BIO NEWS

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2017 年 8 月のニュース

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1．複数の癌に打撃を与えてノックアウトさせる方法 -マウス実験

2017 年 8 月 2 日

Cancer Research UK が資金を提供し、*Journal of the National Cancer Institute* 誌に掲載された研究によると、NOX4 と呼ばれる酵素を標的にすることで癌関連線維芽細胞 (CAF) と呼ばれるタイプの細胞の作用を停止させマウスの腫瘍のサイズを 50%まで縮小させることができることが発見された。
線維芽細胞は、異なるタイプの器官を一緒に保持する役割を果たす健康な細胞であるが、それらががん細胞に乗っ取られると CAF になって腫瘍が増殖して広がることが知られているが、今までこれらを対象とした試みは成功していなかった。
サウスハンプトン大学の研究者らは今回初めて、CAF が多くの癌タイプを形成し腫瘍の成長を助けるのに NOX4 が必要であることを確認し、NOX4 を遮断することによってこの事態を止めることができることを示した。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170802201201.htm

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Scientists deliver knockout blow to multiple cancers

Date:

August 2, 2017

Source:

Cancer Research UK

Summary:

Targeting healthy cells that have been hijacked by cancer cells could help treat many different types of the disease, according to research.

FULL STORY

Targeting healthy cells that have been hijacked by cancer cells could help treat many different types of the disease, according to research funded by Cancer Research UK and published in the *Journal of the National Cancer Institute*.

Scientists found that targeting an enzyme known as NOX4 stops the action of a type of cell called cancer associated fibroblasts (CAFs), reducing the size of tumours in mice by up to 50 per cent.

Fibroblasts are healthy cells whose role is to hold different types of organs together. When they are hijacked by cancer cells, they become CAFs and are known to help tumours grow, spread and evade therapy. Until now, attempts to target them have proved unsuccessful.

In line with previous studies, the team at the University of Southampton found that higher levels of CAFs were associated with poorer survival in several cancers including bowel, head and neck cancers.

For the first time, they identified that NOX4 is needed for CAFs to form and help tumours grow in many cancer types. But they could stop this happening by blocking NOX4 using a drug that is being developed to treat a condition called organ fibrosis.

These findings could form the basis for new treatments and help make cancers respond better to existing drugs. Cancer Research UK is now funding the Southampton scientists to see if this approach improves treatments like immunotherapy and chemotherapy to make them more effective.

Professor Gareth Thomas, lead researcher and Chair of Experimental Pathology at the University of Southampton, said: "By looking at many types of cancer, we have identified a common mechanism responsible for CAF formation in tumours.

"These cells make cancers aggressive and difficult to treat, and we can see exciting possibilities for targeting CAFs in many patients who don't respond well to existing therapies."

Dr Áine McCarthy, Cancer Research UK's senior science information officer, said: "Some cancers are incredibly difficult to treat, and can use the body's own cells to help them grow, evade treatment and

spread around the body. Researchers have been trying to unlock the secrets behind this for many years and this study is a big step forward in understanding how some cancers achieve this.

"These findings show that CAFs can be targeted with a drug and their 'pro-tumour' effects can be reversed in mice, giving researchers a starting point to develop new and potentially more effective treatments in the future."

Story Source:

Materials provided by **Cancer Research UK**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Christopher J. Hanley, Massimiliano Mellone, Kirsty Ford, Steve M. Thirdborough, Toby Mellows, Steven J. Frampton, David M. Smith, Elena Harden, Cedric Szyndralewiez, Marc Bullock, Fergus Noble, Karwan A. Moutasim, Emma V. King, Pandurangan Vijayanand, Alex H. Mirnezami, Timothy J. Underwood, Christian H. Ottensmeier, Gareth J. Thomas. **Targeting the Myofibroblastic Cancer-Associated Fibroblast Phenotype Through Inhibition of NOX4**. *JNCI: Journal of the National Cancer Institute*, 2018; 110 (1) DOI: 10.1093/jnci/djx121

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Cancer Research UK. "Scientists deliver knockout blow to multiple cancers." ScienceDaily. www.sciencedaily.com/releases/2017/08/170802201201.htm (accessed August 8, 2017).

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2. 皮膚を介した遺伝子治療で肥満を含む多くの疾患を治療 -マウス実験

2017 年 8 月 3 日

Cell Stem Cell 誌の 8 月 3 日号に掲載された論文で、シカゴ大学に拠点を置く研究チームの研究者らは、2 つの非常に一般的なヒトの疾患（2 型糖尿病と肥満）を治療する為の新しい形態の遺伝子療法（皮膚移植によって投与される）について記述している。
研究者らは、CRISPR と呼ばれる正確な遺伝子工学ツールを用いて、膵臓を刺激してインスリンを分泌するホルモンであるグルカゴン様ペプチド 1（GLP1）遺伝子を、血流中でホルモンの半減期を延長するよう設計改変し、この遺伝子を皮膚細胞に挿入し培養してそれらの細胞を増殖させた。この遺伝子改変皮膚をマウスに移植したところ、血糖値が低下した、としている。また、正常マウスおよび遺伝子改変マウスに高脂肪食を与えた場合、両群とも急速に体重が増加し肥満になったが、ドキシサイクリンを含む食物で GLP1 放出を誘導すると、正常マウスは引き続き脂肪を増やし、GLP1 を発現するマウスは体重増加が少なかった、としている。

英文記事：
https://medicalxpress.com/news/2017-08-gene-therapy-skin-diseases-obesity.html

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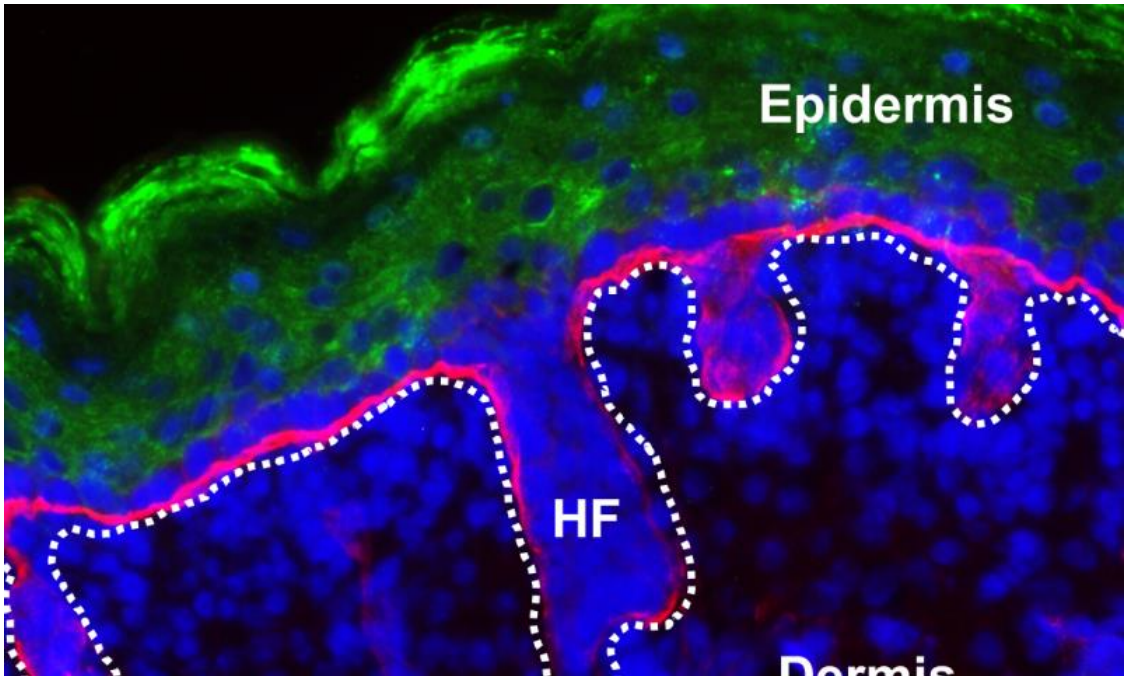
Gene therapy via skin could treat many diseases, even obesity

August 3, 2017



Immunofluorescence imaging shows normal skin differentiation and tissue architecture of transplanted skin grafts.
Credit: Wu Laboratory, University of Chicago

A research team based at the University of Chicago has overcome challenges that have limited gene therapy and demonstrated how their novel approach with skin transplantation could enable a wide range of gene-based therapies to treat many human diseases.

In the August 3, 2017 issue of the journal *Cell Stem Cell*, the researchers provide "proof-of-concept." They describe a new form of gene-therapy – administered through skin transplants – to treat two related and extremely common human ailments: type-2 diabetes and obesity.

"We resolved some technical hurdles and designed a mouse-to-mouse skin transplantation model in animals with intact immune systems," said study author Xiaoyang Wu, PhD, assistant professor in the Ben May Department for Cancer Research

at the University of Chicago. "We think this platform has the potential to lead to safe and durable gene therapy, in mice and we hope, someday, in humans, using selected and modified cells from skin."

Beginning in the 1970s, physicians learned how to harvest skin stem cells from a patient with extensive burn wounds, grow them in the laboratory, then apply the lab-grown tissue to close and protect a patient's wounds. This approach is now standard. However, the application of skin transplants is better developed in humans than in mice.

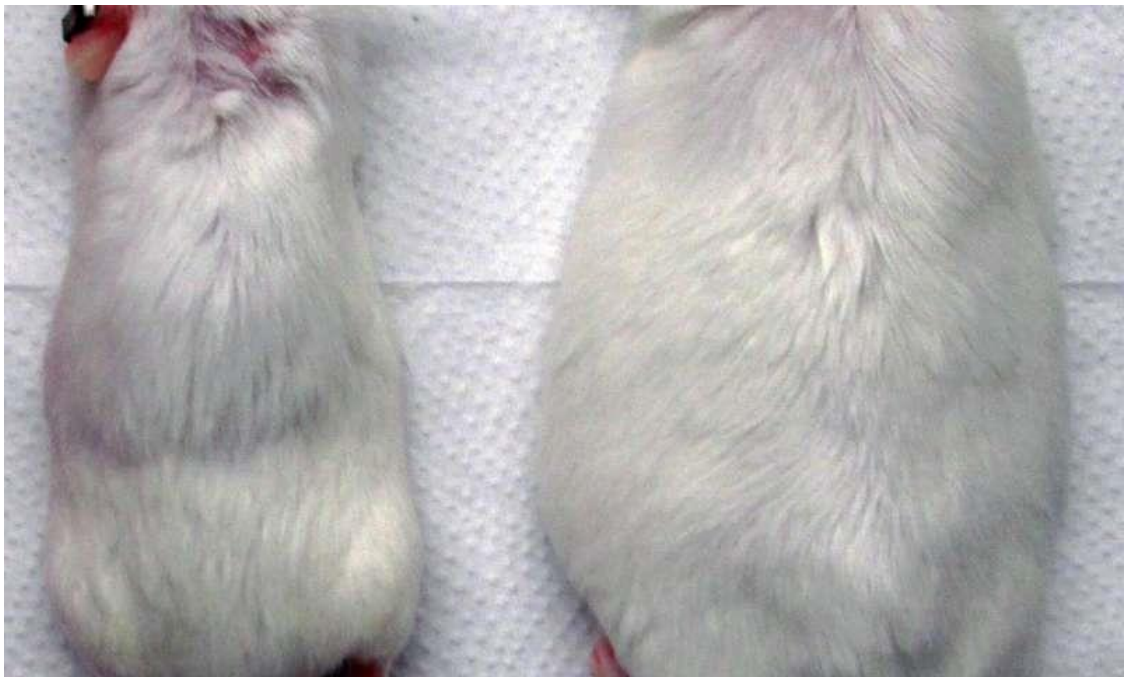
"The mouse system is less mature," Wu said. "It took us a few years to optimize our 3D skin organoid culture system."

This study, "Engineered epidermal progenitor cells can correct diet-induced obesity and diabetes," is the first to show that an engineered skin graft can survive long term in wild-type mice with intact immune systems. "We have a better than 80 percent success rate with skin transplantation," Wu said. "This is exciting for us."

They focused on diabetes because it is a common non-skin disease that can be treated by the strategic delivery of specific proteins.

The researchers inserted the gene for glucagon-like peptide 1 (GLP1), a hormone that stimulates the pancreas to secrete insulin. This extra insulin removes excessive glucose from the bloodstream, preventing the complications of diabetes. GLP1 can also delay gastric emptying and reduce appetite.

Using CRISPR, a tool for precise genetic engineering, they modified the GLP1 gene. They inserted one mutation, designed to extend the hormone's half-life in the blood stream, and fused the modified gene to an antibody fragment so that it would circulate in the blood stream longer. They also attached an inducible promoter, which enabled them to turn on the gene to make more GLP1, as needed, by exposing it to the antibiotic doxycycline. Then they inserted the gene into skin cells and grew those cells in culture.



When normal and gene-altered mice ate the high-fat diet -- along with varying levels of doxycycline to induce GLP1 release -- mice expressing GLP1 (left) gained less weight gain while normal mice (right) grew fat.
Credit: Wu Laboratory, the University of Chicago

When these cultured cells were exposed to an air/liquid interface in the laboratory, they stratified, generating what the authors referred to as a multi-layered, "skin-like organoid." Next, they grafted this lab-grown gene-altered skin onto mice with intact immune systems. There was no significant rejection of the transplanted skin grafts.

When the mice ate food containing minute amounts of doxycycline, they mice released dose-dependent levels of GLP1 into the blood. This promptly increased blood-insulin levels and reduced blood-glucose levels.

When the researchers fed normal or gene-altered mice a high-fat diet, both groups rapidly gained weight. They became obese. When normal and gene-altered mice got the high-fat diet along with varying levels of doxycycline, to induce GLP1 release, the normal mice grew fat and mice expressing GLP1 showed less weight gain.

Expression of GLP1 also lowered glucose levels and reduced insulin resistance.

"Together, our data strongly suggest that cutaneous gene therapy with inducible expression of GLP1 can be used for the treatment and prevention of diet-induced obesity and pathologies," the authors wrote. When they transplanted gene-altered human cells to mice with a limited immune system, they saw the same effect. These results, the authors wrote, suggest that "cutaneous gene therapy for GLP1 secretion could be practical and clinically relevant."

This approach, combining precise genome editing in vitro with effective application of engineered cells in vivo, could provide "significant benefits for the treatment of many human diseases," the authors note.

"We think this can provide a long-term safe option for the treatment of many diseases," Wu said. "It could be used to deliver therapeutic proteins, replacing missing proteins for people with a genetic defect, such as hemophilia. Or it could function as a metabolic sink, removing various toxins."

Skin progenitor cells have several unique advantages that are a perfect fit for gene therapy. Human skin is the largest and most accessible organ in the body. It is easy to monitor. Transplanted skin can be quickly removed if necessary. Skins cells rapidly proliferate in culture and can be easily transplanted. The procedure is safe, minimally invasive and inexpensive.

There is also a need. More than 100 million U.S. adults have either diabetes (30.3 million) or prediabetes (84.1 million), according the Centers for Disease Control and Prevention. More than 2 out of 3 adults are overweight. More than 1 out of 3 are considered obese.

Explore further: Injectable solution may provide weeks of glucose control

More information: "Engineered Epidermal Progenitor Cells Can Correct Diet-Induced Obesity and Diabetes" *Cell Stem Cell* (2017). DOI: 10.1016/j.stem.2017.06.016 , http://www.cell.com/cell-stem-cell/fulltext/S1934-5909(17)30274-6

Journal reference: Cell Stem Cell

Provided by: University of Chicago Medical Center

目次に戻る

3. <ゲノム編集> ヒト受精卵で心臓病遺伝子「修復」米チーム

2017 年 8 月 3 日

生物の遺伝子を効率良く改変できる新技術「ゲノム編集」をヒトの受精卵に使い、遺伝性の心臓病を引き起こす遺伝子変異を高い効率で修復する実験に成功したと、米国などの研究チームが２日付の英科学誌ネイチャー電子版に発表した。今回は子宮に戻していないが、将来技術が確立すれば遺伝性疾患が子孫に伝わるのを防げる可能性を示す内容。だが、限られた好条件での実験で、研究チームは臨床応用には社会的合意も必要としている。

ゲノム編集でヒト受精卵の遺伝子を操作する研究は中国で３例の報告があるが、米国では初めて。改変された影響が次世代に受け継がれるため、安全性や倫理面から否定的な意見が強く、米政府は公的研究費を配分していない。ネイチャーなどの主要科学誌が論文を掲載するのも異例で、研究や応用の是非を巡り論争を呼びそうだ。

研究チームは、世界で初めてヒトクローン胚性幹細胞（ＥＳ細胞）を作ったミタリポフ博士ら米オレゴン健康科学大や韓国の研究所が主体だが、日本の研究者も加わっている。

論文によると、肥大型心筋症の原因とされる遺伝子変異がある精子を健康な女性の卵子に顕微授精すると同時に、クリスパー・キャス９というゲノム編集技術を利用。受精卵５８個のうち約７割で遺伝子が修復でき、異常な細胞が混じる問題も起きないことを確かめた、などとしている。

日本では昨春、政府の生命倫理専門調査会が一部の基礎研究に限って受精卵のゲノム編集を認めるとの報告書をまとめた。今の国の指針では、今回の論文のような目的で受精卵を作る研究は認められていないが、見直しの動きもある。

今回研究に参加した鈴木啓一郎・米ソーク生物学研究所研究員は「ゲノム編集する前の条

件の最適化やテストをしたが、「私自身はヒト受精卵のゲノム編集には全く関わっていない」と話している。
【千葉紀和、荒木涼子】
毎日新聞

[参考]:
http://www.nikkei.com/article/DGXLASDG02H82_S7A800C1CR8000/

心臓病の遺伝子修復に成功　人の受精卵をゲノム編集

2017 年 8 月 3 日

【ワシントン＝共同】人の受精卵をゲノム編集で改変し、心臓病の原因となる遺伝子変異を高い効率で修復することに成功したと、米オレゴン健康科学大のチームが 2 日付の英科学誌ネイチャー電子版に発表した。子宮に戻して成長させるのは避けた。ゲノム編集は狙った遺伝子を効率的に改変できる技術。人の受精卵への応用は中国で実施例があるが、米国では初めて。従来に比べて成功率が大幅に高まり、受精卵が成長する際に正常な細胞と異常な細胞が混じる問題も避けられた。子供が遺伝病になるリスクを減らせる可能性がある。チームのミタリポフ教授は「臨床応用を見据え、精度を上げたい」と話した。
ただ生殖に関わるゲノム編集は安全面の懸念が残る上、改変された遺伝子が将来の子孫に受け継がれるため倫理的な批判が根強い。専門家は「実際の応用には十分な検討が必要だ」と指摘する。
チームは、肥大型心筋症の原因とされる遺伝子変異を持つ精子と、ゲノム編集のための試薬を同時に正常な卵子に注入。体外受精でできた 58 個の受精卵のうち、42 個が正常な遺伝子だけを持っていた。
人のゲノム編集について、米科学アカデミーは技術が向上すれば将来容認しうるとの見解を示している。
日本経済新聞

目次に戻る

４．精神障害における脳の酸性度の問題 -マウス実験

2017 年 8 月 7 日

私達の身体の酸性/アルカリ性の恒常性、組織や器官における適切な pH バランスの維持は、健康にとって重要である。pH の不均衡、特に酸性へのシフトは心血管出力の低下、呼吸困難、腎不全など様々な臨床状態に影響を及ぼす。
そこで、今回 pH が神経障害にも関連しているか、藤田保健大学総合医学研究所の研究者らが、精神障害の 5 つの異なるマウスモデル（統合失調症、双極性障害、自閉症のモデルを含む）を使用して実験を行い、8 月 4 日号の *Neuropsychopharmacology* 誌に発表している。
この研究によると、pH の低下は、精神障害に関連する脳内の基礎病態生理を反映している可能性が高い、とのことである。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170807110404.htm

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Increased brain acidity in psychiatric disorders

Date:

August 7, 2017

Source:

Fujita Health University

Summary:

Decreased brain pH in the patients with schizophrenia and bipolar disorder has been considered to be the result of secondary factors associated with the diseases, such as medication and agonal

state. However, the researchers of the present study suggest that decreased brain pH is a primary feature of the diseases themselves, based on the current findings from systematic investigation using five animal models, which are devoid of such secondary factors.

FULL STORY

Your body's acid/alkaline homeostasis, or maintenance of an adequate pH balance in tissues and organs, is important for good health. An imbalance in pH, particularly a shift toward acidity, is associated with various clinical conditions, such as a decreased cardiovascular output, respiratory distress, and renal failure. But is pH also associated with psychiatric disorders?

Researchers at the Institute for Comprehensive Medical Science at Fujita Health University in Japan, along with colleagues from eight other institutions, have identified decreased pH levels in the brains of five different mouse models of mental disorders, including models of schizophrenia, bipolar disorder, and autism spectrum disorder. This decrease in pH likely reflects an underlying pathophysiology in the brain associated with these mental disorders, according to the study published August 4th in the journal *Neuropsychopharmacology*.

While post-mortem studies have shown that the brains of patients with the abovementioned mental disorders tend to have a lower pH than those of controls, this phenomenon has been considered to be the result of secondary factors associated with the diseases rather than a primary feature of the diseases themselves. Secondary factors that confound the observation of a decreased brain pH level include antipsychotic treatments and agonal experiences associated with these disorders.

Dr. Miyakawa and his colleagues performed a meta-analysis of existing datasets from ten studies to investigate the pH level of postmortem brains from patients with schizophrenia and bipolar disorder. They observed that patients with schizophrenia and bipolar disorder exhibited significantly lower brain pH levels than control participants, even when potential confounding factors were considered (i.e., postmortem interval, age at death, and history of antipsychotic use). "These factors may not be major factors causing a decrease in pH in the postmortem brains of patients with schizophrenia and bipolar disorder," Miyakawa explains.

The researchers then conducted a systematic investigation of brain pH using five mouse models of psychiatric disorders, including models for schizophrenia, bipolar disorder, and autism spectrum disorders. All of the mice used in the study were drug-naive, with equivalent agonal states, postmortem intervals, and ages within each strain. The analyses revealed that in all five mouse models, brain pH was significantly lower than that in the corresponding controls. In addition, the levels of lactate were also elevated in the brains of the model mice, and a significant negative correlation was found between brain pH and lactate levels. The increase in lactate may explain the decreased brain pH levels, as lactate is known to act as a strong acid.

Miyakawa suggests that, "while it is technically impossible to completely exclude confounding factors in human studies, our findings in mouse models strongly support the notion that decreased pH associated with increased lactate levels reflects an underlying pathophysiology, rather than a mere artifact, in at least a subgroup of patients with these mental disorders."

Changes in the brain pH level have been considered an artifact, therefore substantial effort has been made to match the tissue pH among study participants and to control the effect of pH on molecular changes in the postmortem brain. However, given that decreased brain pH is a pathophysiological trait of psychiatric disorders, these efforts could have unwittingly obscured the specific pathophysiological signatures that are potentially associated with changes in pH, such as neuronal hyper-excitation and inflammation, both of which have been implicated in the etiology of psychiatric disorders. Therefore, the present study highlighting that decreased brain pH is a shared endophenotype of psychiatric disorders has significant implications on the entire field of studies on the pathophysiology of mental disorders.

This research raises new questions about changes in brain pH. For example, what are the mechanisms through which lactate is increased and pH is decreased? Are specific brain regions responsible for the decrease in pH? Is there functional significance to the decrease in brain pH observed in psychiatric disorders, and if so, is it a cause or result of the onset of the disorder?. Further studies are needed to address these issues.

Story Source:

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

Journal Reference:

1. Hideo Hagihara, Vibeke S Catts, Yuta Katayama, Hirotaka Shoji, Tsuyoshi Takagi, Freesia L Huang, Akito Nakao, Yasuo Mori, Kuo-Ping Huang, Shunsuke Ishii, Isabella A Graef, Keiichi I Nakayama, Cynthia Shannon Weickert, Tsuyoshi Miyakawa. **Decreased Brain pH as a Shared Endophenotype of Psychiatric Disorders**. *Neuropsychopharmacology*, 2017; DOI: 10.1038/npp.2017.167

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Fujita Health University. (2017, August 7). Increased brain acidity in psychiatric disorders. *ScienceDaily*. Retrieved August 8, 2017 from www.sciencedaily.com/releases/2017/08/170807110404.htm
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目次に戻る

5. 生物時計と老化の関係が明らかに -マウス実験

2017 年 8 月 10 日

老化が新陳代謝の生物時計に及ぼす影響について、低カロリー食がこれらのエネルギー調節プロセスを活気付かせ身体を若く保つ手助けをすることが示された。
カリフォルニア大学アーバイン校 Epigenetics＆Metabolism センターの Paolo Sassone-Corsi 氏と彼の同僚、およびバルセロナ生物医学研究所の共同研究チームは、8 月 10 日に *Cell* 誌に掲載された研究で、どのようにして概日リズム（身体の生物時計）が生理的老化の結果変化するのか明らかにしている。老化プロセスに直接結び付いている時計制御回路は、細胞内のエネルギーの効率的な代謝に基づいており、マウス実験によると、古い細胞はエネルギーを非効率的に処理する。しかし、6 カ月間 30%のカロリー食を与えられた老齢マウスについて、細胞内のエネルギー処理は変化しなかったことを示し、カロリー制限食がマウスの老化を遅らせる理由を説明するものだとしている。
これまでのフルーツフライ研究で、低カロリー食が寿命を延ばす可能性があることが既に示されているが、UCI とバルセロナの研究は、カロリー制限が体内の日内リズムの細胞老化過程に関与することを初めて示した。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170810082416.htm

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Link between biological clock and aging revealed

Date:

August 10, 2017

Source:

University of California, Irvine

Summary:

Scientists studying how aging affects the biological clock's control of metabolism have discovered that a low-calorie diet helps keep these energy-regulating processes humming and the body younger.

FULL STORY

Low-calorie diets can extend longevity, but new research is the first to show that calorie restriction influences the body's circadian rhythms' involvement with the aging process in cells.

Credit: © photka / Fotolia

Scientists studying how aging affects the biological clock's control of metabolism have discovered that a low-calorie diet helps keep these energy-regulating processes humming and the body younger.

In a study appearing Aug. 10 in the journal *Cell*, Paolo Sassone-Corsi, director of the Center for Epigenetics & Metabolism at the University of California, Irvine, and colleagues reveal how circadian rhythms -- or the body's biological clock -- change as a result of physiological aging. The clock-controlled circuit that directly connects to the process of aging is based on efficient metabolism of energy within cells.

The Sassone-Corsi team tested the same group of mice at 6 months and 18 months, drawing tissue samples from the liver, the organ which operates as the interface between nutrition and energy distribution in the body. Energy is metabolized within cells under precise circadian controls.

The researchers found that the 24-hour cycle in the circadian-controlled metabolic system of older mice remained the same, but there were notable changes in the circadian mechanism that turns genes on and off based upon the cells' energy usage. Simply put, the older cells processed energy inefficiently.

"This mechanism works great in a young animal, but it basically shuts off in an old mouse," Sassone-Corsi said.

However, in a second group of aged mice that were fed a diet with 30 percent fewer calories for six months, energy processing within cells was more than unchanged.

"In fact, caloric restriction works by rejuvenating the biological clock in a most powerful way," Sassone-Corsi said. "In this context, a good clock meant good aging."

Collaborative confirmation

For a companion study detailed in *Cell*'s current issue, a research team from the Barcelona Institute for Research in Biomedicine collaborated with the Sassone-Corsi team to test body clock functioning in stem cells from the skin of young and older mice. They too found that a low-calorie diet conserved most of the rhythmic functions of youth.

"The low-calorie diet greatly contributes to preventing the effects of physiological aging," said Salvador Aznar Benitah, who co-led the Spanish study. "Keeping the rhythm of stem cells 'young' is important because in the end these cells serve to renew and preserve very pronounced day-night cycles in tissue. Eating less appears to prevent tissue aging and, therefore, prevent stem cells from reprogramming their circadian activities."

According to the UCI and Barcelona researchers, these studies can help explain why a calorie-restricted diet slows down aging in mice. The implications for human aging could be far-reaching.

The scientists said that it's important to further examine why metabolism has such a dominant effect on the stem cell aging process and, once the link that promotes or delays aging has been identified, to develop treatments that can regulate this link.

It's been shown in previous fruit fly studies that low-calorie diets can extend longevity, but the UCI and Barcelona research is the first to show that calorie restriction influences the body's circadian rhythms' involvement with the aging process in cells.

"These studies also present something like a molecular holy grail, revealing the cellular pathway through which aging is controlled," Sassone-Corsi said. "The findings provide a clear introduction on how to go about controlling these elements of aging in a pharmacological perspective."

The circadian connection

Sassone-Corsi and his colleagues first showed the circadian rhythm-metabolism link some 10 years ago, identifying the metabolic pathways through which a circadian enzyme protein called SIRT1 works. SIRT1 senses energy levels in cells; its activity is modulated by how many nutrients a cell is consuming. In addition, it helps cells resist oxidative and radiation-induced stress. SIRT1 has also been tied to the inflammatory response, diabetes and aging.

Sassone-Corsi, the Donald Bren Professor of Biological Chemistry at UCI, is one of the world's leading researchers on circadian rhythms, epigenetics and metabolism. Shogo Sato, Leonardo Bee and Selma Masri of UCI; Guiomar Solanas, Francisca Oliveira Peixoto and Aikaterini Symeonidi with the Barcelona Institute for Research in Biomedicine; and Mark Schmidt and Charles Brenner of the University of Iowa also contributed to the study, which received support from the National Institutes of Health and the French National Institute of Health & Medical Research, or INSERM.

Story Source:

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

Journal Reference:

1. Guiomar Solanas, Francisca Oliveira Peixoto, Eusebio Perdiguero, Mercè Jardí, Vanessa Ruiz-Bonilla, Debayan Datta, Aikaterini Symeonidi, Andrés Castellanos, Patrick-Simon Welz, Juan Martín Caballero, Paolo Sassone-Corsi, Pura Muñoz-Cánoves, Salvador Aznar Benitah. **Aged Stem Cells Reprogram Their Daily Rhythmic Functions to Adapt to Stress**. *Cell*, 2017; 170 (4): 678 DOI: 10.1016/j.cell.2017.07.035

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University of California, Irvine. (2017, August 10). Link between biological clock and aging revealed. *ScienceDaily*. Retrieved August 15, 2017 from www.sciencedaily.com/releases/2017/08/170810082416.htm
University of California, Irvine. "Link between biological clock and aging revealed." ScienceDaily. www.sciencedaily.com/releases/2017/08/170810082416.htm (accessed August 15, 2017).

目次に戻る

6. <ゲノム編集> ブタ内在性ウイルスのリスク除去 ヒト臓器移植に光

2017 年 8 月 11 日

中国・北京の養豚場の子豚（2017 年 6 月 5 日撮影、資料写真）。【翻訳編集】 AFPBB News

【AFP＝時事】子ブタのゲノムを編集し、内在するウイルスによる感染の危険を取り除くことに成功したとの論文が 10 日、米科学誌サイエンス（Science）のウェブサイトに公開された。ブタから人への臓器移植の実現に道を開く画期的な研究成果だ。

臓器移植の待機患者数は、米国だけでも約 11 万 7000 人に上り、毎日 22 人が移植日を待ち望みながら死亡しているという公式統計がある。今回の研究は、年々増え続ける待機者を大幅に減らし、多くの命を救うことにつながる可能性がある。

ハーバード大学（Harvard University）の遺伝学者、ジョージ・チャーチ（George Church）氏とルーハン・ヤン（Luhan Yang）氏は、デンマークや中国の研究者の協力を得

て、今回の研究を行った。

研究チームは編集した胚細胞を、成長を助け改変過程で起きやすい破壊効果を克服しやすくする化学化合物の中に置き、標準的なクローン技術を使って、編集した DNA を代理母の卵細胞に注入した。これにより、ブタ内在性レトロウイルス（PERV）を保有しない子ブタ 37 匹が生まれたという。

実際に人がブタから臓器提供を受けた場合に PERV に感染するかどうかは不明だが、実験ではペトリ皿に入れたウイルスがヒト細胞に感染し得ることが確認されている。

既にブタの心臓弁や膵臓（すいぞう）のヒト移植例はあるが、科学者たちは人の臓器と同サイズに成長するブタ臓器全てのヒト移植を実現しようと長年研究してきた。とはいえ、異種移植のゴールはまだ遠い。ヒト免疫システムの反応や血液の毒性相互作用を回避するため、ブタの遺伝子をさらに編集する必要がある。【翻訳編集】 AFPBB News

[参考]:
http://www.afpbb.com/articles/-/3083080?utm_source=yahoo&utm_medium=news&cx_from=yahoo&cx_position=r1&cx_rss=afp&cx_id=3138937

異種間臓器移植、ブタの心臓が人の命を救う可能性 研究

2016 年 4 月 6 日 10:28 発信地：パリ/フランス

ブタ。仏西部ロクロナンの養豚場で（2015 年 8 月 18 日撮影、本文とは関係ありません）。(c)AFP/FRED TANNEAU

【4 月 6 日 AFP】将来、心臓病の患者がブタの心臓の鼓動によって元気を取り戻せる日が来るかもかもしれない――異種間臓器移植での大きな進歩について報告する研究論文が 5 日、発表された。

臓器提供者（ドナー）が極度に不足するなか、人の命を救うために動物の心臓、肺、肝臓などを利用することは、長年にわたって医学の目標となってきた。しかし、そこには、臓器拒絶反応という大きな壁が常に立ちはだかっている。

このほど、米国とドイツの研究チームが発表した研究内容は、ヒトの近縁種である霊長類のヒヒにブタの心臓を移植して、過去最高の 2 年半生存させることに成功したというものだ。研究チームは、遺伝子組み換え技術と、標的を絞った免疫抑制剤を組み合わせたという。

論文の共同執筆者で、米国立心肺血液研究所（NHLBI）のモハメド・モヒウディン（Muhammad Mohiuddin）氏は「これは、動物臓器の人での利用に前進の一歩をもたらすという理由で、非常に意義深いことだ」と語る。

モヒウディン氏は、AFP の取材に電子メールで応じ、「異種移植――すなわち異なる生物種の間での臓器移植を通じて、人の移植用臓器の不足が原因で失われている年間数千人もの命を救うことができる可能性がある」と述べた。

ヒヒ 5 匹を使った実験では、移植したブタの心臓の生存状態を最長で 945 日間維持し、同じ研究チームが保持していた過去最高記録を更新した。

ブタの心臓は、ヒヒの心臓と交換するのではなく、ヒヒの腹部にある 2 本の大血管を経由して循環系に接続された。移植した心臓は、正常な心臓と同様に鼓動した。同時にヒヒ自身の心臓も、血液を送り出す機能を継続。これは、臓器拒絶反応の研究でよく知られた手法だ。

ドナーの臓器は、移植患者（レシピエント）の免疫系によって異質なもの、すなわち脅威として認識される可能性があり、免疫系による拒絶反応を引き起こすことが多い。

今回の研究では、免疫反応に対する高い耐性を持つよう遺伝子組み換えを施したブタから、ドナー臓器を採取した。こうすることで、レシピエントの自然の防御システムである免疫系にドナー臓器が認識されないようになるという。

さらに研究チームは、血液凝固を防ぐ助けになるヒトの遺伝因子を、これらのブタに付加し、またレシピエントのヒヒには、免疫反応を抑制する薬剤を投与した。

■人でも安全なのか

心臓がヒトのものと解剖学的に類似しているブタは、最適なドナー候補と考えられていた霊長類に比べ、疾病伝播のリスクが低い、成長が早い、すでに広く飼育されているといった点から、移植用臓器のより優れた供給源となるとみられている。

この種の異種移植の臨床試験では、ヒヒが人間のモデルとなる。

モヒウディン氏によると、次段階の重要な試験は、ブタからヒヒへの心臓の完全移植となる見通しだという。そして、「近い将来」にはブタの心臓が人体に移植されるかもしれないとも述べている。「末期の臓器不全患者が対象のこの手法は、人への応用においても安全である可能性があるように思われる。臓器不全の患者が、異種移植手術の初期臨床試験の候補となるかもしれない」と論文の執筆者らは記している。

今回の成果は、英科学誌ネイチャー・コミュニケーションズ（Nature Communications）に発表された。(c)AFP/Mariëtte Le Roux

目次に戻る

7. 幹細胞を活性化して毛髪を成長させる新しい方法 -マウス実験

2017 年 8 月 14 日

カリフォルニア大学ロサンゼルス校（UCLA）の科学者らは、毛包幹細胞を活性化して毛髪を成長させる新たな方法を発見した。
Nature Cell Biology 誌に掲載されたこの研究は、ホルモンバランスの乱れ、ストレス、高齢、あるいは化学療法治療などのせいで毛髪を喪失する禿頭や脱毛症の人のための毛髪成長促進用新薬の開発に繋がる可能性があるとしている。
毛包幹細胞の刺激は、マウス内の乳酸生成を増やしたり減らしたりすることで行うことができ、遺伝子改変でマウスの乳酸生成をブロックした場合、毛包幹細胞の活性化が妨げられ、ユタ大学の協力で、逆に遺伝子改変でマウスの乳酸生成を増やした場合には、毛包幹細胞の活性化が促進され毛髪サイクルが増加した、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170814134816.htm

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New way to activate stem cells to make hair grow

Date:

August 14, 2017

Source:

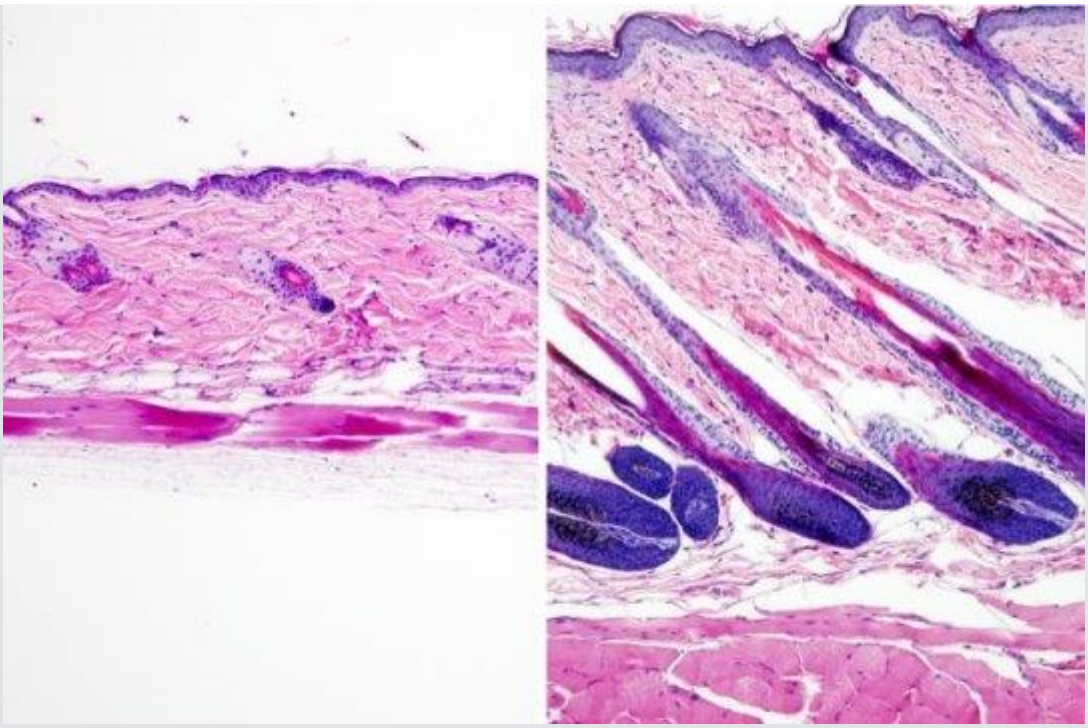
University of California - Los Angeles Health Sciences

Summary:

Researchers have discovered a new way to activate the stem cells in the hair follicle to make hair grow. The research may lead to new drugs that could promote hair growth for people with

baldness or alopecia, which is hair loss associated with such factors as hormonal imbalance, stress, aging or chemotherapy treatment.

FULL STORY



Untreated mouse skin showing no hair growth (left) compared to mouse skin treated with the drug UK5099 (right) showing hair growth.

Credit: UCLA Broad Stem Cell Center/Nature Cell Biology

UCLA researchers have discovered a new way to activate the stem cells in the hair follicle to make hair grow. The research, led by scientists Heather Christofk and William Lowry, may lead to new drugs that could promote hair growth for people with baldness or alopecia, which is hair loss associated with such factors as hormonal imbalance, stress, aging or chemotherapy treatment.

The research was published in the journal *Nature Cell Biology*.

Hair follicle stem cells are long-lived cells in the hair follicle; they are present in the skin and produce hair throughout a person's lifetime. They are "quiescent," meaning they are normally inactive, but they quickly activate during a new hair cycle, which is when new hair growth occurs. The quiescence of hair follicle stem cells is regulated by many factors. In certain cases they fail to activate, which is what causes hair loss.

In this study, Christofk and Lowry, of Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, found that hair follicle stem cell metabolism is different from other cells of the skin. Cellular metabolism involves the breakdown of the nutrients needed for cells to divide, make energy and respond to their environment. The process of metabolism uses enzymes that alter these nutrients to produce "metabolites." As hair follicle stem cells consume the nutrient glucose -- a form of sugar -- from the bloodstream, they process the glucose to eventually produce a metabolite called pyruvate. The cells then can either send pyruvate to their mitochondria -- the part of the cell that creates energy -- or can convert pyruvate into another metabolite called lactate.

"Our observations about hair follicle stem cell metabolism prompted us to examine whether genetically diminishing the entry of pyruvate into the mitochondria would force hair follicle stem cells to make more lactate, and if that would activate the cells and grow hair more quickly," said Christofk, an associate professor of biological chemistry and molecular and medical pharmacology.

The research team first blocked the production of lactate genetically in mice and showed that this prevented hair follicle stem cell activation. Conversely, in collaboration with the Rutter lab at University of Utah, they increased lactate production genetically in the mice and this accelerated hair follicle stem cell activation, increasing the hair cycle.

"Before this, no one knew that increasing or decreasing the lactate would have an effect on hair follicle stem cells," said Lowry, a professor of molecular, cell and developmental biology. "Once we saw how altering lactate production in the mice influenced hair growth, it led us to look for potential drugs that could be applied to the skin and have the same effect."

The team identified two drugs that, when applied to the skin of mice, influenced hair follicle stem cells in distinct ways to promote lactate production. The first drug, called RCGD423, activates a cellular signaling pathway called JAK-Stat, which transmits information from outside the cell to the nucleus of the cell. The research showed that JAK-Stat activation leads to the increased production of lactate and

this in turn drives hair follicle stem cell activation and quicker hair growth. The other drug, called UK5099, blocks pyruvate from entering the mitochondria, which forces the production of lactate in the hair follicle stem cells and accelerates hair growth in mice.

"Through this study, we gained a lot of interesting insight into new ways to activate stem cells," said Aimee Flores, a predoctoral trainee in Lowry's lab and first author of the study. "The idea of using drugs to stimulate hair growth through hair follicle stem cells is very promising given how many millions of people, both men and women, deal with hair loss. I think we've only just begun to understand the critical role metabolism plays in hair growth and stem cells in general; I'm looking forward to the potential application of these new findings for hair loss and beyond."

The use of RCGD423 to promote hair growth is covered by a provisional patent application filed by the UCLA Technology Development Group on behalf of UC Regents. The use of UK5099 to promote hair growth is covered by a separate provisional patent filed by the UCLA Technology Development Group on behalf of UC Regents, with Lowry and Christofk as inventors.

The experimental drugs described above were used in preclinical tests only and have not been tested in humans or approved by the Food and Drug Administration as safe and effective for use in humans.

Story Source:

Materials provided by **University of California - Los Angeles Health Sciences**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Aimee Flores, John Schell, Abigail S. Krall, David Jelinek, Matilde Miranda, Melina Grigorian, Daniel Braas, Andrew C. White, Jessica L. Zhou, Nicholas A. Graham, Thomas Graeber, Pankaj Seth, Denis Evseenko, Hilary A. Coller, Jared Rutter, Heather R. Christofk, William E. Lowry. **Lactate dehydrogenase activity drives hair follicle stem cell activation**. *Nature Cell Biology*, 2017; DOI: 10.1038/ncb3575

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8. ピーナツアレルギー克服に道か＝豪研究者が治療法開発

2017 年 8 月 18 日

【シドニー時事】オーストラリアの研究者らは１６日、ピーナツアレルギー克服に道を開く可能性がある治療法を開発したと発表した。ピーナツアレルギーは、死に至るアナフィラキシーショックを引き起こす恐れがあり、関係者には朗報となりそうだ。

メルボルンの小児医療研究所マードック・チルドレンズ・リサーチ・インスティチュートが臨床試験を実施。ピーナツアレルギーを持つ子供たちに１年半にわたり、免疫強化の効果があるとされる乳酸菌の一種「ラクトバチルス・ラムノサス」と少量のピーナツを徐々に量を増やしながら摂取してもらった。

その結果、被験者の８２％がピーナツ耐性を獲得。耐性を持った子供の８割は、臨床試験終了から４年が経過した今でも、ピーナツを問題なく食べられるという。

https://medical.jiji.com/news/8678

目次に戻る

9. ヒト免疫系を持つマウスモデルは幹細胞研究には適していない

2017 年 8 月 22 日

8 月 22 日の *Cell Reports* 誌に掲載されたスタンフォード大学医学部の研究者らによる新しい研究によると、ヒト免疫系が移植された幹細胞に対してどのように反応するかを評価するために広く使われているマウスモデルは、人間の患者に起こりそうな事象を反映しない、としている。研究者らは、ヒトに広範囲の幹細胞移植を開始するかどうか、またいつ開始するかについての決定を下す前に、この動物モデルの更なる最適化を強く推奨している。
「ヒト化」マウスとして知られるこの動物はヒトの免疫系を有するように操作されており、研究者らは何十年もの間この動物に依存して、とりわけ、糖尿病の膵島細胞の移植時および火傷犠牲者に対する皮膚移植時の免疫反応の研究を行ってきた。しかしながら、実際にヒト患者で起こるのとは異なり、ヒト化マウスでは、遺伝的にミスマッチなヒト幹細胞の移植に対して強い拒絶反応ができないことを発見、そのため移植後に患者が必要とする免疫抑制薬を研究することができない、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170822123842.htm

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Mouse model of human immune system inadequate for stem cell studies

Date:

August 22, 2017

Source:

Stanford University Medical Center

Summary:

A type of mouse widely used to assess how the human immune system responds to transplanted stem cells does not reflect what is likely to occur in patients, according to a new study.

FULL STORY

A type of mouse widely used to assess how the human immune system responds to transplanted stem cells does not reflect what is likely to occur in patients, according to a study by researchers at the Stanford University School of Medicine. The researchers urge further optimization of this animal model before making decisions about whether and when to begin wide-scale stem cell transplants in humans.

Known as "humanized" mice, the animals have been engineered to have a human, rather than a murine, immune system. Researchers have relied upon the animals for decades to study, among other things, the immune response to the transplantation of pancreatic islet cells for diabetes and skin grafts for burn victims.

However, the Stanford researchers found that, unlike what would occur in a human patient, the humanized mice are unable to robustly reject the transplantation of genetically mismatched human stem cells. As a result, they can't be used to study the immunosuppressive drugs that patients will likely require after transplant. The researchers conclude that the humanized mouse model is not suitable for studying the human immune response to transplanted stem cells or cells derived from them.

"In an ideal situation, these humanized mice would reject foreign stem cells just as a human patient would," said Joseph Wu, MD, PhD, director of Stanford's Cardiovascular Institute and professor of cardiovascular medicine and of radiology. "We could then test a variety of immunosuppressive drugs to learn which might work best in patients, or to screen for new drugs that could inhibit this rejection. We can't do that with these animals."

Wu shares senior authorship of the research, which will be published Aug. 22 in *Cell Reports*, with Dale Greiner, PhD, professor in the Program in Molecular Medicine at the University of Massachusetts Medical School, and Leonard Shultz, PhD, professor at the Jackson Laboratory. Former postdoctoral scholars Nigel Kooreman, MD, and Patricia de Almeida, PhD, and graduate student Jonathan Stack, DVM, share lead authorship of the study.

"Although these mice are fully functional in their immune response to HIV infection or after transplantation of other tissues, they are unable to completely reject the stem cells," said Kooreman. "Understanding why this is, and whether we can overcome this deficiency, is a critical step in advancing stem cell therapies in humans."

"Humanized mice are critical preclinical models in many biomedical fields helping to bring basic science into the clinic, but as this work shows, it is critical to frame the question properly," said Greiner. "Multiple laboratories remain committed to advancing our understanding and enhancing the function of engrafted human immune systems."

Greiner and Shultz helped to pioneer the use of humanized mice in the 1990s to model human diseases and they provided the mice used in the study.

Understanding stem cell transplants

The researchers were studying pluripotent stem cells, which can become any tissue in the body. They tested the animals' immune response to human embryonic stem cells, which are naturally pluripotent, and to induced pluripotent stem cells. Although iPS cells can be made from a patient's own tissues, future clinical applications will likely rely on pre-screened, FDA-approved banks of stem cell-derived products developed for specific clinical situations, such as heart muscle cells to repair tissue damaged by a heart attack, or endothelial cells to stimulate new blood vessel growth. Unlike patient-specific iPS cells, these cells would be reliable and immediately available for clinical use. But because they won't genetically match each patient, it's likely that they would be rejected without giving the recipients immunosuppressive drugs.

Humanized mice were first developed in the 1980s. Researchers genetically engineered the mice to be unable to develop their own immune system. They then used human immune and bone marrow precursor cells to reconstitute the animals' immune system. Over the years subsequent studies have shown that the human immune cells survive better when fragments of the human thymus and liver are also implanted into the animals.

Kooreman and his colleagues found that two varieties of humanized mice were unable to completely reject unrelated human embryonic stem cells or iPS cells, despite the fact that some human immune cells homed to and were active in the transplanted stem cell grafts. In some cases, the cells not only thrived, but grew rapidly to form cancers called teratomas. In contrast, mice with unaltered immune systems quickly dispatched both forms of human pluripotent stem cells.

The researchers obtained similar results when they transplanted endothelial cells derived from the pluripotent stem cells.

A new mouse model

To understand more about what was happening, Kooreman and his colleagues created a new mouse model similar to the humanized mice. Instead of reconstituting the animals' nonexistent immune systems with human cells, however, they used immune and bone marrow cells from a different strain of mice. They then performed the same set of experiments again.

Unlike the humanized mice, these new mice robustly rejected human pluripotent stem cells as well as mouse stem cells from a genetically mismatched strain of mice. In other words, their newly acquired immune systems appeared to be in much better working order.

Although more research needs to be done to identify the cause of the discrepancy between the two types of animals, the researchers speculate it may have something to do with the complexity of the immune system and the need to further optimize the humanized mouse model to perhaps include other types of cells or signaling molecules. In the meantime, they are warning other researchers of potential pitfalls in using this model to screen for immunosuppressive drugs that could be effective after human stem cell transplants.

"Many in the fields of pluripotent stem cell research and regenerative medicine are pushing the use of the humanized mice to study the human immune response," said Kooreman. "But if we start to make

claims using this model, assuming that these cells won't be rejected by patients, it could be worrisome. Our work clearly shows that, although there is some human immune cell activity, these animals don't fully reconstitute the human immune system."

The researchers are hopeful that recent advances may overcome some of the current model's limitations.

"The immune system is highly complex and there still remains much we need to learn," said Shultz. "Each roadblock we identify will only serve as a landmark as we navigate the future. Already, we've seen recent improvements in humanized mouse models that foster enhancement of human immune function."

Story Source:

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

Journal Reference:

1. Nigel G. Kooreman, Patricia E. De Almeida, Jonathan P. Stack, Raman V. Nelakanti, Sebastian Diecke, Ning-Yi Shao, Rutger-Jan Swijnenburg, Veronica Sanchez-Freire, Elena Matsa, Chun Liu, Andrew J. Connolly, Jaap F. Hamming, Paul H.a. Quax, Michael A. Brehm, Dale L. Greiner'correspondence Information About the Author Dale L. Greineremail the Author Dale L. Greiner, Leonard D. Shultz, Joseph C. Wu. **Alloimmune Responses of Humanized Mice to Human Pluripotent Stem Cell Therapeutics**. *Cell Reports*, 2017 DOI: 10.1016/j.celrep.2017.08.003

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10. 骨髄タンパク質を標的にして、幹細胞移植を改善し得る

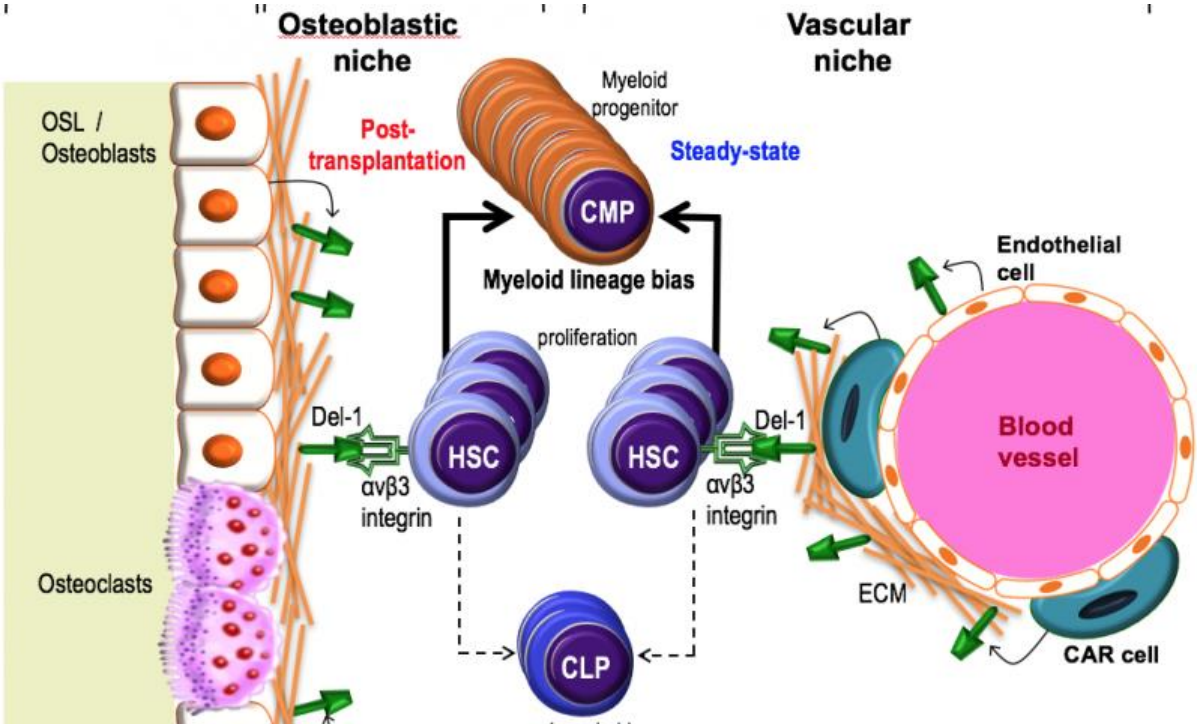
2017 年 8 月 28 日

骨髄にはあらゆる血液細胞の前駆体である造血細胞が含まれており、これらの細胞は骨髄移植および骨髄損傷後に作用して、その造血過程で免疫細胞を含む新しい血液細胞を作り出す。
今回ペンシルベニア大学とドレスデン工科大学の科学者が率いる新しい研究において、この造血の過程で重要な規制因子が、可溶性で容易に操作できる Del-1 というタンパク質であることが同定された。マウス実験で、Del-1 欠損マウスは正常の Del-1 レベルのマウスと比較して、骨髄細胞を再生し始める速度が遅かった、とし、このたんぱく質を標的にすることが、ドナーとレシピエントの両方にとって幹細胞移植を改善する効果的な方法なるだろうとしている。
この研究は、今週の *Journal of Clinical Investigation* 誌に報告されている。

英文記事：
https://medicalxpress.com/news/2017-08-bone-marrow-protein-stem-cell.html

Bone marrow protein may be target for improving stem cell transplants

August 28, 2017



Del–1, a protein previous shown to play a role in gum disease, has now been found to help regulate the production of blood cells. Targeting it could be an effective way to improve stem cell transplants for both donors and recipients. There ⋯more

Bone marrow contains hematopoetic stem cells, the precursors to every blood cell type. These cells spring into action following bone marrow transplants, bone marrow injury and during systemic infection, creating new blood cells, including immune cells, in a process known as hematopoiesis.

A new study led by University of Pennsylvania and Technical University of Dresden scientists has identified an important regulator of this process, a protein called Del–1. Targeting it, the researchers noted, could be an effective way to improve stem cell transplants for both donors and recipients. There may also be ways to modulate levels of Del–1 in patients with certain blood cancers to enhance immune cell production. The findings are reported this week in *The Journal of Clinical Investigation*.

"Because the hematopoetic stem cell niche is so important for the creation of bone marrow and blood cells and because Del–1 is a soluble protein and is easily manipulated, one can see that it could be a target in many potential applications," said George

Hajishengallis, the Thomas W. Evans Centennial Professor in the Department of Microbiology in Penn's School of Dental Medicine and a senior author on the work.

"I think that Del-1 represents a major regulator of the hematopoetic stem cell niche," said Triantafyllos Chavakis, co-senior author on the study and a professor at the Technical University of Dresden. "It will be worthwhile to study its expression in the context of hematopoetic malignancy."

For Hajishengallis, the route to studying Del-1 in the bone marrow began in his field of dental medicine. Working with Chavakis, he had identified Del-1 as a potential drug target for gum disease after finding that it prevents inflammatory cells from moving into the gums.

Both scientists and their labs had discovered that Del-1 was also expressed in the bone marrow and began following up to see what its function was there.

"In the beginning, I thought it would have a simple function, like regulating the exit of mature leukocytes [white blood cells] from the marrow into the periphery," Hajishengallis said, "something analogous to what it was doing in the gingiva. But it turned out it had a much more important and global role than what I had imagined."

The researchers' investigations revealed that Del-1 was expressed by at least three cell types in the bone marrow that support hematopoetic stem cells: endothelial cells, CAR cells and osteoblasts. Using mice deficient in Del-1, they found that the protein promotes proliferation and differentiation of hematopoetic stem cells, sending more of these progenitor cells down a path toward becoming myeloid cells, such as macrophages and neutrophils, rather than lymphocytes, such as T cells and B cells.

In bone marrow transplant experiments, the team discovered that the presence of Del-1 in recipient bone marrow is required for the transplanted stem cells to engraft in the recipient and to facilitate the process of myelopoesis, the production of myeloid cells.

When the researchers mimicked a systemic infection in mice, animals deficient in Del-1 were slower to begin making myeloid cells again compared to those with normal Del-1 levels.

"We saw roles for Del-1 in both steady state and emergency conditions," Hajishengallis said.

Hajishengallis, Chavakis and their colleagues identified the protein on hematopoetic stem cells with which Del-1 interacts, the ß3 integrin, perhaps pointing to a target for therapeutic interventions down the line.

The scientists see potential applications in bone marrow and stem cell transplants, for both donors and recipients. In donors, blocking the interaction between Del-1 and hematopoetic stem cells could enhance the mobilization of those progenitors into the bloodstream. This could be helpful for increasing donor cell numbers for transplantation. Transplant recipients, on the other hand, may need enhanced Del-1 interaction to ensure the transplanted cells engraft and begin making new blood cells more rapidly.

In addition, people undergoing chemotherapy who develop febrile neutropenia, associated with low levels of white blood cells, might benefit from the role of Del-1 in supporting the production of immune-related blood cells such as neutrophils.

"It's easy to think of practical applications for these findings," said Hajishengallis. "Now we need to find out whether it works in practice, so our studies continue."

Explore further: Engineered bone marrow could make transplants safer

More information: Ioannis Mitroulis et al, Secreted protein Del-1 regulates myelopoiesis in the hematopoietic stem cell niche, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI92571

Journal reference: Journal of Clinical Investigation

Provided by: University of Pennsylvania

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11．骨由来のホルモンがマウスの加齢性記憶喪失を改善

2017 年 8 月 29 日

コロンビア大学医療センター（CUMC）の研究者らによるマウス研究によると、骨細胞によって生成されるオステオカルシンというホルモンの血中濃度を上昇させることで、加齢性の記憶喪失が改善される可能性がある、としている。研究チームはまた、脳におけるオステオカルシンの受容体を同定し、加齢性の認知力低下を治療する新しいアプローチの道を開いた。
研究チームの一員である Eric Kandel 博士は、2000 年のノーベル生理学/医学賞の受賞者でもある。
この研究は、今週の *Journal of Experimental Medicine* 誌のオンライン版に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170829091052.htm

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Bone-derived hormone reverses age-related memory loss in mice

Study also identified possible target for novel therapies

Date:

August 29, 2017

Source:

Columbia University Medical Center

Summary:

Researchers have reversed age-related memory loss in mice by boosting blood levels of osteocalcin, a hormone produced by bone cells.

FULL STORY

Age-related memory loss may be reversed by boosting blood levels of osteocalcin, a hormone produced by bone cells, according to mouse studies led by Columbia University Medical Center (CUMC) researchers. The research team also identified a receptor for osteocalcin in the brain, paving the way for a novel approach to treating age-related cognitive decline.

The paper was published in the online edition of the *Journal of Experimental Medicine*.

"In previous studies, we found that osteocalcin plays multiple roles in the body, including a role in memory," said study leader Gerard Karsenty, MD, PhD, Paul A. Marks Professor and Chair, Department of Genetics & Development, and Professor of Medicine at CUMC. "We also observed that the hormone declines precipitously in humans during early adulthood. That raised an important question: Could memory loss be reversed by restoring this hormone back to youthful levels? The answer, at least in mice, is yes, suggesting that we've opened a new avenue of research into the regulation of behavior by peripheral hormones."

Karsenty's group, in collaboration with the laboratory of Eric Kandel, MD, University Professor and Kavli Professor of Brain Science at Columbia University and a key contributor to this study, conducted several experiments to evaluate osteocalcin's role in age-related memory loss. In one experiment, aged mice were given continuous infusions of osteocalcin over a two-month period. The infusions greatly improved the animals' performance on two different memory tests, reaching levels seen only in young mice.

The same improvements were seen when blood plasma from young mice, which is rich in osteocalcin, was injected into aged mice. In contrast, there was no memory improvement when plasma from young, osteocalcin-deficient mice was given to aged mice. But adding osteocalcin to this plasma before injecting it into the aged mice resulted in memory improvement. The researchers also used anti-

osteocalcin antibodies to deplete the hormone from the plasma of young mice, reducing their performance on memory tests.

The researchers then determined that osteocalcin binds to a receptor called Gpr158 that is abundant in neurons of the CA3 region of the hippocampus, the brain's memory center. This was confirmed by inactivating hippocampal Gpr158 in mice, and subsequently giving them infusions of osteocalcin, which failed to improve their performance on memory tests.

The researchers did not observe any toxic effects from giving the mice osteocalcin. "It's a natural part of our body, so it should be safe," said Dr. Karsenty. "But of course, we need to more research to translate our findings into clinical use for humans."

In previous research, Dr. Karsenty found that osteocalcin injections also rejuvenate the muscles of older mice, allowing them to match the running speeds and distances of young mice.

"Our laboratory's long-term interest in the biology of memory and our recent work on age-related memory loss made this a natural collaboration with the Karsenty laboratory, with its background work on osteocalcin," said Eric Kandel, MD, co-director of the Mortimer B. Zuckerman Mind Brain Behavior Institute at Columbia and a senior investigator at the Howard Hughes Medical Institute. Dr. Kandel was awarded a share of the 2000 Nobel Prize in Physiology or Medicine for his studies of the molecular basis of learning and memory.

Story Source:

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

Journal Reference:

1. Gerard Karsenty et al. **Gpr158 mediates osteocalcin's regulation of cognition**. *Journal of Experimental Medicine*, August 2017 DOI: 10.1084/jem.20171320
