BIO NEWS

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1．幹細胞を緑色に発光させる新しいマウスモデル

2018 年 2 月 1 日

多能性間質細胞は医療研究において長い間注目されている。今回ボン大学の科学者らによって、これらの幹細胞を特異的にマーキングする方法が発見された。これにより、これら幹細胞の分布パターンや生物組織内でどのように機能するか分析することが可能になる。
特定の細胞型を調べる為には、最初にそれを他の細胞型とはっきり区別することが必要となるが、多能性間質細胞の場合には、限られた範囲内でしか可能ではなかった。研究チームは、CD73 遺伝子が多能性間質細胞で主に活性であることを利用して、これらの遺伝子の発現が緑の蛍光色をもたらすトランスジェニックマウスを作成した。
この研究には、オックスフォード大学、筑波大学、ストックホルム　カロリンスカ研究所の研究者らも加わっており、現在 *Cell Stem Cell* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180201173107.htm

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New mouse model makes stem cells light up green

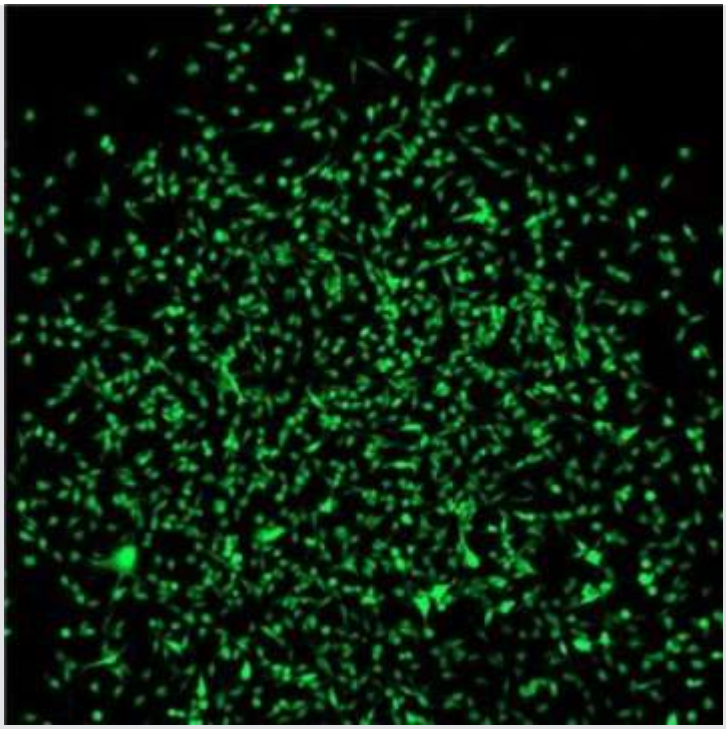
Date:
February 1, 2018

Source:
Universität Bonn

Summary:

Multipotent stromal cells have long been a hot topic in medical research. Scientists have now found a way to specifically mark these stem cells. This makes it possible to analyze their distribution pattern and their function in living organisms.

FULL STORY



Scientists at the University of Bonn have found a way to specifically mark multipotent stromal cells. These cells therefore light up green in the microscope image.

Credit: (c) Martin Breitbach/Uni Bonn

Multipotent stromal cells have long been a hot topic in medical research. Scientists at the University of Bonn have now found a way to specifically mark these stem cells. This makes it possible to analyze their distribution pattern and their function in living organisms. The study, which included researchers from Oxford University, Tsukuba University and the Karolinska Institute Stockholm, is now being published in the journal *Cell Stem Cell.*

In order to examine a particular cell type, one must first be able to clearly distinguish it from others. Biologists and physicians have therefore developed sophisticated methods for the live labeling of specific cells. For multipotent stromal cells however, this has until now only been possible to a limited extent.

This is particularly unsatisfactory, because these cells are a focal point of research interest, especially in regenerative medicine. For instance, it is known that they can become bone, fat or cartilage cells. Additionally, it is believed that they play a role in wound healing processes, but also in pathological events, for instance those that occur during vascular calcification (arteriosclerosis).

"In all these development and disease processes however, there are still many unanswered questions," explains Dr. Martin Breitbach from the Institute of Physiology I at the University of Bonn. "Which is why we looked for a way to mark multipotent stromal cells in the living organism." To this end, the scientists searched for genetic information that is read frequently in the cells of interest, but is rather inactive in other cell types. They found what they were looking for in the so-called CD73 gene.

Live reporter indicates gene activity

They then generated transgenic mice, where expression of the CD73 gene results in green fluorescent labeling of the respective cell. "As CD73 is mainly active in the multipotent stromal cells, these are marked by a green glow," explains Breitbach's co-author Dr. Kenichi Kimura.

This approach has in principle been established for many years. But until now, there was no known adequate marker for multipotent stromal cells that is well-suited to distinguishing them from other cells. "And we have now found this marker with the CD73 gene," explains Kimura.

The dye-labeling made it possible to isolate these cells from the bone marrow. The scientists were then able to show that bone, fat and cartilage cells differentiate from a single multipotent stromal cell in the culture dish. "Our method makes it possible to examine the cells in their original state," says Breitbach. "In future studies, it will for example be possible to clarify directly in the living animal whether and how the stem cells migrate to the different organs in the case of injury or illness, and what they do there."

Chance discovery opens new perspectives

A result that the scientists themselves had not expected also opens up new research perspectives: In addition to the multipotent stromal cells, sinusoidal endothelial cells in the bone marrow are another cell type that appears to have increased CD73 activity.

The researchers were delighted about this discovery: It only became recently known that the maturation and distribution of hematopoietic stem cells are regulated by a variety of endothelial cell types. Sinusoidal endothelial cells probably play a key role here. But the underlying mechanisms are still rather puzzling. Because until recently, they too could not be stained specifically and thus distinguished from the other endothelial cells within the bone marrow.

The scientists have now purified the various cell populations and characterized the genetic fingerprint of the multipotent stromal cells and the sinusoidal endothelial cells in detail. "These findings are extremely interesting," says Breitbach. "They provide deeper insights into these cell types and are a starting point for further studies."

Story Source:

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

Journal Reference:

1. Martin Breitbach, Kenichi Kimura, Tiago C. Luis, Christopher J. Fuegemann, Petter S. Woll, Michael Hesse, Raffaella Facchini, Sarah Rieck, Katarzyna Jobin, Julia Reinhardt, Osamu Ohneda, Daniela Wenzel, Caroline Geisen, Christian Kurts, Wolfgang Kastenmüller, Michael Hölzel, Sten E.W. Jacobsen, Bernd K. Fleischmann. **In Vivo Labeling by CD73 Marks Multipotent Stromal Cells and Highlights Endothelial Heterogeneity in the Bone Marrow Niche**. *Cell Stem Cell*, 2018; 22 (2): 262 DOI: 10.1016/j.stem.2018.01.008

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2. ハダカデバネズミは長寿で癌に罹らない、その謎解明に迫る

2018 年 2 月 6 日

奇妙な外見をしたハダカデバネズミは、平均寿命がげっ歯類で最長の 30 年であり、癌など様々な加齢性疾患に顕著な耐性があるなど、研究者にとっては大変興味深い存在である。また、老化しない唯一の哺乳類であることから、生物学の常識を覆す生き物ともされている。このげっ歯類が細胞老化と呼ばれる抗癌メカニズムを有するかどうかを調べているロチェスター大学の研究者らは、このハダカデバネズミはマウスと似通った細胞老化を示すが、それら老化細胞が長寿や癌耐性に寄与する可能性のある独特な特徴を示すことを発見した。研究者らは、ハダカデバネズミが老化細胞の代謝プロセスをより強く阻害し、老化の有害な影響に対してより高い耐性をもたらすことを見出した。
高齢化研究所（National Institute of Aging）からの助成金とライフ・エクステンション財団によってサポートされているこの研究は、PNAS（国立科学アカデミー紀要）に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180206115143.htm

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Another piece to the puzzle in naked mole rats' long, cancer-free life

Date:
February 6, 2018

Source:
University of Rochester

Summary:
Cellular senescence is an evolutionary adaptation that prevents damaged cells from dividing out of control and developing into cancer. However, senescence has a negative side: by stopping cell division, it also accelerates aging. In a surprising finding, biologists have shown that naked mole rats experience the same cellular senescence as much shorter-lived mice, yet they continue to live long, cancer-free lives.

FULL STORY

Naked mole rats are intriguing for researchers for a variety of reasons: they have the longest life span of rodents (average lifespan is 30 years), they are resistant to a variety of age-related diseases such as cancer, and they tend to remain fit and active until very advanced ages. The

Gorbunova Lab at the University of Rochester studies these rodents in the hopes of unraveling their unique anti-cancer properties.

Credit: University of Rochester photo/J. Adam Fenster

With their large buck teeth and wrinkled, hairless bodies, naked mole rats won't be winning any awards for cutest rodent. But their long life span -- they can live up to 30 years, the longest of any rodent -- and remarkable resistance to age-related diseases, offer scientists key clues to the mysteries of aging and cancer.

That's why University of Rochester biology professors Vera Gorbunova and Andrei Seluanov and postdoctoral associate Yang Zhao studied naked mole rats to see if the rodents exhibit an anticancer mechanism called cellular senescence -- and, if so, "how the mechanism might work differently than in short-lived animals, like mice," says Zhao, the lead author of the study, published in *PNAS*.

Cellular senescence is an evolutionary adaptation that prevents damaged cells from dividing out of control and developing into full-blown cancer. However, senescence has a negative side too: by stopping cell division in order to prevent potential tumors, it also accelerates aging.

Previous studies indicated that when cells that had undergone senescence were removed from mice, the mice were less frail in advanced age as compared to mice that aged naturally with senescent cells intact.

Researchers therefore believed senescence held the key to the proverbial fountain of youth; removing senescent cells rejuvenated mice, so perhaps it could work with human beings. Companies began investigating drugs -- known as senolytic agents -- that would kill senescent cells and translate the anti-aging effects to humans.

But is eliminating senescence actually the key to preventing or reversing age-related diseases, namely cancer?

"In humans, as in mice, aging and cancer have competing interests," Gorbunova says. "In order to prevent cancer, you need to stop cells from dividing. However, to prevent aging, you want to keep cells dividing in order to replenish tissues."

Gorbunova and Seluanov have long researched cancer and its relation to aging and DNA repair. They have identified several mechanisms that contribute to longevity and cancer resistance in naked mole rats, including the chemical HMW-HA (high molecular weight hyaluronan). But they believe there are more pieces to the puzzle.

In their recent study, Zhao, Seluanov, Gorbunova, and their collaborators compared the senescence response of naked mole rats to that of mice, which live a tenth as long -- only about two to three years. "We wanted to look at these animals that pretty much don't age and see if they also had senescent cells or if they evolved to get rid of cell senescence," Seluanov says.

Their unexpected discovery? Naked mole rats do experience cellular senescence, yet they continue to live long, healthy lives; eliminating the senescence mechanism is not the key to their long life span. "It was surprising to us that despite its remarkable longevity the naked mole rat has cells that undergo senescence like mouse cells," Gorbunova says.

The researchers found that although naked mole rats exhibited cellular senescence similar to mice, their senescent cells also displayed unique features that may contribute to their cancer resistance and longevity.

The cellular senescence mechanism permanently arrests a cell to prevent it from dividing, but the cell still continues to metabolize. The researchers found that naked mole rats are able to more strongly inhibit the metabolic process of the senescent cells, resulting in higher resistance to the damaging effects of senescence.

"In naked mole rats, senescent cells are better behaved," Gorbunova says. "When you compare the signals from the mouse versus from the naked mole rat, all the genes in the mouse are a mess. In the naked mole rat, everything is more organized. The naked mole rat didn't get rid of the senescence, but maybe it made it a bit more structured."

Although evolution of a long life span does not eliminate senescence, the more structured response to senescence may have an evolutionary basis, Zhao says: "We believe there was some strategy during the evolution of naked mole rats that allowed them to have more systematic changes in their genes and have more orchestrated pathways being regulated. We believe this is beneficial for longevity and cancer resistance."

The research was supported by grants from the National Institute of Aging and by the Life Extensions Foundation.

Story Source:

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

Journal Reference:

1. Yang Zhao, Alexander Tyshkovskiy, Daniel Muñoz-Espín, Xiao Tian, Manuel Serrano, Joao Pedro de Magalhaes, Eviatar Nevo, Vadim N. Gladyshev, Andrei Seluanov, Vera Gorbunova. **Naked mole rats can undergo developmental, oncogene-induced and DNA damage-induced cellular senescence**. *Proceedings of the National Academy of Sciences*, 2018; 201721160 DOI: 10.1073/pnas.1721160115

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目次に戻る

3. ウィルスが免疫システムを武装解除する方法

2018 年 2 月 5 日

HIV や C 型肝炎などの慢性感染症を引き起こすウィルスは、どのようにして宿主の免疫系を打ち負かすのだろうか？その質問の答えはずっと不明のままであったが、今回マギル大学の新しい研究で、パズルの重要な部分である可能性のある分子メカニズムが解明されている。この発見は広範囲の疾患を治療するための新たな標的を提供する可能性がある、として最近の *Immunity* 誌に発表された。

感染阻止は、感染した細胞を迅速に認識して破壊する能力に大きく依存するが、これは、CD8 + T 細胞として知られる免疫細胞のクラスによって行われる。今回の発見によると、CD8 + T 細胞の表面上の糖タンパク質の改変をもたらし、細胞の機能を低下させるサイトカインの産生が促進されることによってウィルスが持続、すなわち病原体が免疫応答を超えて慢性感染を確立する時間を手に入れることが明らかになった。また、この発見は T 細胞の機能があまり規制されていないがんや自己免疫などの病気にも役立つかもしれない、としている。

英文記事：
https://sciencesources.eurekalert.org/pub_releases/2018-02/mu-hvd020518.php

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PUBLIC RELEASE: 5-FEB-2018

How viruses disarm the immune system

Discovery of molecular mechanism could point toward new targets for treating patients

McGill University

How do viruses that cause chronic infections, such as HIV or hepatitis c virus, manage to outsmart their hosts' immune systems?

The answer to that question has long eluded scientists, but new research from McGill University has uncovered a molecular mechanism that may be a key piece of the puzzle. The discovery could provide new targets for treating a wide range of diseases.

Fighting off infections depends largely on our bodies' capacity to quickly recognize infected cells and destroy them, a job carried out by a class of immune cells known as CD8+ T cells. These soldiers get some of their orders from chemical mediators known as cytokines that make them more or less responsive to outside threats. In most cases, CD8+ T cells quickly recognize and destroy infected cells to prevent the infection from spreading.

"When it comes to viruses that lead to chronic infection, immune cells receive the wrong set of marching orders, which makes them less responsive," says Martin Richer, an assistant professor at McGill's Department of Microbiology & Immunology and senior author of the study, published recently in the journal *Immunity*.

The research, conducted in Richer's lab by graduate student Logan Smith, revealed that certain viruses persist by driving the production of a cytokine that leads to modification of glycoproteins on the surface of the CD8+ T cells, making the cells less functional. That maneuver buys time for the pathogen to outpace the immune response and establish a chronic infection. Importantly, this pathway can be targeted to restore some functionality to the T cells and enhance the capacity to control infection.

The discovery of this regulatory pathway could help identify new therapeutic targets for a variety of diseases. "We might be able to take advantage of the pathways induced by these signals to fight chronic viral infections by making the immune system more responsive," Richer says. "The findings might also prove useful for diseases like cancer and autoimmunity, where T cells function is poorly regulated."

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目次に戻る

４．果糖の過剰摂取が腸にもたらすこと -マウス研究

2018 年 2 月 6 日

プリンストン大学の研究者らがマウス研究によって示した報告によると、今まで肝臓で処理されると見なされていた果糖は、実は主に小腸で処理される。また、小腸が食事後により効率的に果糖を処理消失させることも発見した。
今までのマウスやヒトの研究からの証拠によれば、過剰な糖分摂取は特に肝臓に有害であり、慢性的な過剰摂取は、肥満から糖尿病に進行するインスリン抵抗性へとつながる可能性があり、それはまた、肝硬変や肝臓癌に至り得る非アルコール性脂肪疾患へとつながる可能性がある。
以前の見解では、肝臓が全ての糖分を処理、ということであったが、この研究によって、果糖の90%以上はマウスの小腸で消失したことが示された。これは、適量な果糖であれば肝臓まで届かないということである。また、小腸が食事後により効率的に果糖を処理することから、「甘い物は食後に適量のみ、食事中に甘い飲み物は飲まない」という古くからのアドバイスが正しい、としている。
この研究成果は、2 月 6 日の *Cell Metabolism* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180206140645.htm

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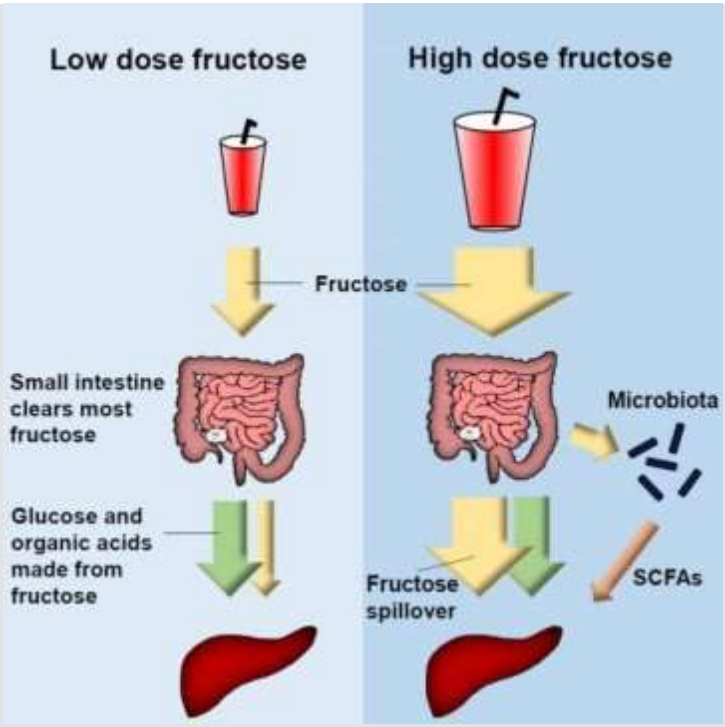
Mouse study reveals what happens in the gut after too much fructose

Date:
February 6, 2018

Source:
Cell Press

Summary:
Researchers report that in mice, fructose, a sugar found in fruit, is processed mainly in the small intestine, not in the liver as had previously been suspected. Sugary drinks and processed high-sugar foods overwhelm the small intestine and spill into the liver for processing. Additionally, the authors learned that the ability of the small intestine to process fructose is higher after a meal.

FULL STORY



This graphical abstract depicts the findings of Jang et al., which show that it is actually the small intestine that clears most dietary fructose, and this is enhanced by feeding. High fructose doses spill over to the liver and to the colonic microbiota for metabolism.

Credit: Jang et al./Cell Metabolism 2018

Princeton University researchers report that in mice, fructose, a sugar found in fruit, is processed mainly in the small intestine, not in the liver as had previously been suspected. Sugary drinks and processed high-sugar foods overwhelm the small intestine and spill into the liver for processing. Additionally, the authors learned that the ability of the small intestine to process fructose is higher after a meal. The work appears February 6 in the journal *Cell Metabolism*.

Evidence from previous animal and human studies has shown that excessive sugar ingestion can be harmful, especially to the liver. Chronic over-consumption can lead to obesity and foster insulin resistance that can progress to diabetes; it also can contribute to non-alcoholic fatty liver disease, which can lead to cirrhosis or liver cancer.

"There is a fundamental physiological difference in how smaller and larger amounts of sugar are processed in the body," explains Joshua D. Rabinowitz of the Lewis-Sigler Institute for Integrative Genomics at Princeton University, whose laboratory led the study. The prior view was that the liver processes all ingested sugar. But this study showed that more than 90 percent of the fructose was cleared by the small intestine in mice.

"We can offer some reassurance -- at least from these animal studies -- that fructose from moderate amounts of fruits will not reach the liver," he says. However, the small intestine probably starts to get overwhelmed with sugar halfway through a can of soda or large glass of orange juice.

In the study, Rabinowitz and his colleagues studied the path of isotope-labeled fructose through the digestive systems of laboratory mice. The researchers observed that excess fructose that is not absorbed by the small intestine continues through the intestine into the colon. As a consequence, it also comes into contact with the natural microbiotic flora of the large intestine and colon, known as the microbiome.

"The microbiome is designed to never see sugar," Rabinowitz says. "One can eat an infinite amount of carbohydrates, and there will be nary a molecule of glucose that enters the microbiome. But as soon as you drink the soda or juice, the microbiome is seeing an extremely powerful nutrient that it was designed to never see."

While the study did not show that fructose influences the microbiome, the authors suggest an effect is likely and should be studied further to learn more about the biological consequences of high sugar intake.

The investigators also found that the small intestine clears fructose more efficiently after a meal. "We saw that feeding of the mice prior to the sugar exposure enhanced the small intestine's ability to process fructose," said Rabinowitz. "And that protected the liver and the microbiome from sugar exposure." The researchers theorize that in a fasting state, such as upon awakening or in the mid-afternoon, one is extra vulnerable to fructose due to a lessened ability to process it in the small intestine.

Although the study was conducted in mice, Rabinowitz encourages "the most old-fashioned advice in the world" for humans. Limit sweets to moderate quantities after meals, and do not have sweet drinks away from meal time.

Story Source:

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

Journal Reference:

1. Jang, C. et al. **The Small Intestine Converts Dietary Fructose into glucose and organic acids**. *Cell Metabolism*, 2018 DOI: 10.1016/j.cmet.2017.12.016

Cite This Page:

- MLA
- APA
- Chicago

Cell Press. "Mouse study reveals what happens in the gut after too much fructose." ScienceDaily. ScienceDaily, 6 February 2018. <www.sciencedaily.com/releases/2018/02/180206140645.htm>.

目次に戻る

5. 牛の胚性幹細胞単離術の発見

2018 年 2 月 9 日

35 年以上にわたり、科学者らは牛の胚性幹細胞を単離しようと試みてきたが、まだ大きな成功は得られていない。適切な条件下では胚性幹細胞は無制限に増殖し、他の細胞型あるいは組織を作ることができるため、これによって遺伝的に優れた牛の作製の可能性が非常に高くなる。

今週の米国科学アカデミー紀要に掲載されたカリフォルニア大学デイビス校の研究によると、研究者らは、ほぼ全ての試みにおいて効率的に幹細胞を抽出することができる新しい培養システムの開発に成功した、としている。

マウスやラットでは特定の治療法がヒトに対して機能するかどうかを実証するには小さ過ぎるという点から、遺伝子検査、ゲノム工学、ヒトの疾患研究には牛のような比較的大きな家畜から胚性幹細胞を生産することが重要という考えがあり、その意味でもこの細胞はヒト幹細胞治療のためのより良いモデルを提供し得る、としている。また、胚性幹細胞株から配偶子、精子や卵子を作ることができれば、このような「in vitro」育種で、遺伝的に優れた牛の生産に要する時間を短縮できる；すなわち、将来の牛はより多くの筋肉を持ち、より多くの牛乳を生産し、より少ないメタンガスを放出し、気候にもより容易に適応することができる、と。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180209170526.htm

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Efficient technique discovered for isolating embryonic stem cells in cows

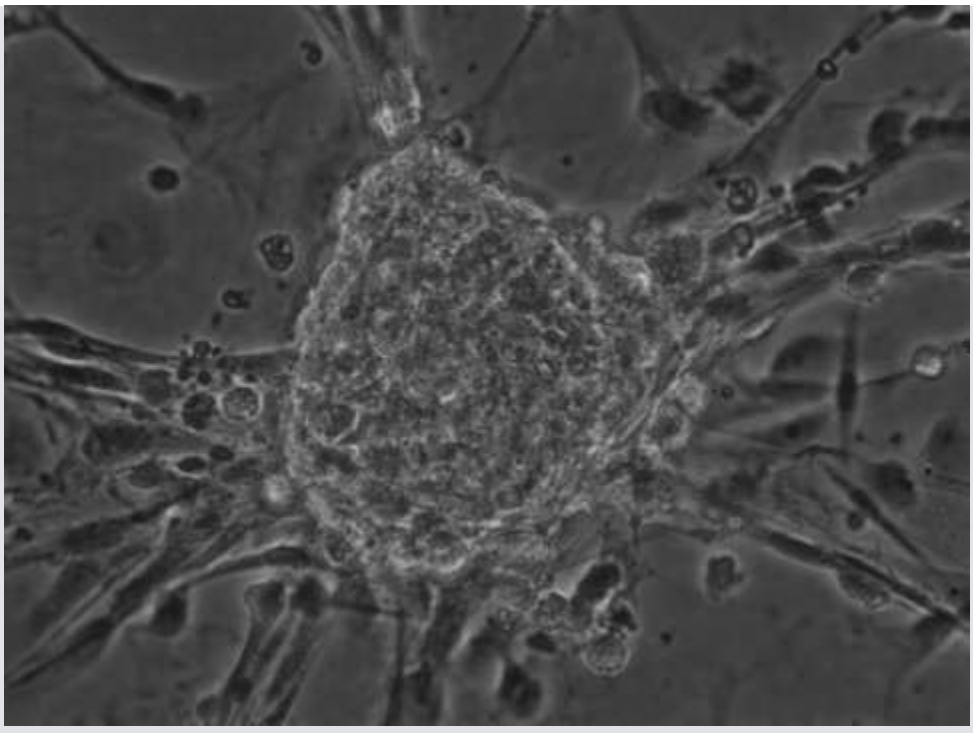
Findings could advance cattle production, help study human disease

Date:
February 9, 2018

Source:
University of California - Davis

Summary:
Scientists have developed a highly efficient method of isolating embryonic stem cells in cows. Producing embryonic stem cells from large livestock species like cattle is important for genetic testing, genome engineering, and studying human disease.

FULL STORY



A colony of cow embryonic stem cells.

Credit: Pablo Ross / UC Davis

For more than 35 years, scientists have tried to isolate embryonic stem cells in cows without much success. Under the right conditions, embryonic stem cells can grow indefinitely and make any other cell type or tissue, which has huge implications for creating genetically superior cows.

In a study published this week in the journal *Proceedings of the National Academy of Sciences*, scientists at the University of California, Davis, were able to develop a new culture system that allows them to efficiently derive stem cells on almost every single attempt.

Producing embryonic stem cells from large livestock species like cattle is important for genetic testing, genome engineering and studying human disease. The cells may offer a better model for human stem cell therapies. Mice and rats are sometimes too small to demonstrate whether certain therapies will work on humans.

BREEDING A BETTER COW, FASTER

If researchers can generate gametes, or sperm and eggs cells, from the stem cell lines, the ramifications are profound. Such "in vitro" breeding could decrease the amount of time it takes to produce genetically superior cattle.

"That could revolutionize the way we do genetics by orders of magnitude," said study author Pablo Ross, an associate professor in the Department of Animal Science at UC Davis' College of Agricultural and Environmental Sciences.

In just a few years, scientists could speed up the process of improving generations by decades. "In two and a half years, you could have a cow that would have taken you about 25 years to achieve. It will be like the cow of the future. It's why we're so excited about this," said Ross.

The cow of the future could have more muscle, produce more milk, emit less methane, or more easily adapt to a warmer climate.

Ross envisions the findings helping the cattle industry become more sustainable. "Animals that are more efficient and have improved welfare, that may have more disease resistance is better for everyone," said Ross.

Story Source:

Materials provided by **University of California - Davis**. Original written by Amy Quinton. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yanina Soledad Bogliotti, Jun Wu, Marcela Vilarino, Daiji Okamura, Delia Alba Soto, Cuiqing Zhong, Masahiro Sakurai, Rafael Vilar Sampaio, Keiichiro Suzuki, Juan Carlos Izpisua Belmonte, Pablo Juan Ross. **Efficient derivation of stable primed pluripotent embryonic stem cells from bovine blastocysts**. *Proceedings of the National Academy of Sciences*, 2018; 201716161 DOI: 10.1073/pnas.1716161115

Cite This Page:

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University of California - Davis. "Efficient technique discovered for isolating embryonic stem cells in cows: Findings could advance cattle production, help study human disease." ScienceDaily. ScienceDaily, 9 February 2018. <www.sciencedaily.com/releases/2018/02/180209170526.htm>.

目次に戻る

6. 脂肪燃焼を制御する脳内スイッチ -マウス実験

2018 年 2 月 13 日

オーストラリアのモナシュ大学の研究者らは脂肪燃焼を調節するマウスの脳内の分子スイッチを発見、これによりダイエット後の体重増加をコントロールする方法を提供し得るとして、今日発行の *Cell Reports* 誌に発表している。
このスイッチは特にダイエットとリバウンドを繰り返すヨーヨーダイエットの根底にあるプロセスを引き起こすとし、このスイッチを制御することができれば、肥満および 2 型糖尿病などの代謝障害の治療法になり得る、としている。
この分子は、カルニチンアセチルトランスフェラーゼ（Crat）と呼ばれるタンパク質で、このたんぱく質を遺伝的にスイッチオフしたマウスを開発、このマウスは絶食後または絶食後に給餌されると通常の速度よりも大きな蓄積量を消費した。また、繰り返されるダイエット（ヨーヨーダイエット）は、脳がこれらのダイエットを短い飢饉と解釈し脳細胞における Crat タンパク質のスイッチをオフにし身体を脂肪燃焼から貯蔵へと変える、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180213120451.htm

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The end of yo-yo dieting? Brain switch that controls fat burning uncovered

Date:
February 13, 2018

Source:
Monash University

Summary:
Scientists have discovered a molecular switch in the brain that regulates fat burning -- and could provide a way to control weight gain following dieting.

FULL STORY

Scientists have discovered a molecular switch in the brain that regulates fat burning -- and could provide a way to control weight gain following dieting.

Monash University researchers have identified a molecular switch in the brain that potentially controls the human body's capacity to store fat, particularly after long periods of "famine" or weight loss -- a process that underlies yo-yo dieting, where we regain the weight lost caused by dieting.

Being able to control this switch may be a therapy for obesity and other metabolic disorders such as Type 2 diabetes.

Associate Professor Zane Andrews and his colleagues at the Monash Biomedicine Discovery Institute have identified a protein in mice, called carnitine acetyltransferase (Crat), in hunger-processing brain cells that regulate fat storage after dieting. These findings were published today in the international journal *Cell Reports*.

When we are dieting (or evolutionarily when there is a famine) our bodies burn more fat to provide enough energy. But at the same time our brains fight to conserve energy and, as soon as food becomes available, the body switches from burning to storing fat and instead uses ingested calories from food. The international research team discovered the Crat protein and developed a mouse that had this protein genetically switched off. These mice, when fasted or fed after a fast, consume their fat reserves at a greater than normal rate.

According to Associate Professor Andrews, repeated dieting, or yo-yo dieting, may lead to weight gain because the brain interprets these diets as short famines and urges the person to store more fat for future shortages. For the first time the Crat protein in hunger-processing brain cells has

been identified as the switch that instructs the body to replace the lost weight through increased fat storage.

"Manipulating this protein offers the opportunity to trick the brain and not replace the lost weight through increased appetite and storage of fat," Associate Professor Andrews said.

"By regulating this protein we can ensure that diet-induced weight loss stays off rather than sneaking back on."

Story Source:

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

Journal Reference:

1. Alex Reichenbach, Romana Stark, Mathieu Mequinion, Raphael R.G. Denis, Jeferson F. Goularte, Rachel E. Clarke, Sarah H. Lockie, Moyra B. Lemus, Greg M. Kowalski, Clinton R. Bruce, Cheng Huang, Ralf B. Schittenhelm, Randall L. Mynatt, Brian J. Oldfield, Matthew J. Watt, Serge Luquet, Zane B. Andrews. **AgRP Neurons Require Carnitine Acetyltransferase to Regulate Metabolic Flexibility and Peripheral Nutrient Partitioning**. *Cell Reports*, 2018; 22 (7): 1745 DOI: 10.1016/j.celrep.2018.01.067

Cite This Page:

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Monash University. "The end of yo-yo dieting? Brain switch that controls fat burning uncovered." ScienceDaily. ScienceDaily, 13 February 2018. <www.sciencedaily.com/releases/2018/02/180213120451.htm>.

目次に戻る

7. iPS 細胞で癌を予防しうる -マウス実験

2018 年 2 月 15 日

iPS 細胞（人工多能性幹細胞）は、身体の外側では外傷や疾患による損傷の修復を助けることができる異なるタイプの細胞や組織になることで知られているが、今回スタンフォード大学医学部のマウス研究では、iPS 細胞の別の使用法が示唆されている。
その使用法とは、いろいろなタイプの癌の発症を予防するワクチンとして、であり、iPS 細胞が多くの癌細胞と同様、身体の組織を構成する成熟細胞に組み込まれた増殖制限のない発達途上の未熟な前駆細胞に似ているため、抗癌ワクチンとして機能する、としている。
実際に、単に照射で不活性化しただけの iPS 細胞が抗腫瘍 T 細胞反応を促して癌の発現や再発を防ぐ抗癌ワクチンとなりうることがマウス実験で示されたことが、2 月 15 日の *Cell Stem Cell* 誌で発表されている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180215125026.htm

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Induced pluripotent stem cells could serve as cancer vaccine

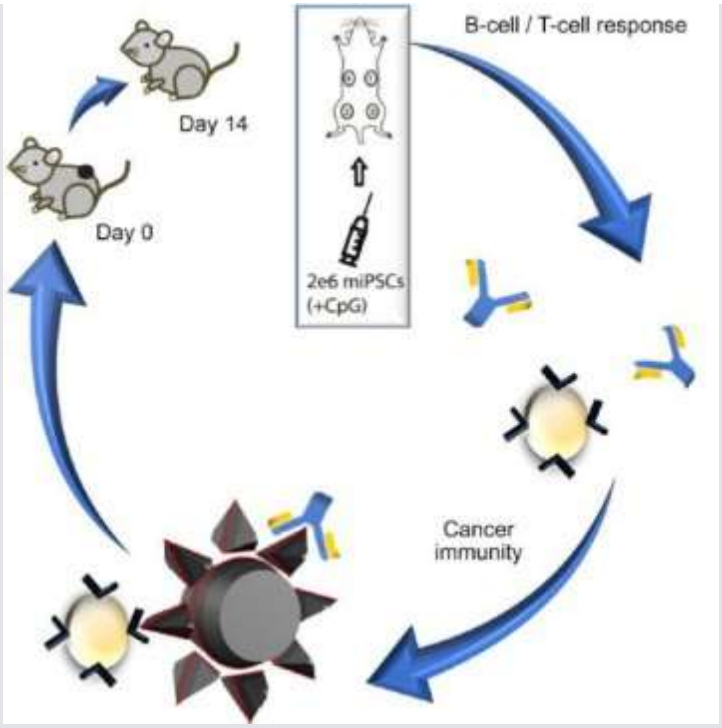
Date:
February 15, 2018

Source:

Stanford Medicine

Summary:
Induced pluripotent stem cells, or iPS cells, are a keystone of regenerative medicine. Outside the body, they can be coaxed to become many different types of cells and tissues that can help repair damage due to trauma or disease. Now, a study in mice suggests another use for iPS cells: training the immune system to attack or even prevent tumors.

FULL STORY



This visual abstract depicts how cancer immunity against multiple types of cancer can be achieved using an easily generable iPSC-based cancer vaccine. This immunity is based on overlapping epitopes between iPSCs and cancer cells and can also be achieved by reactivating the immune system as an adjuvant.

Credit: Kooreman and Kim et al./Cell Stem Cell

Induced pluripotent stem cells, or iPS cells, are a keystone of regenerative medicine. Outside the body, they can be coaxed to become many different types of cells and tissues that can help repair damage due to trauma or disease. Now, a study in mice from the Stanford University School of Medicine suggests another use for iPS cells: training the immune system to attack or even prevent tumors.

The results suggest it may one day be possible to vaccinate an individual with his or her own iPS cells to protect against the development of many types of cancer.

The iPS cells work as an anti-cancer vaccine because, like many cancer cells, they resemble developmentally immature progenitor cells, which are free from the growth restrictions built into mature cells that make up the body's tissues. Injecting iPS cells that genetically match the recipient, but that are unable to replicate, can safely expose the immune system to a variety of cancer-specific targets, the researchers found.

"We've learned that iPS cells are very similar on their surface to tumor cells," said Joseph Wu, MD, PhD, director of Stanford's Cardiovascular Institute and professor of cardiovascular medicine and of radiology. "When we immunized an animal with genetically matching iPS cells, the immune system could be primed to reject the development of tumors in the future. Pending replication in humans, our findings indicate these cells may one day serve as a true patient-specific cancer vaccine."

Wu is the senior author of the study, which will be published online Feb. 15 in *Cell Stem Cell*. Former postdoctoral scholar Nigel Kooreman, MD, is the lead author.

"These cells, as a component of our proposed vaccine, have strong immunogenic properties that provoke a systemwide, cancer-specific immune response," said Kooreman, who is now a surgery resident in the Netherlands. "We believe this approach has exciting clinical potential."

Similarities between cancer, iPS cells

To make iPS cells, researchers collect cell samples from an easily accessible source like skin or blood. The cells are then treated with a panel of genes that make them rewind their developmental clock to become pluripotent, allowing them to become nearly any tissue in the body. One key test of pluripotency is the ability of the cells to form a tumor called a teratoma, which is composed of many different cell types, after the cells are injected into animals. (IPS cells used in regenerative-

medicine therapies are grown in the presence of other proteins to encourage them to specialize, or differentiate, into specific cell populations before being used clinically.)

Cancer cells also have long been known to echo many features of developmentally immature cells. As part of their cancerous transformation, they often shed the naturally occurring mechanisms that serve to block inappropriate cell division and instead begin proliferating rapidly.

Wu and Kooreman wondered exactly how closely iPS and cancer cells resemble one another. They compared the gene expression panels of the two types of cells in mice and humans and found some remarkable similarities, suggesting that these cells share proteins on their surfaces called epitopes that could serve as targets for the immune system.

To test this theory, they used four groups of mice. One was injected with a control solution, one received genetically matching iPS cells that had been irradiated to prevent the formation of teratomas, one received a generic immune-stimulating agent known as an adjuvant, and one received a combination of irradiated iPS cells and adjuvant. All animals in each group were injected once a week for four weeks. Lastly, a mouse breast cancer cell line was transplanted into the animals to observe the potential growth of tumors.

One week after transplantation, all mice were found to have developed tumors of the breast cancer cells at the injection site. Although the tumors grew robustly in the control groups, they shrank in size in 7 out of 10 mice vaccinated with iPS cells plus the adjuvant. Two of these mice were able to completely reject the breast cancer cells and live for more than one year after tumor transplantation. Similar results were obtained when Kooreman and his colleagues transplanted a mouse melanoma and mesothelioma (a type of lung cancer) cell line into mice.

Kooreman and his colleagues further found that immune cells called T cells from vaccinated mice were able to slow the growth of breast cancer cells in unvaccinated mice. Conversely, these T cells also blocked the growth of teratomas in mice injected with nonirradiated iPS cells, showing that the activated T cells were recognizing epitopes that are shared between the breast cancer cells and the iPS cells.

Putting the immune system on alert

"This approach is particularly powerful because it allows us to expose the immune system to many different cancer-specific epitopes simultaneously," Kooreman said. "Once activated, the immune system is on alert to target cancers as they develop throughout the body."

The researchers next would like to study whether the approach works in samples of human cancers and immune cells in a laboratory setting. If successful, they envision a future in which people could receive a vaccine comprised of their own irradiated iPS cells as a way to prevent the development of cancers months or years later. Alternatively, the iPS cells could potentially be used as a part of the standard of adjuvant care after primary surgery; chemotherapy or radiation therapy, or both; or immunotherapy as a way to treat established cancers.

"Although much research remains to be done, the concept itself is pretty simple," Wu said. "We would take your blood, make iPS cells and then inject the cells to prevent future cancers. I'm very excited about the future possibilities."

Story Source:

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

Journal Reference:

1. Nigel G. Kooreman, Youngkyun Kim, Patricia E. de Almeida, Vittavat Termglinchan, Sebastian Diecke, Ning-Yi Shao, Tzu-Tang Wei, Hyoju Yi, Devaveena Dey, Raman Nelakanti, Thomas P. Brouwer, David T. Paik, Idit Sagiv-Barfi, Arnold Han, Paul H.A. Quax, Jaap F. Hamming, Ronald Levy, Mark M. Davis, Joseph C. Wu. **Autologous iPSC-Based Vaccines Elicit Anti-tumor Responses In Vivo**. *Cell Stem Cell*, 2018; DOI: 10.1016/j.stem.2018.01.016

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Stanford Medicine. "Induced pluripotent stem cells could serve as cancer vaccine." ScienceDaily. ScienceDaily, 15 February 2018. <www.sciencedaily.com/releases/2018/02/180215125026.htm>.

目次に戻る

8. 知的障害のマウスモデルから、学習と記憶、知的障害の研究に新たな切り口

2018 年 2 月 19 日

ヒトにおいて、遺伝子 CRBN の突然変異は知能指数の低さで定義される知的障害の原因とされる。知的障害はこれまで自閉症スペクトル障害、脆弱 X およびダウン症候群のような複雑な疾患と関連して研究されてきており、このことが認知障害を選択的に理解することを困難にしてきた。

今回コーネル大学医学部の Weill Cornell Medicine の自閉症研究プログラムの研究者らが *JNeurosci* 誌で発表した研究によると、CRBN 遺伝子を欠損させた雄マウスが、CRBN 遺伝子を有するマウスと比較して、海馬に依存する学習・記憶能力をテストするために作られた迷路をナビゲートするのが困難であること、ただし、社会的または反復的な行動に変化はないこと、また、海馬における酵素の活性を阻害する化合物でマウスを処置することで、学習・記憶障害が改善されること、が示されている。

研究者らは、CRBN 遺伝子を欠損させたマウスモデルが、学習・記憶における CRBN 遺伝子の役割を研究する新しい方法を提供し、純粋な知的障害のげっ歯類モデルを提供する、としている。

英文記事：

https://sciencesources.eurekalert.org/pub_releases/2018-02/sfn-mmo021418.php

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PUBLIC RELEASE: 19-FEB-2018

Mouse model of intellectual disability isolates learning gene

A new way to study learning and memory, intellectual disability

Society for Neuroscience

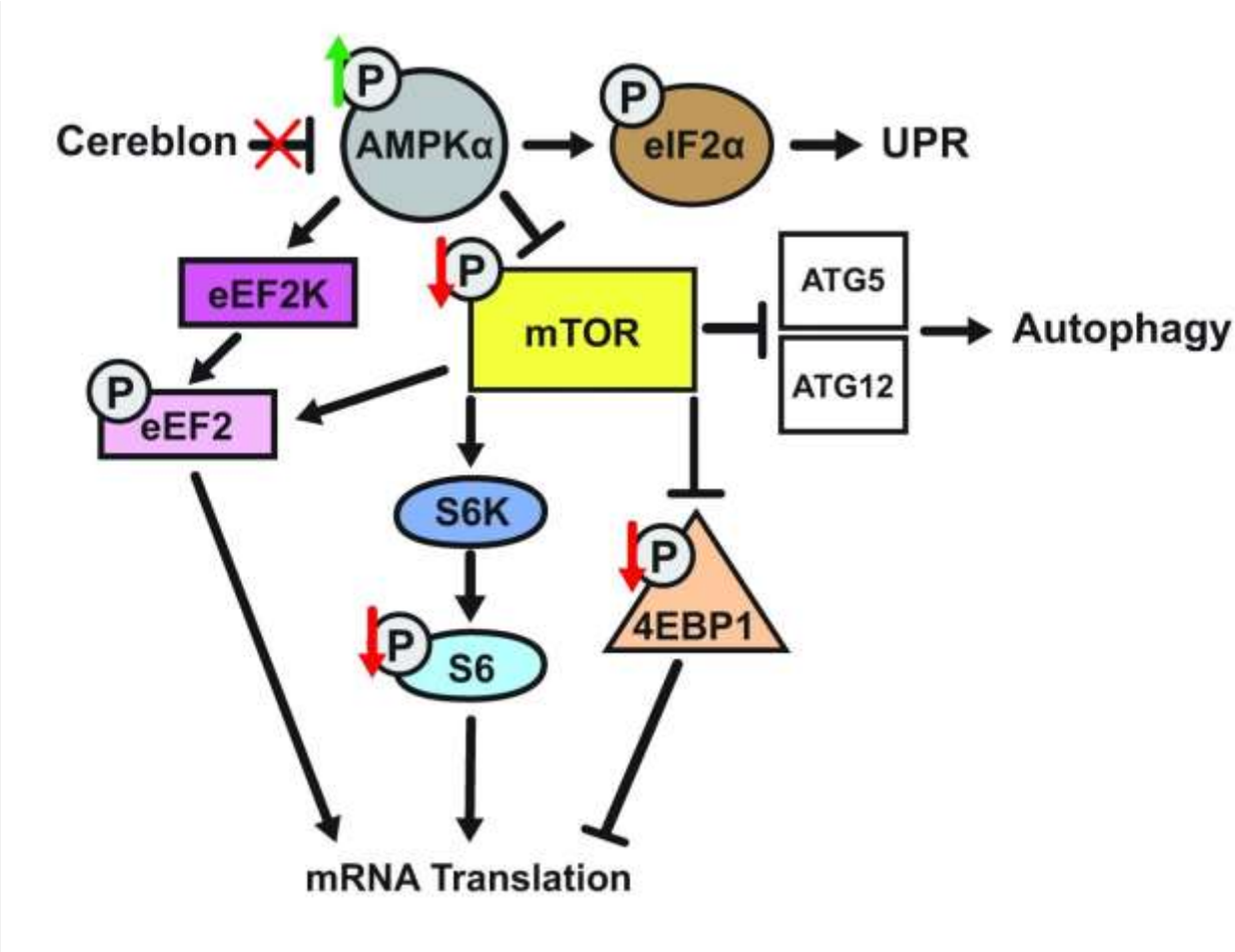

IMAGE: CrbnKO mice show altered mTORC1 signaling in the hippocampus. Schematic of proposed molecular mechanism. **view more**

Credit: Bavley et al., JNeurosci (2018)

Adult male mice lacking a gene linked to intellectual disability have trouble completing and remembering mazes, with no changes in social or repetitive behavior, according to new research published in *JNeurosci*. This animal model provides a new way to study the role of this gene in learning and memory and provides a rodent model of pure intellectual disability.

A mutation in the gene CRBN causes a type of intellectual disability in humans that is defined by a low intelligence quotient. Intellectual disability has been studied in the context of complex disorders like autism spectrum disorder, Fragile X and Down syndrome that co-occur with other conditions, which has made it difficult to selectively understand cognitive impairment.

Anjali Rajadhyaksha, director of the Weill Cornell Autism Research Program, associate professor of neuroscience in pediatrics and of neuroscience at the Feil Family Brain and Mind Research Institute at Weill Cornell Medicine, and colleagues deleted the mouse Crbn gene and demonstrated that these mice, compared to mice with the intact gene, have difficulty navigating mazes designed to test learning and memory abilities, dependent on the hippocampus. Treating the mice with a compound that inhibits the activity of an enzyme in the hippocampus improved the learning and memory deficits. The researchers did not observe any differences in the preference of altered mice to interact with a fellow mouse or in repetitive grooming behavior, indicating that the gene is not associated with behaviors that often co-occur with intellectual disability, as in autism.

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Article: Rescue of learning and memory deficits in the human non-syndromic intellectual disability cereblon knockout mouse model by targeting the AMPK-mTORC1 translational pathway

DOI: https://doi.org/10.1523/JNEUROSCI.0599-17.2018

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About *JNeurosci*

JNeurosci, the Society for Neuroscience's first journal, was launched in 1981 as a means to communicate the findings of the highest quality neuroscience research to the growing field. Today

the journal remains committed to publishing cutting-edge neuroscience that will have an immediate and lasting scientific impact while responding to authors' changing publishing needs, representing breadth of the field and diversity in authorship.

About The Society for Neuroscience

The Society for Neuroscience is the world's largest organization of scientists and physicians devoted to understanding the brain and nervous system. The nonprofit organization, founded in 1969, now has nearly 37,000 members in more than 90 countries and over 130 chapters worldwide.

目次に戻る

9．マウスモデルでアルツハイマー病の認知機能が改善

2018 年 2 月 19 日

Cleveland Clinic Lerner Research Institute の研究チームは、脳内で Aβ ペプチド生成を開始させる BACE1 と呼ばれる酵素を徐々に枯らすことでアルツハイマー病マウスの脳内アミロイド沈着が完全に解消しシナプス機能が回復、認知機能を改善させることに成功した。この酵素を標的とした薬剤がヒトにおけるアルツハイマー病の治療に成功することが期待される。
BACE1 を阻害する薬剤は、これまでも潜在的アルツハイマー病治療薬として開発されてきているが、アミロイド前駆体タンパク質（APP）以外のたんぱく質も切断するため、多くの重要なプロセスを制御し重大な副作用を有する可能性がある。実際に BACE1 を完全に欠くマウスは重度の精神発達欠損を患う。
そこで、有害性をより少なくできるか調べるために、成長に応じてこの酵素を徐々に失うマウスを作ったところ、これらのマウスは正常に発達、経時的に完全に健康なままであったとして、この研究成果を *Journal of Experimental Medicine* 誌で発表した。

英文記事：
https://psychcentral.com/news/2018/02/19/alzheimers-signs-reversed-in-mouse-study/132747.html

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Alzheimer’s Signs Reversed in Mouse Study

By Rick Nauert PhD

Researchers have successfully reversed the formation of amyloid plaques in the brains of mice with Alzheimer's disease, thereby improving the animals' cognitive function.

Investigators from the Cleveland Clinic Lerner Research Institute discovered that gradually depleting an enzyme called BACE1 eliminates the plaques.

The study, which appears in the *Journal of Experimental Medicine*, raises hopes that drugs targeting this enzyme will be able to successfully treat Alzheimer's disease in humans. The vast majority of experimental treatments using a rodent model — whether for diabetes or cancer or Alzheimer's — fail to work in humans.
Researchers explain that one of the earliest events in Alzheimer's disease is an abnormal buildup of beta-amyloid peptide, which can form large, amyloid plaques in the brain and disrupt the function of neuronal synapses.

Also known as beta-secretase, BACE1 helps produce beta-amyloid peptide by cleaving amyloid precursor protein (APP). Drugs that inhibit BACE1 are therefore being developed as potential Alzheimer's disease treatments. However, the drugs may have serious side-effects because BACE1 controls many important processes.

Mice completely lacking BACE1 suffer severe neurodevelopmental defects. To investigate whether inhibiting BACE1 in adults might be less harmful, researcher Dr. Riqiang Yan and

colleagues generated mice that gradually lose this enzyme as they grow older. These mice developed normally and appeared to remain perfectly healthy over time.

The researchers then bred these rodents with mice that start to develop amyloid plaques and Alzheimer's disease when they are 75 days old. The resulting offspring also formed plaques at this age, even though their BACE1 levels were approximately 50 percent lower than normal.

Remarkably, however, the plaques began to disappear as the mice continued to age and lose BACE1 activity, until, at 10 months old, the mice had no plaques in their brains at all.

"To our knowledge, this is the first observation of such a dramatic reversal of amyloid deposition in any study of Alzheimer's disease mouse models," Yan said.

Decreasing BACE1 activity also resulted in lower beta-amyloid peptide levels and reversed other hallmarks of Alzheimer's disease, such as the activation of microglial cells and the formation of abnormal neuronal processes.

Loss of BACE1 also improved the learning and memory of mice with Alzheimer's disease. However, when the researchers made electrophysiological recordings of neurons from these animals, they found that depletion of BACE1 only partially restored synaptic function, suggesting that BACE1 may be required for optimal synaptic activity and cognition.
"Our study provides genetic evidence that preformed amyloid deposition can be completely reversed after sequential and increased deletion of BACE1 in the adult," Yan said.

"Our data show that BACE1 inhibitors have the potential to treat Alzheimer's disease patients without unwanted toxicity. Future studies should develop strategies to minimize the synaptic impairments arising from significant inhibition of BACE1 to achieve maximal and optimal benefits for Alzheimer's patients."

Source: Rockefeller University Press/Science Daily

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10. 腸内細菌が敗血症から保護してくれる -マウス研究

2018 年 2 月 22 日

敗血症というのは、細菌や毒素が血流へ拡散し、それに対して身体が組織や器官を損傷するように反応して起こる。
今回ペンシルベニア大学医学部ペレルマン校の研究者らが 2 月 22 日の *Cell Host & Microbe* 誌で報告した研究によると、マウスに特定の腸内微生物を与えることで、免疫グロブリン A（IgA）抗体の血中濃度が上昇し、敗血症に至る広範な細菌の襲撃からの保護効果があることが分かった。以前の研究では、腸内細菌の成分に特異的な IgA がマウスの血清で検出され、IgA 欠損症を有する人々は、敗血症に陥る可能性がより高いことが示されていたが、これらの 2 つの観察が何らかの方法で関連しているかどうかは未解決であった。
研究者らは、これらの知見に基づき、IgA が敗血症に対する防御を与えるメカニズムをさらに解明し、これらの抗体特定の特性を利用してヒト疾患に適用される治療法を開発する方法を模索する、としている。

英文記事：
https://www.sciencedaily.com/releases/2018/02/180222145002.htm

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Gut microbes protect against sepsis: Mouse study

Date:

February 22, 2018

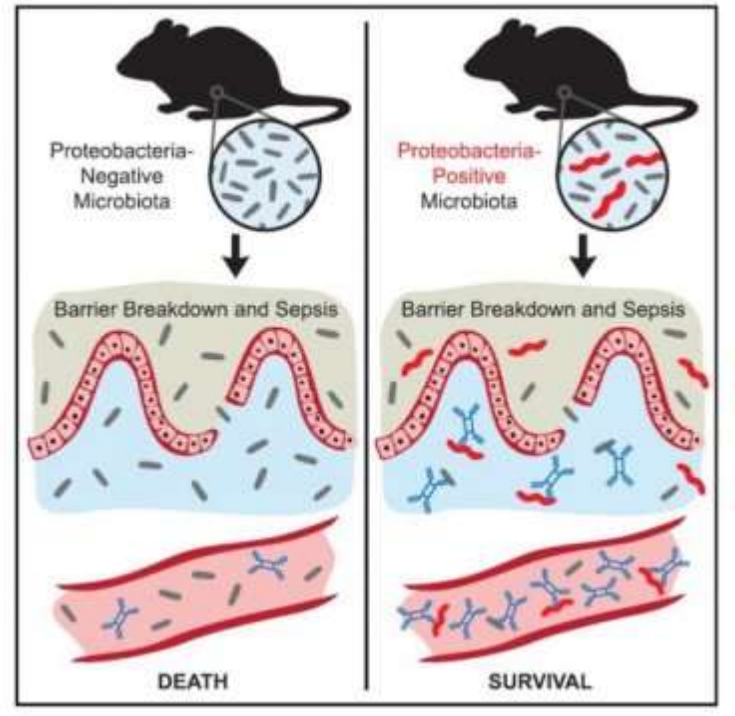
Source:

Cell Press

Summary:

Sepsis occurs when the body's response to the spread of bacteria or toxins to the bloodstream damages tissues and organs. The fight against sepsis could get a helping hand from a surprising source: gut bacteria. Researchers found that giving mice particular microbes increased blood levels of immunoglobulin A (IgA) antibodies, which protected against the kind of widespread bacterial invasion that leads to sepsis.

FULL STORY



This visual abstract depicts the findings of Wilmore et al., who demonstrate a role for serum IgA in protection against polymicrobial sepsis. Induction of protective concentrations of T cell dependent serum IgA requires colonization of the gut with a complex microbiota that includes bacteria in the phylum Proteobacteria.

Credit: Wilmore et al./Cell Host & Microbe 2018

Sepsis occurs when the body's response to the spread of bacteria or toxins to the bloodstream damages tissues and organs. The fight against sepsis could get a helping hand from a surprising source: gut bacteria. Researchers reporting February 22 in the journal *Cell Host & Microbe* found that giving mice particular microbes increased blood levels of immunoglobulin A (IgA) antibodies, which protected against the kind of widespread bacterial invasion that leads to sepsis.

Prior work has linked IgA responses to gut microbes and IgA specific to components of intestinal bacteria have been detected in sera of mice. Additionally, people with IgA deficiencies are more likely to succumb to sepsis. However, whether these two observations were linked in any way remained an open question.

Previous research showed that immunoglobulin M (IgM) antibodies quickly respond to blood-borne bacteria in sepsis and that gut microbes trigger immunoglobulin G (IgG) antibody responses that can block bacterial infection. The researchers of the current work asked whether gut microbes could trigger IgA responses that protect against sepsis.

"We propose that serum IgA and IgG antibodies may play roles similar to the protective role proposed for natural IgM antibodies, with the IgA component providing a non-inflammatory mechanism for keeping invading bacteria in check," says first author Joel Wilmore of the Perelman School of Medicine at the University of Pennsylvania.

To investigate this possibility, senior author David Allman, also at UPenn's Perelman School of Medicine, and his team looked at IgA antibodies, which are readily detected in mice and humans but whose role in host protection against sepsis was unknown. The researchers found that exposing mice to a unique but natural microflora that included several members of the Proteobacteria phylum led to increases in IgA levels in the blood. Moreover, shifting the mouse gut to a Proteobacteria-rich microbiota led to IgA-mediated resistance to sepsis in mice.

When the researchers transferred blood lacking IgA into mice with sepsis, all but one animal died within two days. By contrast, mice that received blood enriched in IgA survived much longer. Taken together, the findings suggest that commensal microbes can have a substantial impact on IgA levels in the blood, resulting in protection against bacterial sepsis.

Based on these findings, the researchers plan to further dissect the mechanism by which IgA confers protection against sepsis and explore ways to harness the specific properties of these antibodies to develop a treatment that may be applied to human disease. In the meantime, they urge caution against over-interpreting the new findings.

"The study is limited by the fact that the microbiome in every person or animal is unique to some degree, and our study is in the context of the animal facility at the Perelman School of Medicine at the University of Pennsylvania," Allman says. "While IgA protected mice in our study, it should not be assumed that IgA could replace standard treatments provided to patients in a clinical setting."

This work was supported by National Institutes of Health.

Story Source:

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

Journal Reference:

1. Joel R. Wilmore, Brian T. Gaudette, Daniela Gomez Atria, Tina Hashemi, Derek D. Jones, Christopher A. Gardner, Stephen D. Cole, Ana M. Misic, Daniel P. Beiting, David Allman. **Commensal Microbes Induce Serum IgA Responses that Protect against Polymicrobial Sepsis**. *Cell Host & Microbe*, 2018; DOI: 10.1016/j.chom.2018.01.005

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