Bio News – July, 2019

In-Vivo Science International, Inc.

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6/13　AbbVie、Humira の後を担う乾癬薬 SKYRIZI の良好な長期治療成績を報告

6/13　去年の製薬会社 CEO 高収入番付～女性はおらず、規模と手取りは無関係

6/13　AstraZeneca の英国本拠地建設費は予定の 2 倍を超える 7 億 5,000 万ポンド

6/14　Bain Capital が生命科学への投資資金集めの 2 回めで 9 億ドルを確保/Bloomberg

6/14　GSK が CRISPR 特許係争で Broad Institute に勝ったカリフォルニア大学（バークレー校）と手を組む

米国東海岸ケンブリッジの Broad Institute との遺伝子編集技術 CRISPR 特許の訴訟で 2 月に勝利した西海岸のカリフォルニア大学の研究者 2 人・Jennifer Doudna 氏と Jonathan Weissman 氏、GlaxoSmithKline（GSK）の研究開発（R&D）の頭・Hal Barron 氏の着想により、病因変異がどう病気を引き起こすかを CRISPR 技術を使って調べて創薬へといち早く結びつけることに取り組む研究所 Laboratory for Genomics Research（LGR）が設立され、GSK は今後 5 年間に最大 6,700 万ドルを LGR に提供する。

https://www.statnews.com/2019/06/13/gsk-partners-with-crispr-pioneer-doudna-to-search-for-new-drugs/?utm_source=STAT+Newsletters&utm_campaign=1ae9cfcf5f-Daily_Recap&utm_medium=email&utm_term=0_8cab1d7961-1ae9cfcf5f-150065641

6/14　加齢で減る酵素注射→若返り　マウスで成功 -米ワシントン大や国立長寿医療研究センターなどのチーム

https://headlines.yahoo.co.jp/hl?a=20190614-00000005-asahi-soci

6/14　トランプ大統領が J&J の新しい抗うつ薬をべた褒め

製薬会社をあまり良く言わないドナルド・トランプ米国大統領が、珍しく J&J の新しい抗うつ薬、ケタミンの S 型鏡像異性体 esketamine 点鼻薬 SPRAVATO に夢中になっており、悩めるどの退役軍人にも与えるべきであり、同剤で自殺が激減しうると言っている。
J&J は気前よく分けてくれるだろうし、必要なら J&J との仲を取り持つとトランプ大統領は退役軍人局（VA）長官 Robert Wilkie 氏に話している。
また Wilkie 氏も同剤はとても有効だと言っており、年内に全ての VA 病院に備わることを目指して手続きが進められている。

6/17　40 兆個もある腸内細菌の中から大腸がん発症に関わる菌種を見つけた 早期診断の新検査法に道 -阪大など

https://headlines.yahoo.co.jp/hl?a=20190617-00010000-sportal-sctch

6/18　糞中微生物移植の試験を米国 FDA が差し止め～深刻な感染症の発生を受けて

6/18　AstraZeneca が韓国の研究開発（R&D）に 6 億 3,000 万ドルを投じる

6/18　アレルギー反応誘発抗体・IgE を発見した女性免疫学者・石坂照子氏が 92 歳で死去

6/18　テレビ広告での薬価表示義務廃止を求めて米国製薬会社 3 社（Merck & Co、Eli Lilly、Amgen）が米国政府を告訴

6/19　ファイザーのがん治療薬「ベバシズマブ」（アバスチン）に国内初のバイオ後続品

https://www.mixonline.jp/tabid55.html?artid=67666

6/20　ゲノム編集食品、表示義務化見送りへ -消費者庁

6/20　遺伝子編集で、胎児の疾患を「子宮の中」で治療する

https://headlines.yahoo.co.jp/article?a=20190620-00010004-wired-sctch

6/21　Merck & Co、Keytruda を始めとする癌治療、ワクチン、病院製品の展望発表

Merck & Co の 5 年ぶりの投資家向け説明会 2019 Investor Day で抗 PD-1 薬 Keytruda（pembrolizumab）の更なる成長の可能性が示された。また、Lynparza や Lenvima 等の癌分野の製品や開発の備え、ワクチン、病院治療製品の展望が発表された。

6/21　アルツハイマー関与の変異を発見　日本人の免疫活性化遺伝子で -国立長寿医療研究センター（愛知県大府市）など研究グループ

6/22　中国成人のおよそ 4%が喘息

6/23　Sanofi が米国で早期退職者を募っている

製薬ニュース Endpointo によると、欧州のフランスとドイツの R&D 再編で 466 職を削減する Sanofi が米国では早期退職者を募ってる。

6/25　Humira の後が欲しい AbbVie が不振の Allergan を 630 億ドルで買収

欧州で安い類似品（バイオシミラー）との競争に直面している売り上げ世界一の薬 Humira（adalimumab）依存からの脱却が必要な AbbVie が、株価低迷を背景に会社分割間近と報じられていた BOTOX メーカーAllergan をおよそ 630 億ドルで買収。

6/26　サンフランシスコが電子タバコを全面禁止

急成長の電子タバコ（蒸気タバコ）市場の売り上げの今や 72%を占める Juul の発祥の地サンフランシスコでの電子タバコの全面禁止が知事 London Breed 氏の署名を経て決定する。
店が製品を撤収する 6 か月間の猶予期間を経て電子タバコを売ることも使うことも製造することも禁止となり、決まりを破れば罰金やその他の刑が科される。
米国の高校生の電子タバコ使用が去年 78%増えたことが示されており、健康への影響がよく分かっていない電子タバコが若者の手に渡らないようにあらゆる手段を講じる、とサンフランシスコの相談役 Shamann Walton 氏は言っている。

6/26　ネイチャー誌が糾弾～日本発最悪の研究不正が暴く日本の大学の「不備」

https://news.yahoo.co.jp/byline/enokieisuke/20190626-00131623/

6/27　参天製薬、Oxford Biomedica の技術頼りの網膜疾患遺伝子治療に取り組む

6/27　iPS心筋シート移植　冬に延期　大阪大、安全性を検証

https://headlines.yahoo.co.jp/hl?a=20190627-00000622-san-sctch

6/28　ImmunoGen が従業員の大半を削減して卵巣癌薬の Ph3 をやり直す

6/28　遠隔操作のロボット手術解禁へ　厚労省検討会が了承

6/28　オナラの匂いをバラの香りに変えるサプリが、フランスで発売！ チョコ、すみれなど種類も豊富

https://headlines.yahoo.co.jp/article?a=20190628-00010001-finders-sctch

6/29　Pfizer、Roche のアバスチンのバイオシミラー製品 ZIRABEV が FDA に承認された

-企業関連ニュース/他のトップページに戻る

今月の研究関連ニュース/他

1. リチウムが筋ジストロフィーマウスの筋力を増強
2. Pfizer の大ヒット商品「Enbrel」にはアルツハイマー病を予防する可能性への手がかりがあったのに公表しなかったのはなぜか？
3. 腸内微生物叢を増やすことはより健康的な老後につながるのか？
4. アルツハイマー病の悪性化に関わるタンパク質の発見
5. EvaluatePharma ワールドプレビュー2018 年、2024 年までの展望
6. パーキンソン病を発症する前にくい止める
7. 不健康な腸が乳癌の拡大を促進
8. ゲノム編集技術で、新しい自閉症モデル開発
9. ビスフェノール（BPA）曝露が世代を超えて自閉症関連遺伝子に影響 – マウス研究

1. リチウムが筋ジストロフィーマウスの筋力を増強

新薬ターゲットの特定

セントルイスのワシントン大学医学部の研究者らは、リチウムが肩や腰の脱力を引き起こす稀な形の筋ジストロフィーを持つマウスの筋肉の大きさと強度を改善することを発見した。この調査結果は、治療薬につながる可能性があるとして、4 月 18 日の *Neurology Genetics* 誌に発表されている。

肢帯型筋ジストロフィーと呼ばれるこの病気は、米国内で数千人が罹患している。他の希少疾患と同様に、研究者や資金提供機関からあまり注目されていないため、治療法開発が遅れているという現実がある。この論文の上席著者で大学の神経筋疾患センターで筋ジストロフィー患者を治療する C. Chris Weihl 医学博士とその同僚らは、家族内で数人がこの病気に罹患している 2 家族を同定し、両家の罹患者および非罹患者の DNA を分析することにより、遺伝子 DNAJB6 の変異が筋力低下の原因であることを見い出した。そして、この DNAJB6 がなければ、筋繊維はその通常サイズの 3 倍に成長した、としている。

研究者らが遺伝子操作したマウスを用いて調べた結果、これらのマウスはヒトの患者と同様に、成人期に進行性の筋力低下を発症した。これらのマウスからの筋肉を使用して、病気の変種が筋肉の成長を抑制するたんぱく質を過剰に活性化することを発見、このたんぱく質（GSK3β と呼ばれる）を塩化リチウムで阻害すると、マウスの筋肉の強度と量が向上した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/06/190603124717.htm

Lithium boosts muscle strength in mice with rare muscular dystrophy

New drug target identified

Date:

June 3, 2019

Source:

Washington University School of Medicine

Summary:

Researchers have found that lithium improves muscle size and strength in mice with a rare form of muscular dystrophy that causes weakness in the shoulders and hips. The findings could lead to a drug for the disabling condition.

FULL STORY

Standing up from a chair, climbing stairs, brushing one's hair -- all can be a struggle for people with a rare form of muscular dystrophy that causes progressive weakness in the shoulders and hips. Over time, many such people lose the ability to walk or to lift their arms above their heads.

This form of the disease -- called limb girdle muscular dystrophy -- affects a few thousand people nationwide. Like other rare illnesses, it tends not to attract much attention from researchers and funding agencies, so progress toward developing therapies has been slow. But a team at Washington University School of Medicine in St. Louis that identified a subtype of the disease in 2012 has shown that lithium improves muscle size and strength in mice with this form of muscular dystrophy. The findings, published April 18 in *Neurology Genetics*, could lead to a drug for the disabling condition.

"There are no medications available for people with limb girdle muscular dystrophy, so we are very excited to have a good therapeutic target and a potential therapy," said senior author C. Chris Weihl, MD, PhD, a professor of neurology who treats people with muscular dystrophy at the university's Neuromuscular Disease Center. "This has been an amazing project. It all began when we diagnosed a patient with muscular dystrophy of unknown cause. Genetic sequencing then helped us identify a new subtype, and we've been able to take that all the way through to a possible therapy."

Limb girdle muscular dystrophy can be caused by variations in any one of more than a dozen different genes. Several years ago, Weihl and colleagues -- including neurologists Robert Baloh, MD, PhD, and Matthew Harms, MD -- identified two families in which several members had symptoms of the condition but none of the known genetic variants. By analyzing the DNA of affected and unaffected members of both families, the researchers found that a variation in the gene DNAJB6was responsible for their muscle weakness.

While the researchers had found the faulty gene, it wasn't immediately clear why an alteration to that gene caused people's muscles to atrophy. To find out, Weihl and co-first authors Andrew Findlay, MD, a clinical fellow in neurology, and Rocio Bengoechea Ibaceta, PhD, a staff scientist, cut the gene out entirely, expecting to see even more muscle loss when the gene was absent.

They found the opposite: Without DNAJB6, muscle fibers grew to three times their normal size.

"When Drew showed me these enormous muscle fibers, I just didn't understand it," Weihl said. "But Drew pointed out that we were on the right pathway, but perhaps going the wrong direction. Something in this pathway is important for muscle growth."

The researchers tried again, this time using genetically modified mice that Weihl and colleagues had engineered in 2015. These mice carried the same genetic variant as the patients, and like the patients, they developed progressive muscle weakness in adulthood. Using muscle from these mice, the researchers discovered that disease variants overactivate a protein that suppresses muscle growth. Moreover, inhibiting the protein -- called GSK3beta -- with lithium chloride improves mice's strength and muscle mass.

"Before treatment, mutant mice had roughly one-fifth the strength of the normal mice," Findlay said. "After a month of treatment, they improved to 75 percent of the normal mice. It's a big jump."

Lithium chloride was once sold as table salt but was taken off the shelves in 1949, when doctors realized that sprinkling it liberally on food can be deadly. But other forms of lithium such as lithium carbonate and lithium citrate are used to treat some psychiatric illnesses, so it's possible a safe form of lithium can be found to treat the rare muscular dystrophy.

"I don't want people to go out and take lithium chloride right now," Findlay said. "We've shown that this protein is a promising therapeutic target, but more work needs to be done."

Before any compound targeting the protein is tested in humans, a better understanding of limb girdle muscular dystrophy is needed. The disease is so rare that doctors have not defined how quickly different people lose strength and how the course of the disease differs in people whose condition is caused by variations in different genes.

"We're at a point where therapeutic development has outpaced our understanding of the natural history of this disease," Weihl said. "We have a therapeutic target, but we don't fully understand how patients progress when they're not treated. We need to understand as many people with this rare disease as possible so when we do start testing an investigational drug, we can be confident that it is changing the course of the disease."

Weihl, Findlay, and colleagues around the U.S. and U.K. are planning a study of people with limb girdle muscular dystrophy caused by variations in any gene. The study will map disease progression in such people in preparation for upcoming treatment trials. Participants will make annual visits to the neuromuscular clinic to undergo functional assessments such as timed stair climbs and fill out questionnaires rating their ability to perform tasks of daily life.

Story Source:

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

Journal Reference:

1. Andrew R. Findlay, Rocio Bengoechea, Sara K. Pittman, Tsui-Fen Chou, Heather L. True, Conrad C. Weihl. **Lithium chloride corrects weakness and myopathology in a preclinical model of LGMD1D**. *Neurology Genetics*, 2019; 5 (2): e318 DOI: 10.1212/NXG.0000000000000318

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2. Pfizer の大ヒット商品「Enbrel」にはアルツハイマー病を予防する可能性への手がかりがあったのに公表しなかったのはなぜか？

ワシントンポスト紙が入手した Pfizer の内部資料によると、2015 年に同社の研究者チームは、強力な抗炎症薬であり、同社の大ヒット商品でもある、リウマチ性関節炎治療薬「Enbrel」が、アルツハイマー病のリスクを 64%減少させるようだ、という驚異的な発見をした。その結果は、何十万もの保険請求の分析から得られたものであった。ただ、その薬が実際にその効果をもたらすことを確認するには高価な臨床試験を必要とするため、数年間の内部議論の末に同社はそれ以上の調査をせずデータの公表をしないことを選んだ、とのことである。実際に、同社は、3 年間の社内レビューの中で、Enbrel は直接脳の組織に到達しないためアルツハイマー病の予防には有効ではないと判断した、とポスト紙に語っている。
ある評論家によると、Pfizer がアルツハイマー病の臨床試験に投資することを推奨しなかった時に働いたより大きな市場原理は、ブランド薬製造業者がその薬から独占利益を享受する時の 20 年間の独占権に根差している。
しかしながら、Enbrel のアルツハイマー病予防に対する Pfizer の評価に反対する科学者も多い。これらの科学者らは、Pfizer が少なくともそのデータを公表するべきだと主張している。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.washingtonpost.com/business/economy/pfizer-had-clues-its-blockbuster-drug-could-prevent-alzheimers-why-didnt-it-tell-the-world/2019/06/04/9092e08a-7a61-11e9-8bb7-0fc796cf2ec0_story.html?noredirect=on&utm_term=.5b38afdc5544

Business

Pfizer had clues its blockbuster drug could prevent Alzheimer's. Why didn't it tell the world?

Pfizer had clues its drug could prevent Alzheimer's. What happened?

Pfizer's arthritis drug appeared to reduce the risk of getting Alzheimer's disease. The Washington Post's Chris Rowland explains why Pfizer did not pursue it. (Luis Velarde/The Washington Post)

By Christopher Rowland

Business reporter focused on the health-care economy's effects on patient health, costs, and privacy

June 4

A team of researchers inside Pfizer made a startling find in 2015: The company's blockbuster rheumatoid arthritis therapy Enbrel, a powerful anti-inflammatory drug, appeared to reduce the risk of Alzheimer's disease by 64 percent.

The results were from an analysis of hundreds of thousands of insurance claims. Verifying that the drug would actually have that effect in people would require a costly clinical trial — and after several years of internal discussion, Pfizer opted against further investigation and chose not to make the data public, the company confirmed.

Researchers in the company's division of inflammation and immunology urged Pfizer to conduct a clinical trial on thousands of patients, which they estimated would cost $80 million, to see if the signal contained in the data was real, according to an internal company document obtained by The Washington Post.

"Enbrel could potentially safely prevent, treat and slow progression of Alzheimer's disease," said the document, a PowerPoint slide show that was prepared for review by an internal Pfizer committee in February 2018.

[The most expensive drug on the planet will treat infants with rare disease. The market fight focused on cost and safety is just getting started]

The company told The Post that it decided during its three years of internal reviews that Enbrel did not show promise for Alzheimer's prevention because the drug does not directly reach brain tissue. It deemed the likelihood of a successful clinical trial to be low. A synopsis of its statistical findings prepared for outside publication, it says, did not meet its "rigorous scientific standards."

The surprising reasons why drug prices in the U.S. are higher than in the rest of the world

Pharma companies have raised prices for new drugs and commonly used medications, prompting many patients to order medications across the border. (Luis Velarde/The Washington Post)

Science was the sole determining factor against moving forward, company spokesman Ed Harnaga said.

Likewise, Pfizer said it opted against publication of its data because of its doubts about the results. It said publishing the information might have led outside scientists down an invalid pathway.

Pfizer's deliberations, which previously have not been disclosed, offer a rare window into the frustrating search for Alzheimer's treatments inside one of the world's largest drug companies. Despite billions spent on research, Alzheimer's remains a stubbornly prevalent disease with no effective prevention or treatment.

Some outside scientists disagree with Pfizer's assessment that studying Enbrel's potential in Alzheimer's prevention is a scientific dead end. Rather, they say, it could hold important clues to combating the disease and slowing cognitive decline in its earliest stages.

[Why coming up with a drug for Alzheimer's is so devilishly hard]

Despite promising preliminary data in an internal analysis, Pfizer opted against conducting a clinical trial to see if its drug Enbrel could prevent Alzheimer's disease. (Spencer Platt/Getty Images)

Pfizer did share the data privately with at least one prominent scientist, but outside researchers contacted by The Post believe Pfizer also should at least have published its data, making the findings broadly available to researchers.

"Of course they should. Why not?'' said Rudolph E. Tanzi, a leading Alzheimer's researcher and professor at Harvard Medical School and Massachusetts General Hospital.

"It would benefit the scientific community to have that data out there,'' said Keenan Walker, an assistant professor of medicine at Johns Hopkins who is studying how inflammation contributes to Alzheimer's. "Whether it was positive data or negative data, it gives us more information to make better informed decisions.''

Internal discussions about possible new uses of drugs are common in pharmaceutical companies. In this case, Pfizer's deliberations show how decisions made by industry

executives — who are ultimately accountable to shareholders — can have an impact well beyond corporate board rooms.

[This $1,650 pill will tell your doctors whether you've taken it. Is it the future of medicine?]

As its Enbrel deliberations ended early last year, Pfizer was getting out of Alzheimer's research. It announced in January 2018 that it would be shutting down its neurology division, where Alzheimer's treatments were explored, and laying off 300 employees.

Meanwhile, Enbrel has reached the end of its patent life. Profits are dwindling as generic competition emerges, diminishing financial incentives for further research into Enbrel and other drugs in its class.

"I'm frustrated myself really by the whole thing,'' said Clive Holmes, a professor of biological psychiatry at the University of Southampton in Great Britain who has received past support from Pfizer for Enbrel research in Alzheimer's, a separate 2015 trial in 41 patients that proved inconclusive.

He said Pfizer and other companies do not want to invest heavily in further research only to have their markets undermined by generic competition.

"Someone can pop up and say, 'Look, I've got a me-too drug here,'" Holmes said, referring to the advent of generic versions of Enbrel. "I think that is what this is all about.''

Enbrel's 'life cycle'

The broader market forces that critics say discouraged Pfizer from investing in Alzheimer's clinical trials are rooted in Enbrel's "life cycle,'' the 20-year period of patent exclusivity when a brand manufacturer reaps monopoly profits from a drug. By industry standards, Enbrel, an injectable biologic drug, is relatively old, with FDA approval for rheumatoid arthritis in 1998. It also has been approved to treat psoriasis.

[Drugmakers alleged scare tactics may hold back generic competition]

Pfizer got rights to market it internationally when it acquired drugmaker Wyeth in 2009. But Enbrel, which earned Pfizer $2.1 billion in 2018, now faces generic competition.

Drug companies often are criticized for extending the patent life of a drug — and winning new profits — by merely tweaking a drug's molecule or changing the method of delivery into the body. But it is a "heavy lift'' for a company to win regulatory approval to use a drug for a completely different disease, said Robert I. Field, a professor of law and health care management at Drexel University.

“Our patent laws do not provide the appropriate incentives,’’ Field said. Drug therapy for early Alzheimer’s “would be a godsend for American patients, so we should be doing everything we can as a country to encourage development of treatments. It’s frustrating that there may be a missed opportunity.’’

As Enbrel’s life cycle winds down, Pfizer has introduced a new rheumatoid arthritis drug, Xeljanz, that works differently from Enbrel. Pfizer is putting its marketing muscle behind the new treatment. While Enbrel revenue is shrinking, Xeljanz revenue is growing. The Xeljanz patent expires in 2025 in the United States and 2028 in Europe, according to Pfizer’s public disclosures. The drug is on track to make Pfizer billions more each year for the foreseeable future.

[Pharma giant profits from HIV treatment funded by taxpayers and patented by the government]

Wagering money on a clinical trial of Enbrel for an entirely different disease, especially when Pfizer had doubts about the validity of its internal analysis, made little business sense, said a former Pfizer executive who was aware of the internal debate and spoke on the condition of anonymity to discuss internal Pfizer matters.

“It probably was high risk, very costly, very long term drug development that was off-strategy,’’ the former executive said.

Another former executive, who also spoke on the condition of anonymity to discuss Pfizer operations, said Pfizer offered virtually no explanation internally for opting against further investigation in early 2018, when the internal debate ended.

“I think the financial case is they won’t be making any money off of it,’’ the second former executive said.

'Impeding research'

Drug companies frequently have been pilloried for not fully disclosing negative side effects of their drugs. What happens when the opposite is the case? What obligation does a company have to spread potentially beneficial information about a drug, especially when the benefits in question could improve the outlook for treating Alzheimer’s, a disease that afflicts at least 500,000 new patients per year?

A medical ethics expert argued that Pfizer has a responsibility to publicize positive findings, although it is not as strong as an imperative to disclose negative findings.

“Having acquired the knowledge, refusing to disclose it to those who might act upon it hides a potential benefit, and thereby wrongs and probably harms those at risk of developing Alzheimer’s by impeding research,’’ said Bobbie Farsides, professor of

clinical and biomedical ethics at Brighton and Sussex Medical School in the United Kingdom.

Another health-care ethics specialist cautioned that the demand for drug company disclosure should remain focused on information collected during clinical trials.

"I do think you have to draw some limits, and say that not every piece of information they have in their files has to be disclosed with others," said Marc A. Rodwin, a law professor at Suffolk University Law School in Boston.

Pfizer markets Enbrel outside North America. Another drug company, Amgen, which holds rights to market Enbrel in the United States and Canada, says it knew of the Pfizer data and similarly decided the findings held little promise. Amgen said market factors played no role in its deliberations.

"Unfortunately, our exploratory work did not yield results strong enough to warrant further studies," Amgen said.

Analyzing insurance claims

Sometimes doctors prescribe drugs for uses that have not been approved by the Food and Drug Administration. But none of the experts interviewed for this story said such "off-label" use of Enbrel would be appropriate for Alzheimer's, because of the very limited nature of the data thus far. Nor, they said, do they believe such prescribing is happening to any significant extent.

The role of brain inflammation in Alzheimer's recently has been getting closer attention among academics after the failure of multiple experimental drugs that targeted the buildup of plaques on brain tissue. In 2016, researchers from Dartmouth and Harvard universities published a study of insurance claims data — similar to Pfizer's internal findings — that showed a potential benefit of Enbrel. Enbrel "shows promise as a potential treatment" for Alzheimer's, the study found.

Pfizer's analysis about potential Enbrel benefits in the brain sprang from the company's division of immunology and inflammation, based in a large Pfizer office complex in Collegeville, Pa.

Statisticians in 2015 analyzed real world data, hundreds of thousands of medical insurance claims involving people with rheumatoid arthritis and other inflammatory diseases, according to the Pfizer PowerPoint obtained by The Post.

They divided those anonymous patients into two equal groups of 127,000 each, one of patients with an Alzheimer's diagnosis and one of patients without. Then they checked for Enbrel treatment. There were more people, 302, treated with Enbrel in the group

without Alzheimer's diagnosis. In the group with Alzheimer's, 110 had been treated with Enbrel.

The numbers may seem small, but they were mirrored in the same proportion when the researchers checked insurance claims information from another database. The Pfizer team also produced closely similar numbers for Humira, a drug marketed by AbbVie that works like Enbrel. The positive results also showed up when checked for "memory loss'' and "mild cognitive impairment,'' indicating Enbrel may have benefit for treating the earliest stages of Alzheimer's.

A clinical trial to prove the hypothesis would take four years and involve 3,000 to 4,000 patients, according to the Pfizer document that recommended a trial. The document said Pfizer would gain a positive public relations "halo effect'' by investigating an Alzheimer's treatment.

Enbrel reduces inflammation by targeting a specific protein called TNF-a. The Pfizer claims data analysis added to a growing body of evidence that broadly targeting TNF-a in the body has the potential to prevent Alzheimer's, said Holmes, the professor of biological psychiatry at the University of Southampton.

Holmes is among the few researchers who has gained access to the Pfizer data; he won the company's permission to use it in a grant application for a small clinical trial he is undertaking in England.

"If it's true in reality, if you did it in a clinical trial setting, it's massive — it would be huge,'' Holmes said. "That's why it's so exciting.''

One reason for caution: another class of anti-inflammatory therapies, called non-steroidal anti-inflammatory drugs (NSAIDS), showed no effect against mild-to-moderate Alzheimer's in several clinical trials a decade ago. Still, a long-term follow-up of one of those trials indicated a benefit if NSAID use began when the brain was still normal, suggesting the timing of therapy could be key.

Pfizer said it also was skeptical because Enbrel has only a limited effect on the brain. The Enbrel molecule is too large to pass through the "blood-brain barrier'' and directly target TNF-a in brain tissue, the company said.

Yet Alzheimer's researchers believe inflammation outside the brain — called peripheral inflammation — influences inflammation within the brain.

"There is a lot of evidence suggesting that peripheral or systemic inflammation may be a driver of Alzheimer's disease,'' said Walker, the Johns Hopkins researcher. It is a fair hypothesis that fighting inflammation outside the brain with Enbrel will have a similar effect inside the brain, he said.

“I don’t believe Enbrel would need to cross the blood brain barrier to modulate the inflammatory/immune response within the brain,’’ Walker said.

“There is increasing evidence that peripheral inflammation can influence brain function,’’ said rheumatologist Christopher Edwards, of the University of Southampton in Britain.

“It’s important that that’s published, and in the public domain,’’ Edward added of the Pfizer data. “It needs to be out there.’’

Correction: An earlier version of this story misstated the location of the Brighton and Sussex Medical School.

Christopher RowlandChris Rowland joined The Washington Post business team in 2018 after serving as the Washington bureau chief for the Boston Globe, leading coverage of two presidential elections and overseeing political enterprise reporting. He previously covered health care for the Globe in Boston. Follow

3. 腸内微生物叢を増やすことは本当により健康的な老後につながるのか？

ケンブリッジのバブラハム研究所の免疫学者らの研究によると、若年マウスから老齢マウスへの糞便移植は、腸内微生物叢を刺激し、腸の免疫系を回復させることができる。この研究は今日の *Nature Communications* 誌に掲載されている。
腸は、加齢によって最も深刻な影響を受ける臓器の 1 つであり、ヒトの腸内微生物叢に対する年齢依存の変化は、腸免疫系の機能低下と並行して起こるが、これまでこの 2 つの変化が関連しているかどうかは分かっていなかった。
若年マウスと老齢マウスを共飼いすること、また若年マウスから老齢マウスへの糞便移植をより直接的に行うことで、老齢マウスの腸免疫系が促進された。関与する免疫細胞の数をみると、老齢マウスは腸管免疫反応を有し、若年マウスの腸管免疫反応とほとんど見分けがつかなかった。この研究結果は、貧弱な腸の免疫反応が不可逆的ではないこと、免疫反応は適切な刺激を与えることによって強化し得ること、本質的に若年マウスの状況により密接に類似するように腸の免疫系の時計の針を巻き戻せること、を示している。

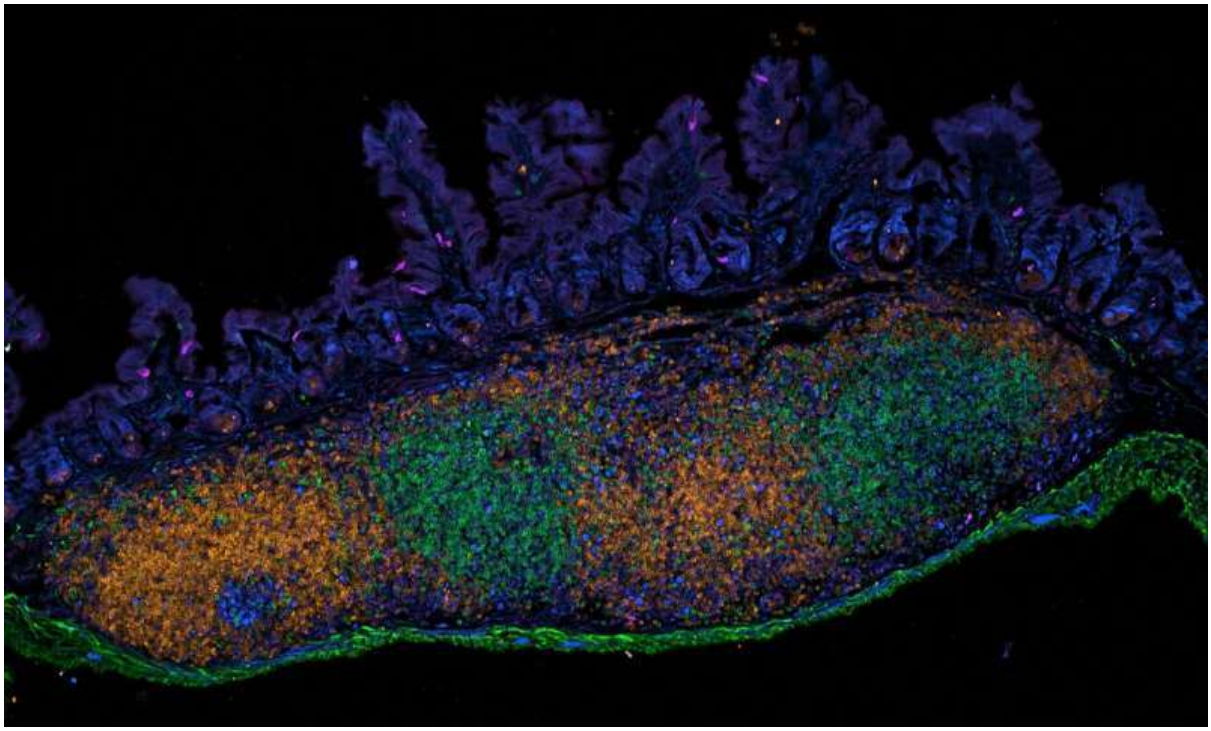
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-06-boosting-gut-microbiome-secret-healthier.html

JUNE 4, 2019

Could boosting the gut microbiome be the secret to healthier older age?

by Babraham Institute



A confocal microscope image of immune cells in the epithelial lining of the intestine of a young mouse. The cells are localised within specialised lymphoid tissue in the epithelial lining of the intestine called a Peyer's patch. Here, B and T cells interact to mediate an effective antibody response against the gut microbiota. Naïve B cells are shown in orange, while proliferating cells - including germinal centre B cells - are blue. All T cells are stained green and regulatory Foxp3+ T cells can be recognised by their purple centre. Credit: Marisa Stebegg, Babraham Institute.

Faecal transplants from young to aged mice can stimulate the gut microbiome and revive the gut immune system, a study by immunologists at the Babraham Institute, Cambridge, has shown. The research is published in the journal *Nature Communications* today.

The gut is one of the organs that is most severely affected by ageing and age-dependent changes to the human gut microbiome have been linked to increased frailty, inflammation and increased susceptibility to intestinal disorders. These age-dependent changes to the gut microbiome happen in parallel with a decrease in function of the gut immune system but, until now, it was unknown whether the two changes were linked.

"Our gut microbiomes are made up of hundreds of different types of bacteria and these are essential to our health, playing a role in our metabolism, brain function and immune response," explains lead researcher Dr. Marisa Stebegg. "Our immune system is constantly interacting with the bacteria in the gastrointestinal tract. As immunologists who study why our immune system doesn't work as well as we age, we were interested to explore whether the make-up of the gut microbiome might influence the strength of the gut immune response."

Co-housing young and aged mice (mice naturally like to sample the faecal pellets of other mice!) or more directly performing faecal transfer from young to aged mice boosted the gut immune system in the aged mice, partly correcting the age-related decline.

"To our surprise, co-housing rescued the reduced gut immune response in aged mice. Looking at the numbers of the immune cells involved, the aged mice possessed gut immune responses that were almost indistinguishable from those of the younger mice." commented Dr. Michelle Linterman, group leader in the Immunology programme at the Babraham Institute.

The results show that the poor gut immune response is not irreversible and that the response can be strengthened by challenging with appropriate stimuli, essentially turning back the clock on the gut immune system to more closely resemble the situation in a young mouse.

The results of the study have relevance for treating age-related symptoms, confirming a link between the effects of the ageing immune system and age-associated changes in the gut microbiome. By demonstrating the effectiveness of interventions that have a positive impact on the composition of the gut microbiome, this research suggests that faecal transplants, probiotics, co-habitation and diet might all prove to be ways to facilitate healthy ageing.

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4. アルツハイマー病の悪性化に関わるタンパク質の発見

http://www.riken.jp/pr/press/2019/20190604_2/

2019 年 6 月 4 日
理化学研究所

アルツハイマー病の悪性化に関わるタンパク質の発見

－タウタンパク質の凝集と脳の萎縮を加速する－

理化学研究所（理研）脳神経科学研究センター神経老化制御研究チームの橋本翔子基礎科学特別研究員、斉藤貴志副チームリーダー、西道隆臣チームリーダーらの研究チームは、「CAPON」というタンパク質がアルツハイマー病の悪性化に関わることを発見しました。

本研究成果により、今後、新たな CAPON の機能を阻害するような薬剤（手法）[1]が開発されれば、アルツハイマー病の進行を抑制できると期待できます。

アルツハイマー病の病理形成機構としては、アミロイドβペプチド（Aβ）[2]の沈着（アミロイド病理）が引き金となって、タウタンパク質[3]が凝集する神経原線維変化[3]（タウ病理）の形成、神経細胞死に至るという「アミロイドカスケード仮説」が支持されています。しかし、アミロイド病理からタウ病理、神経細胞死への遷移機構は不明でした。

今回、研究チームはインタラクトーム解析[4]により、CAPON がタウタンパク質と結合することを見いだしました。そして、ヒトのアミロイド病理を再現するモデルマウスの脳で CAPON を強制発現させると、タウ病理と神経細胞死に伴う脳の萎縮が促進されること、逆に、タウ病理と神経細胞死を再現するモデルマウスで *CAPON* 遺伝子を欠損させると、脳の萎縮が抑制されることが明らかになりました。このことから、CAPON はアミロイド病理下において、タウ病理、神経細胞死を誘導する重要な因子であると考えられます。

本研究は、英国のオンライン科学雑誌『*Nature Communications*』（6 月 3 日付け）に掲載されました。

※研究支援

本研究は、アステラス製薬株式会社との共同研究、日本医療研究開発機構（AMED）「革新的技術による脳機能ネットワークの全容解明プロジェクト」などによる支援を受けて行われました。

背景

日本では高齢化に伴って認知症患者数が急増しており、厚生労働省の推計によると、2026 年には 65 歳以上の 5 人に 1 人が認知症に罹患すると算定されています[注 1)]。なかでも、アルツハイマー型認知症（アルツハイマー病、AD）は、認知症患者のうち半数以上を占めるため、早急な治療・予防法の確立が求められています。

AD の病理形成機構としては、脳内の神経細胞外でアミロイドβペプチド（Aβ）が凝集・沈着する老人斑（アミロイド病理）が引き金となって、微小管結合タンパク質の一つであるタウタンパク質がリン酸化されて、細胞質中で線維化・凝集する神経原線維変化（タウ病理）の形成、神経細胞死に至るという「アミロイドカスケード仮説」が支持されています。しかし、アミロイド病理からタウ病理形成、神経細胞死への遷移機構は不明でした。

西道チームリーダーらは、2014 年にノックイン技法[5]を用いて、アミロイド病理を再現する「*App*$^{NL\text{-}G\text{-}F}$ ノックインマウス[6]」という新しい AD モデルマウスを作製していました[注 2)]。そこで、研究チームはこのマウスを用いて、タウ病理形成、神経細胞死への遷移機構の解明を試みました。

注 1）厚生労働省 認知症施策推進総合戦略（新オレンジプラン）～認知症高齢者等にやさしい地域づくりに向けて～
注 2）2014 年 4 月 14 日プレスリリース「次世代型アルツハイマー病モデルマウスの開発に成功」

研究手法と成果

研究チームはまず、タウ病理形成に関わるタンパク質を調べるために、インタラクトーム解析を行った結果、CAPON（C-terminal PDZ ligand of nNOS[7]）というタンパク質がタウタンパク質に結合することを見いだしました。CAPON は nNOS（神経型一酸化窒素合成酵素）と結合し、NMDA 受容体[8]を介した興奮毒性などに関わることなどが知られていましたが、AD における機能は不明でした。

そこで、アミロイド病理を再現する *App*$^{NL\text{-}G\text{-}F}$ ノックイン（KI）マウスの脳において、CAPON の発現を解析したところ、海馬[9]の錐体細胞層に CAPON が蓄積していることが分かりました。AD 患者の脳でも同様であることが報告されている[注 3)]ことから、アミロイド病理下における CAPON の海馬での蓄積がその後の AD 病理に影響を及ぼすと考えられます。

次に、マウスでヒトの脳と同じ様式でタウタンパク質を発現する *MAPT* KI マウス（ヒト型タウ KI マウス）を作製しました。そして、*App*$^{NL\text{-}G\text{-}F}$ KI マウスと *MAPT* KI マウスを掛け合わせたダブル KI マウスにおいて、アデノ随伴ウイルスベクター[10]を用いて CAPON を過剰発現させました。すると、タウ病理および神経細胞死が誘導され、海馬が萎縮することが分かりました（図 1）。

さらに、どのような機構で神経細胞死が誘発されるのか調べたところ、プログラムされた細胞死のアポトーシス[11]マーカーだけではなく、炎症性細胞死のパイロトーシス[12]マーカーの上昇も認められました。このことから、単一の経路ではなく、複雑なメカニズムを経て神経細胞死が誘発されると考えられます。

また、タウ病理と神経細胞死を再現する P301S-タウトランスジェニックマウス[13]（P301S-Tau-Tg）において、*CAPON* 遺伝子をノックアウト（欠損）すると、脳の萎縮が抑制されることが分かりました（図2）。

以上の結果から、CAPON はアミロイド病理下において、タウ病理、神経細胞死を誘導する重要な因子であると考えられます。

注 3）Masakazu Hashimoto *et al*, “Analysis of microdissected neurons by 18O mass spectrometry reveals altered protein expression in Alzheimer’s disease” *J. Cell. Mol. Med*. Vol 16, No 8, 2012 pp. 1686-1700

今後の期待

本研究において、CAPON が AD におけるタウ病理形成・神経細胞死の促進に重要な役割を果たすことが明らかになりました。今後、CAPON 機能を阻害する方法を開発できれば、AD の新しい治療法となると期待できます。

また今回、新たに発表した *MAPT* KI マウスは、ヒトの脳と同じ様式でタウタンパク質を発現することから、今後の AD 研究において有用なツールとなると期待できます。

原論文情報

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補足説明

1. **CAPON の機能を阻害するような薬剤（手法）**

   これまでに、shRNA やアンチセンスオリゴヌクレオチドにより遺伝子発現を抑制する治療、遺伝子を破壊する遺伝子治療、CAPON と nNOS などのタンパク質との相互作用（protein-protein interaction: PPI）を阻害する治療などが開発されている。

2. **アミロイドβペプチド（Aβ）**

   アミロイドβ前駆体タンパク質からプロテアーゼにより切断されて産生される生理的ペプチド。アルツハイマー病で見られるアミロイド斑（老人斑）の構成成分として発見されたことから、Aβの過剰な蓄積がアルツハイマー病発症の引き金と考えられている。

3. **タウタンパク質、神経原線維変化**

   タウタンパク質は、*MAPT* 遺伝子から発現する微小管結合タンパク質。アルツハイマー病においては、リン酸化されたタウタンパク質が、神経細胞内に蓄積して神経原線維変化を形成する。タウタンパク質の蓄積は、神経細胞死と深く関係していると考えられている。

4. インタラクトーム解析

特定のタンパク質と相互作用するタンパク質を、免疫沈降法などにより抽出し、質量分析によって網羅的に同定する解析方法。

5. ノックイン技法

遺伝子組換え法の一つで、標的遺伝子の目的とする塩基のみを置換する方法。トランスジェニックのように過剰発現を行わず、また、ノックアウトのように遺伝子を欠損させることもない。

6. *App*$^{NL\text{-}G\text{-}F}$ ノックインマウス

家族性アルツハイマー病変異を含むアミロイド前駆体タンパク質（*App*）遺伝子のノックインマウス。アミロイド病理を再現する。

7. nNOS

神経型一酸化窒素合成酵素。神経細胞において一酸化窒素（NO）を合成する酵素。NO の合成を介して、神経細胞の機能維持や神経細胞死を制御する。

8. NMDA 受容体

神経伝達物質グルタミン酸の受容体の一種。グルタミン酸が結合すると、ナトリウムイオン（Na^{+}）やカルシウムイオン（Ca^{2+}）を細胞外から取り込み、神経細胞を興奮させる。カルシウムイオン透過性の特徴により、神経細胞間の情報伝達の効率が変化するシナプス可塑性に関わるとされる。

9. 海馬

脳の中で、記憶をつかさどる領域。解剖学的には大脳新皮質の内側に位置し、タツノオトシゴに似た形をしていることから「海馬」（タツノオトシゴの別名）と呼ばれる。

10. アデノ随伴ウイルスベクター

動物個体への遺伝子導入に適したウイルスベクター。とくに神経細胞などの非分裂細胞において長期間安定な目的遺伝子発現を可能にする。

11. アポトーシス

プログラムされた細胞死を指し、生理的には個体の正常な発生に必要であり、またがん化した細胞などの除去の目的でも積極的に引き起こされる。

12. パイロトーシス

炎症誘導性のプログラム細胞死。カスパーゼ 1 を介した炎症性サイトカインの分泌によって細胞死を引き起こす。

13. トランスジェニックマウス

特定の遺伝子の機能や発現パターンを解析することを目的として、種々の遺伝子操作を行い、外来性遺伝子を導入したマウス。DNA 断片を受精卵にマイクロインジェクションで導入して作製する。

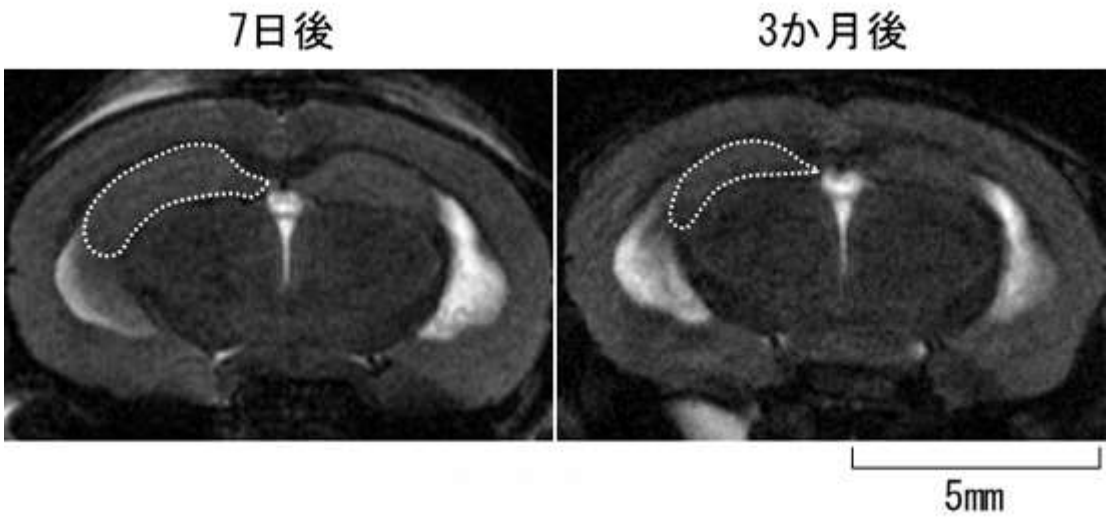

図 1 CAPON 過剰発現マウス脳の MRI 画像

App$^{NL\text{-}G\text{-}F}$ KI と *MAPT* KI のダブルノックインマウスに、アデノ随伴ウイルスを用いて *CAPON* 遺伝子を過剰発現させ、7 日後と 3 カ月後に MRI の撮像を行った。CAPON を過剰発現させて 3 カ月経つと、有意に海馬が萎縮していることが認められた。

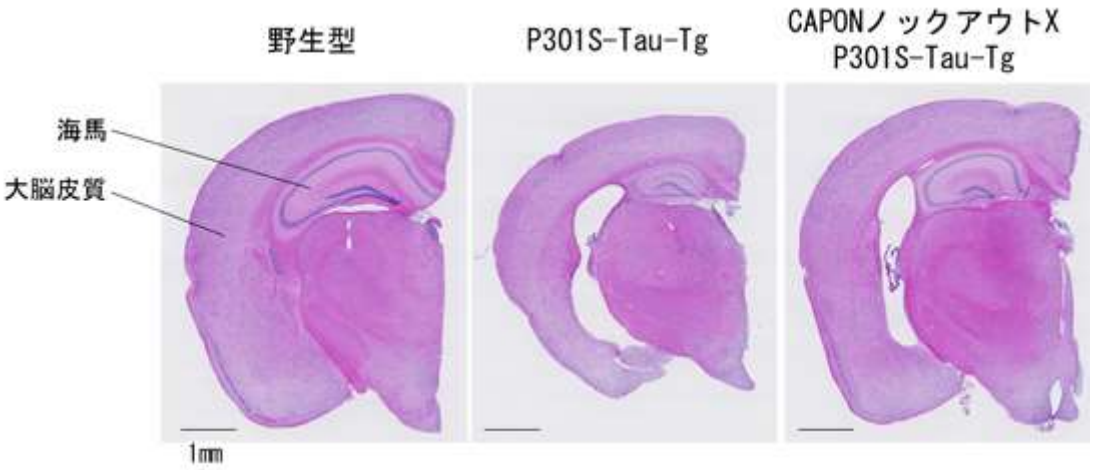

図 2 CAPON ノックアウト X P301S-Tau-Tg マウスの脳

右の画像は、*CAPON* ノックアウトマウスと P301S-Tau-Tg マウスを掛け合わせたマウスの脳切片（H&E 染色画像）。P301S-Tau-Tg マウス（中央の画像）で見られる脳の萎縮が、CAPON の欠損によって有意に抑制されていることが分かる。また右画像では、神経細胞死が起きて白く見える部分が減少し、かつ海馬や大脳皮質の大きさや厚みが中央画像ほど縮小していないことが分かる。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/06/190606133824.htm

Alzheimer's disease protein links plaques to cell death in mice

Date:

June 6, 2019

Source:

RIKEN

Summary:

A new protein involved in Alzheimer's disease (AD) has been identified by researchers. CAPON may facilitate the connection between the two most well-known AD culprits, amyloid plaques and tau pathology, whose interactions cause brain cell death and symptoms of dementia.

FULL STORY

Illustration of amyloid plaques on a nerve cell in Alzheimer's disease (stock image).

Credit: © Sebastian Kaulitzki / Adobe Stock

A new protein involved in Alzheimer's disease (AD) has been identified by researchers at the RIKEN Center for Brain Science (CBS). CAPON may facilitate the connection between the two most well-known AD culprits, amyloid plaques and tau pathology, whose interactions cause brain cell death and symptoms of dementia. This latest finding from the Takaomi Saido group at RIKEN CBS uses a novel mouse model of AD. The study was published in *Nature Communications* on June 3.

Alzheimer's disease is a complex and devastating condition characterized by plaques of amyloid-β and neurofibrillary tangles, also known as tau pathology, in the brain. Investigating the connection between these features, the research team identified CAPON, a protein that binds to tau. The CAPON gene is a known risk for other psychiatric disorders, and because AD can be accompanied by psychiatric symptoms, the team guessed that CAPON could form a link between these conditions. Indeed, when they examined one type of AD mouse, they found accumulation of CAPON in the hippocampus, an important memory center in the brain. Furthermore, CAPON accumulation was even greater in the presence of amyloid-β pathology.

After creating another type of AD mouse model using a novel App/MAPT double knock-in process, the team inserted CAPON DNA into the brain, which resulted in CAPON overexpression. These mice exhibited significant neurodegeneration, elevated tau, and hippocampal shrinkage. "The implication is that accumulating CAPON increases AD-related pathology," says lead author Shoko Hashimoto of RIKEN CBS. "Although cell death resulting from CAPON can occur through many different pathways, we definitely think this protein is a facilitator between neuroinflammation and tau pathology." This is the first study to use App/MAPT double knock-in mice, which are engineered to have human-like MAPT and App genes containing pathogenic mutations.

If CAPON accumulation exacerbates AD pathology, the team reasoned that CAPON deficiency could have the opposite effect. For this test, the team knocked out CAPON in another type of AD model mouse that typically has increased tau pathology. They found that CAPON deficiency led to less tau,

less amyloid-β, less neurodegeneration, and less brain atrophy. Thus, reducing CAPON levels in AD mice effectively reduced many of the physiological AD symptoms.

"Neurodegeneration is complex but we think CAPON is an important mediator between amyloid-β, tau, and cell death. Breaking this link with drugs is a promising avenue for treating AD," says Saido. "The App/MAPT double knock-in mice developed by our lab are an improved tool for the entire Alzheimer's research field."

Story Source:

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

Journal Reference:

1. Shoko Hashimoto, Yukio Matsuba, Naoko Kamano, Naomi Mihira, Naruhiko Sahara, Jiro Takano, Shin-ichi Muramatsu, Takaomi C. Saido, Takashi Saito. **Tau binding protein CAPON induces tau aggregation and neurodegeneration**. *Nature Communications*, 2019; 10 (1) DOI: 10.1038/s41467-019-10278-x

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Cite This Page:

- MLA
- APA
- Chicago

RIKEN. "Alzheimer's disease protein links plaques to cell death in mice." ScienceDaily. ScienceDaily, 6 June 2019. <www.sciencedaily.com/releases/2019/06/190606133824.htm>.

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5. EvaluatePharma ワールドプレビュー2018 年、2024 年までの展望

EvaluatePharma が発表した『ワールドプレビュー2018 年、2024 年までの展望』によると、世界の処方薬の売上は 2024 年までに 1 兆 2,000 億ドルまでに加速して跳ね上がる。また、研究開発費は、2024 年の処方薬販売の 16.9%と予想されている。オンコロジーが引き続き業界の主要な原動力であり、2017 年から 2024 年までの予測 CAGR は 12%。
Novartis は、2024 年には、大手処方薬会社となり、その売上高は 532 億ドルになる。長い間売上世界一の処方薬、AbbVie の Humira (adalimumab) は、主に米国外でのバイオシミラーの台頭により今後 7 年間で CAGR は-3%となるにもかかわらず、引き続き売れ行き世界一の座を守る、としている。
2024 年の全世界売上順位予想は以下の通り:

1 位	Humira (adalimumab)	AbbVie + Eisai	-3%
2 位	Keytruda (pembrolizumab)	Merck & Co + Otsuka Holdings	+19%
3 位	Revlimid (lenalidomide)	Celgene + BeiGene	+6%
4 位	Opdivo (nivolumab)	Bristol-Myers Squibb	+10%
5 位	Eliquis (apixaban)	Bristol-Myers Squibb	+12%
6 位	Imbruvica (ibrutinib)	AbbVie + Johnson & Johnson	+17%
7 位	Ibrance (palbociclib)	Pfizer	+15%
8 位	Dupixent (dupilumab)	Sanofi	+64%
9 位	Eylea (aflibercept)	Regeneron + Bayer + Santen	+1%
10 位	Stelara (ustekinumab)	Johnson & Johnson	+7%

研究関連ニュース/他のトップページに戻る

＜英文＞https://info.evaluategroup.com/WP2018-CS.html

全47ページのレポートはこちら:
https://www.evaluate.com/sites/default/files/media/download-files/WP2018.pdf

EvaluatePharma World Preview 2018, Outlook to 2024

Worldwide prescription drug sales accelerate to $1.2 trillion by 2024

Unmet need in the pharmaceutical industry is forecast to drive annual compound growth to over 6%. Take advantage of forward-looking insights that help you maximise the opportunities for growth at your organisation.

Our report also shows that the threat of biosimilars or genericisation for some of the industry's biggest products could act as a brake on industry growth. $251bn of sales are at risk between 2018 and 2024, teeing up a second patent cliff for the industry.

KEY HIGHLIGHTS

- Prescription drug sales expected to reach $1.2trn in 2024 (+6.4% CAGR 2018-2024)
- R&D spend is forecast at 16.9% of prescription sales in 2024
- Oncology continues to be a key industry driver, with a forecasted CAGR of 12% from 2017 to 2024
- Novartis will be the leading prescription drug company in 2024 with sales of $53.2bn
- Humira remains the top selling drug in 2024, despite a CAGR of -3% over the next 7 years

6. パーキンソン病を発症前にくい止める

パーキンソン病（PD）は、世界中で何百万人もが罹患している進行性の神経変性疾患で、タンパク質αシヌクレインの蓄積を特徴とするが、今現在 PD の治療法は存在していない。
今回、大阪大学主導の研究チームは、世界中の PD 患者に希望の光を与える調査結果を *Scientific Reports* 誌に発表した。PD の正確な原因はまだ謎であるが、研究者らは遺伝学と環境の両方が関係している可能性が高いと考えている。研究者らは、新規 PD 治療の標的としてαシヌクレインに焦点を当て、このαシヌクレインの発現を防ぎ、PD の生理学的原因を効果的に排除する方法を調べた。
彼らはαシヌクレイン遺伝子産物の一部の鏡像である DNA の短い断片を設計し、アミノ架橋を加えることによってその設計物を安定化させた。得られたアミド架橋核酸修飾アンチセンスオリゴヌクレオチド（ASO）と呼ばれるフラグメントを、それらと適合する mRNA 配列に結合し、それがタンパク質に変換されるのを防いだ。50 の異なる ASO をスクリーニングして、αシヌクレイン mRNA レベルを 81%現象させる 15 ヌクレオチド配列を決定した。
PD マウスモデルでこの ASO をテストしたところ、ASO がマウスのαシヌクレイン産生を効果的に減少させ、投与後 27 日以内に疾患の症状の重症度を有意に減少させることが示された。この方法は、PD を治療するだけでなく、αシヌクレインの蓄積によって引き起こされる認知症も治療する、としている。

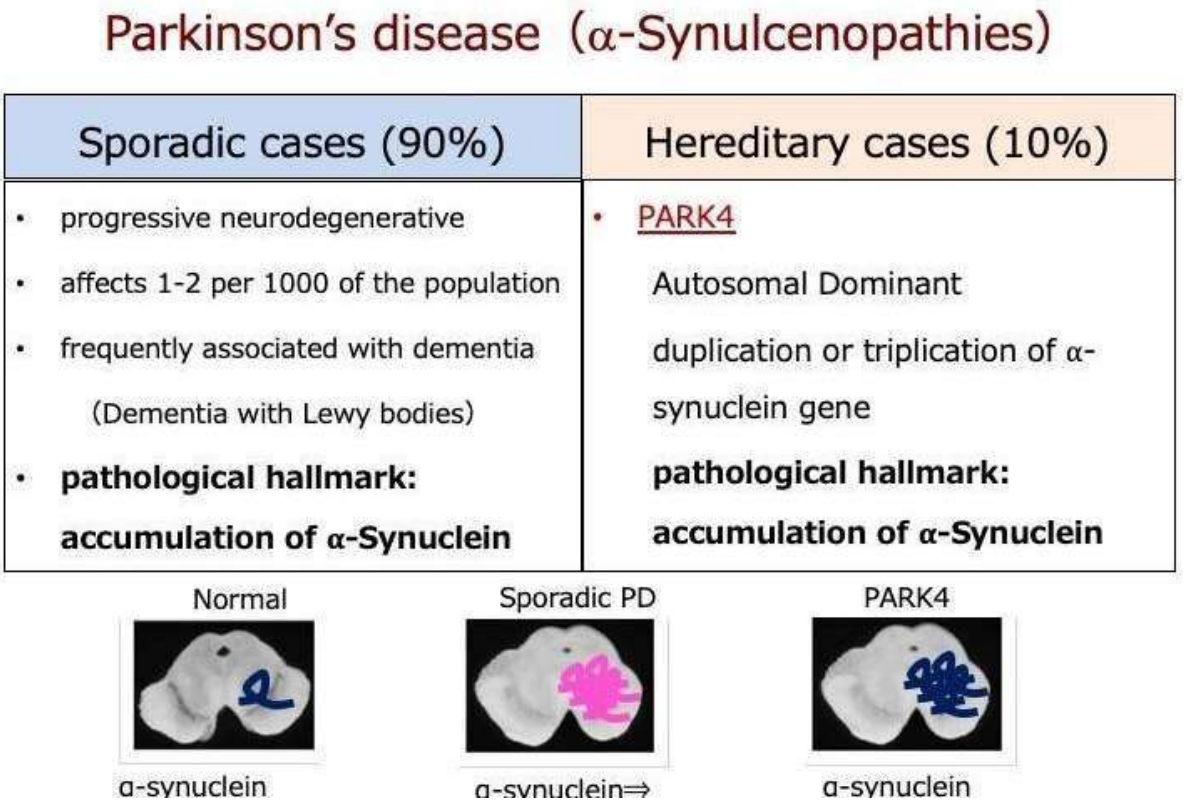
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-06-parkinson-disease.html

JUNE 5, 2019

Stopping Parkinson's disease before it starts

by Osaka University



Genetics and pathology of Parkinson's disease (PD). 90 % cases of PD are sporadic, whereas 10 % cases are hereditary. α-synuclein (SNCA) protein is shown to be a major component of Lewy body, a pathological hallmark of both sporadic and familial form of PD, suggesting that dysfunction or toxicity caused by SNCA protein results in the pathology of PD. Importantly, duplication and triplication of SNCA gene cause dominant form of PD, PARK4. Hence, decreasing levels of SNCA expression is thought to be an attractive treatment for suppressing progression of PD. Credit: Osaka University

An Osaka University-led research team has recently published findings that provide a ray of hope for the millions of Parkinson's disease (PD) sufferers worldwide. Although more common in those aged over sixty, PD can strike at any age, with an estimated prevalence of 41 per 100,000 people in their forties. And while not fatal in and of itself, the progressive neurodegeneration that is characteristic of PD can often cause secondary effects that lead to death.

The exact cause of PD is still a mystery, but researchers believe that both genetics and the environment are likely to play a part. Importantly though, all PD patients show a loss of dopaminergic neurons in the brain and increased levels of a protein called α-synuclein, which accumulates in Lewy bodies. Lewy bodies are a pathological feature of both familial and sporadic forms of the disease, as well as some types of dementia.

In the study published this month in *Scientific Reports*, the team led by researchers from Osaka University's Graduate School of Medicine focused on α-synuclein as a target for a novel PD treatment.

"Although there are drugs that treat the symptoms associated with PD, there is no fundamental treatment to control the onset and progression of the disease," explains lead author Takuya Uehara. "Therefore, we looked at ways to prevent the expression of α-synuclein and effectively eliminate the physiological cause of PD."

To do this, the researchers designed short fragments of DNA that are mirror images of sections of the α-synuclein gene product. The constructs were stabilized by the addition of amido-bridging. The resulting fragments, called amido-bridged nucleic acid-modified antisense oligonucleotides (ASOs), bind to their matching mRNA sequence, preventing it from being translated into protein. After screening 50 different ASOs, the researchers settled on a 15-nucleotide sequence that decreased α-synuclein mRNA levels by 81%.

"When we tested the ASO in a mouse model of PD, we found that it was delivered to the brain without the need for chemical carriers," says co-lead author Chi-Jing Choong. "Further testing showed that the ASO effectively decreased α-synuclein production in the mice and significantly reduced the severity of disease symptoms within 27 days of administration."

Explains senior author of the study Hideki Mochizuki, "Our results showed that gene therapy using α-synuclein-targeting ASOs is a promising strategy for the control and prevention of PD. We expect that in the future, this method will be used to not only successfully treat PD, but also dementia caused by α-synuclein accumulation."

Explore further

Novel device opens new doors for Parkinson's disease diagnostics

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More information: Takuya Uehara et al. Amido-bridged nucleic acid (AmNA)-modified antisense oligonucleotides targeting α-synuclein as a novel therapy for Parkinson's disease, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-43772-9

Journal information: Scientific Reports

Provided by Osaka University

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7. 不健康な腸が乳癌の拡大を促進

バージニア大学（UVA）医学部およびUVA癌センターのMelanie Rutkowski博士らは、不健康なマイクロバイオームがホルモン受容体陽性乳癌の拡大を促進することを発見し、その調査結果を*Cancer Research*誌に発表した。この研究には、強力な抗生物質で天然腸内細菌を破壊されたマウスが使用された。
研究者らが抗生物質を慢性的に与えてマウスのマイクロバイオームの平衡を崩した時、全身にまた乳房組織内に炎症が生じた。この炎症環境では、腫瘍細胞は組織から血液中および肺へと広がることがより可能になる。そしてこれがホルモン受容体陽性乳癌の転移する主要部位である。65%以上の乳癌はこのホルモン受容体陽性であり、これはその成長がホルモン、エストロゲンかプロゲステロンのどちらか、によって促進されることを意味する。結局マウスはヒトではないので、慢性的な抗生物質の使用と癌の転移との間の関連性については、もっと多くの研究を行う必要があるが、健康な微生物叢が健康の多くの側面に不可欠であることを示す証拠が増えている、としている。

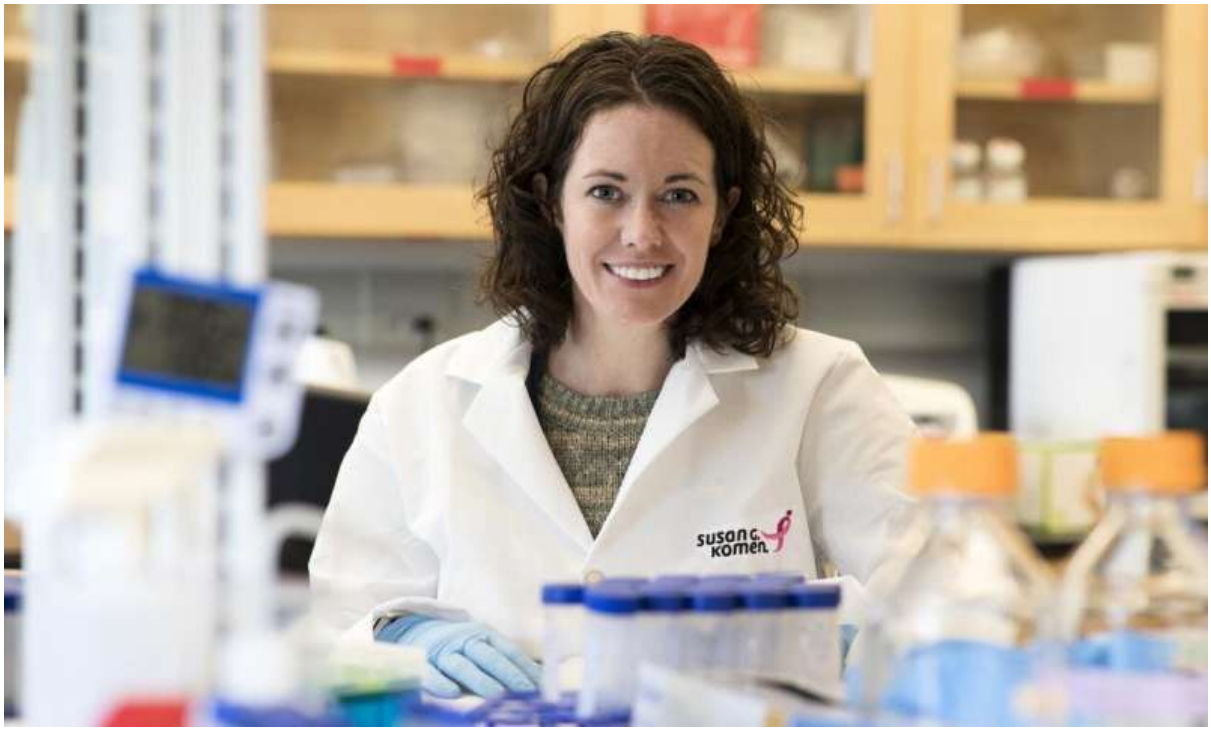
研究関連ニュース/他のトップページに戻る

＜英文＞https://medicalxpress.com/news/2019-06-unhealthy-gut-breast-cancer.html

June 10, 2019

Unhealthy gut promotes spread of breast cancer, study finds

by Joshua Barney, University of Virginia



Melanie Rutkowski, PhD, of the UVA School of Medicine and the UVA Cancer Center, has found that an unhealthy microbiome promotes the spread of hormone receptor-positive breast cancer. Credit: Dan Addison/UVA

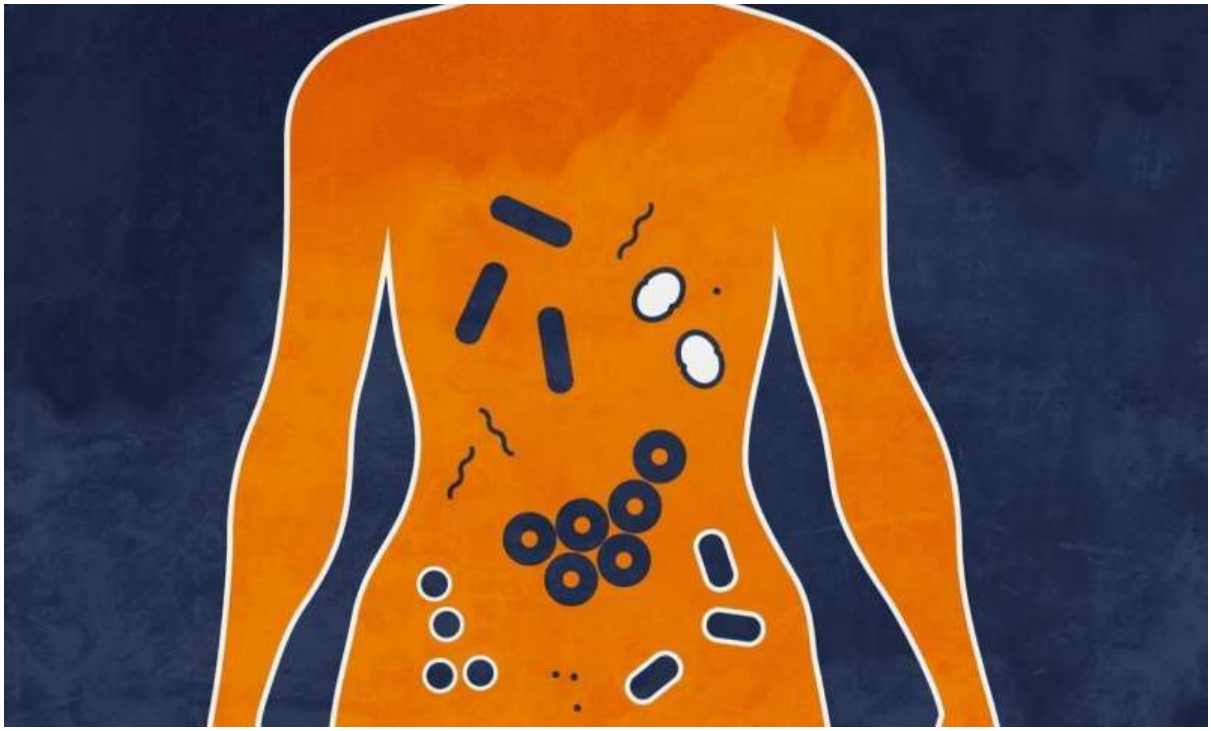
An unhealthy, inflamed gut causes breast cancer to become much more invasive and spread more quickly to other parts of the body, new research from the University of Virginia Cancer Center suggests.

Melanie Rutkowski, Ph.D., of UVA's Department of Microbiology, Immunology and Cancer Biology, found that disrupting the microbiome of mice caused hormone receptor-positive breast cancer to become more aggressive. Altering the microbiome, the collection of microorganisms that live in the gut and elsewhere, had dramatic effects in the body, priming the cancer to spread.

"When we disrupted the microbiome's equilibrium in mice by chronically treating them antibiotics, it resulted in inflammation systemically and within the mammary tissue," she said. "In this inflamed environment, tumor cells were much more able to disseminate from the tissue into the blood and to the lungs, which is a major site for hormone receptor-positive breast cancer to metastasize."

Hormone Receptor-Positive Breast Cancer

Most breast cancers—65 percent or more—are hormone receptor positive. That means their growth is fueled by a hormone, either estrogen or progesterone. The good news is that these types of cancers are likely to respond well to hormone therapy.



The microbiome is the collection of microorganisms that live in and on us. New research from the University of Virginia School of Medicine suggests an unhealthy microbiome can promote the spread of breast cancer. Credit: Alexandra Angelich/UVA

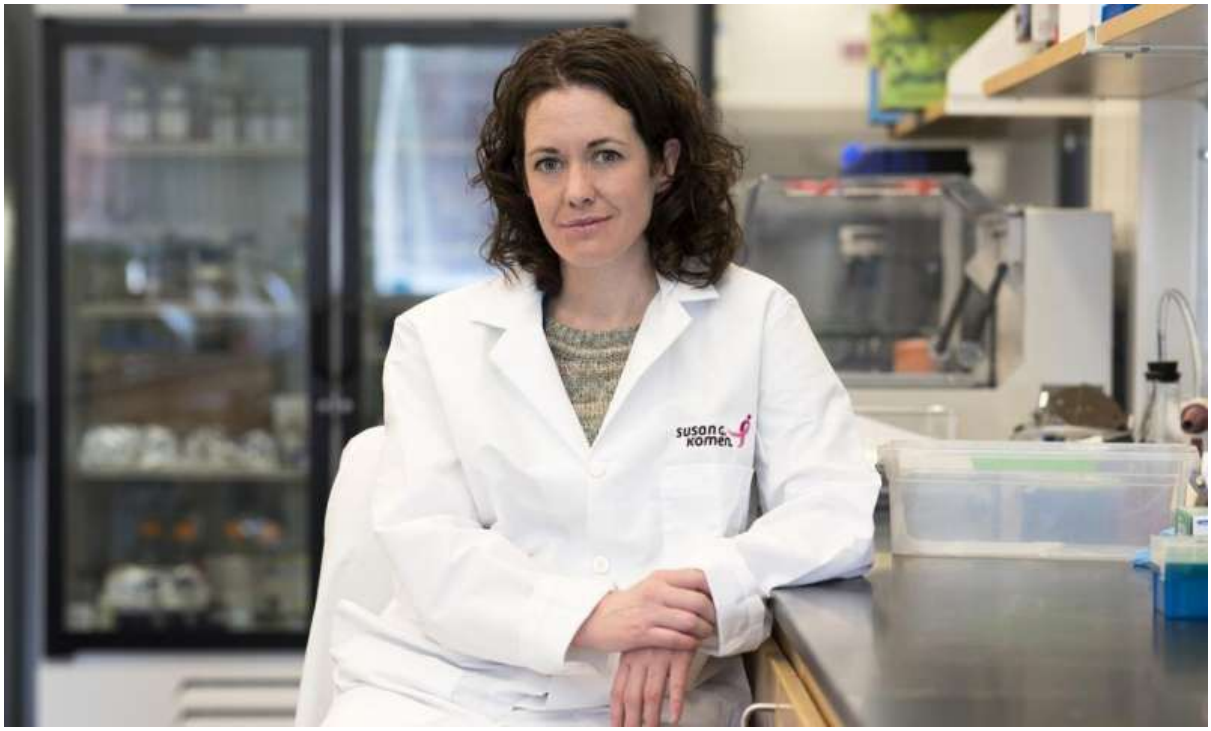
Predicting whether such cancers will spread beyond the breast to other parts of the body (a process called metastasis) is a major challenge within the field, and is primarily driven by clinical characteristics at the time of diagnosis. Early metastasis is affected by a variety of factors, Rutkowski explained. "One of them is having a high level of [immune] cells called macrophages present within the tissue," she said. "There have also been studies that have demonstrated that increased amounts of the structural protein collagen in the tissue and tumor also lead to increased breast cancer metastasis."

Having an unhealthy microbiome prior to breast cancer increased both, and the effect was powerful and sustained. "Disrupting the microbiome resulted in long-term inflammation within the tissue and the tumor environment," Rutkowski said. "These findings suggest that having an unhealthy microbiome, and the changes that occur within the tissue that are related to an unhealthy microbiome, may be early predictors of invasive or metastatic breast cancer. Ultimately, based upon these findings, we would speculate that an unhealthy microbiome contributes to increased invasion and a higher incidence of metastatic disease."

Maintaining a Healthy Microbiome

While Rutkowski used powerful antibiotics to disrupt the mice's natural gut bacteria, she emphasized that antibiotics are not dangerous and should not be avoided by women with breast cancer or anyone who needs them to treat infections. Mice, after all, are not people, and substantially more research needs to be done to define whether an

association exists between chronic antibiotics usage and cancer outcome. For this study, the antibiotics were only a means to an end, a simple way to create a long-term imbalance to the microbiome, similar to what individuals may experience with chronically unhealthy microbiomes. The effect was far, far more exaggerated than would occur in a person taking a normal course of antibiotics, or even multiple rounds.



Melanie Rutkowski, PhD, of the UVA School of Medicine and the UVA Cancer Center, has found that an unhealthy microbiome promotes the spread of hormone receptor-positive breast cancer. Credit: Dan Addison/UVA Health System

Thanks in part to Rutkowski's research, doctors eventually may be able to manipulate the microbiome to benefit patients with breast cancer. But the key message for now, Rutkowski said, is the importance of a healthy microbiome. The finding adds to the growing evidence demonstrating that a healthy microbiome is vital for many aspects of good health.

While she is a cancer researcher rather than a medical doctor, Rutkowski noted there are things that are generally accepted to promote a healthy microbiome. "A healthy diet, high in fiber, along with exercise, sleep—all of those things that contribute to positive overall health," she said. "If you do all of those things, in theory, you should have a healthy microbiome. And that, we think, is very much associated with a favorable outcome in the long term for breast cancer."

The researchers have published their findings in the journal *Cancer Research*.

8. ゲノム編集技術で、新しい自閉症モデル開発

MIT および中国の研究者らは、ゲノム編集システム CRISPR を使用して、ヒトの自閉症およびその他の神経発達障害に関連する遺伝子突然変異を発現するマカクザルを設計した。これらのサルは、ヒトで見られるのと同様の行動特性と脳の接続パターンを示す。
自閉症およびその他の神経発達障害のマウス研究は、臨床試験でテストされた薬物候補を生み出したが、実際それらのどれも成功してはいない。そういう結果をふまえて、多くの製薬会社がそのような薬のテストを諦めつつあるのが現実だ。
研究者らは Shank3 として知られる 1 つの遺伝子に注目した。自閉症との関連性に加えて、Shank3 の突然変異または欠失は、最も一般的な特徴として知的障害、言語障害および睡眠障害、ならびに反復行動を含む、フェラン – マクダーミド症候群と呼ばれる関連するまれな障害を引き起こす可能性がある。症状の多くが重なるので、これらは全て自閉症スペクトラム障害とされている。
彼らは以前に Shank3 突然変異を持つマウスを研究し、それらが社会的相互作用の回避や強迫観念、反復行動を含む自閉症に関連したいくつかの形質を示すことを発見した。マウスの研究は疾患の分子的基盤について多くの情報を提供することができるが、神経発達障害を研究するためにそれらを使用することには欠点がある。というのも、マウスには、意思決定、集中的な注意の持続、社会的合図の解釈など、脳障害の影響を受けることが多い、霊長類独特の多くの特徴である高度に発達した前頭前野が欠けているからだ。
米国に比べて霊長類の生殖技術がはるかに進んでいる中国に拠点を置く研究チームのメンバーは、Shank3 変異を持つ胚を生み出す受精マカク卵に CRISPR コンポーネントを注入。研究者らは、この Shank3 突然変異を持つマカクザルが、突然変異した遺伝子を持つ人間に見られるのと類似した行動パターンを示した、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/06/190612141431.htm

Using gene editing, neuroscientists develop a new model for autism

Date:

June 12, 2019

Source:

Massachusetts Institute of Technology

Summary:

By introducing a gene variant associated with autism into monkeys, researchers hope to study treatment options for severe neurodevelopmental disorders.

FULL STORY

Using the genome-editing system CRISPR, researchers at MIT and in China have engineered macaque monkeys to express a gene mutation linked to autism and other neurodevelopmental disorders in humans. These monkeys show some behavioral traits and brain connectivity patterns similar to those seen in humans with these conditions.

Mouse studies of autism and other neurodevelopmental disorders have yielded drug candidates that have been tested in clinical trials, but none of them have succeeded. Many pharmaceutical companies have given up on testing such drugs because of the poor track record so far.

The new type of model, however, could help scientists to develop better treatment options for some neurodevelopmental disorders, says Guoping Feng, who is the James W. and Patricia Poitras Professor of Neuroscience, a member of MIT's McGovern Institute for Brain Research, and one of the senior authors of the study.

"Our goal is to generate a model to help us better understand the neural biological mechanism of autism, and ultimately to discover treatment options that will be much more translatable to humans," says Feng, who is also an institute member of the Broad Institute of MIT and Harvard and a senior scientist in the Broad's Stanley Center for Psychiatric Research.

"We urgently need new treatment options for autism spectrum disorder, and treatments developed in mice have so far been disappointing. While the mouse research remains very important, we believe that primate genetic models will help us to develop better medicines and possibly even gene therapies for some severe forms of autism," says Robert Desimone, the director of MIT's McGovern Institute for Brain Research, the Doris and Don Berkey Professor of Neuroscience, and an author of the paper.

Huihui Zhou of the Shenzhen Institutes of Advanced Technology, Andy Peng Xiang of Sun Yat-Sen University, and Shihua Yang of South China Agricultural University are also senior authors of the study, which appears in the June 12 online edition of *Nature*. The paper's lead authors are former MIT postdoc Yang Zhou, MIT research scientist Jitendra Sharma, Broad Institute group leader Rogier Landman, and Qiong Ke of Sun Yat-Sen University. The research team also includes Mriganka Sur, the Paul and Lilah E. Newton Professor in the Department of Brain and Cognitive Sciences and a member of MIT's Picower Institute for Learning and Memory.

Gene variants

Scientists have identified hundreds of genetic variants associated with autism spectrum disorder, many of which individually confer only a small degree of risk. In this study, the researchers focused on one gene with a strong association, known as Shank3. In addition to its link with autism, mutations or deletions of Shank3 can also cause a related rare disorder called Phelan-McDermid Syndrome, whose most common characteristics include intellectual disability, impaired speech and sleep, and repetitive behaviors. The majority of these individuals are also diagnosed with autism spectrum disorder, as many of the symptoms overlap.

The protein encoded by Shank3 is found in synapses -- the junctions between brain cells that allow them to communicate with each other. It is particularly active in a part of the brain called the striatum, which is involved in motor planning, motivation, and habitual behavior. Feng and his colleagues have previously studied mice with Shank3 mutations and found that they show some of

the traits associated with autism, including avoidance of social interaction and obsessive, repetitive behavior.

Although mouse studies can provide a great deal of information on the molecular underpinnings of disease, there are drawbacks to using them to study neurodevelopmental disorders, Feng says. In particular, mice lack the highly developed prefrontal cortex that is the seat of many uniquely primate traits, such as making decisions, sustaining focused attention, and interpreting social cues, which are often affected by brain disorders.

The recent development of the CRISPR genome-editing technique offered a way to engineer gene variants into macaque monkeys, which has previously been very difficult to do. CRISPR consists of a DNA-cutting enzyme called Cas9 and a short RNA sequence that guides the enzyme to a specific area of the genome. It can be used to disrupt genes or to introduce new genetic sequences at a particular location.

Members of the research team based in China, where primate reproductive technology is much more advanced than in the United States, injected the CRISPR components into fertilized macaque eggs, producing embryos that carried the Shank3 mutation.

Researchers at MIT, where much of the data was analyzed, found that the macaques with Shank3 mutations showed behavioral patterns similar to those seen in humans with the mutated gene. They tended to wake up frequently during the night, and they showed repetitive behaviors. They also engaged in fewer social interactions than other macaques.

Magnetic resonance imaging (MRI) scans also revealed similar patterns to humans with autism spectrum disorder. Neurons showed reduced functional connectivity in the striatum as well as the thalamus, which relays sensory and motor signals and is also involved in sleep regulation. Meanwhile, connectivity was strengthened in other regions, including the sensory cortex.

Drug development

Within the next year, the researchers hope to begin testing treatments that may affect autism-related symptoms. They also hope to identify biomarkers, such as the distinctive functional brain connectivity patterns seen in MRI scans, that would help them to evaluate whether drug treatments are having an effect.

A similar approach could also be useful for studying other types of neurological disorders caused by well-characterized genetic mutations, such as Rett Syndrome and Fragile X Syndrome. Fragile X is the most common inherited form of intellectual disability in the world, affecting about 1 in 4,000 males and 1 in 8,000 females. Rett Syndrome, which is more rare and almost exclusively affects girls, produces severe impairments in language and motor skills and can also cause seizures and breathing problems.

"Given the limitations of mouse models, patients really need this kind of advance to bring them hope," Feng says. "We don't know whether this will succeed in developing treatments, but we will see in the next few years how this can help us to translate some of the findings from the lab to the clinic."

The research was funded, in part, by the Shenzhen Overseas Innovation Team Project, the Guangdong Innovative and Entrepreneurial Research Team Program, the National Key R&D Program of China, the External Cooperation Program of the Chinese Academy of Sciences, the Patrick J. McGovern Foundation, the National Natural Science Foundation of China, the Shenzhen Science, Technology Commission, the James and Patricia Poitras Center for Psychiatric Disorders Research at the McGovern Institute at MIT, the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, and the Hock E. Tan and K. Lisa Yang Center for Autism Research at the McGovern Institute at MIT. The research facilities in China where the primate work was conducted are accredited by AAALAC International, a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.

Story Source:

Materials provided by **Massachusetts Institute of Technology**. Original written by Anne Trafton.
Note: Content may be edited for style and length.

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9. ビスフェノール（BPA）曝露が世代を超えて自閉症関連遺伝子に影響 – マウス研究

内分泌学会のジャーナル内分泌学（*Endocrinology* 誌）に掲載されたマウス研究によると、ビスフェノール（BPA）曝露は世代を超えて自閉症の一因となる可能性がある。
内分泌攪乱化学物質（EDC）は、身体のホルモンの働きを妨げる化学物質または化学物質の混合物である。BPA は、プラスチックや食品貯蔵材料に使用される一般的な EDC であり、それらは既にほとんどのヒトの尿や血液に含まれている。動物実験では、BPA は不安、攻撃性、貧弱な学習および社会的相互作用と結び付けられてきた。ヒトにおいては、注意欠陥多動性障害や自閉症のような神経行動問題との関連が報告されている。
今回、バージニア大学医学部（Charlottesville, VA）およびノースキャロライナ州立大学（Raleigh, N.C.）などの研究者らは、「マウスの胎児を BPA に晒すと脳内の神経細胞結合の形成が乱され、世代を超えた影響を受ける」とし、このマウス研究において、研究者らは、BPA に暴露されたマウスの子孫であるマウスを試験し、それらが自閉症行動のような社会的欠陥を示すことを発見した。

研究関連ニュース/他のトップページに戻る

＜英文＞https://www.sciencedaily.com/releases/2019/06/190612092937.htm

Mouse study finds BPA exposure has transgenerational effects on gene linked to autism

Social recognition test used for first time in mice shows behavioral deficit

Date:

June 12, 2019

Source:

The Endocrine Society

Summary:

Transgenerational bisphenol A (BPA) exposure may contribute to autism, according to a mouse study.

FULL STORY

BPA chemical structure (stock image).

Credit: © Zerbor / Adobe Stock

Transgenerational bisphenol A (BPA) exposure may contribute to autism, according to a mouse study published in the Endocrine Society's journal *Endocrinology*.

Endocrine disrupting chemicals (EDCs) are chemicals or mixtures of chemicals that interfere with the way the body's hormones work. BPA is a common EDC used in plastics and food storage material, and it is already present in most humans' urine or blood. Animal studies have linked BPA to anxiety, aggression, and poor learning and social interactions. Studies of human populations report associations between BPA and neurobehavioral issues like attention deficit hyperactivity disorder and autism.

"Exposure of mouse fetuses to BPA disrupts formation of nerve cell connections in the brain, and this is a transgenerational effect," said the study's senior author, Emilie F. Rissman, Ph.D., of University of Virginia School of Medicine in Charlottesville, Va. and North Carolina State University in Raleigh, N.C. "To put this in human terms, if your great grandmother was exposed to BPA during her pregnancy and none of your other relatives ever came into contact with BPA, your brain would still show these effects."

In this mouse study, researchers tested mice descended from those exposed to BPA for social recognition and found that they showed a social behavioral deficient like autistic behavior. Mice whose great grandmothers were exposed to BPA during pregnancy were more active and took longer to habituate to strangers than other mice. More strikingly, they didn't explore the new mice that were introduced to the group. Mice are very social and curious, so this is an exciting finding.

"Even if we ban all BPA right now, that will not change these long-term effects on the brain," Rissman said.

Other authors of the study include: Jennifer T. Wolstenholme of the University of Virginia School of Medicine in Charlottesville, Va., and Virginia Commonwealth University in Richmond, Va.; Zuzana

Drobná and Joshua W. Irvin of North Carolina State University; Anne D. Henriksen of James Madison University in Harrisonburg, Va.; Jessica A. Goldsby of the University of Virginia School of Medicine; Rachel Stevenson of Virginia Commonwealth University; and Jodi A. Flaws of the University of Illinois in Urbana, Ill.

The study received funding support from the National Institutes of Health and the Environmental Protection Agency.

Story Source:

Materials provided by **The Endocrine Society**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Jennifer T Wolstenholme, Zuzana Drobná, Anne D Henriksen, Jessica A Goldsby, Rachel Stevenson, Joshua W Irvin, Jodi A Flaws, Emilie F Rissman. **Transgenerational Bisphenol A causes deficits in social recognition and alters post-synaptic density genes in mice**. *Endocrinology*, 2019; DOI: 10.1210/en.2019-00196

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