすると、マウスの枯れた筋肉の質量と強度が回復し、トレッドミルでのランニング時間が長くなり、逆に、若いマウスでこのタンパク質の発現を増加させると、筋肉が萎縮して弱まる、として 12 月 10 日に「Science」のオンライン版で公開している。
加齢における筋肉喪失はサルコペニアとして知られ、人々が自分自身をケアする能力を失い、より多くの転倒を経験し、ますます動きを少なくさせる。米国ではこれによる医療費が毎年数十億ドルを占める。
研究者らは、以前の研究でプロスタグランジン E2 と呼ばれる分子が、損傷した筋線維を修復するために作用する筋幹細胞を活性化できることを発見し、この同じ経路が老化にも重要なのではないかと考えた。プロスタグランジン E2 レベルは、プロスタグランジン E2 を分解する 15-PGDH によって調節される。そこで研究者らは、高感度の質量分析を使用して、老齢マウスの筋肉では若いマウスと比較して 15-PGDH レベルが高く、プロスタグランジン E2 のレベルが低いことを確認した。又、15-PGDH の活性をブロックする小分子を 1 か月間毎日マウスに投与し、老齢マウスと若齢マウスに対する治療の効果を評価したところ、老齢マウスでは、15-PGDH を部分的に阻害するだけでもプロスタグランジン E2 が若齢マウスに見られる生理学的レベルに回復することが分かり、若齢マウスで 15-PGDH を過剰発現させたときには、反対のことが起こった。
最後に、研究者らは、実験用皿で成長するヒトの筋管（未成熟な筋線維）に対するプロスタグランジン E2 の効果を観察した。彼らは、筋管をプロスタグランジン E2 で処理すると直径が大きくなり、筋管でのタンパク質合成が増加することを発見、これは、プロスタグランジン E2 が組織微小環境の他の細胞ではなく、筋肉細胞に直接作用したことの証拠である、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＞Blocking protein restores strength, endurance in old mice -- ScienceDaily

BLOCKING PROTEIN RESTORES STRENGTH, ENDURANCE IN OLD MICE

Date:

December 10, 2020

Source:

Stanford Medicine

Summary:

A single protein is a master regulator of mouse muscle function during aging, a new study finds. Blocking this protein increased muscle strength and endurance in old animals. It may play a role in age-related muscle weakening in humans.

FULL STORY

Blocking the activity of a single protein in old mice for one month restores mass and strength to the animals' withered muscles and helps them run longer on a treadmill, according to a study by researchers at the Stanford University School of Medicine. Conversely, increasing the expression of the protein in young mice causes their muscles to atrophy and weaken.

"The improvement is really quite dramatic" said Helen Blau, PhD, professor of microbiology and immunology. "The old mice are about 15% to 20% stronger after one month of treatment, and their muscle fibers look like young muscle. Considering that humans lose about 10% of muscle strength per decade after about age 50, this is quite remarkable."

The protein hasn't previously been implicated in aging. The researchers show that the amount of the protein, called 15-PGDH, is elevated in old muscle and is widely expressed in other old tissues. Experiments they conducted in human tissue raise hopes for a future treatment for the muscle weakness that occurs as people age.

Blau, the Donald E. and Delia B. Baxter Foundation Professor and director of the Baxter Laboratory for Stem Cell Biology, is the senior author of the study, which will be published online Dec. 10 in *Science*. Senior scientist Adelaida Palla, PhD, is the lead author.

Muscle loss in aging

Muscle loss during aging is known as sarcopenia, and it accounts for billions of dollars of health care expenditures in the United States each year as people lose the ability to care for themselves, experience more falls and become increasingly less mobile. It is due to changes in muscle structure and function: The muscle fibers shrink and the number and function of the cellular powerhouses known as mitochondria dwindle.

Blau and her colleagues have long been interested in understanding muscle function after muscle injury and in diseases like Duchenne muscular dystrophy. Previously, they found that a molecule called prostaglandin E2 can activate muscle stem cells that spring into action to repair damaged muscle fibers.

"We wondered whether this same pathway might also be important in aging," Blau said. "We were surprised to find that PGE2 not only augments the function of stem cells in regeneration, but also acts on mature muscle fibers. It has a potent dual role."

Prostaglandin E2 levels are regulated by 15-PGDH, which breaks down prostaglandin E2. The researchers used a highly sensitive version of mass spectrometry, a method for differentiating closely related molecules, to determine that compared with young mice, the 15-PGDH levels are elevated in the muscles of older animals, and the levels of prostaglandin E2 are lower.

They found a similar pattern of 15-PGDH expression in human muscle tissues, as those from people in their 70s and early 80s expressed higher levels than those from people in their mid-20s.

"We knew from our previous work that prostaglandin E2 was beneficial for regeneration of young muscles," Palla said. "But its short half-life makes it difficult to translate into a therapy. When we inhibited 15-PGDH, we observed a systemic elevation of prostaglandin E2 levels leading to a bodywide muscle improvement in aged mice."

Inhibiting 15-PGDH

The researchers administered a small molecule that blocks the activity of 15-PGDH to the mice daily for one month and assessed the effect of the treatment on the old and young animals.

"We found that, in old mice, even just partially inhibiting 15-PGDH restored prostaglandin E2 to physiological levels found in younger mice," Blau said. "The muscle fibers in these mice grew larger, and were stronger, than before the treatment. The mitochondria were more numerous, and looked and functioned like mitochondria in young muscle."

Treated animals were also able to run longer on a treadmill than untreated animals.

When Palla and her colleagues performed the reverse experiment -- overexpressing 15-PGDH in young mice -- the opposite occurred. The animals lost muscle tone and strength, and their muscle fibers shrank and became weaker, like those of old animals.

Finally, the researchers observed the effect of prostaglandin E2 on human myotubes -- immature muscle fibers -- growing in a lab dish. They found that treating the myotubes with prostaglandin E2 caused them to increase in diameter, and protein synthesis in the myotubes was increased -- evidence that prostaglandin E2 worked directly on the muscle cells, not on other cells in the tissue microenvironment.

"It's clear that this one regulator, 15-PGDH, has a profound effect on muscle function," Blau said. "We're hopeful that these findings may lead to new ways to improve human health and impact the quality of life for many people. That's one of my main goals."

Blau and Palla are studying more about what controls the levels and activity of 15-PGDH during normal aging, and how it might affect the function of other tissues in the body.

"The mice perform better on a treadmill, but that requires more than just an increase in muscle strength," Blau said. "Other organ systems are involved -- the heart and lungs, for example. It suggests an overall improvement in the function of the whole animal."

Story Source:

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

Journal Reference:

1. A. R. Palla, M. Ravichandran, Y. X. Wang, L. Alexandrova, A. V. Yang, P. Kraft, C. A. Holbrook, C. M. Schürch, A. T. V. Ho, H. M. Blau. **Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength**. *Science*, 2020; eabc8059 DOI: 10.1126/science.abc8059

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4. ワクチン研究用のマウスを生成するためのワンステップ法

日付：2020 年 12 月 15 日
ソース：マサチューセッツ総合病院
概要：

ワクチンを開発し、ヒトの免疫反応を調査するために、科学者らはマウスを含むさまざまな動物モデルに依存している。これらの動物モデルには、遺伝子操作された B 細胞受容体を介してヒト抗体（B 細胞膜に結合した特殊な抗体）を産生できるマウスが含まれるが、これらのマウスは、発育に数年かかることが多く、遺伝子組み換えと慎重な繁殖の複雑なプロセスを必要とする。これらの特殊なマウスを生成するのにかかる時間は、ワクチン開発を遅らせる主な要因である。
マサチューセッツ工科大学およびハーバード大学のラゴン研究所の研究者らは CRISPR/Cas9 テクノロジーを使用するワンステップの方法を開発し、わずか数週間で遺伝子操作されたヒト B 細胞受容体を備えたマウス作製に成功した。
この研究成果は、「The EMBO Journal」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＞One-step method to generate mice for vaccine research -- ScienceDaily

ONE-STEP METHOD TO GENERATE MICE FOR VACCINE RESEARCH

Date:

December 15, 2020

Source:

Massachusetts General Hospital

Summary:

Researchers have developed a one-step method, which uses CRISPR/Cas9 technology, to produce mice with genetically engineered human B cell receptors in just a few weeks.

FULL STORY

To develop vaccines and investigate human immune responses, scientists rely on a variety of animal models, including mice that can produce human

antibodies through genetically engineered B cell receptors, which are specialized antibodies bound to the B cell membrane. These mice, however, often take several years to develop, requiring a complicated process of genetic modification and careful breeding.

"The time it takes to generate these specialized mice has been a major factor in delaying vaccine development," says Facundo Batista, PhD, associate director of the Ragon Institute of MGH, MIT and Harvard. "With the recent advances in gene editing technology like CRISPR/Cas9, we knew there had to be a way to speed up this process significantly."

Batista's group has developed a new method for generating mouse lines for pre-clinical vaccine evaluation that dramatically shortens this timeline. In a study published recently in the journal *EMBO*, this one-step method, which uses CRISPR/Cas9 technology, can produce mice with genetically engineered human B cell receptors in just a few weeks.

To test this technology, the researchers engineered mice to have human B cell receptors that are precursors to what are called broadly neutralizing HIV antibodies. These antibodies are known to be effective in combating HIV, but they are difficult to stimulate through vaccination. The precursors responded to an antigen currently being used in clinical HIV trials by generating broadly neutralizing antibody-like mutations. The ability to quickly evaluate the ability of different antigens to active these precursors has the potential to significantly accelerate vaccine development.

The engineered B cells were not just capable of making high-quality antibodies; some became a specialized form of B cell known as memory B cells, which are used to maintain long-lasting immunity once antibodies are produced against a pathogen. This means the mice can likely be used to quickly validate good candidate vaccines for HIV and other pathogens.

"This new technique may allow scientists studying vaccines and antibody evolution to tremendously speed up their research," says Ragon research fellow Xuesong Wang, PhD, co-first author on the paper.

Rashmi Ray, PhD, also co-first author and a Ragon research fellow, agrees: "It will allow researchers to respond much more quickly and flexibly to new developments in the field."

Story Source:

Materials provided by **Massachusetts General Hospital**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Xuesong Wang, Rashmi Ray, Sven Kratochvil, Eleonora Melzi, Ying-Cing Lin, Sophie Giguere, Liling Xu, John Warner, Diane Cheon, Alessia Liguori, Bettina Groschel, Nicole Phelps, Yumiko Adachi, Ryan Tingle, Lin Wu, Shane Crotty, Kathrin H Kirsch, Usha Nair, William R Schief, Facundo D Batista. **Multiplexed CRISPR/CAS9-mediated engineering of pre-clinical mouse models bearing native human B cell receptors**. *The EMBO Journal*, 2020; DOI: 10.15252/embj.2020105926

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5. マウスの卵子をかたち作る遺伝子群を同定
～卵細胞質の大量作製が可能に～

日付：2020 年 12 月 16 日
ソース：九州大学
概要：https://www.kyushu-u.ac.jp/ja/researches/view/538

九州大学大学院医学研究院の林克彦教授、浜崎伸彦助教（現ワシントン大学/HHMI 特別研究員）、理化学研究所生命機能科学研究センターの北島智也チームリーダー、京極博久客員研究員の研究グループは、マウスの卵子をかたち作る遺伝子群を同定しました。また、この遺伝子群を胚性幹(ES)細胞や人工多能性幹(iPS)細胞に導入することで、短期間のうちに大量の卵子様細胞を作製することに成功しました。
卵子の細胞質（卵細胞質）は個体発生能を司る特殊な機能をもち、不妊治療やクローン動物の作製にも用いられています。しかしながら、これまでにこの特殊な卵細胞質がどのようにつくられるかについては不明な点が多く残されていました。本研究では卵子ができあがる過程を丹念に調べた結果、卵細胞質の形成に必要な 8 つの遺伝子（転写因子）を突き止めました。驚くべきことに、その 8 つの遺伝子を ES 細胞や iPS 細胞に発現させると、急激に細胞質が成長し、受精能をもった卵子様細胞に変化しました。また、これらの遺伝子の数を最小 4 つに減らしても同様の作用があることがわかりました。この方法を用いると、生物学・医学的に貴重な卵細胞質をこれまでより短期間で大量に作製することができます。この成果により、個体の発生に必要な卵細胞質の形成機構の解明や人工的に作られた卵細胞質を用いた不妊治療技術の開発が期待されます。
本研究成果は 2020 年 12 月 16 日（水）16 時（英国標準時間）に国際学術雑誌「Nature」に掲載されました。なお、本研究は文部科学省科研費、日本医療研究開発機構（AMED）、武田科学振興財団、The Open Philanthropy Project の支援を受けました。

研究関連ニュース/他のトップページに戻る

＜英文＞Oh so simple: Eight genes enough to convert mouse stem cells into oocyte-like cells: Surprisingly simple method could provide a new tool for producing specialized cytoplasm for reproductive medicine -- ScienceDaily

OH SO SIMPLE: EIGHT GENES ENOUGH TO CONVERT MOUSE STEM CELLS INTO OOCYTE-LIKE CELLS

Surprisingly simple method could provide a new tool for producing specialized cytoplasm for reproductive medicine

Date:

December 16, 2020

Source:

Kyushu University

Summary:

By activating just eight genes for transcription factors, researchers have directly converted mouse stem cells into oocyte-like cells that mature and can even be fertilized like egg cells. In addition to giving new insight into egg cell development, the research may lead to a simple route for generating large amounts of oocyte cytoplasm for use in reproductive biology and medicine.

FULL STORY

In a new study published in the journal *Nature*, researchers in Japan report that activating just eight genes for producing gene-controlling proteins is enough to convert mouse stem cells directly into oocyte-like cells that mature and can even be fertilized like egg cells.

On top of providing new insights into the mechanisms of egg cell development, the research may lead to a simple route for generating highly specialized substances unique to oocytes for use in reproductive biology and medicine.

Stored in the body until they mature into egg cells ready for fertilization, oocytes represent the very first step in the creation a new human life.

Oocytes are extremely unique because of their ability to bring forth the over two hundred kinds of highly differentiated cells needed to create an individual person, and one key to this ability is the complex mixture of substances within the fluid-like cytoplasm filling the cells.

So extraordinary are oocytes and their cytoplasm that replacing an oocyte's DNA-containing nucleus with that of a body cell -- a process called somatic cell nuclear transfer -- can produce a new life, as famously demonstrated with Dolly the sheep.

Thus, a fundamental understanding of oocytes and their development is important for both advancing reproductive medicine and better grasping how life propagates, but knowledge of the many genes that orchestrate oocyte development is still far from complete.

Analyzing the development of oocytes from mice, researchers led by Katsuhiko Hayashi, professor at Kyushu University's Faculty of Medical Sciences, have now identified eight genes for gene-triggering proteins known as transcription factors that not only are necessary for oocyte growth but also can directly convert mouse stem cells into oocyte-like cells.

"I was initially in complete disbelief to see mouse stem cells so quickly and easily take the form of oocytes based on introducing just a handful of factors, but repeated experiments proved it was true," says Nobuhiko Hamazaki, first author on the study reporting the results and assistant professor at Kyushu University at the time of the research. "To find that eight transcription factors could lead to such big changes was quite astonishing."

Working in collaboration with researchers at RIKEN, Hayashi's group found that both mouse embryonic stem cells and induced pluripotent stem (iPS) cells -- which can be created from adult

body cells -- consistently converted into oocyte-like cells when forced to produce the set of eight transcription factors, with only four factors being sufficient in some cases though with worse reproducibility.

"That stem cells can be directly converted into oocyte-like cells without following the same sequence of steps that happen naturally is remarkable," says Hayashi.

When grown in the presence of other cells usually found around oocytes, the oocyte-like cells developed structures similar to mature egg cells but with an abnormal chromosome structure. Despite this, the mature oocyte-like cells could be fertilized in vitro and exhibited early development, with some even progressing to an eight-cell stage.

Though the modified nuclei of the oocyte-like cells may not be useable in the long run, this is no problem for applications needing mainly the oocyte cytoplasm, such as for studies of reproductive biology and for treatments like mitochondrial replacement therapy, in which parts of oocytes are replaced to prevent mothers from passing to their children diseases related to the mitochondria.

"Cytoplasm from oocytes is an invaluable resource in reproductive biology and medicine, and this method could provide a novel tool for producing large amounts of it without any invasive procedures," comments Hayashi. "While the processes could still be much more complex for humans, these initial results in mice are very promising."

Story Source:

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

Journal Reference:

1. Nobuhiko Hamazaki, Hirohisa Kyogoku, Hiromitsu Araki, Fumihito Miura, Chisako Horikawa, Norio Hamada, So Shimamoto, Orie Hikabe, Kinichi Nakashima, Tomoya S. Kitajima, Takashi Ito, Harry G. Leitch, and Katsuhiko Hayashi. **Reconstitution of the oocyte transcriptional network with transcription factors**. *Nature*, 2020 DOI: 10.1038/s41586-020-3027-9

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6. COVID-19 ウイルスは脳に侵入できる

日付：2020 年 12 月 17 日
ソース：ワシントン大学健康科学/ワシントン大学医学部
概要：

COVID-19 に感染した人々が脳の霧や倦怠感などの認知効果に苦しんでいるという証拠がどんどん出てきている。そして、研究者らはその理由を発見しつつある。
「Nature Neuroscience」で 12 月 16 日に公開された研究で、ワシントン大学医学部の研究者らは、SARS-CoV-2 ウイルスの赤い腕として描かれることが多い細胞結合蛋白質・スパイクタンパク質 S1 サブユニット（S1）が血液脳関門（BBB）を通過してマウスの脳に入りうることが示された。ウイルスからちぎれたタンパク質は BBB を通り抜けて神経炎症や中枢神経系を故障させることが知られており、S1 もそういう害を及ぼす可能性がある。これは、COVID-19 の原因である SARS-CoV-2 ウイルスが脳に侵入する可能性があることを強く示唆している。

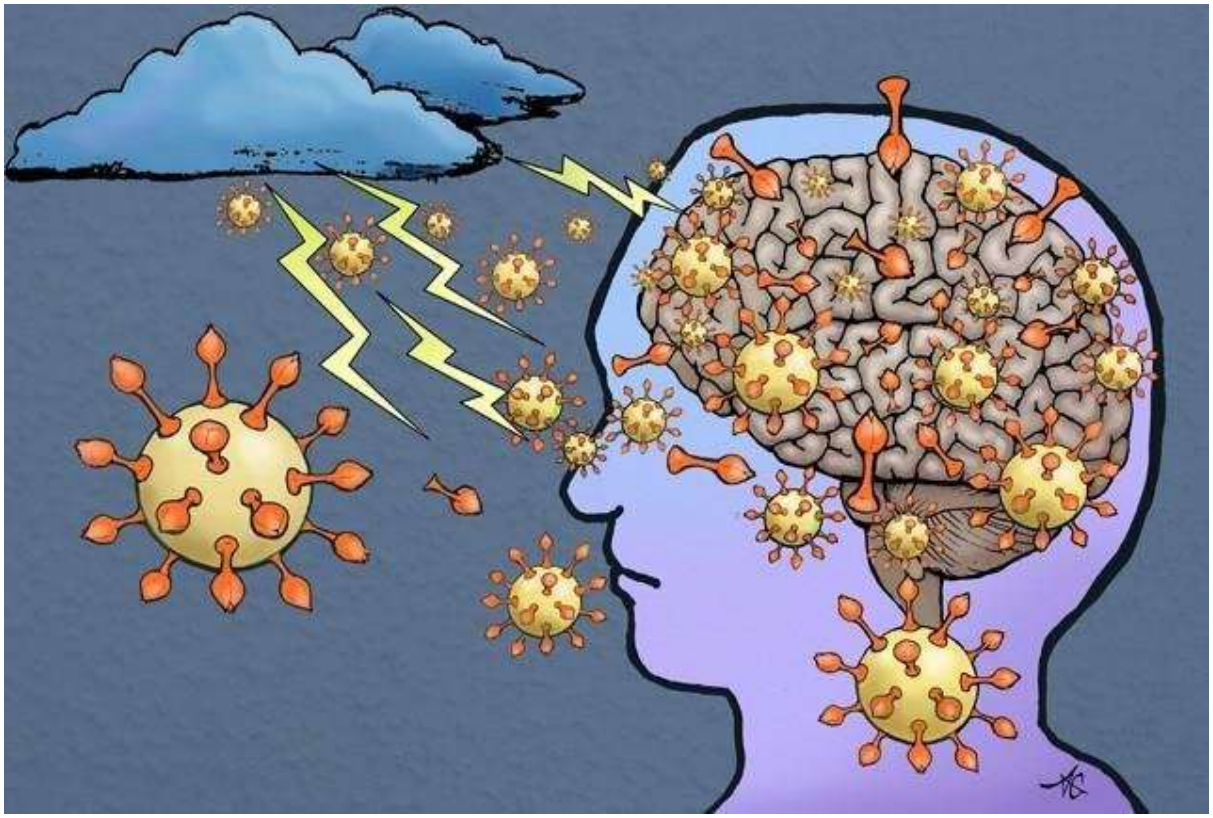
研究関連ニュース/他のトップページに戻る

＜英文＞Research strongly suggests COVID-1 virus enters the brain (medicalxpress.com)

DECEMBER 17, 2020

RESEARCH STRONGLY SUGGESTS COVID-19 VIRUS ENTERS THE BRAIN

by Bobbi Nodell, University of Washington



The S1 protein likely causes the brain to release inflammatory products causing a storm in the brain, researchers said. Credit: Alice Gray

More and more evidence is coming out that people with COVID-19 are suffering from cognitive effects, such as brain fog and fatigue.

And researchers are discovering why. The SARS-CoV-2 virus, like many viruses before it, is bad news for the brain. In a study published Dec.16 in *Nature Neuroscience*, researchers found that the spike protein, often depicted as the red arms of the virus, can cross the blood-brain barrier in mice.

This strongly suggests that SARS-CoV-2, the cause of COVID-19, can enter the brain.

The spike protein, often called the S1 protein, dictates which cells the virus can enter. Usually, the virus does the same thing as its binding protein, said lead author William A. Banks, a professor of medicine at the University of Washington School of Medicine and a Puget Sound Veterans Affairs Healthcare System physician and researcher. Banks said binding proteins like S1 usually by themselves cause damage as they detach from the virus and cause inflammation.

"The S1 protein likely causes the brain to release cytokines and inflammatory products," he said.

In science circles, the intense inflammation caused by the COVID-19 infection is called a cytokine storm. The immune system, upon seeing the virus and its proteins,

overreacts in its attempt to kill the invading virus. The infected person is left with brain fog, fatigue and other cognitive issues.

Banks and his team saw this reaction with the HIV virus and wanted to see if the same was happening with SARS CoV-2.

Banks said the S1 protein in SARS-CoV2 and the gp 120 protein in HIV-1 function similarly. They are glycoproteins—proteins that have a lot of sugars on them, hallmarks of proteins that bind to other receptors. Both these proteins function as the arms and hand for their viruses by grabbing onto other receptors. Both cross the blood-brain barrier and S1, like gp120, is likely toxic to brain tissues.

"It was like déjà vu," said Banks, who has done extensive work on HIV-1, gp120, and the blood-brain barrier.

The Banks' lab studies the blood-brain barrier in Alzheimer's, obesity, diabetes, and HIV. But they put their work on hold and all 15 people in the lab started their experiments on the S1 protein in April. They enlisted long-time collaborator Jacob Raber, a professor in the departments of Behavioral Neuroscience, Neurology, and Radiation Medicine, and his teams at Oregon Health & Science University.

The study could explain many of the complications from COVID-19.

"We know that when you have the COVID infection you have trouble breathing and that's because there's infection in your lung, but an additional explanation is that the virus enters the respiratory centers of the brain and causes problems there as well," said Banks.

Raber said in their experiments transport of S1 was faster in the olfactory bulb and kidney of males than females. This observation might relate to the increased susceptibility of men to more severe COVID-19 outcomes.

As for people taking the virus lightly, Banks has a message:

"You do not want to mess with this virus," he said. "Many of the effects that the COVID virus has could be accentuated or perpetuated or even caused by virus getting in the brain and those effects could last for a very long time."

Explore further

COVID-19 vaccines focus on the spike protein – but here's another target

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More information: Elizabeth M. Rhea et al, The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice, *Nature Neuroscience* (2020). DOI: 10.1038/s41593-020-00771-8

Journal information: Nature Neuroscience

7. マウスに制御されたマウスで、脳が意図的な制御をどのように表すかを理解

日付：2020 年 12 月 22 日
ソース：Sainsbury Wellcome Center (University College London)
概要：

我々は脳が思考を導くことができると知っているが、これがどのように達成されるかを理解することは困難である。
Sainsbury Wellcome Center の研究者らは、今日の「Neuron」で、マウスが脳の活動のみを使用してカーソルをガイドすることを学習できるようにするブレインマシンインターフェイス（BMI）を考案した、と発表している。この研究で、研究者らは、報酬を受け取るためにターゲットの場所に移動するこのマウスに制御されたマウスを監視することにより、脳が意図的な制御をどのように表すかを研究することができた、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＞Mouse-controlled mouse helps researchers understand intentional control: Study sheds light on how the brain represents causally-controlled objects -- ScienceDaily

MOUSE-CONTROLLED MOUSE HELPS RESEARCHERS UNDERSTAND INTENTIONAL CONTROL

Study sheds light on how the brain represents causally-controlled objects

Date:

December 22, 2020

Source:

Sainsbury Wellcome Centre

Summary:

Researchers have devised a brain machine interface (BMI) that allows mice to learn to guide a cursor using only their brain activity. By monitoring this mouse-controlled mouse moving to a target location to receive a reward, the researchers were able to study how the brain represents intentional control.

FULL STORY

We know that the brain can direct thoughts, but how this is achieved is difficult to determine. Researchers at the Sainsbury Wellcome Centre have devised a brain machine interface (BMI) that allows mice to learn to guide a cursor using only their brain activity. By monitoring this mouse-controlled mouse moving to a target location to receive a reward, the researchers were able to study how the brain represents intentional control.

The study, published today in *Neuron,* sheds light on how the brain represents causally-controlled objects. The researchers found that when mice were controlling the cursor, brain activity in the higher visual cortex was goal-directed and contained information about the animal's intention. This research could one day help to improve BMI design.

"Brain machine interfaces are devices that allow a person or animal to control a computer with their mind. In humans, that could be controlling a robotic arm to pick up a cup of water, or moving a cursor on a computer to type a message using the mind. In animals, we are using these devices as models for understanding how to make BMIs better," said the paper's first author, Dr Kelly Clancy, who completed the study at the Sainsbury Wellcome Centre, University College London, following previous work at Biozentrum, University of Basel.

"Right now, BMIs tend to be difficult for humans to use and it takes a long time to learn how to control a robotic arm for example. Once we understand the neural circuits supporting how intentional control is learned, which this work is starting to elucidate, we will hopefully be able to make it easier for people to use BMIs," said co-author of the paper, Professor Tom Mrsic-Flogel, Director of the Sainsbury Wellcome Centre, University College London.

Traditionally it has been difficult to study how causally-controlled objects are represented in the brain. Imagine trying to determine how the brain represents a cursor it is controlling versus a cursor it is passively watching. There are motor signals in the first case but not in the second, so it is difficult to compare the two. With BMIs, the subject doesn't physically move, so a cleaner comparison can be made.

In this study, the researchers used a technique called widefield brain imaging, which allowed them to look at the whole dorsal surface of the cortex while the animal was using the BMI. This technique enabled an unbiased screen of the cortex to locate the areas that were involved in learning to intentionally control the cursor.

Visual cortical areas in mice were found to be involved during the task. These areas included the parietal cortex, an area of the brain implicated in intention in humans.

"Researchers have been studying the parietal cortex in humans for a long time. However, we weren't necessarily expecting this area to pop out in our unbiased screen of the mouse brain. There seems to be something special about parietal cortex as it sits between sensory and motor areas in the brain and may act as a way station between them," added Dr Kelly Clancy.

By delving deeper into how this way station works, the researchers hope to understand more about how control is exerted by the brain. In this study, mice learned to map their brain activity to sensory feedback. This is analogous to how we learn to interact with the world -- for example, we adjust how we use a computer mouse depending on its gain setting. Our brains build representations of how objects typically behave, and execute actions accordingly. By understanding more about how such rules are generated and updated in the brain, the researchers hope to be able to improve BMIs.

Story Source:

Materials provided by **Sainsbury Wellcome Centre**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Kelly B. Clancy, Thomas D. Mrsic-Flogel. **The sensory representation of causally controlled objects**. *Neuron*, 2020; DOI: 10.1016/j.neuron.2020.12.001

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8. 健康な妊娠を確保する上で忘れられた臓器の重要性

日付：2020 年 12 月 23 日
ソース：ブリティッシュ コロンビア大学（カナダ）
概要：

ブリティッシュ コロンビア大学（UBC）が率いる国際的な研究チームは、妊娠中の女性の流産と糖尿病を防ぐために働く胸骨の後ろに隠れている小さな胸腺の重要性を初めて明らかにした。「Nature」に本日発表された研究では、この胸腺が、妊娠中の代謝制御と免疫の両方で重要な役割を果たしていると特定されている。
研究者らはまた、メカニズムの背後にある重要な分子として、上皮と呼ばれる胸腺の一部で発現する受容体である RANK を特定した。そして、より良い理解を得るために、RANK が胸腺から削除されたマウスを研究した。
RANK を欠くマウスは、妊娠中の胸腺での制御性 T 細胞の産生が妨げられ、その結果、胎盤での制御性 T 細胞が少なくなり、流産率が上昇した。又、RANK を欠く妊娠中のマウスは、血中のブドウ糖とインスリンのレベルが高く、妊娠糖尿病など他の多くの指標があった。
研究者らは、この研究により、胸腺に対して、妊娠を保護するために必要な活動的な器官として今までの見方が変わるはずだ、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＞New research highlights the importance of a forgotten organ in ensuring healthy pregnancies -- ScienceDaily

NEW RESEARCH HIGHLIGHTS THE IMPORTANCE OF A FORGOTTEN ORGAN IN ENSURING HEALTHY PREGNANCIES

Date:

December 23, 2020

Source:

University of British Columbia

Summary:

An international research team has uncovered for the first time the importance of a small gland tucked behind the sternum that works to prevent miscarriage and diabetes in pregnant women.

FULL STORY

An international research team led by the University of British Columbia (UBC) has uncovered for the first time the importance of a small gland tucked behind the sternum that works to prevent miscarriage and diabetes in pregnant women.

The organ in question is the thymus, identified in a study published today in the journal *Nature* as playing a significant role in both metabolic control and immunity in pregnancy.

How the immune system adapts to support mother and fetus has puzzled researchers for decades. The study -- conducted by an international research team, including UBC's Dr. Josef Penninger -- reveals an answer. The researchers have found that female sex hormones instruct important changes in the thymus, a central organ of the immune system, to produce specialized cells called Tregs to deal with physiological changes that arise in pregnancy.

The researchers also identified RANK, a receptor expressed in a part of the thymus called the epithelium, as the key molecule behind this mechanism.

"We knew RANK was expressed in the thymus, but its role in pregnancy was unknown," says the study's senior author Dr. Penninger, professor in the department of medical genetics and director of the Life Sciences Institute at UBC.

To get a better understanding, the authors studied mice where RANK had been deleted from the thymus.

"The absence of RANK prevented the production of Tregs in the thymus during pregnancy. That resulted in less Tregs in the placentas, leading to elevated rates of miscarriage," says the study's lead author Dr. Magdalena Paolino, assistant professor in the department of medicine at the Karolinska Institutet.

The findings also offer new molecular insights into the development of diabetes during pregnancy, known as gestational diabetes, a disease that affects approximately 15 percent of women in pregnancy worldwide, and about which scientists still know little.

In healthy pregnancies, the researchers found that Tregs migrated to the mother's fat tissue to prevent inflammation and help control glucose levels in the body. Pregnant mice lacking RANK had high levels of glucose and insulin in their blood and many other indicators of gestational diabetes, including larger-than-average young.

"Similar to babies of women with diabetes in pregnancy, the newborn pups were much heavier than average," says Dr. Paolino.

The deficiency of Tregs during pregnancy also resulted in long-lasting, transgenerational effects on the offspring. The pups remained prone to diabetes and overweight throughout their life spans. Giving the RANK-deficient mice thymus-derived Tregs isolated from normal pregnancies reversed all their health issues, including miscarriage and maternal glucose levels, and also normalized the body weights of the pups.

The researchers also analyzed women with diabetes in pregnancy, revealing a reduced number of Tregs in their placentas, similar to the study on mice.

"The discovery of this new mechanism underlying gestational diabetes potentially offers new therapeutic targets for mother and fetus in the future," says co-author Dr. Alexandra Kautzky-Willer, a clinician-researcher based at the Medical University of Vienna.

"The thymus changes massively during pregnancy and how such rewiring of an entire tissue contributes to a healthy pregnancy has been one of the remaining mysteries of immunology," adds Dr. Penninger. "Our work over many years has now not only solved this puzzle -- pregnancy hormones rewire the thymus via RANK -- but uncovered a new paradigm for its function: the thymus not only changes the immune system of the mother so it does not reject the fetus, but the thymus also controls metabolic health of the mother.

"This research changes our view of the thymus as an active and dynamic organ required to safeguard pregnancies," says Dr. Penninger.

Story Source:

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

Journal Reference:

1. Magdalena Paolino, Rubina Koglgruber, Shane J. F. Cronin, Iris Uribesalgo, Esther Rauscher, Jürgen Harreiter, Michael Schuster, Dagmar Bancher-Todesca, Blanka Pranjic, Maria Novatchkova, Juan P. Fededa, Andrea J. White, Verena Sigl, Sabine Dekan, Thomas Penz, Christoph Bock, Lukas Kenner, Georg A. Holländer, Graham Anderson, Alexandra Kautzky-Willer, Josef M. Penninger. **RANK links thymic regulatory T cells to fetal loss and gestational diabetes in pregnancy**. *Nature*, 2020; DOI: 10.1038/s41586-020-03071-0

9. 造血幹細胞の老化メカニズムの発見 –マウス実験

日付:2020 年 12 月 24 日
ソース:東京大学医科学研究所
概要:

マウスの老化した造血幹細胞(老化した HSC)を若いマウスの環境(骨髄ニッチ)に移すことにより、幹細胞の遺伝子発現パターンが若い造血幹細胞のパターンに活性化することが実証された。一方、老化した HSC の機能は、若い骨髄ニッチでは回復しなかった。老化した HSC のエピゲノム(DNA メチル化)は、若い骨髄ニッチでも有意な変化はなく、DNA メチル化プロファイルは老化した HSC の遺伝子発現パターンよりも優れた指標であることが分かった。
東京大学医科学研究所(IMSUT)幹細胞分子医学部の岩間敦教授を中心とした研究グループが、これら世界初の成果を発表し、「Journal of Experimental Medicine」のオンライン版に掲載された。研究者らは、この結果が、加齢に伴う血液疾患の治療法の開発に貢献するだろう、としている。

参考: 研究により、造血幹細胞に対する加齢の影響が明らかになりました – BRAIN&MIND NEWS (revolusynapse.com)

研究関連/他のトップページに戻る

＜英文＞Discovery of aging mechanism for hematopoietic stem cells: Limited rejuvenation of aged hematopoietic stem cells in young bone marrow niche -- ScienceDaily

DISCOVERY OF AGING MECHANISM FOR HEMATOPOIETIC STEM CELLS

Limited rejuvenation of aged hematopoietic stem cells in young bone marrow niche

Date:

December 24, 2020

Source:

The Institute of Medical Science, The University of Tokyo

Summary:

By transferring mouse aged hematopoietic stem cells (aged HSCs) to the environment of young mice (bone marrow niche), it was demonstrated that the pattern of stem cell gene expression was rejuvenated to that of young hematopoietic stem cells.

FULL STORY

By transferring mouse aged hematopoietic stem cells (aged HSCs, *1) to the environment of young mice (bone marrow niche, *2), it was demonstrated that the pattern of stem cell gene expression was rejuvenated to that of young hematopoietic stem cells. On the other hand, the function of aged HSCs did not recover in the young bone marrow niche. The epigenome (DNA methylation, *3) of aged HSCs did not change significantly even in the young bone marrow niche, and DNA methylation profiles were found to be a better index than the gene expression pattern of aged HSCs.

A research group led by Professor Atsushi Iwama at the Division of Stem Cell and Molecular Medicine, The Institute of Medical Science, The University of Tokyo (IMSUT) announced these world-first results and was published in the *Journal of Experimental Medicine* (online) on November 24th.

"The results will contribute to the development of treatments for age-related blood diseases," states lead scientist, Professor Iwama at IMSUT.

Focus on changes in aged HSCs in the bone marrow niche

The research group investigated whether rejuvenating aged HSCs in a young bone marrow niche environment would rejuvenate.

Tens of thousands of aged hematopoietic stem/progenitor cells collected from 20-month-old mice were transplanted into 8-week-old young mice without pretreatment such as irradiation. After two months of follow-up, they collected bone marrow cells and performed flow cytometric analysis.

The research team also transplanted 10-week-old young mouse HSCs for comparison. In addition, engrafted aged HSCs were fractionated and RNA sequence analysis and DNA methylation analysis were performed.

They found that engrafted aged HSCs were less capable of producing hematopoietic cells than younger HSCs. They also showed that differentiation of aged HSCs into multipotent progenitor cells was persistently impaired even in the young bone marrow niche, and that the direction of differentiation was biased. It was found that the transfer of aged HSCs to the young bone marrow niche does not improve their stem cell function.

A more detailed analysis may reveal mechanisms that irreversibly affect aged HSC function

Aging studies focusing on HSCs have been actively pursued in mice using a bone marrow transfer model. However, the effect of aging on HSCs remains to be clarified.

Professor Iwama states as follows."This study has a significant impact because it clarified the effect of aging on HSCs. Our results are expected to contribute to further elucidation of the

mechanism of aging in HSCs and understanding of the pathogenic mechanism of age-related blood diseases."

Story Source:

Materials provided by **The Institute of Medical Science, The University of Tokyo**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Wakako Kuribayashi, Motohiko Oshima, Naoki Itokawa, Shuhei Koide, Yaeko Nakajima-Takagi, Masayuki Yamashita, Satoshi Yamazaki, Bahityar Rahmutulla, Fumihito Miura, Takashi Ito, Atsushi Kaneda, Atsushi Iwama. **Limited rejuvenation of aged hematopoietic stem cells in young bone marrow niche**. *Journal of Experimental Medicine*, 2021; 218 (3) DOI: 10.1084/jem.20192283
