BIO NEWS

August, 2018

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1. D 型肝炎に有効な治療法開発のための遺伝的ヒト化マウス

2018 年 6 月 27 日

肝炎デルタウィルス（HDV -D 型肝炎ウィルス）は、ヒトに最も攻撃的な形態のウィルス性肝炎を引き起こし、少なくとも 2,000 万人の人々が肝線維症、肝硬変および肝臓癌を発症する可能性がある。しかしながら、実験用マウスはこのウィルスに感受性でないという事実に阻まれて、HDV に対する有効な治療法を開発する努力は実っていない。
今回 6 月 27 日に *Science Translational Medicine* 誌で発表されたプリンストン大学の研究では、HDV に持続的に感染するように遺伝的にヒト化されたマウスについて、述べられている。HDV は小さな RNA ベースの「サテライト」ウィルスで、それ自体が単一のタンパク質を産生するため、別の肝臓ウィルス、B 型肝炎ウィルス（HBV）によって提供されるたんぱく質を必要とする。HDV は既に HBV を保有している患者に感染することができ、抗 HBV ワクチンで感染予防はできるが、HDV 感染を治す為の抗ウィルス療法は存在しない。
研究者らは、肝細胞にヒト NTCP タンパク質を発現するマウスを作製し、これらの細胞を HBV および HDV に感染させた。これらの免疫不全マウスは、HDV 感染の治療として既に現在開発されている 2 つの薬物の有効性の試験を可能にしている。

英文記事：
https://www.sciencedaily.com/releases/2018/06/180627160514.htm

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Genetically humanized mice could boost fight against aggressive hepatitis

Date:

June 27, 2018

Source:

Princeton University

Summary:

In research that could lead to treatments for an aggressive type of liver disease, scientists describe a genetically humanized mouse that can be persistently infected with hepatitis delta virus.

FULL STORY

Hepatitis delta virus (HDV) causes the most aggressive form of viral hepatitis in humans, putting at least 20 million people worldwide at risk of developing liver fibrosis, cirrhosis, and liver cancer. Efforts to develop effective treatments against HDV have been hampered by the fact that laboratory mice are not susceptible to the virus. But, in a study published June 27, 2018, in the journal *Science Translational Medicine*, Alexander Ploss and colleagues describe a genetically humanized mouse that can be persistently infected with HDV.

HDV is a small, RNA-based "satellite" virus that produces just a single protein of its own and therefore requires additional proteins provided by another liver virus, hepatitis B virus (HBV). HDV can infect patients already carrying HBV, or both viruses can infect patients simultaneously. Though infections can be prevented with an anti-HBV vaccine, there are no antiviral therapies available to cure existing HDV infections.

HDV and HBV infect the liver by binding to a protein called NTCP that is present on the surface of liver cells. But the viruses only recognize the version of NTCP present in humans and a few other primates, and therefore can't infect mice or other small mammals that produce their own versions of NTCP. This has made it difficult to study HBV and HDV infections in the laboratory. Researchers have tried transplanting human liver cells into immunocompromised mice before infecting them with virus, but this approach has produced inconsistent results and is both expensive and time-consuming.

Ploss and colleagues, led by graduate student Benjamin Winer, took a different approach. They generated mice that express the human NTCP protein in their liver cells, allowing these cells to be infected by HBV and HDV.

In these mice, HBV failed to replicate after entering mouse liver cells but HDV was able to establish persistent infection when provided with the HBV proteins it needs to propagate. For example, mice genetically engineered to produce both human NTCP and the entire HBV genome could be infected with HDV for up to 14 days. "To our knowledge, this is the first time the entire HDV life cycle has been recapitulated in a mouse model with inheritable susceptibility to HDV," Ploss said.

The mice were able to rid themselves of HDV before they developed any liver damage, apparently by mounting an immune response involving antiviral interferon proteins and various white blood cell types, including Natural Killer (NK) cells and T cells. Accordingly, mice expressing human NTCP and the HBV genome, but lacking functional B, T, and NK cells could be infected with HDV for two months or more.

These immunocompromised animals allowed Ploss and colleagues to test the effectiveness of two drugs that are currently being developed as treatments for HDV infection. Both drugs -- either alone or in combination -- suppressed the levels of HDV in immunocompromised mice after viral infection. But the drugs were not able to completely clear the mice of HDV; viral levels rose again within weeks of stopping treatment.

"This is largely in line with recently reported data from clinical trials, showing the utility of our model for preclinical antiviral drug testing," Winer said.

"Our model is amenable to genetic manipulations, robust, and can be adopted as a method to rapidly screen for potential treatments," Ploss added.

Timothy M. Block, president of the Hepatitis B Foundation and its Baruch S. Blumberg Institute, who was not involved in the study, said "These systems should be able to provide practical, and presumably economical tools. Their work is urgently needed, and a desperate community welcomes it. I emphasize that it is often the new methods in science that revolutionize a field such as drug discovery, almost as much as the new drugs themselves."

Story Source:

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

Journal Reference:

1. Benjamin Y. Winer, Elham Shirvani-Dastgerdi, Yaron Bram, Julie Sellau, Benjamin E. Low, Heath Johnson, Tiffany Huang, Gabriela Hrebikova, Brigitte Heller, Yael Sharon, Katja Giersch, Sherif Gerges, Kathleen Seneca, Mihai-Alexandru Pais, Angela S. Frankel, Luis Chiriboga, John Cullen, Ronald G. Nahass, Marc Lutgehetmann, Jared E. Toettcher, Michael V. Wiles, Robert E. Schwartz, Alexander Ploss. **Preclinical assessment of antiviral combination therapy in a genetically humanized mouse model for hepatitis delta virus infection**. *Science Translational Medicine*, 2018; 10 (447): eaap9328 DOI: 10.1126/scitranslmed.aap9328

Cite This Page:

- MLA
- APA
- Chicago

Princeton University. "Genetically humanized mice could boost fight against aggressive hepatitis." ScienceDaily. ScienceDaily, 27 June 2018. <www.sciencedaily.com/releases/2018/06/180627160514.htm>.

目次に戻る

2. 実験薬物がマウスにおけるパーキンソン病の進行を阻止

2018 年 7 月 2 日

ジョンズ・ホプキンズ大学医学部の研究者らは、マウスにおいてパーキンソン病そのものの症状やその症状の進行を遅らせる実験薬を開発した、として 6 月 11 日の *Nature Medicine* 誌に報告した。

ヒト脳細胞の培養および生きたマウスモデルで実施された実験において、この NLY01 と呼ばれる薬物がパーキンソン病の特徴である脳細胞の分解を阻止したとして、今年この薬剤は臨床試験に移行される予定である。

研究者らによると、この NLY01 は、特定の細胞の表面上のグルカゴン様ペプチド-1 受容体に結合することによって作用する。類似した薬物は血液中のインスリンレベルを上昇させるための 2 型糖尿病治療に広く使用されている。過去のマウス実験では、このクラスの薬物の神経保護能力について示唆されていたものの、脳内でどのように作用したか未だ示せていなかった。

英文記事：

https://www.sciencedaily.com/releases/2018/07/180702120505.htm

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Experimental drug stops Parkinson's disease progression in mice

Date:

July 2, 2018

Source:

Johns Hopkins Medicine

Summary:

Researchers say they have developed an experimental drug, similar to compounds used to treat diabetes, that slows the progression of Parkinson's disease itself -- as well as its symptoms -- in mice.

FULL STORY

Johns Hopkins researchers say they have developed an experimental drug, similar to compounds used to treat diabetes, that slows the progression of Parkinson's disease itself -- as well as its symptoms -- in mice. In experiments performed with cultures of human brain cells and live mouse models, they report the drug blocked the degradation of brain cells that is the hallmark of Parkinson's disease. The drug is expected to move to clinical trials this year.

"It is amazingly protective of target nerve cells," says Ted Dawson, M.D., Ph.D., director of the Institute for Cell Engineering and professor of neurology at the Johns Hopkins University School of Medicine.

Dawson explains that if planned clinical trials for the drug, named NLY01, are successful in humans, it could be one of the first treatments to directly target the progression of Parkinson's disease, not just the muscle rigidity, spasmodic movements, fatigue, dizziness, dementia and other symptoms of the disorder.

A report of the study's results was published June 11 in *Nature Medicine*.

According to the investigators, NLY01 works by binding to so-called glucagon-like peptide-1 receptors on the surface of certain cells. Similar drugs are used widely in the treatment of type 2 diabetes to increase insulin levels in the blood. Though past studies in animals suggested the neuroprotective potential of this class of drugs, researchers had not shown directly how it operated in the brain.

To find out, Dawson and his team tested NLY01 on three major cell types in the human brain: astrocytes, microglia and neurons. They found that microglia, a brain cell type that sends signals

throughout the central nervous system in response to infection or injury, had the most sites for NLY01 to bind to -- two times higher than the other cell types, and 10 times higher in humans with Parkinson's disease compared to humans without the disease.

Dawson and his team knew that microglia secreted chemical signals that converted astrocytes -- the star shaped cells that help neurons communicate with their neighbors -- into aggressive "activated" astrocytes, which eat away at the connections between cells in the brain, causing neurons to die off. They speculated that NLY01 might stop this conversion.

"The activated astrocytes we focused on go into a revolt against the brain," says Dawson, "and this structural breakdown contributes to the dead zones of brain tissue found in those with Parkinson's disease. The ideas was that if we could find a way to calm those astrocytes, we might be able to slow the progression of Parkinson's disease."

In a preliminary experiment in laboratory-grown human brain cells, Dawson's team treated human microglia with NLY01 and found that they were able to turn the activating signals off. When healthy astrocytes were combined with the treated microglia, they did not convert into destructive activated astrocytes and remained healthy neuroprotective cells. Dawson's team suspected that neurons throughout the body could be protected in the same way.

They explored this hypothesis by testing the drug's effectiveness in mice engineered to have a rodent version of Parkinson's disease.

In one experiment, Dawson's team injected the mice with alpha-synuclein, the protein known to be the primary driver of Parkinson's disease, and treatedmice with NLY01. Similar but untreated mice injected with alpha-synuclein showed pronounced motor impairment over the course of six months in behavioral tests such as the pole test, which allows researchers to measure motor impairment such as that caused by Parkinson's disease. However, Dawson's team found that the mice treated with NLY01 maintained normal physical function and had no loss of dopamine neurons, indicating that the drug protected against the development of Parkinson's disease.

In a second experiment, Dawson's team used mice that were genetically engineered to naturally produce more human-type alpha-synuclein typically used to model human Parkinson's disease that runs in families. Under normal conditions, these so-called transgenic mice will succumb to the disease in 387 days. However, Dawson's team found that treatment with NLY01 extended the lives of the 20 mice treated with the drug by over 120 days.

Upon further investigation, Dawson's team found that the brains of the mice treated with NLY01 showed few signs of the neurodegenerative characteristics of Parkinson's disease.

Parkinson's disease is a progressive disorder of the nervous system that affects approximately 1 million people in the U.S., according to the Parkinson's Foundation. Early symptoms include tremors, trouble sleeping, constipation and trouble moving or walking, which ultimately give way to more severe symptoms such as loss of motor function and the ability to speak, and dementia. Most people begin showing symptoms in their 60s, but cases have been reported in patients as young as 2 years old.

Dawson cautions that the experimental drug must still be tested for safety as well as effectiveness in people, but based on the safety profile of other similar drugs, he does not anticipate any major roadblocks to its use in humans.

Dawson says he and his team have reason to be hopeful that NLY01 could, in a relatively short period of time, make an impact on the lives of those with Parkinson's.

Similar drugs to NLY01 already approved by the Food and Drug Administration for the treatment of type 2 diabetes include exenatide, lixisenatide, liraglutide and dulaglutide, each of which can cost approximately $2,000 for a 90-day supply. NLY01 is a long-acting drug with improved the brain penetration compared to these approved drugs for diabetes.

Story Source:

Materials provided by **Johns Hopkins Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Seung Pil Yun, Tae-In Kam, Nikhil Panicker, SangMin Kim, Yumin Oh, Jong-Sung Park, Seung-Hwan Kwon, Yong Joo Park, Senthilkumar S. Karuppagounder, Hyejin Park, Sangjune Kim, Nayeon Oh, Nayoung Alice Kim, Saebom Lee, Saurav Brahmachari, Xiaobo Mao, Jun Hee Lee, Manoj Kumar, Daniel An, Sung-Ung Kang, Yunjong Lee, Kang Choon Lee, Dong Hee Na, Donghoon Kim, Sang Hun Lee, Viktor V. Roschke, Shane A. Liddelow, Zoltan Mari, Ben A. Barres, Valina L. Dawson, Seulki Lee, Ted M. Dawson, Han Seok Ko. **Block of A1 astrocyte conversion by microglia is**

neuroprotective in models of Parkinson's disease. *Nature Medicine*, 2018; DOI: 10.1038/s41591-018-0051-5

Cite This Page:

- MLA
- APA
- Chicago

Johns Hopkins Medicine. "Experimental drug stops Parkinson's disease progression in mice." ScienceDaily. ScienceDaily, 2 July 2018. <www.sciencedaily.com/releases/2018/07/180702120505.htm>.

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3. 神経発達障害が女性よりも男性にリスクが高い理由 -マウス研究

2018 年 7 月 3 日

最近、生物学的な性が病気の危険性に重要な役割を果たすことが認識され始めている。鬱病と不安は女性により影響を与え、自閉症スペクトラム障害、早期発症統合失調症、注意欠陥多動症を含む神経発達障害は男性により影響を与える。その他、男性は、妊娠中のストレス、母体感染、薬物暴露などの出生前傷害に対してもより敏感だとされている。
この分子的基盤の不一致についてよく理解するために、メリーランド大学医学部の研究者らは、胎盤の健康に重要な役割を果たす分子に注目した。そして、マウス研究において、O-統合 N-アセチルグルコサミントランスフェラーゼ（OGT）が、遺伝子発現の性別特異的パターンを確立することによって作用することを発見した。
この研究は今週の *Nature Communications* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180703141329.htm

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Why males are more at risk than females for neurodevelopmental disorders

New research unravels potential genetic mechanism behind this disparity

Date:

July 3, 2018

Source:

University of Maryland School of Medicine

Summary:

Researchers have recently begun to realize that biological sex plays a key role in disease risk. Sex plays a role in hypertension, diabetes, arthritis -- and in many neurological and psychiatric disorders. Depression and anxiety affect females more, while neurodevelopmental disorders, including autism spectrum disorders, early onset schizophrenia, and attention deficit hyperactivity, affect more males. Males are also more sensitive to prenatal insults, such as gestational stress, maternal infection and drug exposure.

FULL STORY

Researchers have recently begun to realize that biological sex plays a key role in disease risk. Sex plays a role in hypertension, diabetes, arthritis -- and in many neurological and psychiatric disorders. Depression and anxiety affect females more, while neurodevelopmental disorders, including autism spectrum disorders, early onset schizophrenia, and attention deficit hyperactivity, affect more males. Males are also more sensitive to prenatal insults, such as gestational stress, maternal infection and drug exposure.

To better understand the molecular underpinnings of this disparity, Tracy Bale of the University of Maryland School of Medicine, along with several colleagues, focused on a molecule that plays a key role in placental health. In a study of mice, they found that the molecule, O-linked N-acetylglucosamine transferase (OGT) works by establishing sex-specific patterns of gene expression.

The study was published this week in the journal *Nature Communications*.

OGT seems to work via an epigenetic modification that broadly controls transcription, H3K27me3. Epigenetics is the study of changes in how genes are expressed. Dr. Bale showed that high levels of H3K27me3 in the female placenta produce resilience to stress experienced by the mother. This indicates at least one molecular pathway that allows females to be more resilient to maternal stress than males.

"This pathway could help explain why we see this profound neurodevelopmental difference in humans," said Dr. Bale. "OGT and H3K27me3 in the placenta are crucial to a lot of protein encoding that occurs during pregnancy, and so this process has a lot of downstream effects. The OGT gene is on the X chromosome, and seems to provide a level of protection for the female fetus to perturbations in the maternal environment."

Dr. Bale has focused much of her research on the links between stress and subsequent risk for neurodevelopmental disorders, including autism and schizophrenia in offspring. Her previous work on the placenta has found novel sex differences that may predict increased prenatal risk for disease in males.

She has previously found that, in mice, a father's stress can affect the brain development of offspring. This stress can alter the father's sperm, which can alter the brain development of the child. Dr. Bale has also found that male mice experiencing chronic mild stress have offspring with a reduced hormonal response to stress; this response has been linked to some neuropsychiatric disorders, including PTSD. This suggests that even mild environmental challenges can have a significant effect on the health of offspring.

Story Source:

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

Journal Reference:

1. Bridget M. Nugent, Carly M. O'Donnell, C. Neill Epperson, Tracy L. Bale. **Placental H3K27me3 establishes female resilience to prenatal insults**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-04992-1

Cite This Page:

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University of Maryland School of Medicine. "Why males are more at risk than females for neurodevelopmental disorders: New research unravels potential genetic mechanism behind this disparity." ScienceDaily. ScienceDaily, 3 July 2018. <www.sciencedaily.com/releases/2018/07/180703141329.htm>.

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４．セノリティック ドラッグが老化細胞原因の損傷を逆転 -マウス実験

2018 年 7 月 9 日

7 月 9 日に *Nature Communications* 誌で発表された、ミネソタ州ロチェスターのメイヨークリニックの新しい研究によると、老化細胞を若いマウスに注入すると健康や機能が失われるが、２つの既存の薬物を組み合わせてマウスを治療すると老化細胞が組織から除去され、身体機能が回復する。
この薬は、ダサチニブとケルセチンで、ダサチニブは通常白血病の治療に使用されており、ケルセチンは果物や野菜に含まれる植物フラバノールで、この薬は自然に老化したマウスに対してもその寿命と健康の両方を延長させた、としている。
この研究は、国立衛生研究所（NHI）の一部である国立老化研究所（NIA）によってサポートされた。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180709111137.htm

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Senolytic drugs reverse damage caused by senescent cells in mice

Date:

July 9, 2018

Source:

NIH/National Institute on Aging

Summary:

Injecting senescent cells into young mice results in a loss of health and function but treating the mice with a combination of two existing drugs cleared the senescent cells from tissues and restored physical function. The drugs also extended both life span and health span in naturally aging mice.

FULL STORY

Mouse. (stock image)

Credit: © HYUNGKEUN / Fotolia

Injecting senescent cells into young mice results in a loss of health and function but treating the mice with a combination of two existing drugs cleared the senescent cells from tissues and restored physical function. The drugs also extended both life span and health span in naturally aging mice, according to a new study in *Nature Medicine*, published on July 9, 2018.

A research team led by James L. Kirkland, M.D., Ph.D., of the Mayo Clinic in Rochester, Minnesota, found that injecting even a small number of senescent cells into young, healthy mice causes damage that can result in physical dysfunction. The researchers also found that treatment with a combination of dasatinib and quercetin could prevent cell damage, delay physical dysfunction, and, when used in naturally aging mice, extend their life span.

"This study provides compelling evidence that targeting a fundamental aging process -- in this case, cell senescence in mice -- can delay age-related conditions, resulting in better health and longer life," said NIA Director Richard J. Hodes, M.D. "This study also shows the value of investigating biological mechanisms which may lead to better understanding of the aging process."

Many normal cells continuously grow, die, and replicate. Cell senescence is a process in which cells lose function, including the ability to divide and replicate, but are resistant to cell death. Such cells have been shown to affect neighboring ones because they secrete several pro-inflammatory and tissue remodeling molecules. Senescent cells increase in many tissues with aging; they also occur in organs associated with many chronic diseases and after radiation or chemotherapy.

Senolytics are a class of drugs that selectively eliminate senescent cells. In this study, Kirkland's team used a combination of dasatinib and quercetin (D+Q) to test whether this senolytic combination could slow physical dysfunction caused by senescent cells. Dasatinib is used to treat some forms of leukemia; quercetin is a plant flavanol found in some fruits and vegetables.

To determine whether senescent cells caused physical dysfunction, the researchers first injected young (four-month-old) mice with either senescent (SEN) cells or non-senescent control (CON) cells. As early as two weeks after transplantation, the SEN mice showed impaired physical function as determined by maximum walking speed, muscle strength, physical endurance, daily activity, food intake, and body weight. In addition, the researchers saw increased numbers of senescent cells, beyond what was injected, suggesting a propagation of the senescence effect into neighboring cells.

To then analyze whether a senolytic compound could stop or delay physical dysfunction, researchers treated both SEN and CON mice for three days with the D+Q compound mix. They found that D+Q selectively killed senescent cells and slowed the deterioration in walking speed, endurance, and grip strength in the SEN mice.

In addition to young mice injected with senescent cells, the researchers also tested older (20-month-old), non-transplanted mice with D+Q intermittently for 4 months. D+Q alleviated normal

age-related physical dysfunction, resulting in higher walking speed, treadmill endurance, grip strength, and daily activity.

Finally, the researchers found that treating very old (24- to 27-month-old) mice with D+Q biweekly led to a 36 percent higher average post-treatment life span and lower mortality hazard than control mice. This indicates that senolytics can reduce risk of death in old mice.

"This is exciting research," said Felipe Sierra, Ph.D., director of NIA's Division of Aging Biology. "This study clearly demonstrates that senolytics can relieve physical dysfunction in mice. Additional research will be necessary to determine if compounds, like the one used in this study, are safe and effective in clinical trials with people."

The researchers noted that current and future preclinical studies may show that senolytics could be used to enhance life span not only in older people, but also in cancer survivors treated with senescence-inducing radiation or chemotherapy and people with a range of senescence-associated chronic diseases.

The research was supported primarily by the National Institute on Aging (NIA), part of the National Institutes of Health (NIH).

Story Source:

Materials provided by **NIH/National Institute on Aging**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ming Xu, Tamar Pirtskhalava, Joshua N. Farr, Bettina M. Weigand, Allyson K. Palmer, Megan M. Weivoda, Christina L. Inman, Mikolaj B. Ogrodnik, Christine M. Hachfeld, Daniel G. Fraser, Jennifer L. Onken, Kurt O. Johnson, Grace C. Verzosa, Larissa G. P. Langhi, Moritz Weigl, Nino Giorgadze, Nathan K. LeBrasseur, Jordan D. Miller, Diana Jurk, Ravinder J. Singh, David B. Allison, Keisuke Ejima, Gene B. Hubbard, Yuji Ikeno, Hajrunisa Cubro, Vesna D. Garovic, Xiaonan Hou, S. John Weroha, Paul D. Robbins, Laura J. Niedernhofer, Sundeep Khosla, Tamara Tchkonia, James L.

Kirkland. **Senolytics improve physical function and increase lifespan in old age**. *Nature Medicine*, 2018; DOI: 10.1038/s41591-018-0092-9

Cite This Page:

- MLA
- APA
- Chicago

NIH/National Institute on Aging. "Senolytic drugs reverse damage caused by senescent cells in mice." ScienceDaily. ScienceDaily, 9 July 2018. <www.sciencedaily.com/releases/2018/07/180709111137.htm>.

目次に戻る

5. CRISPR システムでゲノム編集失敗の原因を発見

2018 年 7 月 10 日

イリノイ大学シカゴ校の研究者らは、CRISPR ゲノム編集がなぜうまくいかないか、そしてそのプロセスがより効率的になる方法を初めて説明し、*Molecular Cell* 誌に発表した。
CRISPR は、DNA から不要な遺伝子や遺伝物質を切り出したり、時には所望の配列を追加する遺伝子編集ツールである。望ましくない DNA を切り取るためにはさみのように機能する Case9 という酵素を使用する。
研究者らは、CRISPR を用いたゲノム編集が失敗した場合、これは切断部位の DNA に Case9 タンパク質が永続的に結合するためであることが多く、DNA 修復酵素が切断にアクセスするのを阻止する、としている。さらに調査したところ、Case9 を誘導して DNA 二重らせんを構成する鎖のうちの 1 つにアニールすると、Case9 と RNA ポリメラーゼとの相互作用が促進され、Case9 を効率的なゲノムエディターに変えることができた、としている。

英文と記事：
https://www.sciencedaily.com/releases/2018/07/180710185347.htm

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Biochemists discover cause of genome editing failures with hyped CRISPR system

New study sheds light on biology of most-used Cas9 target

Date:

July 10, 2018

Source:

University of Illinois at Chicago

Summary:

Researchers are the first to describe why CRISPR gene editing sometimes fails to work, and how the process can be made to be much more efficient.

Share:

FULL STORY

Researchers from the University of Illinois at Chicago are the first to describe why CRISPR gene editing sometimes fails to work, and how the process can be made to be much more efficient.

CRISPR is a gene-editing tool that allows scientists to cut out unwanted genes or genetic material from DNA, and sometimes add a desired sequence or genes. CRISPR uses an enzyme called Cas9 that acts like scissors to cut out unwanted DNA. Once cuts are made on either side of the DNA to be removed, the cell either initiates repair to glue the two ends of the DNA strand back together, or the cell dies.

In a study published in the journal *Molecular Cell*, the researchers showed that when gene editing using CRISPR fails, which occurs about 15 percent of the time, it is often due to persistent binding of the Cas9 protein to the DNA at the cut site, which blocks the DNA repair enzymes from accessing the cut.

Senior author Bradley Merrill, associate professor of biochemistry and molecular genetics in the UIC College of Medicine, says that before now, researchers did not know why the process randomly failed.

"We found that at sites where Cas9 was a 'dud' it stayed bound to the DNA strand and prevented the cell from initiating the repair process," Merrill said. The stuck Cas9 is also unable to go on to make additional cuts in DNA, thus limiting the efficiency of CRISPR, he said.

Merrill, UIC graduate student Ryan Clarke, and their colleagues also found that Cas9 was likely to be ineffective at sites in the genome where RNA polymerases -- enzymes involved in gene activity -- were not active. Further investigation revealed that guiding Cas9 to anneal to just one of the strands making up the DNA double helix promoted interaction between Cas9 and the RNA polymerase, helping to transform a "dud" Cas9 into an efficient genome editor.

Specifically, they found that consistent strand selection for Cas9 during genome editing forced the RNA polymerases to collide with Cas9 in such a way that Cas9 was knocked off the DNA.

"I was shocked that simply choosing one DNA strand over the other had such a powerful effect on genome editing," said Clarke, the lead author of the paper. "Uncovering the mechanism behind this phenomenon helps us better understand how Cas9 interactions with the genome can cause some editing attempts to fail and that, when designing a genome editing experiment, we can use that understanding to our benefit."

"This new understanding is important for those of us who need genome editing to work well in the lab and for making genome editing more efficient and safer in future clinical uses," Merrill said.

The study findings are also significant because, in the genome editing process, the interaction between Cas9 and the DNA strand is now known to be the "rate-limiting step," said Merrill. This means that it is the slowest part of the process; therefore, changes at this stage have the most potential to impact the overall duration of genome editing.

"If we can reduce the time that Cas9 interacts with the DNA strand, which we now know how to do with an RNA polymerase, we can use less of the enzyme and limit exposure," Merrill said. "This means we have more potential to limit adverse effects or side effects, which is vital for future therapies that may impact human patients."

Additional co-authors on the study are Matthew MacDougall, Maureen Regan and Leslyn Hanakahi of UIC; Robert Heller and Dr. Luciano Marraffini of Rockefeller University; and Nan Cher Yeo, Alejandro Chavez and George Church of Harvard Medical School.

Grants from the National Institutes of Health (R01-HD081534 and 1DP2AI104556) and the UIC Center for Clinical and Translational Sciences supported this research. Marraffini and Church both noted financial disclosures relevant to the study.

Story Source:

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

Journal Reference:

1. Ryan Clarke, Robert Heler, Matthew S. MacDougall, Nan Cher Yeo, Alejandro Chavez, Maureen Regan, Leslyn Hanakahi, George M. Church, Luciano A. Marraffini, Bradley J. Merrill. **Enhanced Bacterial Immunity and Mammalian Genome Editing via RNA-Polymerase-Mediated Dislodging of Cas9 from Double-Strand DNA Breaks**. *Molecular Cell*, 2018; 71 (1): 42 DOI: 10.1016/j.molcel.2018.06.005

Cite This Page:

- MLA
- APA
- Chicago

University of Illinois at Chicago. "Biochemists discover cause of genome editing failures with hyped CRISPR system: New study sheds light on biology of most-used Cas9 target." ScienceDaily. ScienceDaily, 10 July 2018. <www.sciencedaily.com/releases/2018/07/180710185347.htm>.

目次に戻る

6. 動物実験よりも信頼性の高いデータベース分析

2018 年 7 月 11 日

7 月 11 日の *Toxicological Sciences* 誌に掲載されたジョンズ・ホプキンズ大学ブルームバーグ公衆衛生学校の研究では、化学構造と毒性の関係をマッピングするために開発した既知の化学物質のデータベースを採掘した。研究者らは、その後このマッピングを利用して単一の動物実験が行うよりも正確に、あらゆる化合物の毒性を自動的に予測できることを示した。
マウス、ウサギ、モルモット、イヌなどの動物は世界中の研究室で毎年数百万の化学毒性試験を受けているとされる。この動物試験は、通常、消費者保護のために法律で義務付けられているが、道徳的根拠に反していると言わざるを得ず、高コストと不確実性のため製品メーカーにとっては不評である。
食品医療薬品局（FDA）と環境保護庁（EPA）も、食品、医薬品などの化学物質の安全性を評価するために現在使用されている動物実験の大部分を代替えできるかどうか、この技術を用いて判断できるかどうか検討を始めている。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180711093127.htm

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Database analysis more reliable than animal testing for toxic chemicals

Study shows that computer algorithms could replace standard toxicology tests on animals

Date:

July 11, 2018

Source:

Johns Hopkins University Bloomberg School of Public Health

Summary:

Advanced algorithms working from large chemical databases can predict a new chemical's toxicity better than standard animal tests, suggests a new study.

Share:

FULL STORY

Advanced algorithms working from large chemical databases can predict a new chemical's toxicity better than standard animal tests, suggests a study led by scientists at Johns Hopkins Bloomberg School of Public Health.

The researchers, in the study that appears in the journal *Toxicological Sciences* on July 11, mined a large database of known chemicals they developed to map the relationships between chemical structures and toxic properties. They then showed that one can use the map to automatically predict the toxic properties of any chemical compound -- more accurately than a single animal test would do.

The most advanced toxicity-prediction tool the team developed was on average about 87 percent accurate in reproducing consensus animal-test-based results -- across nine common tests, which account for 57 percent of the world's animal toxicology testing. By contrast, the repetition of the same animal tests in the database were only about 81 percent accurate -- in other words, any given test had only an 81 percent chance, on average, of obtaining the same result for toxicity when repeated.

"These results are a real eye-opener -- they suggest that we can replace many animal tests with computer-based prediction and get more reliable results," says principal investigator Thomas Hartung, MD, PhD, the Doerenkamp-Zbinden Chair and professor in the Department of Environmental Health and Engineering at the Bloomberg School.

The computer-based approach could also be applied to many more chemicals than animal testing, which could lead to wider safety assessments. Due to costs and ethical challenges only a small

fraction of the roughly 100,000 chemicals in consumer products have been comprehensively tested.

Animals such as mice, rabbits, guinea pigs and dogs annually undergo millions of chemical toxicity tests in labs around the world. Although this animal testing is usually required by law to protect consumers, it is opposed on moral grounds by large segments of the public, and is also unpopular with product manufacturers because of the high costs and uncertainties about testing results.

"A new pesticide, for example, might require 30 separate animal tests, costing the sponsoring company about 20 million dollars," says Hartung, who also directs the Center for Alternatives to Animal Testing, which is based in the Bloomberg School's Department of Environmental Health and Engineering.

The most common alternative to animal testing is a process called read-across, in which researchers predict a new compound's toxicity based on the known properties of few chemicals that have a similar structure. Read-across is much less expensive than animal testing, yet requires expert evaluation and somewhat subjective analysis for every compound of interest.

As a first step towards optimizing and automating the read-across process, Hartung and colleagues two years ago assembled the world's largest machine-readable toxicological database. It contains information on the structures and properties of 10,000 chemical compounds, based in part on 800,000 separate toxicology tests.

"There is enormous redundancy in this database -- we found that often the same chemical has been tested dozens of times in the same way, such as putting it into rabbits' eyes to check if it's irritating," says Hartung. This waste of animals, however, gave the researchers information they needed to develop a benchmark for a better approach.

For their study, the team enlarged the database and used machine-learning algorithms, with computing muscle provided by Amazon's cloud server system, to read the data and generate a "map" of known chemical structures and their associated toxic properties. They developed related software to determine precisely where any compound of interest belongs on the map, and whether -- based on the properties of compounds "nearby" -- it is likely to have toxic effects such as skin irritation or DNA damage.

"Our automated approach clearly outperformed the animal test, in a very solid assessment using data on thousands of different chemicals and tests," Hartung says. "So it's big news for toxicology." Underwriter's Laboratories (UL), a company that specializes in developing public safety standards

and testing against them, co-sponsored this work and is making the read-across software tool commercially available.

The U.S. Food and Drug Administration and the Environmental Protection Agency have begun formal evaluations of the new method, to test if read-across can substitute for a significant proportion of the animal tests currently used to evaluate the safety of chemicals in foods, drugs and other consumer products. The researchers also are starting to use it to help some large corporations, including major technology companies, to determine if they have potentially toxic chemicals in their products.

"One day perhaps, chemists will use such tools to predict toxicity even before synthesizing a chemical so that they can focus on making only non-toxic compounds," Hartung says.

"Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility" was written by Tom Luechtefeld, Dan Marsh, Craig Rowlands, and Thomas Hartung.

Disclosures: Craig Rowlands is an employee of Underwriters Laboratories (UL). The other authors consult UL on computational toxicology, especially read-across, and have a share of their respective sales. Tom Luechtefeld and Dan Marsh have created ToxTrack LLC to develop such computational tools. Thomas Hartung's arrangement with UL has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

Funding was provided by the National Institute of Environmental Health Sciences (Grant T32 ES007141) and the European Commission's Horizon 2020 program (Grant 681002).

Story Source:

Materials provided by **Johns Hopkins University Bloomberg School of Public Health**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Thomas Luechtefeld, Dan Marsh, Craig Rowlands, Thomas Hartung. **Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility**. *Toxicological Sciences*, 2018; DOI: 10.1093/toxsci/kfy152

目次に戻る

7. 脊髄損傷で麻痺したマウスが再び歩行可能に

2018 年 7 月 19 日

脊椎損傷患者のほとんどは、コードが完全に切断されていなくても、傷害部位から下方が麻痺する。脊椎の予備部分がなぜ機能しないのか？ボストン子供病院の研究者らは、この疑問についての洞察を、7 月 19 日の *Cell* 誌のオンライン版に提供している。研究者らは、また、全身に投与された小分子化合物によって、麻痺したマウスがこれらの回路を復活させ歩く能力を回復させることも示している。
研究者らは、ニューロンの興奮性を変化させることで知られ、血液ー脳の壁を通過できる化合物をいくつか選択し、腹腔内注射により 10 匹単位で麻痺したマウスに化合物を投与した。選択肢の中で、CLP290 と呼ばれる化合物は、最も強力な効果があり、麻痺したマウスは 4~5 週間の治療後、踏み台能力を回復することができ、歩行スコアは処置停止後 2 週間対照マウスよりも高いままで、副作用も最小限だった、としている。

英文記事：
https://medicalxpress.com/news/2018-07-paralyzed-mice-spinal-cord-injury.html

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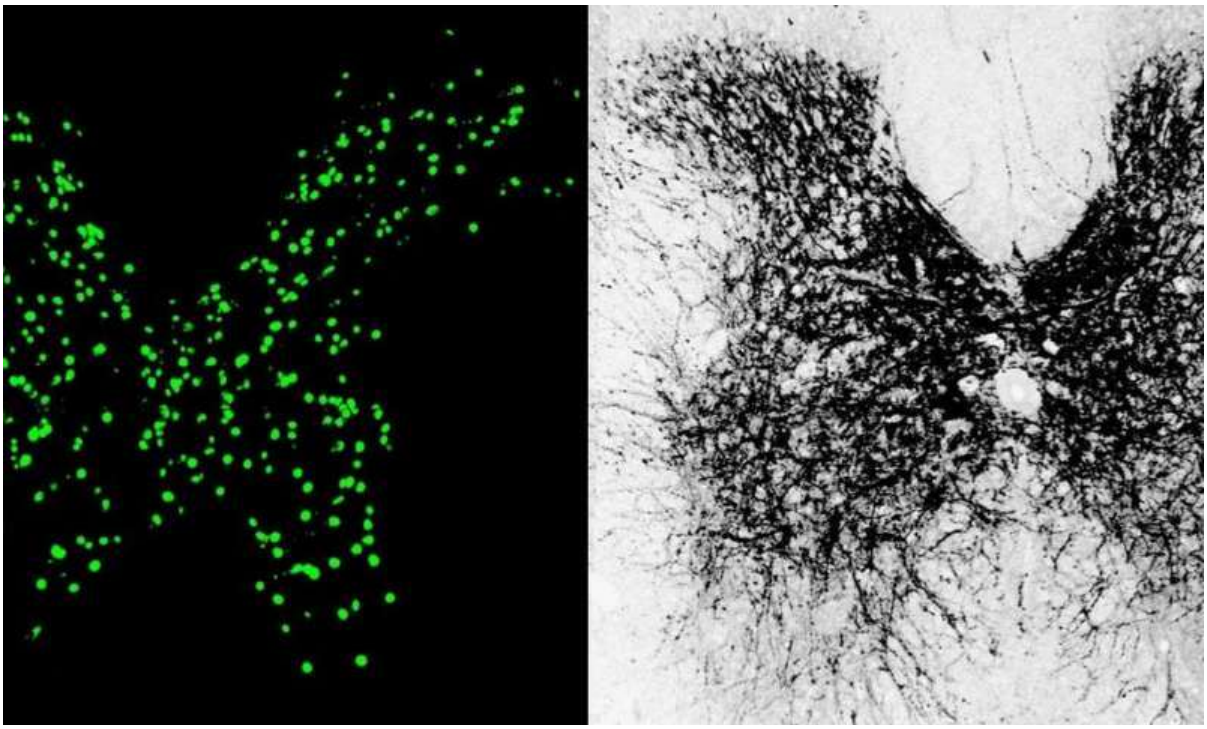
Paralyzed mice with spinal cord injury made to walk again

July 19, 2018, Children's Hospital Boston



A cross section of a mouse spinal cord, stained two different ways, showing increased expression of KCC2 in inhibitory neurons. This increased expression correlated with improved motor function, including ankle movement and stepping.
Credit: Zhigang He Lab, Boston Children's Hospital

Most people with spinal cord injury are paralyzed from the injury site down, even when the cord isn't completely severed. Why don't the spared portions of the spinal cord keep working? Researchers at Boston Children's Hospital now provide insight into why these nerve pathways remain quiet. They also show that a small-molecule compound, given systemically, can revive these circuits in paralyzed mice, restoring their ability to walk.

The study, led by Zhigang He, Ph.D., in Boston Children's F.M. Kirby Neurobiology Center, was published online July 19 by the journal *Cell*.

"For this fairly severe type of spinal cord injury, this is most significant functional recovery we know of," says He. "We saw 80 percent of mice treated with this compound recover their stepping ability."

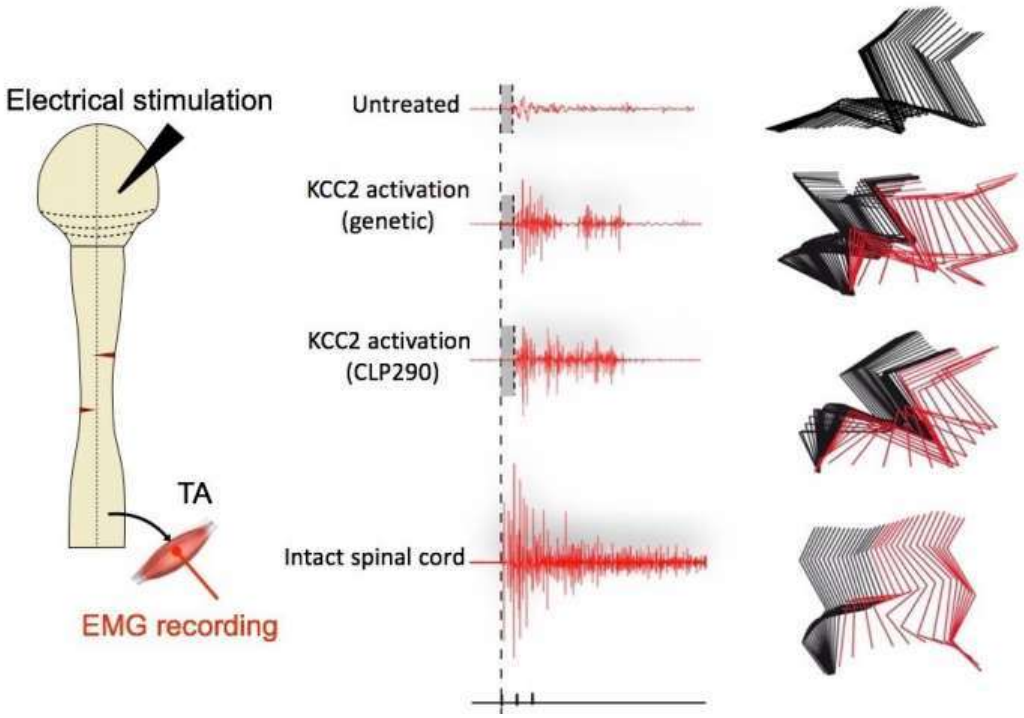
Waking up dormant spinal circuits

Many animal studies looking to repair spinal cord damage have focused on getting nerve fibers, or axons, to regenerate, or to getting new axons to sprout from healthy ones. While impressive axon regeneration and sprouting have been achieved, by He's lab and others, their impacts on the animals' motor function after a severe injury are less clear. Some studies have tried using neuromodulators such as serotonergic drugs to simulate the spinal circuits, but have gotten only transient, uncontrolled limb movement.

He and colleagues took another approach, inspired by the success of epidural electrical stimulation-based strategies, the only treatment known to be effective in patients with spinal cord injury. This treatment applies a current to the lower portion of the spinal cord; combined with rehabilitation training, it has enabled some patients to regain movement.

"Epidural stimulation seems to affect the excitability of neurons," says He. "However, in these studies, when you turn off the stimulation, the effect is gone. We tried to come up with a pharmacologic approach to mimic the stimulation and better understand how it works."

He, first author Bo Chen and colleagues selected a handful of compounds that are already known to alter the excitability of neurons, and are able to cross the blood-brain barrier. They gave each compound to paralyzed mice in groups of 10 via intraperitoneal injection. All mice had severe spinal cord injury, but with some nerves intact. Each group (plus a control group given placebo) was treated for eight to ten weeks.



This schematic compares electromyography (EMG) recordings of right hindlimb electrical activity in different groups of mice, together with observed walking movement. Mice that had KCC2 activated in their inhibitory neurons after severe ⋯more

Inhibiting inhibition by re-activating KCC2

One compound, called CLP290, had the most potent effect, enabling paralyzed mice to regain stepping ability after four to five weeks of treatment. Electromyography recordings showed that the two relevant groups of hindlimb muscles were active. The animals' walking scores remained higher than the controls' up to two weeks after stopping treatment. Side effects were minimal.

CLP290 is known to activate a protein called KCC2, found in cell membranes, that transports chloride out of neurons. The new research shows that inhibitory neurons in the injured spinal cord are crucial to recovery of motor function. After spinal cord injury, these neurons produce dramatically less KCC2. As a result, He and colleagues found, they can't properly respond to signals from the brain. Unable to process inhibitory signals, they respond only to excitatory signals that tell them to

keep firing. And since these neurons' signals are inhibitory, the result is too much inhibitory signaling in the overall spinal circuit. In effect, the brain's commands telling the limbs to move aren't relayed.

By restoring KCC2, with either CLP290 or genetic techniques, the inhibitory neurons can again receive inhibitory signals from the brain, so they fire less. This shifts the overall circuit back toward excitation, the researchers found, making it more responsive to input from the brain. This had the effect of reanimating spinal circuits disabled by the injury.

"Restoring inhibition will allow the whole system to be excited more easily," He explains.

"Too much excitation not good, and too much inhibition is not good either. You really need to get a balance. This hasn't been demonstrated in a rigorous way in spinal cord injury before."

Combination treatment?

He and colleagues are now investigating other compounds that act as KCC2 agonists. They believe such drugs, or perhaps gene therapy to restore KCC2, could be combined with epidural stimulation to maximize a patient's function after spinal cord injury.

"We are very excited by this direction," says He. "We want to test this kind of treatment in a more clinically relevant model of spinal cord injury and better understand how KCC2 agonists work."

Explore further: **Spinal cord injury affects the heart**
More information: *Cell* (2018). **DOI: 10.1016/j.cell.2018.06.005**
Journal reference: Cell
Provided by: Children's Hospital Boston

目次に戻る

8. マウスモデルで老化に伴うしわと脱毛解消に成功

2018 年 7 月 20 日

アラバマ大学バーミンガム校の研究者らは、その学校で開発されたマウスモデルを用いて、老化の特徴であるしわと脱毛の現象を逆転させることに成功した。
ミトコンドリアの機能不全に至る突然変異が誘発された場合、数週間でマウスにはしわができ、広範で目で見てそれと分かる脱毛を発症する。そこで、ミトコンドリア機能障害の原因遺伝子を消すことによってミトコンドリア機能を回復させると、そのマウスには滑らかな皮膚と厚い毛皮が戻り、同じ年齢の健常マウスと区別がつかなくなった、としている。
この研究は、*Cell Death & Disease* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180720112808.htm

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Scientists reverse aging-associated skin wrinkles and hair loss in a mouse model

A gene mutation causes wrinkled skin and hair loss; turning off that mutation restores the mouse to normal appearance.

Date:

July 20, 2018

Source:

University of Alabama at Birmingham

Summary:

Researchers have reversed wrinkled skin and hair loss, hallmarks of aging, in a mouse model. When a mutation leading to mitochondrial dysfunction is induced, the mouse develops wrinkled skin and extensive, visible hair loss in a matter of weeks. When the mitochondrial function is restored by turning off the gene responsible for mitochondrial dysfunction, the mouse returns to smooth skin and thick fur, indistinguishable from a healthy mouse of the same age.

FULL STORY

The mouse in the center photo shows aging-associated skin wrinkles and hair loss after two months of mitochondrial DNA depletion. That same mouse, right, shows reversal of wrinkles and hair loss one month later, after mitochondrial DNA replication was resumed. The mouse on the left is a normal control, for comparison.

Credit: UAB

Wrinkled skin and hair loss are hallmarks of aging. What if they could be reversed?

Keshav Singh, Ph.D., and colleagues have done just that, in a mouse model developed at the University of Alabama at Birmingham. When a mutation leading to mitochondrial dysfunction is induced, the mouse develops wrinkled skin and extensive, visible hair loss in a matter of weeks. When the mitochondrial function is restored by turning off the gene responsible for mitochondrial dysfunction, the mouse returns to smooth skin and thick fur, indistinguishable from a healthy mouse of the same age.

"To our knowledge, this observation is unprecedented," said Singh, a professor of genetics in the UAB School of Medicine.

Importantly, the mutation that does this is in a nuclear gene affecting mitochondrial function, the tiny organelles known as the powerhouses of the cells. Numerous mitochondria in cells produce 90 percent of the chemical energy cells need to survive.

In humans, a decline in mitochondrial function is seen during aging, and mitochondrial dysfunction can drive age-related diseases. A depletion of the DNA in mitochondria is also implicated in human mitochondrial diseases, cardiovascular disease, diabetes, age-associated neurological disorders and cancer.

"This mouse model," Singh said, "should provide an unprecedented opportunity for the development of preventive and therapeutic drug development strategies to augment the mitochondrial functions for the treatment of aging-associated skin and hair pathology and other human diseases in which mitochondrial dysfunction plays a significant role."

The mutation in the mouse model is induced when the antibiotic doxycycline is added to the food or drinking water. This causes depletion of mitochondrial DNA because the enzyme to replicate the DNA becomes inactive.

In four weeks, the mice showed gray hair, reduced hair density, hair loss, slowed movements and lethargy, changes that are reminiscent of natural aging. Wrinkled skin was seen four to eight weeks after induction of the mutation, and females had more severe skin wrinkles than males.

Dramatically, this hair loss and wrinkled skin could be reversed by turning off the mutation. The photos below show the hair loss and wrinkled skin after two months of doxycycline induction, and the same mouse a month later after doxycycline was stopped, allowing restoration of the depleted mitochondrial DNA.

Little change was seen in other organs when the mutation was induced, suggesting an important role for mitochondria in skin compared to other tissues.

The wrinkled skin showed changes similar to those seen in both intrinsic and extrinsic aging -- intrinsic aging is the natural process of aging, and extrinsic aging is the effect of external factors that influence aging, such as skin wrinkles that develop from excess sun or long-term smoking.

Among the details, the skin of induced-mutation mice showed increased numbers of skin cells, abnormal thickening of the outer layer, dysfunctional hair follicles and increased inflammation

that appeared to contribute to skin pathology. These are similar to extrinsic aging of the skin in humans. The mice with depleted mitochondrial DNA also showed changed expression of four aging-associated markers in cells, similar to intrinsic aging.

The skin also showed disruption in the balance between matrix metalloproteinase enzymes and their tissue-specific inhibitor -- a balance of these two is necessary to maintain the collagen fibers in the skin that prevent wrinkling.

The mitochondria of induced-mutation mice had reduced mitochondrial DNA content, altered mitochondrial gene expression, and instability of the large complexes in mitochondria that are involved in oxidative phosphorylation.

Reversal of the mutation restored mitochondrial function, as well as the skin and hair pathology. This showed that mitochondria are reversible regulators of skin aging and loss of hair, an observation that Singh calls "surprising."

"It suggests that epigenetic mechanisms underlying mitochondria-to-nucleus cross-talk must play an important role in the restoration of normal skin and hair phenotype," Singh said, who has a secondary UAB appointment as professor of pathology. "Further experiments are required to determine whether phenotypic changes in other organs can also be reversed to wildtype level by restoration of mitrochondrial DNA."

Story Source:

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

Journal Reference:

1. Bhupendra Singh, Trenton R. Schoeb, Prachi Bajpai, Andrzej Slominski, Keshav K. Singh. **Reversing wrinkled skin and hair loss in mice by restoring mitochondrial function**. *Cell Death & Disease*, 2018; 9 (7) DOI: 10.1038/s41419-018-0765-9

Cite This Page:

- MLA
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University of Alabama at Birmingham. "Scientists reverse aging-associated skin wrinkles and hair loss in a mouse model: A gene mutation causes wrinkled skin and hair loss; turning off that mutation restores the mouse to normal appearance.." ScienceDaily. ScienceDaily, 20 July 2018. <www.sciencedaily.com/releases/2018/07/180720112808.htm>.

目次に戻る

9．肥満マウスの肝臓では脂肪生成と燃焼が同期している

2018 年 7 月 26 日

ペンシルベニア大学医学部ペレルマン校の研究者らが *Cell* 誌に発表した新しい研究によると、肥満飼料を与えられたマウスは、脂肪が蓄積されると同時に、燃焼方法に影響を与える新しい肝臓の概日リズムを発症する。研究者らは、肝臓脂肪の産生増加に伴い、脂肪を燃焼させる身体能力も増加するという驚くべき事実を発見した。
この脂肪生成と燃焼を左右するのが概日リズムであり、これは約 24 時間毎に生じる生理学的過程であることから、このスケジュールのミスアラインメントが代謝障害の危険因子として益々認識されている。言い換えれば、夜勤労働者や睡眠障害のある人は代謝性疾患のリスクが非常に高くなる。概日リズムと代謝障害の関係に影響を与えるメカニズムを理解することは、肥満関連疾患を治療する為の有意義な治療戦略である、と言える。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180726162757.htm

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Fat production and burning are synchronized in livers of mice with obesity

Date:

July 26, 2018

Source:

University of Pennsylvania School of Medicine

Summary:

Mice fed a fattening diet develop new liver circadian rhythms that impact the way fat is accumulated and simultaneously burned. The team found that as liver fat production increases, surprisingly, so does the body's ability to burn fat. These opposing physiological processes reach their peak activity each day around 5 p.m., illustrating an unexpected connection between overeating, circadian rhythms, and fat accumulation in the liver.

FULL STORY

The image depicts transcription factors SREBP and PPAR-alpha, which develop circadian rhythms that control the newly oscillating fat metabolism. SREBP, the rear wheel, directly drives fat synthesis and indirectly drives synchronous changes in fat burning via the front wheel, PPAR-alpha. The water bottle contains an agonist ligand for PPAR-alpha, which adds driving force to PPAR-alpha.

Credit: Annie Spikes, Dongyin Guan and Mitchell A. Lazar, Perelman School of Medicine, University of Pennsylvania; Cell

Mice fed a fattening diet develop new liver circadian rhythms that impact the way fat is accumulated and simultaneously burned, according to a new study published in *Cell* by researchers in the Perelman School of Medicine at the University of Pennsylvania. The team found that as liver fat production increases, surprisingly, so does the body's ability to burn fat. These opposing physiological processes reach their peak activity each day around 5 p.m., illustrating an unexpected connection between overeating, circadian rhythms, and fat accumulation in the liver.

"We know that obesity leads to accumulation of fat in the liver, which can cause inflammation and possibly hepatitis, liver failure, and even liver cancer," said senior author Mitchell Lazar, MD, PhD, director of Penn's Institute for Diabetes, Obesity, and Metabolism, and chief of the division of Endocrinology, Diabetes and Metabolism. "This is rapidly becoming a huge problem, as these conditions can lead to an increased need for liver transplantation, and worse, can be deadly."

While one billion people worldwide are adversely affected by malnutrition, there are another billion who experience excess calorie intake, or "overnutrition," which leads to obesity and other metabolic disorders including type-2 diabetes, cardiovascular disease, fatty liver, hypertension, and cancer. "Studying the harmful effects of overnutrition is a top priority, especially in the United States where metabolic disorders have reached epidemic proportions," Lazar said.

The circadian rhythms that fat creation and burning follow are physiological processes that occur with about every 24 hours. At the molecular level, these cycles involve feedback loops of core clock proteins expressed in virtually every cell of the body. This internal timekeeper functions to integrate environmental stimuli and genetic information to control rhythmic gene expression in a tissue-specific way.

A misalignment of this schedule is increasingly recognized as a risk factor for metabolic disorders. For example, night shift workers and individuals with sleep disorders have an increased risk of metabolic diseases. Understanding the mechanisms that impact the relationship between circadian rhythms and metabolic disorders are necessary for the development of meaningful therapeutic strategies for treating obesity-related diseases.

"We speculate that the diet-induced synchronization of these opposing liver fat metabolic processes is a response to an environment of overnutrition, leading to fat burning outpacing fat

accumulation in the liver," said first author Dongyin Guan, PhD, a postdoctoral fellow in Lazar's lab.

The 24-hour clock aspect of this physiology informs the practice of chronotherapy, which involves administering drugs at times when they are most impactful and tolerated in order to enhance effectiveness and reduce toxicity. The team discovered that the rhythm of fat burning is controlled by a protein called PPAR-alpha, which is the target of drugs called fibrates, which are already used to lower lipids in the blood. The amount of PPAR-alpha in the liver also peaked around 5 p.m.

From this coordination, Lazar's team asked whether there would be a benefit to giving short-acting PPAR-alpha drugs at the specific time of day when PPAR-alpha is at its highest level. The researchers observed that a short-acting PPAR-alpha drug reduced liver fat more when it was given in the afternoon than when it was given in the morning.

Similar to how statins (cholesterol-lowering drugs) are prescribed to be taken at bedtime, "our results support that due to the rhythmicity of PPAR-alpha, drugs that lower liver and blood lipid levels could be more effective at specific times of day," Lazar said. "Following this principle more closely to treat liver metabolic disease may indeed benefit patients, as recent studies have shown that PPAR-alpha expression oscillates in the human liver."

The study was supported by the National Institutes of Health (R01-DK045586, R01-HL54926, R01-DK098542, F32DK116519), the JPB Foundation and an American Diabetes Association Training Grant (1-17-PDF-076, 1-18-PDF-132).

Story Source:

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

Journal Reference:

1. Dongyin Guan, Ying Xiong, Patricia C. Borck, Cholsoon Jang, Paschalis-Thomas Doulias, Romeo Papazyan, Bin Fang, Chunjie Jiang, Yuxiang Zhang, Erika R. Briggs, Wenxiang Hu, David Steger, Harry Ischiropoulos, Joshua D. Rabinowitz, Mitchell A. Lazar. **Diet-Induced Circadian Enhancer**

Remodeling Synchronizes Opposing Hepatic Lipid Metabolic Processes. *Cell*, 2018; DOI: 10.1016/j.cell.2018.06.031

Cite This Page:

- MLA
- APA
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University of Pennsylvania School of Medicine. "Fat production and burning are synchronized in livers of mice with obesity." ScienceDaily. ScienceDaily, 26 July 2018. <www.sciencedaily.com/releases/2018/07/180726162757.htm>.

目次に戻る

10. 骨転移調査に信頼性が高く使用が簡単なマウスモデル

2018 年 7 月 30 日

東京工業大学の研究者らは、骨転移研究に革命を起こす可能性のある、改良されたマウスモデルを提案している。彼らの方法は、マウスの尻尾のいわゆる尾動脈を介して癌細胞を注入するのだが、従来のマウスモデルの多くの限界を克服するものだとしている。また、この新しいマウスモデルは、骨転移および癌進行の為の治療戦略開発における新たな道を開くことができる、としている。
東工大、生命理工学院 口丸高弘助教授および近藤科江教授が率いるこの研究は、*Nature Communications* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/07/180730120350.htm

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A reliable, easy-to-use mouse model for investigating bone metastasis

Date:

July 30, 2018

Source:

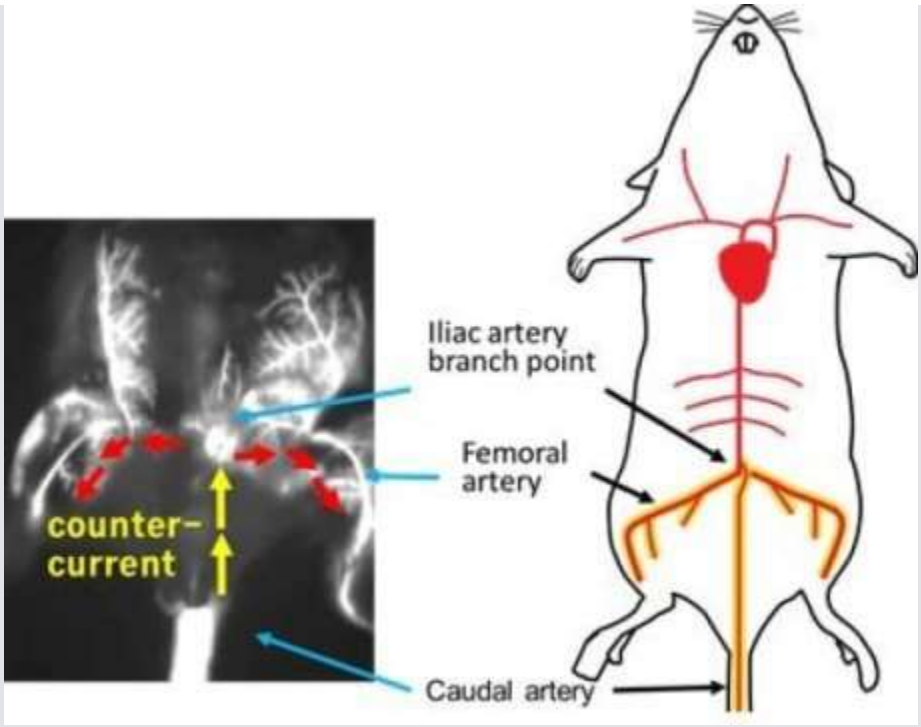
Tokyo Institute of Technology

Summary:

Researchers propose an improved mouse model that could revolutionize bone metastasis research. Their method, which involves injecting cancer cells via the so-called caudal

artery in the mouse tail, overcomes many limitations of traditional mouse models. The new model could thus open a new chapter in the development of therapeutic strategies for bone metastasis and cancer progression.

FULL STORY



The study showed that cancer cells can be delivered in a direction counter to the blood flow in order to reach the branch point of the iliac artery, which sends blood to the lower limbs via the femoral arteries. The delivery route was confirmed using real-time near infrared fluorescent imaging.

Credit: Shinae Kondoh, Nature Communications

Researchers at Tokyo Institute of Technology propose an improved mouse model that could revolutionize bone metastasis research. Their method, which involves injecting cancer cells via the so-called caudal artery in the mouse tail, overcomes many limitations of traditional mouse models. The

new model could thus open a new chapter in the development of therapeutic strategies for bone metastasis and cancer progression.

In a study published in *Nature Communications*, a group of researchers led by Takahiro Kuchimaru and Shinae Kondoh of Tokyo Institute of Technology (Tokyo Tech) present a mouse model that could greatly improve understanding of the underlying biology of bone metastasis.

It is widely known that metastasis -- the spread of cancer cells from a primary tumor to other parts of the body -- is one of the main causes of cancer mortality in humans. Bone metastasis commonly occurs when cancer cells spread to the bone from tumors originating, for example, in the prostate, breast, lung and kidney.

Experimental mouse models provide vital clues as to how cancer cells proliferate and how treatments could be developed. For the last 20 years, a model based on intracardiac (IC) injection has been considered the "gold standard" for inducing bone metastasis. This model involves injecting cancer cells directly into the left ventricle of the mouse heart. It requires a high degree of technical expertise, and even when performed successfully, the number of cancer cells that can be injected at any one time is limited. Another drawback is that the IC model tends to be more suitable for studying cancer cell lines that have a relatively high metastatic ability, ruling out analysis of "weaker" cancer cell lines.

In contrast, the new method developed by Kondoh's group involves injecting cancer cells via the caudal artery (CA) in the mouse tail -- a procedure that can be performed much more easily as the artery is visible on the body surface. This method allows researchers to inject a larger number of cancer cells without causing acute death: In the present study, around one million cells were injected without any acute death. Moreover, the new method provides a new way of studying cancer cell lines with low bone metastatic potential.

The researchers emphasize that the CA model predominantly ensures that bone metastasis develops in the hind limbs with much higher efficiency.

Using bioluminescence (BL) imaging, the team was able to detect bone metastasis just five to twelve days after CA injection of all cell lines examined.

"Overall, the results demonstrated that CA injection provides a reliable method to develop bone metastasis by increasing the delivery efficiency of a wide variety of cancer cell lines to the bone marrow of the hind limbs in mice," they say.

In addition, the CA model enables scientists to monitor the progression of bone metastasis over a longer period of time compared with the IC model due to reduced incidence of lethal metastasis in other organs. This represents a big step forward for investigating cancer cell dormancy and reactivation in greater depth.

The researchers conclude: "Our model may open a new avenue for understanding the bone metastatic processes and development of drugs preventing bone metastasis and recurrence."

Story Source:

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

Journal Reference:

1. Takahiro Kuchimaru, Naoya Kataoka, Kenji Nakagawa, Tatsuhiro Isozaki, Hitomi Miyabara, Misa Minegishi, Tetsuya Kadonosono, Shinae Kizaka-Kondoh. **A reliable murine model of bone metastasis by injecting cancer cells through caudal arteries**. *Nature Communications*, 2018; 9 (1) DOI: 10.1038/s41467-018-05366-3

Cite This Page:

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Tokyo Institute of Technology. "A reliable, easy-to-use mouse model for investigating bone metastasis." ScienceDaily. ScienceDaily, 30 July 2018. <www.sciencedaily.com/releases/2018/07/180730120350.htm>.