Bio News – September, 2022

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1. トリクロサン曝露が脂肪肝疾患発症の原因となる可能性 –マウス実験

日付：2022 年 7 月 27 日
ソース：カリフォルニア大学サンディエゴ校医学部
概要：

トリクロサンは、石鹸、歯磨き粉、化粧品、衣料品、家具、台所用品、殺虫剤、おもちゃなど、微生物汚染を軽減または防止するためにさまざまな消費者向け製品に添加される成分である。2 年前、UC サンディエゴ校医学部の研究者らは、高脂肪食を与えられたマウスのトリクロサン曝露が脂肪肝疾患を悪化させるという証拠を発表した。最新の研究は、それがどのように起こるかを基に構築されており、トリクロサンが授乳中の母親から子供に渡され、脂肪肝の初期兆候が現れ、おそらくその後脂肪肝疾患の可能性が高くなることを示している。
非アルコール性脂肪性肝疾患（NAFLD）は、米国で最も一般的な慢性肝疾患であり、推定 1 億人の成人が罹患している。過度のアルコール摂取以外の原因で肝細胞に脂肪が蓄積し、臓器の機能が損なわれた場合に発生する。正確な原因は分かっていないが、食事と遺伝が重要な役割を果たしているとされ、肥満者の最大 50% が NAFLD に罹っていると考えられている。更に NAFLD 患者の約 20% が非アルコール性脂肪性肝炎（NASH）に移行する。NASH は、もっと深刻な炎症と臓器損傷を特徴とし、肝臓の瘢痕化、肝硬変、および肝癌を引き起こす可能性がある、より進行した形態の疾患である。
研究者らは、妊娠中の雌マウスをトリクロサンにさらし、それが授乳によって子供マウスに効率的に移行し、授乳期間中に重大な脂肪肝を引き起こし、脂肪肝、トリグリセリド蓄積、小胞体ストレス、炎症の徴候、および肝線維症を引き起こすことを発見した。研究者らは、トリクロサンへの初期の曝露が、NAFLD および NASH に似た病状を引き起こすように思われること、そしてこれが小児 NAFLD および NASH の発症の素因となる可能性がある、としている。また、最近の小児 NAFLD の増加は、トリクロサンのような環境毒性物質の母子感染の結果である可能性がある、としている。
この結果は、「Nature Communications」誌の 2022 年 7 月 27 日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＞Lactating mice pass along common antimicrobia | EurekAlert!

NEWS RELEASE 27-JUL-2022

Lactating mice pass along common antimicrobial to pups, initiating liver damage

Triclosan is used in everything from cleaners to pesticides to toys; researchers say exposure early in life may lay groundwork for future development of fatty liver disease

Peer-Reviewed Publication

UNIVERSITY OF CALIFORNIA – SAN DIEGO

PrintEmail

IMAGE: ROBERT TUKEY, PHD, IS PROFESSOR OF PHARMACOLOGY AT UC SAN DIEGO SCHOOL OF MEDICINE. view more

CREDIT: UC SAN DIEGO HEALTH SCIENCES

In mouse studies, researchers at University of California San Diego School of Medicine report that lactating mothers expose their feeding pups to triclosan, an antimicrobial commonly used in consumer products, resulting in early signs of liver damage that can eventually lead to more serious impairment and illness, such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

The findings published in the July 27, 2022 online issue of *Nature Communications*.

NAFLD is the most common chronic liver condition in the United States, affecting an estimated 100 million adults. It occurs when fat accumulates in liver cells due to causes other than excessive alcohol use, impairing organ function. The precise cause is not known, but diet and genetics play substantial roles. Up to 50 percent of obese people are believed to have NAFLD.

Approximately 20 percent of persons with NAFLD transition to NASH, a more advanced form of the disease characterized by increasingly severe inflammation and organ damage that may result in scarring of the liver, cirrhosis and cancer.

According to a study published by UC San Diego scientists in June 2022, NASH is the fastest growing cause of liver cancer deaths globally, especially in the Americas. It is driven by rapidly rising obesity rates. The prevalence of obesity in the U.S. in 2017 was 42.4 percent, according to the Centers for Disease Control, up from 30.5 percent in 2000.

The prevalence of NAFLD in children is rising, along with obesity rates in the young. It is estimated that 9.6 percent of children ages 2 to 19 years have NAFLD. A recent study by UC San Diego scientists found that pediatric NAFLD increases the risk of developing type 2 diabetes later in life.

Triclosan is an ingredient added to diverse consumer products to reduce or prevent microbial contamination, including soaps, toothpaste, cosmetics, clothing, furniture, kitchenware, pesticides and toys.

“Triclosan is a broad-spectrum antimicrobial agent that is used in many personal care products, and impregnated in numerous different materials, ranging from clothing to food packaging. It has been linked to multiple adverse health effects,” said the study’s corresponding author Robert H. Tukey, PhD, professor in the Department of Pharmacology at UC San Diego School of Medicine.

In 2016, fueled by rising evidence and public health concerns, the U.S. Food and Drug Administration banned the use of triclosan in some products and required premarket approval for others. It remains an ingredient in many products.

Two years ago, Tukey, study co-author Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology at UC San Diego School of Medicine, and colleagues published evidence that triclosan exposure worsened fatty liver disease in mice fed a high-fat diet. The latest research builds upon how that happens, showing that triclosan is passed from nursing mothers to pups, who develop early signs of fatty liver pathogenesis and perhaps a greater likelihood of fatty liver disease later in life.

The researchers exposed pregnant females to triclosan in their diet and found that it was efficiently transferred by lactation to newborn mice, causing significant fatty liver during the

suckling period, and resulting in hepatosteatosis, triglyceride accumulation, endoplasmic reticulum stress, signs of inflammation and liver fibrosis. Two key metabolic regulators responsible for triclosan-induced fatty liver disease were identified.

“Early exposure to triclosan appears to trigger pathologies that resemble NAFLD and NASH: toxicant associated fatty liver disease and toxicant associated fatty liver disease, which may predispose development of pediatric NAFLD and NASH,” said Tukey. “Recent increases in pediatric NAFLD could be a consequence of mother-to-child transmission of environmental toxicants like triclosan.”

Co-authors include: Andre A. Weber, Xiaojing Yang, Elvira Mennillo, Jeffrey Ding, Jeramie D. Watous, Mohit Jain and Shujuan Chen, all at UC San Diego.

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JOURNAL

Nature Communications

ARTICLE PUBLICATION DATE

27-Jul-2022

2. 涼しい室温がマウスの癌増殖を抑制

日付：2022 年 8 月 3 日
ソース：カロリンスカ研究所
概要：

スウェーデンのカロリンスカ研究所の研究者らによるマウス研究によると、室温を下げると、癌細胞が増殖し難くなるようだ。「Nature」誌に掲載されたこの研究では、寒冷な気温が、腫瘍の増殖に必要な糖を消費する熱を生成する褐色脂肪を活性化し、同様の代謝メカニズムが、低い室温にさらされた癌患者でも発見された。
この研究では、結腸直腸癌、乳癌、膵臓癌など、さまざまな種類の癌を患ったマウスの腫瘍の成長率と生存率を、寒い環境と暖かい環境にさらした場合で比較した。摂氏 4 度の温度に順応させたマウスは、腫瘍の成長が著しく遅く、摂氏 30 度の部屋のマウスと比較してほぼ 2 倍長生きした。
その理由を調べるために、研究者は組織内のマーカーを分析して細胞反応を研究し、画像検査を使用してブドウ糖の代謝を調べた。癌細胞は、通常、増殖するために大量のブドウ糖または砂糖を必要とする。彼らは、低温が、褐色脂肪組織における有意なブドウ糖の取り込みを引き起こすことを発見、同時に、ブドウ糖のシグナルは腫瘍細胞ではほとんど検出されなかった。研究者らが褐色脂肪またはその代謝に重要な UCP1 と呼ばれるタンパク質のいずれかを除去すると、寒冷暴露の有益な効果は本質的に一掃され、腫瘍はより高い温度に暴露されたものと同等のペースで成長した。同様に、腫瘍を持つマウスに糖分の多い飲み物を与えると、低温の影響がなくなり、腫瘍の成長が回復した。
調査結果におけるヒトとの関連性を研究するために、研究者らは健康な志願者と化学療法を受けている癌患者に対して、陽電子放出断層撮影法（PET）スキャンを使用して、摂氏 16 度のやや肌寒い室温にさらされたときに、かなりの量の褐色脂肪が活性化されることを特定した。イメージング スキャンでは、温度が高い場合と比べて低い場合に、褐色脂肪の増加と腫瘍へのブドウ糖の取り込みの低下が検出された。研究者らは、寒冷療法と薬物などの他のアプローチによる褐色脂肪組織の活性化が、癌治療の別のツールになる可能性が高い、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＞Cool room temperature inhibited cancer growth in mice (medicalxpress.com)

AUGUST 3, 2022

Cool room temperature inhibited cancer growth in mice

by Karolinska Institutet

Credit: Pixabay/CC0 Public Domain

Turning down the thermostat seems to make it harder for cancer cells to grow, according to a study in mice by researchers at Karolinska Institutet in Sweden. The study, published in the journal *Nature*, found that chilly temperatures activate heat-producing brown fat that consumes the sugars the tumors need to thrive. Similar metabolic mechanisms were found in a cancer patient exposed to a lowered room temperature.

"We found that cold-activated brown adipose tissue competes against tumors for glucose and can help inhibit tumor growth in mice," says Professor Yihai Cao at the Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, and corresponding author. "Our findings suggest that cold exposure could be a promising novel approach to cancer therapy, although this needs to be validated in larger clinical studies."

The study compared tumor growth and survival rates in mice with various types of cancer, including colorectal, breast and pancreatic cancers, when exposed to cold versus warm living conditions. Mice acclimatized to temperatures of 4 degrees Celsius had significantly slower tumor growth and lived nearly twice as long compared with mice in rooms of 30 degrees Celsius.

To find out why that is, the researchers analyzed markers in the tissue to study cellular reactions and used imaging tests to examine glucose metabolism. Cancer cells typically need large amounts of glucose, or sugar, to grow.

They found that cold temperatures triggered significant glucose uptake in brown adipose tissue, also known as brown fat, a type of fat that is responsible for keep the body warm during cold conditions. At the same time, the glucose signals were barely detectable in the tumor cells.

When the researchers removed either the brown fat or a protein crucial for its metabolism called UCP1, the beneficial effect of the cold exposure was essentially wiped out and the tumors grew at a pace on par with those that were exposed to

higher temperatures. Similarly, feeding tumor-bearing mice with a high sugar drink also obliterated the effect of cold temperatures and restored tumor growth.

"Interestingly, high sugar drinks seem to cancel out the effect of cold temperatures on cancer cells, suggesting that limiting glucose supply is probably one of the most important methods for tumor suppression," Yihai Cao says.

To study the human relevance of the findings, the researchers recruited six healthy volunteers and one patient with cancer undergoing chemotherapy. Using positron emission tomography (PET) scanning, the researchers identified a significant amount of brown fat activated in the neck, spine and chest area of healthy adults wearing shorts and T-shirts while being exposed to a slightly chilly room temperature of 16 degrees Celsius for up to six hours per day for two weeks.

The patient with cancer wore light clothing while spending time in rooms of 22 degrees Celsius for a week and then in rooms of 28 degrees Celsius for four days. Prior research has shown that even though there are significant individual differences, 28 degrees Celsius is generally considered a comfortable environmental temperature (the thermoneutral temperature) for most inactive humans. The imaging scans picked up increased brown fat and lowered tumor glucose uptake during the lower versus the higher temperature.

"These temperatures are considered tolerable by most people," Yihai Cao says. "We are therefore optimistic that cold therapy and activation of brown adipose tissue with other approaches such as drugs could represent another tool in the toolbox for treating cancer."

Explore further

Cold temps may help to combat obesity and related metabolic diseases by reducing inflammation, researchers find

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More information: Yihai Cao, Brown-fat-mediated tumour suppression by cold-altered global metabolism, *Nature* (2022). DOI: 10.1038/s41586-022-05030-3. www.nature.com/articles/s41586-022-05030-3

Journal information: Nature

Provided by Karolinska Institutet

3. 不妊マウス内でラットの精子を生産

日付：2022 年 8 月 4 日
ソース：ETH チューリッヒ
概要：

ETH チューリッヒの研究者らは、胚盤胞補完と呼ばれる技術を使用して、無菌マウス内でラットの精子細胞を生成することに成功し、その成果を、8 月 4 日付けの「Stem Cell Reports」誌で発表している。
多能性幹細胞（PSC）は、生物医学研究のための強力なツールを提供するが、PSC から卵子または精子細胞の形で配偶子を生成することは非常に困難な試みである。以前の研究では、研究者は胚盤胞補完と呼ばれる技術を使用して、特定の器官を生成できない PSC と変異マウス胚を使用して、マウス内でラット器官を生成した。この研究に基づいて、この研究チームは、マウス内でラットの精子を生成することが可能かどうか、疑問に思っていた。このアイデアをテストするために、研究者らはラットの PSC をマウス胚に注入して、マウスとラットのキメラを作成した。マウスの胚盤胞で、精子の生産に不可欠な遺伝子が変異していた。ラットの幹細胞はマウスの細胞と一緒に発生し、それによって 2 つの種の遺伝子型から構成されるキメラ動物が生成された。遺伝的不稔誘発突然変異の結果として、空のニッチが精巣内に発達し、ラット細胞がそれらにコロニーを形成し、マウスとラットのキメラでラット精子のみを生成することが可能になった。精子細胞はラットの卵細胞を受精させることができたが、胚は正常に発達せず、生きた子孫を生み出さなかった。
彼らの研究は、他の動物種から生殖細胞を生成するための宿主として不妊動物を使用できることを示しており、この概念は絶滅危惧種の動物の配偶子をより一般的な動物の内部で生産するために利用できる、としている。生物医学研究用のラット トランスジェニック モデルを作成するための改善された方法が含まれる可能性もある、としている。

研究関連ニュース/他のトップページに戻る

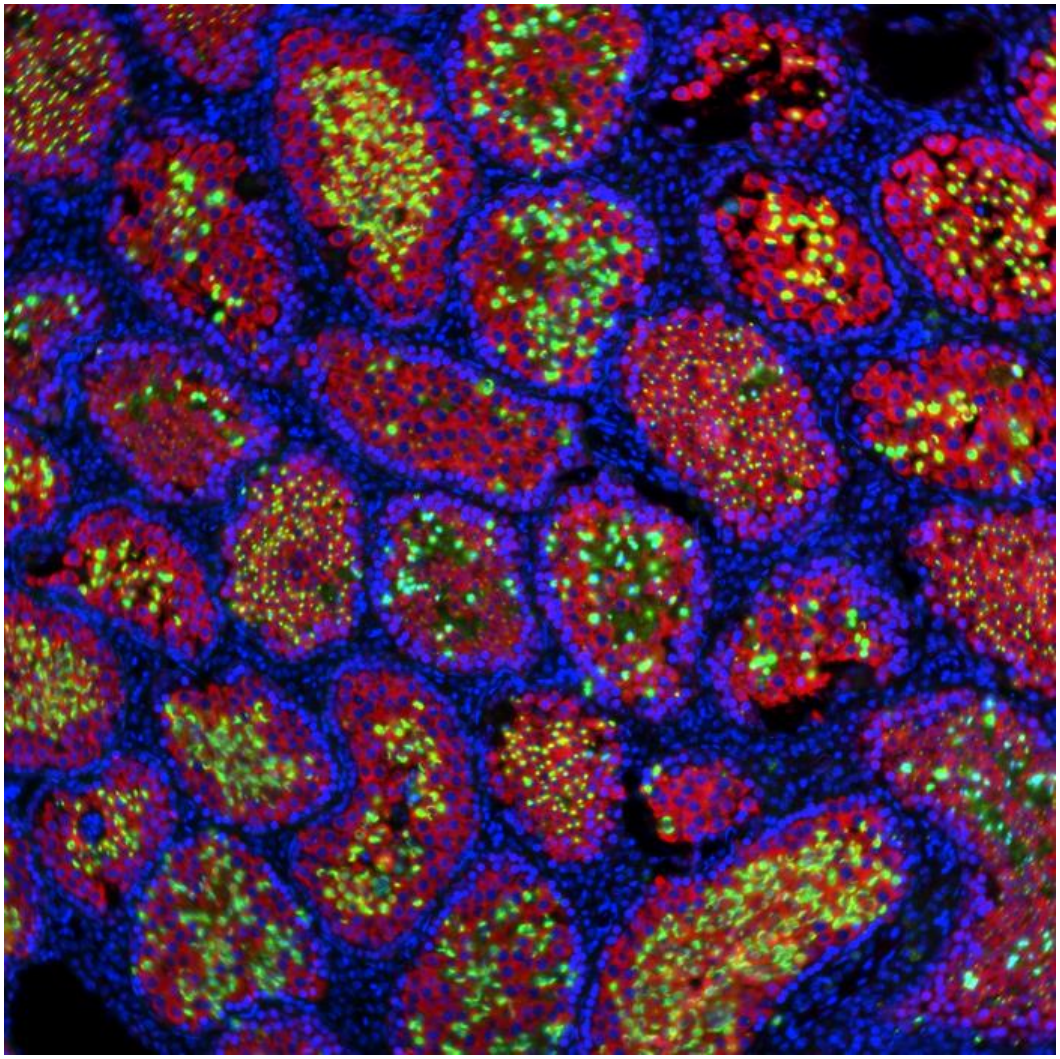
＜英文＞Sterile mice produce rat sperm (bioengineer.org)

Sterile mice produce rat sperm

BY **BIOENGINEER**

August 4, 2022

Researchers generated rat sperm cells inside sterile mice using a technique called blastocyst complementation. The advance appears August 4 in the journal *Stem Cell Reports*.



Credit: Joel Zvick/ETH Zurich

Researchers generated rat sperm cells inside sterile mice using a technique called blastocyst complementation. The advance appears August 4 in the journal *Stem Cell Reports*.

“Our study shows that we can use sterile animals as hosts for the generation of germ cells from other animal species,” says senior author Ori Bar-Nur, a stem cell biologist at ETH Zurich. “Aside from a conceptual advancement, this notion can be utilized to produce endangered animal species gametes inside more prevalent animals. Other implications may involve an improved method to produce rat transgenic models for biomedical research.”

Pluripotent stem cells (PSCs) provide a powerful tool for biomedical research, but the generation of gametes in the form of eggs or sperm cells from PSCs is a highly challenging endeavor. In prior studies, researchers used a technique called blastocyst

complementation to generate rat organs in mice using PSCs and mutated mouse embryos that cannot produce specific organs. Building on this work, Bar-Nur and his collaborators wondered whether it would be possible to generate rat sperm inside mice that carry a genetic mutation that otherwise renders them sterile.

To test this idea, the researchers injected rat PSCs into mouse embryos to produce mouse-rat chimeras. An essential gene for sperm production was mutated in the mouse blastocysts. The rat stem cells developed together with the mouse cells, thereby generating a chimeric animal composed of genotypes from the two species. As a consequence of the genetic sterility-inducing mutation, an empty niche developed inside the testes, which enabled the rat cells to colonize them and exclusively generate rat sperm in mouse-rat chimeras. The sperm cells could fertilize rat egg cells, but the embryos did not develop normally or give rise to live offspring.

“We were surprised by the relative simplicity by which we could mix the two species to produce viable mouse-rat chimeras. These animals, by large, appeared healthy and developed normally, although they carried both mouse and rat cells in a chimeric animal,” Bar-Nur says. “The second surprise was that indeed all the sperm cells inside the chimeras were of rat origin. As such, the mouse host environment, which was sterile due to a genetic mutation, was still able to support efficient sperm cell production from a different animal species.”

Although the researchers were able to generate rat sperm cells that morphologically appeared indistinguishable from normal rat sperm cells, these cells were immotile and the fertilization rates of rat eggs was significantly lower in comparison to rat sperm cells produced in rats. Nonetheless, the work provides a proof-of-principle that one can generate sperm cells of one animal species in another by mixing the two species in an artificially generated organism called a chimera. Using sterile mice for genetically modified rat PSCs may speed up the production of transgenic rats to model human diseases in biomedical research.

Moving forward, the researchers will try to produce live animals from rat sperm cells that have been produced in mouse-rat chimeras. “We will need to improve the technique and demonstrate that rat sperm produced in mice can give rise to adult rats when fertilizing rat eggs,” Bar-Nur says.

A more distant plan is to adapt this technique for the production of gametes from endangered rodent species to support animal species conservation efforts. “For example, to the extent we can procure stem cells from an endangered rodent, which at some point in time might become extinct, we may be able to employ the same method to produce its germ cells via chimera production with mice,” Bar-Nur says. “However, it is important to note that several scientific hurdles will need to be overcome to adapt this technique to other animal species. In addition, one still needs to showcase the production of female reproductive cells (i.e., eggs) in female sterile mice, especially if we envision utilizing this technology for species conservation efforts.”

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This work was supported by startup funds from ETH Zurich. Other support was provided by the Swiss National Science Foundation, the Good Food Institute Foundation, the Novartis Foundation for Medical-Biological Research, the Helmut Horten Foundation, and the European Research Council.

Stem Cell Reports, Zvick et al. “Exclusive generation of rat spermatozoa in sterile mice utilizing blastocyst complementation with pluripotent stem cells.” https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(22)00364-2
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JOURNAL

Stem Cell Reports

DOI

10.1016/j.stemcr.2022.07.005

METHOD OF RESEARCH

Experimental study

SUBJECT OF RESEARCH

People

ARTICLE TITLE

Exclusive generation of rat spermatozoa in sterile mice utilizing blastocyst complementation with pluripotent stem cells

ARTICLE PUBLICATION DATE

4-Aug-2022

4. アルコール飲酒によって腸内微生物が変化するが、我々が考えるほどではない –マウス研究

過度のアルコール摂取は腸内細菌の過増殖を引き起こす可能性があるが、マウス研究では、この不均衡がアルコール性肝疾患のリスクに大きな役割を果たしているようには見えない

日付：2022 年 8 月 11 日
ソース：カリフォルニア大学サンディエゴ校
概要：

慢性的アルコール飲酒は、肝障害と死亡の主な原因であり、米国では、毎年約 3 万人が肝硬変などのアルコール性肝疾患で死亡している。過剰なアルコール摂取の悪影響としては、腸内微生物叢への影響があるが、消費されたアルコールの大部分は口と胃で吸収され、腸に到達しないため、それがどのように起こるかは謎である。2022 年 8 月 8 日に「Nature Communications」誌に掲載された新しい研究で、カリフォルニア大学サンディエゴ校の研究者らがその答えを提案している。
酢酸は、細胞の代謝に使用される栄養素であり、食欲の調節、エネルギー消費、および免疫応答に大切な役割を果たす。中程度のレベルでは、心機能の改善から赤血球産生および記憶機能の強化まで、全体的な健康を促進するが、過剰なレベルでは、癌を含む疾患に関連する代謝変化に関連する。
今回の研究では、研究チームは、げっ歯類の腸内で 3 つのアセテートに分解できる分子をマウスに与えた。その結果、マウスにアルコールを与えたときに観察されたのと同様に、追加の酢酸塩によって動物の腸内微生物叢が変化したが、肝臓に損傷を与えることはなかった。この発見は、微生物のエタノール代謝が腸内微生物叢の異常（不均衡）には大きく寄与しておらず、酢酸塩によって変化した微生物叢が肝臓の損傷に大きな役割を果たしていないことを示唆している。研究者らは、この発見は、アルコール性肝疾患の差し迫った新しい治療法につながるわけではないものの、微生物叢に対する酢酸塩の影響を明らかにし、将来の研究デザインを改良するのに役立つものだ、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＞Alcohol use can alter gut microbes, but not i | EurekAlert!

NEWS RELEASE 11-AUG-2022

Alcohol use can alter gut microbes, but not in the way you might think

Excessive alcohol consumption can cause bacterial overgrowth in gut, but mouse studies found this imbalance doesn't appear to play major role in alcoholic liver disease risk

Peer-Reviewed Publication

UNIVERSITY OF CALIFORNIA - SAN DIEGO

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Chronic alcohol use is a major cause of liver damage and death: Approximately 30,000 persons in the United States die annually from alcoholic liver diseases, such as cirrhosis. Among the negative impacts of excessive alcohol use is its ability to adversely affect the gut microbiome, though how that happens has been a mystery, since the majority of consumed alcohol is absorbed in the mouth and stomach and does not reach the intestines.

In a new study, published August 8, 2022 in *Nature Communications*, researchers at University of California San Diego, with colleagues elsewhere, propose an answer: Reprogramming of gut microbiota is caused by acetate produced by the liver diffusing back into the intestines where it becomes a carbon source to support bacterial growth.

“You can think of this a bit like dumping fertilizer on a garden,” said co-corresponding author Karsten Zengler, PhD, professor in the departments of Pediatrics and Bioengineering at UC San Diego School of Medicine and Jacobs School of Engineering, respectively. “The result is an explosion of imbalanced biological growth, benefitting some species but not others.”

Bernd Schnabl, MD, professor of medicine and gastroenterology at UC San Diego School of Medicine, is the other co-corresponding author.

Acetate is a nutrient used in cellular metabolism and has roles in appetite regulation, energy expenditure and immune response. In moderate levels, it promotes overall health, from improved cardiac function to enhanced red blood cell production and memory function. In excessive levels, it is associated with metabolic changes linked to disease, including cancer.

In the latest study, Zengler and colleagues fed mice a molecule that could be broken down into three acetates in the rodents’ gut. The researchers noted the animals’ intestinal microbiota were altered by the additional acetate in a way similar to what they observed when feeding alcohol to the mice, but without damaging effects to their livers.

“Chronic alcohol consumption is associated with lower intestinal expression of antimicrobial molecules. Persons will alcohol-related liver disease commonly have bacterial overgrowth in their guts,” said Zengler. “These findings suggest that microbial ethanol metabolism does not contribute significantly to gut microbiome dysbiosis (imbalance) and that the microbiome altered by acetate does not play a major role in liver damage.”

“The situation is more complicated than previously assumed. It’s not as simple as more ethanol equals microbiome changes and thus, microbiome dysbiosis equals more liver disease. While this finding does not translate to imminent new treatments for alcoholic liver

disease, it will help to delineate the effect of acetate on the microbiota and help refining future study designs."

The authors said the findings are important because they move the investigation past whether "changes in the gut microbiome are related to ethanol consumption per se are critical … and towards identifying bacteria that are causal for deleterious effects of alcohol consumption, rather than side-effects either of consumption or disease."

Co-authors include: Camerson Martino, Livia S. Zaramela, Bei Gao, Mallory Embree, Janna Tarasova, Seth J. Parker, Yanhan Wang, Huikuan Chu, Peng Chen, Kuei-Chuan Lee, Daniela Domingos Glazerani, Asama Lekbua, Maxwell Neal and Rob Knight, all at UC San Diego; Jivani M. Gengatharan and Christian M. Metallo, UC San Diego and Salk Institute for Biological Studies; and Hidekazu Tsukamoto, Southern California Research Center for ALPD and Department of Veterans Affairs Greater Los Angeles Healthcare System.

# # #

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Media Contact

Scott La Fee
University of California – San Diego
slafee@ucsd.edu
Office: 858-249-0431

5. マウスの腫瘍成長を抑制する脂肪細胞からのホルモンを特定

日付:2022 年 8 月 15 日
ソース:ミシガン大学
概要:

ミシガン大学生命科学研究所の新しい研究によると、脂肪細胞から分泌されるホルモンは、マウスの肝臓腫瘍の成長を抑えることができる。この調査結果は、最も一般的な肝臓癌である肝細胞癌に対する治療法を開発するための概念実証を提供する、として「Cell Metabolism」誌で発表している。
研究チームは、モデルとしてマウスを使用し、分子および細胞の変化が非アルコール性脂肪肝疾患によってどのように影響を受けるか、またこれらの変化が結果としてこの疾患の進行にどのようにつながるかを研究している。肝臓に比較的良性の脂肪が蓄積することから始まり、これが後に非アルコール性脂肪性肝炎(NASH)に発展する可能性があり、肝臓癌のリスクが高まる。肝臓には、さまざまな免疫細胞を含むさまざまな種類の細胞が多数含まれているが、今回の研究で、科学者らは、NASH から癌への進行を逆転させる潜在的な治療標的として、これらの細胞タイプのバランスと相互作用を混乱させる特定の分子変化を特定したいと考えていた。
研究チームは以前、主に脂肪細胞から分泌されるホルモンである NRG4 がマウスの肝臓を NASH から保護し、このホルモンの減少または喪失がより深刻なレベルの肝疾患につながることを明らかにした。今回、チームは、このホルモンが NASH マウスの肝細胞癌を抑制できることを発見。彼らの発見は、ホルモン NRG4 を欠くマウスは、正常レベルの NRG4 を持つマウスよりも、より深刻な NASH とより多くの肝臓腫瘍を発症することを示した。科学者らは、脂肪組織での NRG4 の発現を遺伝的に上昇させるか、組換え NRG4 融合体でマウスを治療することにより、マウスのホルモンのレベルを高めると、NRG4 のレベルの増加が NASH 肝癌の進行を抑制した。「我々の発見は、肝臓中心の枠組みから抜け出し、脂肪由来のホルモンが実際に肝臓環境を再プログラムし、肝臓癌の発生に非常に大きな影響を与える可能性があることを示している。NRG4 を肝細胞癌の治療薬として追求するには、さらなる研究が必要だ。」としながらも、研究チームは現在、ホルモンの有効性を改善するためのアプローチを調査し、肝臓のマクロファージと T 細胞の調節の根底にある性質をよりよく理解するべく研究を進めている。

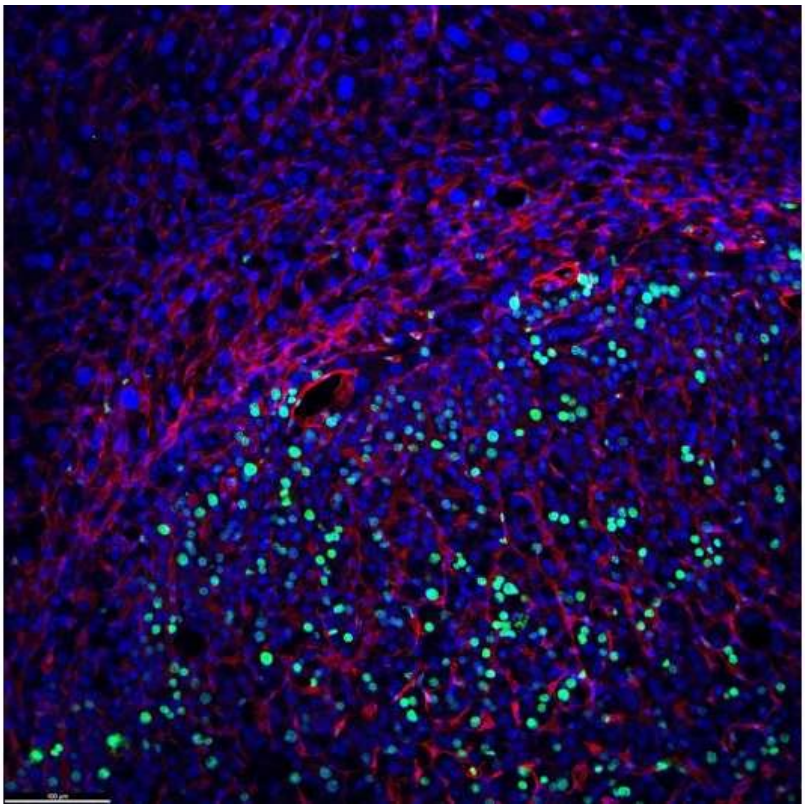
研究関連ニュース/他のトップページに戻る

＜英文＞Researchers identify hormone from fat cells that restrains tumor growth in mice (medicalxpress.com)

AUGUST 15, 2022

Researchers identify hormone from fat cells that restrains tumor growth in mice

by Emily Kagey, University of Michigan



Normal liver tissue (top) and a liver cancer nodule (bottom) containing many dividing cells (labeled in green). Red color indicates blood vessels. Credit: Jiandie Lin, Ph.D., University of Michigan Life Sciences Institute.

A hormone secreted by fat cells can restrain the growth of liver tumors in mice, according to a new study from the University of Michigan Life Sciences Institute.

The findings offer a proof-of-concept for developing therapies against hepatocellular carcinoma, the most common form of liver cancer.

Jiandie Lin and his team use mice as a model to study how molecular and cellular changes are affected by nonalcoholic fatty liver disease, and how these changes consequently lead to the progression of this disease. While it begins as a relatively benign accumulation of fat in the liver, the disorder can develop into nonalcoholic steatohepatitis, or NASH, which increases the risk for liver cancer.

The liver contains scores of different cell types, including various immune cells. Using single-cell RNA sequencing, a technology for probing gene expression of individual cells within complex tissues, Lin and his team previously constructed a liver cell atlas and a blueprint of intercellular signaling in healthy and NASH mouse livers.

For this latest study, published in *Cell Metabolism*, the scientists wanted to identify specific molecular changes in the NASH state that disrupt balance and interactions of these cell types, as potential therapeutic targets to reverse the progression from NASH to cancer.

"Liver cancer in NASH patients is different from cancers caused by viral hepatitis, in that it often develops in the absence of liver cirrhosis," said Lin, a faculty member at the U-M Life Sciences Institute and the study's senior author. "We suspect that different disease mechanisms may be engaged in NASH-related liver cancer."

Lin and colleagues observed changes in two types of immune cells in particular that appear to contribute to the development of HCC. In mouse livers with NASH, T cells—the immune cells that normally fight infected or damaged cells, such as cancerous cells—showed hallmarks of functional impairments. At the same time, the team found that a second type of immune cell, called macrophages, acquired molecular features typically associated with cancers.

"These changes we saw in macrophages and T cells resemble the tumor microenvironment, but they are happening even before any cancer becomes apparent," said Lin, who is also a professor of cell and developmental biology at the U-M Medical School. "It gives us a hint that maybe these changes in the liver microenvironment could provide fertile ground for liver cancer cells to appear and grow. It almost looks like the liver, once it develops NASH, is already preparing for cancer cells to thrive."

The team also identified a hormone that serves as a checkpoint for disease progression, and it appears to have potential as a treatment: neuregulin 4, or NRG4.

Lin's team previously revealed that NRG4—a hormone that is secreted primarily by fat cells—can protect mouse livers against NASH, and that a decrease or loss of this hormone leads to more severe levels of liver disease.

Now, the team has found that the hormone can suppress hepatocellular carcinoma in NASH mice. Their findings show that mice lacking the hormone NRG4 develop more severe NASH and more liver tumors than mice with normal levels of NRG4.

When the scientists boosted levels of the hormone in mice—either by genetically elevating the expression of NRG4 in fat tissues or by treating mice with a recombinant NRG4 fusion—the increased levels of NRG4 suppressed NASH liver cancer progression.

"A lot of studies on liver cancer focus on the cancerous liver cells themselves: how they proliferate and how they evade the immune system," Lin said. "But our findings break out of this liver-centered framework, showing a fat-derived hormone could actually reprogram the liver environment and have a very big impact on liver cancer development."

More research is needed before NRG4 can be pursued as a therapeutic for hepatocellular carcinoma. Lin and his team now plan to investigate approaches for improving the hormone's effectiveness and to better understand the nature underlying its regulation of macrophages and T cells in the liver.

Explore further

Fat hormone linked to progression of fatty liver disease may hold key to new treatments

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More information: Jiandie Lin, Neuregulin 4 suppresses NASH-HCC development by restraining tumor-prone liver microenvironment, *Cell Metabolism* (2022). DOI: 10.1016/j.cmet.2022.07.010. www.cell.com/cell-metabolism/f … 1550-4131(22)00309-6

Journal information: Cell Metabolism

Provided by University of Michigan

6. 極端な気候変動に最も苦しむ動物と生き残る動物は？

日付：2022 年 8 月 19 日
ソース：南デンマーク大学
概要：

長生きして、子孫が少ない動物、ラマ、クマ、ゾウは、マウスやレミングよりも気候変動に耐える可能性が高い、と南デンマーク大学の研究者らが言っている。
極端な気候変動（主に温暖化）がより一般的になるにつれて、全ての動物が暑さを感じるようになるが、一部の動物は他の動物より脆弱だ。
過去 10 年間、研究者らは 157 の哺乳類個体群の個体数変動を分析した。このデータを異常気象に関する情報とクロスチェックした後、彼らはどの種が最も生存確率が高いかを判断した。チンパンジーやその他の寿命の長い大型哺乳類は、異常気象に耐える可能性が高い。また、ハイイログマ、アメリカバイソン、クリップスプリンガー、シュライバーコウモリも同様だ。一方、極端な天候は、アザラのグラスマウス、オリーブグラスマウス、エレガントなファットテールマウスのオポッサム、カナダのレミングに大きな打撃を与える。ツンドラハタネズミ、ホッキョクギツネ、オコジョ、トガリネズミ、ヨゴレ、ホッキョクジリスも苦労する。これは、短命の動物が短期間の個体数の変化に対してより脆弱であるためである。
ただし、これは、大型の動物が絶滅の危機に瀕しているという意味でも、小型の動物が絶滅の運命にあるという意味でもない。寿命が短い小型の哺乳類は、繁殖率が高いため、より早く「ブーム」に戻ることもある。「これらの小さな哺乳類は極端な天候に素早く反応し、双方向に変化します。したがって、異常気象に対する脆弱性を絶滅のリスクと同一視すべきではありません」と、レポートの共著者であるジョン・ジャクソンは述べている。
極端な天候に最もよく耐えることができる大型の動物を含むすべての動物は、他のさまざまな生存上のリスクにも脅かされている。「生息地の破壊、密猟、汚染、侵入種は、多くの動物種を脅かす要因です。多くの場合、気候変動よりもさらに深刻です」とジャクソンは説明する。国連の生物多様性条約によると、我々は毎日約 150 種を失っている、とのことだ。

研究関連ニュース/他のトップページに戻る

＜英文＞Which animals will suffer most from extreme climate change - and which will survive? | Euronews

Which animals will suffer most from extreme climate change - and which will survive?

The new study can be used to make predictions for species not directly included in the research, such as this sugar glider possum.

By **Charlotte Elton** • Updated: 23/08/2022 - 13:01

Llamas, bears and elephants are more likely to withstand climate change than mice and lemmings, according to a new study.

This is because they live longer and have fewer offspring, University of Southern Denmark researchers have found.

As extreme weather events become more common, all animals will feel the heat - but some are **more vulnerable** than others.

“We can see a clear pattern,” says biologist Owen Jones, one of the study’s authors.

“Animals that live a long time and have few offspring are less vulnerable when **extreme weather** hits than animals that live for a short time and have many offspring.

“Examples are llamas, long-lived bats and elephants versus mice, possums and rare marsupials such as the Woylie.”

*Llamas are one of the species well placed to withstand extreme weather events, according to a new study*Canva

- **Cheetahs are being reintroduced to India after 70 years of extinction**
- **Long lost iguana 'born again' on Galapagos Island after nearly two centuries of extinction**

WHICH SPECIES CAN WITHSTAND CLIMATE CHANGE BEST?

Over the past 10 years, researchers analysed **population fluctuations** in 157 mammal populations.

After cross-checking this data with information on extreme weather events, they determined which species have the best survival odds.

The African **elephant**, Siberian tiger, chimpanzee, greater horseshoe bat, llama, vicuña and white rhinoceros are likely to survive heavy rainfall or prolonged drought.

*Chimpanzees - and other large mammals with long life spans - are more likely to withstand extreme weather events*canva

So too are the grizzly bear, American bison, klipspringer and Schreibers's bat.

On the other hand, extreme weather will hit the Azara's grass mouse, olive grass mouse, elegant fat-tailed mouse opossum and Canadian lemming hard.

The Tundra vole, Arctic fox, stoat, common shrew, woylie and arctic ground **squirrel** will also struggle.

This is because short-lived **animals** are more vulnerable to short-term population changes.

For example, a **drought** might decimate a mice population by destroying most of its food. Many of its reproductive members may perish before the drought is over.

In comparison, larger mammals can wait for better times to reproduce, or invest all of their energy in one offspring.

*Short-lived animals like shrews are more vulnerable to short-term population changes.*Canva

DOES THIS MEAN THAT LARGER ANIMALS ARE SAFE FROM EXTINCTION?

This does not mean that larger animals are safe from **extinction** - or that smaller animals are inevitably doomed.

Smaller mammals with shorter lifespans can also 'boom' back more quickly, due to prolific rates of **reproduction**.

"These small mammals react quickly to extreme weather, and it goes both ways. Their vulnerability to extreme weather should therefore not be equated with a risk of **extinction**," says report co-author John Jackson.

However, all animals - including large ones that are best able to withstand **extreme weather** - are also threatened by various other **existential risks.**

"**Habitat destruction**, poaching, **pollution** and invasive species are factors that threaten many animal species - in many cases even more than climate change," Jackson explains.

According to the UN Convention on Biological Diversity, we lose around 150 species every single day.

7. 栄養価のない甘味料がヒトの腸内細菌叢に影響を与え、血糖反応を変える可能性 – マウス研究

日付：2022 年 8 月 19 日
ソース：ワイツマン科学研究所/Cell Press
概要：

1800 年代後半以来、栄養価のない甘味料は、砂糖のすべての甘さをカロリーなしで提供することを約束してきた。更にそれらは人体に影響を及ぼさないと長い間信じられてきた。今回、8 月 19 日に「Cell」誌に発表された研究では、これらの砂糖代用品が不活性ではなく、実際にヒト消費者のマイクロバイオームを変化させ血糖値を変える可能性があることを発見して、この概念に異議を唱えている。
2014 年、ワイツマン科学研究所とドイツ国立がんセンター（DKFZ）の免疫学者でマイクロバイオームの研究者である上級著者の Eran Elinav と彼のチームは、非栄養甘味料がマウスのマイクロバイオームに影響を与え、血糖反応に影響を与える可能性があることを発見。チームは、これらの結果がヒトにも見られるかどうか関心を持っていた。
非栄養甘味料のヒト消費者をグループとして調べたところ、非栄養甘味料の 2 つであるサッカリンとスクラロースが、健康な成人の耐糖能に大きな影響を与えることが分かった。興味深いことに、微生物の変化は、ヒトの血糖反応に見られた変化と高度に相関していた。因果関係を確立するために、研究者は研究対象からの微生物サンプルを無菌マウス（完全に無菌状態で飼育され、独自のマイクロバイオームを持たないマウス）に移した。その結果、非栄養甘味料群のすべてで、これらの無菌マウスに、それぞれの非栄養甘味料を消費していた時点で収集されたトップ レスポンダー個人のマイクロバイオームを移したとき、レシピエントマウスは、ドナー個体のものを非常に顕著に反映する血糖変化を発症した。対照的に、ボトム レスポンダーのマイクロバイオームは、そのような血糖反応を誘発することがほとんどできなかった。
これらの結果から、非栄養甘味料の消費に応じたマイクロバイオームの変化が、高度にパーソナライズされた方法でヒト消費者の血糖変化を引き起こす可能性があることを示唆している、と研究者は結論している。

研究関連ニュース/他のトップページに戻る

＜英文＞Non-nutritive sweeteners affect human microbiomes and can alter glycemic responses -- ScienceDaily

Non-nutritive sweeteners affect human microbiomes and can alter glycemic responses

Date:

August 19, 2022

Source:

Cell Press

Summary:

Since the late 1800s non-nutritive sweeteners have promised to deliver all the sweetness of sugar with none of the calories. They have long been believed to have no effect on the human body, but researchers challenge this notion by finding that these sugar substitutes are not inert, and, in fact, some can alter human consumers' microbiomes in a way that can change their blood sugar levels.

FULL STORY

Since the late 1800s non-nutritive sweeteners have promised to deliver all the sweetness of sugar with none of the calories. They have long been believed to have no effect on the human body, but researchers publishing in the journal *Cell* on August 19 challenge this notion by finding that these sugar substitutes are not inert, and, in fact, some can alter human consumers' microbiomes in a way that can change their blood sugar levels.

In 2014, senior author Eran Elinav an immunologist and microbiome researcher at the Weizmann Institute of Science and the German National Cancer Center (DKFZ) and his team found that non-nutritive sweeteners affected the microbiomes of mice in ways that could impact their glycemic responses. The team was interested in whether these results would also be found in humans.

To address this important question, the research team carefully screened over 1300 individuals for those who strictly avoid non-nutritive sweeteners in their day-to-day lives, and identified a cohort of 120 individuals. These participants were broken into six groups: two controls and four who ingested well below the FDA daily allowances of either aspartame, saccharin, stevia, or sucralose.

"In subjects consuming the non-nutritive sweeteners, we could identify very distinct changes in the composition and function of gut microbes, and the molecules they secret into peripheral blood. This seemed to suggest that gut microbes in the human body are rather responsive to each of these sweeteners," says Elinav. "When we looked at consumers of non-nutritive sweeteners as groups, we found that two of the non-nutritive sweeteners, saccharin and sucralose, significantly impacted glucose tolerance in healthy adults. Interestingly, changes in the microbes were highly correlated with the alterations noted in people's glycemic responses."

To establish causation, the researchers transferred microbial samples from the study subjects to germ-free mice -- mice that have been raised in completely sterile conditions and have no microbiome of their own.

"The results were quite striking," says Elinav. "In all of the non-nutritive sweetener groups, but in none of the controls, when we transferred into these sterile mice the microbiome of the top responder individuals collected at a time point in which they were consuming the respective non-

nutritive sweeteners, the recipient mice developed glycemic alterations that very significantly mirrored those of the donor individuals. In contrast, the bottom responders' microbiomes were mostly unable to elicit such glycemic responses," he adds. "These results suggest that the microbiome changes in response to human consumption of non-nutritive sweetener may, at times, induce glycemic changes in consumers in a highly personalized manner."

Elinav says that he expects the effects of the sweeteners will vary person to person because of the incredibly unique composition of our microbiome. "We need to raise awareness of the fact that non-nutritive sweeteners are not inert to the human body as we originally believed. With that said, the clinical health implications of the changes they may elicit in humans remain unknown and merit future long-term studies."

"In the meantime, we need to continue searching for solutions to our sweet tooth craving, while avoiding sugar, which is clearly most harmful to our metabolic health," says Elinav. "In my personal view, drinking only water seems to be the best solution."

Story Source:

Materials provided by **Cell Press**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Jotham Suez, Yotam Cohen, Rafael Valdés-Mas, Uria Mor, Mally Dori-Bachash, Sara Federici, Niv Zmora, Avner Leshem, Melina Heinemann, Raquel Linevsky, Maya Zur, Rotem Ben-Zeev Brik, Aurelie Bukimer, Shimrit Eliyahu-Miller, Alona Metz, Ruthy Fischbein, Olga Sharov, Sergey Malitsky, Maxim Itkin, Noa Stettner, Alon Harmelin, Hagit Shapiro, Christoph K. Stein-Thoeringer, Eran Segal, Eran Elinav. **Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance**. *Cell*, 2022; DOI: 10.1016/j.cell.2022.07.016

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8. マイクロバイオームを標的にして、マウスの食物アレルギーを逆転

日付：2022 年 8 月 21 日
ソース：シカゴ大学/American Chemical Society（米国化学会：ACS）
概要：

健康なマイクロバイオームによって作られる酪酸塩と呼ばれるバクテリア化合物は、実験室でのテストでアレルギー反応に対して有望であることが示されているが、酷い悪臭があり、味も悪いため経口摂取するのは厄介である。更に、例え飲み込むことができたとしても、酪酸は下部腸の目的地に到達する前に消化されてしまう。今回、UChicago の科学者らは、この化合物をより美味しく届ける方法を説明し、彼らの「高分子ミセル」がマウスのピーナッツアレルギーに対して効果的であることを報告している。
次は、より大きな動物での試験であり、その後に臨床試験が続くのだが、これらの試験が成功し、米国食品医薬品局に承認された場合、ミセルは小さなパケットで販売される可能性がある。消費者はパケットを引き裂き、内容物をグラスの水またはジュースにかき混ぜる。チームはまた、注射による投与についても調査しており、この注射アプローチがマウスのピーナッツアレルギーの治療に効果的であることを発見した。これは、体全体ではなく局所的に免疫活性化を抑制するためにも使用できる可能性があり、たとえば、臓器移植を受けた患者や、関節リウマチなどの局所的な自己免疫および炎症状態を患っている患者に役立つ可能性がある、としている。

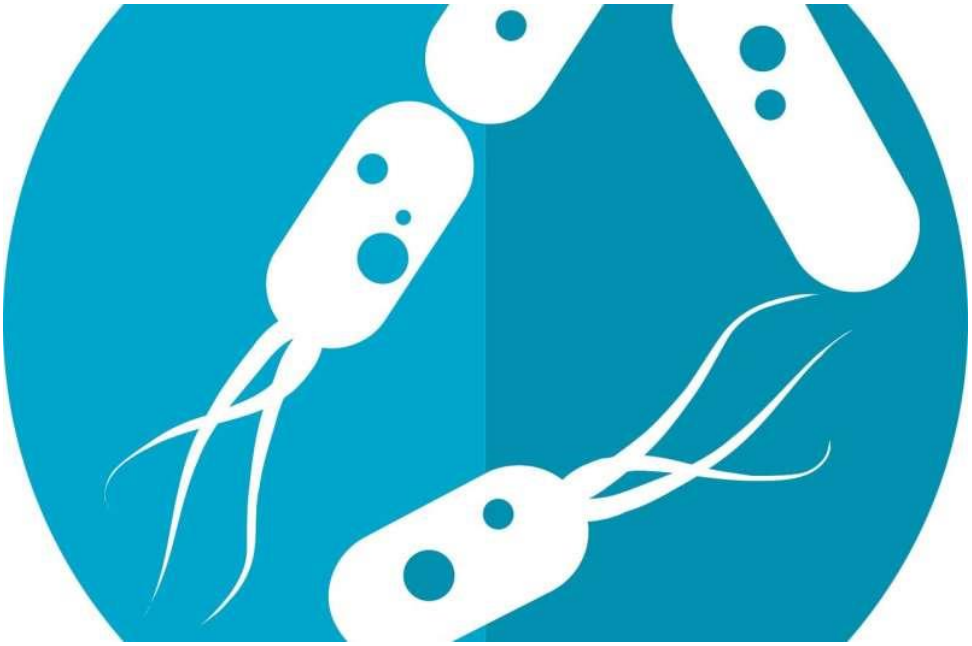
研究関連ニュース/他のトップページに戻る

＜英文＞Food allergies can be reversed in mice by targeting the microbiome (medicalxpress.com)

AUGUST 21, 2022

Food allergies can be reversed in mice by targeting the microbiome

by American Chemical Society



Credit: Pixabay/CC0 Public Domain

Although many people with dietary allergies experience mild symptoms when exposed to triggering foods, some face potentially fatal consequences. A bacterial compound called butyrate that's made by healthy microbiomes has shown promise against allergic reactions in lab tests, but it's nasty to take orally. Today, scientists describe a more palatable way to deliver this compound and report that their "polymeric micelles" are effective against peanut allergies in mice. The treatment could someday counteract many types of food allergies and inflammatory diseases.

The researchers will present their results at the fall meeting of the American Chemical Society (ACS).

Some of the bacteria in the gut microbiome produce metabolites, such as butyrate, that foster the growth of beneficial bacteria and maintain the lining of the gut. If a person's microbiome is unhealthy and lacks these butyrate-producing bacteria, fragments of partially digested food can leak out of the gut and produce an immune reaction that results in an allergic response.

One way to treat those with allergies would be to provide the missing bugs to them orally or with a fecal transplant, but that hasn't worked well in the clinic, according to Jeffrey Hubbell, Ph.D., one of the project's principal investigators (PIs). "So we thought, why don't we just deliver the metabolites—like butyrate—that a healthy microbiome produces?"

"But butyrate has a very bad smell, like dog poop and rancid butter, and it also tastes bad, so people wouldn't want to swallow it," says Shijie Cao, Ph.D., who is presenting the results at the meeting for the team, which is at the University of Chicago. And even if people could choke it down, butyrate would be digested before reaching its destination in the lower gut.

To overcome these challenges, the researchers, including co-PI Cathryn Nagler, Ph.D., and Ruyi Wang, Ph.D., designed a new delivery system. They polymerized butanoyloxyethyl methacrylamide—which has a butyrate group as a side chain—with methacrylic acid or hydroxypropyl methacrylamide. The resulting polymers self-assembled into aggregates, or polymeric micelles, that tucked the butyrate side chains in their core, thus cloaking the compound's foul smell and taste.

The researchers administered these micelles to the digestive systems of mice lacking either healthy gut bacteria or a properly functioning gut lining. After digestive juices released the butyrate in the lower gut, the inert polymers were eliminated in the feces. The treatment restored the gut's protective barrier and microbiome, in part by increasing production of peptides that kill off harmful bacteria, which made room for butyrate-producing bacteria.

Most importantly, dosing allergic mice with the micelles prevented a life-threatening anaphylactic response when they were exposed to peanuts. "This type of therapy is not antigen specific," Cao notes. "So theoretically, it can be broadly applied to any food allergies through the modulation of gut health."

Next up are trials in larger animals, followed by clinical trials. If those trials succeed and the U.S. Food and Drug Administration approves the oral treatment, the micelles could be marketed in small packets; consumers would tear open a packet and stir the contents into a glass of water or juice. In other work with the micelles, the team is analyzing data on treating inflammatory bowel diseases with the oral therapy.

The team is also investigating administration via injection. The researchers have shown that this method allows the micelles and their butyrate cargo to accumulate in lymph nodes, which are part of the immune system. They found that this approach is effective in treating peanut allergies in mice, but it could also be used to suppress immune activation locally—rather than throughout the body. For example, injections could be helpful in patients who have had an organ transplant or who have a localized autoimmune and inflammatory condition, such as rheumatoid arthritis.

Explore further

Link between intestinal inflammation and microbiome

More information: Microbial metabolite butyrate-prodrug polymeric micelles promote gut health and treat food allergies, ACS Fall 2022. www.acs.org/content/acs/en/mee … tings/fall-2022.html

Provided by American Chemical Society

9. ミトコンドリア病マウスモデルの作製に成功

日付：2022 年 8 月 30 日
ソース：筑波大学
概要：https://www.tohoku.ac.jp/japanese/2022/08/press20220824-01-rna.html

ミトコンドリアは、細胞内のエネルギー工場として知られる細胞小器官です。生物の遺伝情報である DNA のほとんどは細胞内の核に存在していますが、ミトコンドリアにも独自のゲノムであるミトコンドリア DNA が存在しています。このミトコンドリア DNA に突然変異が生じると、ミトコンドリア病と呼ばれる代謝性疾患の原因となることや、さらに最近では、糖尿病、がん、老化などの原因になる可能性が示唆されています。ミトコンドリア病の症例が報告されてから 50 年以上の年月が経ちますが、ミトコンドリア DNA に病原性変異を有するモデル動物の作出例はごくわずかしかありません。そのため、ミトコンドリア病やミトコンドリア DNA の突然変異が関与するとされるさまざまな疾患の発症機構の解明はもとより、治療法の探索や創薬開発は進んでいないのが現状です。

本研究では、ミトコンドリア DNA の中の $tRNA^{Leu(UUR)}$遺伝子領域に病原性点突然変異を有するモデルマウスを、世界に先駆けて樹立することに成功しました。このモデルマウスでは、ミトコンドリア病の症例と類似した病態だけでなく、ミトコンドリア DNA の変異で生じるとされる糖尿病や肝機能障害が再現されていました。このようなモデルマウスは、ミトコンドリア DNA 変異に関する研究に資する貴重な動物資源であり、将来的には、ミトコンドリア病や多様なミトコンドリア関連疾患の治療法の探索や治療薬開発に役立つことが期待されます。

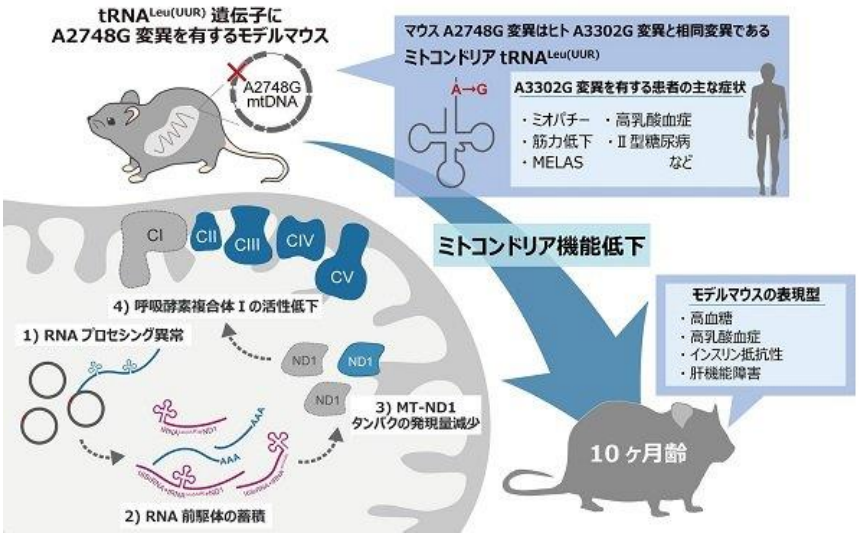


図　本研究の概略図

mtDNA の tRNA$^{Leu(UUR)}$領域に A2748G 変異を有するモデルマウスを作出した。A2748G 変異はヒト A3302G 変異と相同であり、ヒト患者ではミオパチー（筋疾患）や高乳酸血症などが主な臨床症状である。A2748G 変異は 1) RNA プロセシングを阻害することで、2）ミトコンドリア内に未成熟な RNA 前駆体を蓄積させ、3) MT-ND1 遺伝子の発現量が低下し、4）呼吸酵素複合体 I の顕著な活性低下を引き起こす。こうした分子機序により誘導されるミトコンドリア機能不全を介し、10 ヶ月齢のモデルマウスでは、高血糖、高乳酸血症、インスリン抵抗性、肝機能障害を伴う代謝疾患を呈する。

研究関連ニュース/他のトップページに戻る

＜英文＞First mouse model with mitochondrial tRNALeu mutation developed -- ScienceDaily

First mouse model with mitochondrial tRNALeu mutation developed

Date:

August 30, 2022

Source:

University of Tsukuba

Summary:

Researchers have developed the first mouse model for a mitochondrial tRNALeu mutation, showing that the associated metabolic disorder results from faulty RNA processing.

FULL STORY

Studying the role of mitochondria -- the specialized structures within cells responsible for energy production -- in metabolic diseases has been difficult because of a lack of animal models with the necessary mitochondrial mutations to observe these tiny organelles. However, a team from the University of Tsukuba have now generated the first mouse model carrying a disease-associated mitochondrial mutation and have shown that the resulting disease is caused by faulty RNA processing.

Mitochondria are surrounded by a membrane and contain a small amount of their own DNA. This mitochondrial DNA codes for some components of the energy-generating machinery, as well as genes for both ribosomal RNAs (components of the machinery that makes proteins) and transfer RNAs that play a key role in protein synthesis. Mutations in the mitochondrial genome are known

to be linked to some human disorders such as diabetes, neurodegenerative diseases, infertility, and cancer.

Researchers at the University of Tsukuba fused cells that contained mitochondria carrying mutant DNA, but no nucleus, with embryonic stem cells that had had all their mitochondria removed by a drug called rhodamine 6G, thus creating a mouse model containing the A2748G mutation. This mutation is found in human patients, where it is known as the A3302G mutation, and is one of the common mitochondrial mutations associated with some human diseases, such as certain neuromuscular diseases, encephalopathy (brain damage), and metabolic disorders.

The mice carrying this mutant mitochondrial DNA developed metabolic disorders that mimicked the symptoms shown by human patients carrying the equivalent human mutation. This enabled further study to uncover the underlying molecular mechanism of the associated disease, which showed that this mutation affected the processing of RNAs by interfering with protein synthesis in the affected mice.

"The faulty processing of the RNA containing the A2748G mutation led to a decrease in the translation of a protein known as ND1," explains main author Professor Kazuto Nakada. "ND1 is a component of a protein complex known as Complex 1, the first of five key protein complexes in the process of energy generation known as oxidative phosphorylation." The resulting Complex I deficiency affected the function of the cellular energy-generating pathway, which then went on to cause mitochondrial dysfunction and metabolic disorders.

The development of this model will open new avenues for scientific discovery in the study of mitochondria and multiple diseases.

Story Source:

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

Journal Reference:

1. Haruna Tani, Kaori Ishikawa, Hiroaki Tamashiro, Emi Ogasawara, Takehiro Yasukawa, Shigeru Matsuda, Akinori Shimizu, Dongchon Kang, Jun-Ichi Hayashi, Fan-Yan Wei, Kazuto Nakada. **Aberrant RNA processing contributes to the pathogenesis of mitochondrial diseases in trans-mitochondrial mouse model carrying mitochondrial tRNALeu(UUR) with a pathogenic A2748G mutation**. *Nucleic Acids Research*, 2022; DOI: 10.1093/nar/gkac699
