致远人刊

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How to get published in high-impact journals: Big research and better writing

http://blogs.nature.com/naturejobs/2014/11/03/how-to-get-published-in-high-impact-journals-big-research-and-better-writing Posted by Julie Gould

Getting your research into an influential journal is certain to give a healthy boost to both academic standing and future career prospects (scientific or otherwise). Accordingly, it is a competitive business: many articles are put forward but few accepted. In fact, of the almost 11,000 articles submitted to Nature last year only 856 (7.8%) were published. What does it take?

“Data should be at the heart of everything you do,” says Peter Gorsuch, an editor at Macmillan Publishers Ltd., Nature’s parent company. Indeed, without excellent data, it is virtually impossible to publish in high-impact journals — if at all. Still, even with high-quality data, you can jeopardise your chances of publication if you don’t have a high-quality paper.

At the Naturejobs Expo on 19 September in London, Macmillan publishers hosted two workshops on how to publish in high impact journals. Gorsuch was joined by Sadaf Shadan, an editor at Nature and they offered insights on the dos and don’ts of scientific publishing. The second workshop was run by Nicky Dean, a senior editor and team manager at Nature Communications. He gave some insights into what makes research worthy of a high impact journal.

Here are some of their combined tips.

Imagine your research as telling a story.

Start by asking a big question, and form a logical argument. “High-impact papers need strong evidence and noteworthy conclusions,” says Shadan. Look to fill as many gaps in your story as possible; great research builds up a whole picture of a system. A paper should tell a “clear, compelling story” and be written with a chosen scientific publication in mind, says Dean. For example, is your research better suited to the Journal of Virology or Infectious Diseases?

Know your audience.

Nobody is obliged to read anything you write, and if you do not pitch your paper appropriately, you can reduce its potential impact.

The readership for a scientific paper is specialised, but you should never assume too much knowledge on readers’ parts. This is particularly important in high-impact journals, as one of the acceptance criteria is research with broad relevance. So, while your readers will likely be scientists, they will not all be experts in your field.

Be short, clean and clear.

Don’t underestimate the importance of a good title and abstract, says Dean. These short blocks of text — often the final consideration when constructing a paper — will receive far more views than the paper itself. They should be used as a hook, to pull readers (and editors) in. This means not using superfluous, specialised jargon, especially in the headline and abstract. For example, ‘Sylvilagus nuttallii: a semi-arboreal lagomorph’ could be better put as ‘Tree climbing behaviour in Mountain Cottontail; Sylvilagus nuttallii’, says Shadan.

After the headline, the abstract is the second most important section. It should briefly introduce the topic, state the problem that the paper is trying to address, summarise the main findings and then give a perspective on possible benefits and utilities of these findings. Demonstrate the wider context of your research by asking questions like “What are the conclusions of your paper really telling us, and who does that impact on? How relevant is that beyond your immediate community?”

Pay attention to the structure and language of the papers you read. Papers from fields other than yours that you enjoy and find accessible should provide good inspiration for your own.

Editing services can assist you with style and other issues. But do not undersell your research. “If you find something big, tell us!” says Shadan.

Make good use of figures.

Figures must visually represent your findings: they must be in a logical order and correspond to your story. In the age of ‘big data’, figures can become overwhelming, but you can cut them to size. “Consider using the subset of your data that best describes your point,” says Gorsuch, although you must inform readers of any such manipulation.

One of the most fundamental principles of scientific research is the ability to build upon and find inspiration in the ideas of your peers. Says Gorsuch, “The most important thing in scientific publishing is to reach the people who need to know about your research. Publishing in top journals is one of the best ways of achieving that.”

Samuel Brod caught up with Dean at the end of the workshop and asked him if he thought researchers were aware of the importance of good writing and communication skills when submitting to his journal. The reply was frank.

“You can tell a lot of them don’t,” he said. “There are scientists who get it, though. They know how to put all it together and their papers do well. People say ‘Oh you always publish papers by so and so’. Well — they write really good papers, they’re well thought out and carefully constructed… They bring out what’s important, and that increases the interest and the impact of the paper.”

As an immunology graduate student, Brod knows it’s easy, after months or years of grueling research, to approach the writing of a paper with a ‘Look at what I’ve done’ mindset — when if you truly want to maximise the value of your research, it seems that you should instead focus on saying — ‘Look why this matters’

虽然我们刊登的这篇文章题目是“How to get published in high-impact journals”，我们还是希望提醒大家注意，impact factor 并不能完全反映文章的好坏，我们追求的还是 good research 哟~

数学快递

New theorem determines age distribution of populations from fruit flies to humans

Date: October 6, 2014

Source: Medical College of Georgia at Georgia Regents University

The initial motivation was to estimate the age structure of a fruit fly population, the result a fundamental theorem that can help determine the age distribution of essentially any group.

This emerging theorem on stationary populations shows that you can determine the age distribution of a population by looking at how long they still have to live.

The mathematical discovery can help produce data with a wide range of implications, from predicting rates of infectious diseases, such as West Nile virus spread by mosquitoes, to anticipating the health care needs of an aging population.

"The idea is you can't look at an insect and say: How much longer are you going to live?" said Dr. James R. Carey, entomologist at the University of California, Davis. "If you understand the age structure of the population, you can better understand the risks and needs," said Dr. Arni S.R Srinivasa Rao, a mathematical modeler at the Medical College of Georgia at Georgia Regents University. "If there are more children, you need to worry about schools; if there are more older people, you need to worry about health benefits." Rao noted that while many countries, including the United States, have good population data generated by regular surveys, others, including some European and many Third World countries, still don't.

The new theorem is published in the Journal of Mathematical Biology and Notices of the American Mathematical Society.

The work began about a decade ago, when Carey deduced that by keeping tabs on how long a large fruit fly population lived in captivity, he could determine the age structure -- how many flies are how old -- of the general fruit fly population. It's called Carey's Equality.

Figuring that out without knowing the age of the fruit flies at

capture was Carey's eureka moment.

Flash forward to a mathematical demography meeting last year at The Ohio State University Mathematical Biosciences Institute where Carey was explaining his observation and Rao was listening.

"I saw a pattern in what he observed," Rao said, and within 45 minutes, he had put together the complex mathematics behind it, helping prove the relationship, and making it more readily transferrable to diverse populations, from humans to the mosquito population they are now studying. He presented the math to his new colleague the next day.

"We went back a few more steps and said how is this true; what are the biological factors; what are the symmetries; what are the patterns in biology," Rao said.

In fact, putting two graphs -- one depicting the usual course of individual fruit flies from birth to death and the other charting how long flies lived after capture -back-to-back creates a symmetrical mountain that starts at the peak of one day of life and trails off at the base at about 60 days of life on either side.

Their theorem can be applied to human and non-humans in stationary populations -- meaning the birth and death rate and age composition are stable and similar -- such as the fruit fly or more dynamic populations like China.

In terms of broader application beyond age distribution, instead of farmer's guesstimating how many wolves are needed to keep their elk population in an ideal range and vice versa in Montana, they can apply this theorem.

"It's not about how many wolves there are; it's about what is needed to make them both live together," said Rao. "We need to know at what rate wolves are killing elk and how many elk are dying." The age structure of the wolves and elks also yields evidence of how many are in their reproductive years. Taking it to the next step, how much food do the elks need to live, Rao said.

Back to the mosquito, "Understanding age structure in these insect populations is a huge deal worldwide because it's the older mosquitoes that vector the West Nile fever, malaria, yellow fever, and so forth," Carey said.

Biochemical and gene expression studies to collect age data are crude and don't reveal much, and programs to capture, mark, release, then recapture often yield too few recaptures, Carey noted.

http://www.sciencedaily.com/releases/2014/10/141006114101.htm

Math model designed to replace invasive kidney biopsy for lupus patients Date: September 17, 2014

Source: Ohio State University

Mathematics might be able to reduce the need for invasive biopsies in patients suffering kidney damage related to the autoimmune disease lupus.

In a new study, researchers developed a math model that can predict the progression from nephritis – kidney inflammation – to interstitial fibrosis, scarring in the kidney that current treatments cannot reverse. A kidney biopsy is the only existing way to reach a definitive diagnosis of the damage and its extent.

The model could also be used to monitor the effectiveness of experimental treatments for inflammation and fibrosis.

This fibrosis can follow development of lupus nephritis, which occurs in about 60 percent of lupus patients, according to the National Institutes of Health. Inflammation is linked to the most common type of lupus, called systemic lupus erythematosus. The cause of lupus is unknown and it cannot be cured.

The research is published this week in the online early edition of Proceedings of the National Academy of Sciences.

The math model comprises a series of equations that account for the complex inflammatory process leading from nephritis to fibrosis in damaged kidneys. As designed, the model can detect the extent of kidney damage and predict how inflammatory processes will react to different therapies.

“The most important use of this model will be improving the design of clinical trials for new medications to treat the kidneys before they develop fibrosis,” said lead author Avner Friedman, a Distinguished University Professor in The Ohio State University’s Department of Mathematics. “Establishing a dose of an experimental therapy is the most difficult part of testing new drugs. The model could give a starting point for an effective dose.”

Better management of kidney damage in lupus is an urgent medical need because patients with moderate or severe fibrosis are more likely to develop chronic or end-stage kidney disease, said Brad Rovin, professor and director of the division of nephrology at Ohio State’s Wexner Medical Center and a co-author of the paper.

“If a kidney is already damaged, we can’t expect to go back in frequently to extract more tissue for multiple biopsies,” Rovin said.

Modeling by mathematicians with expertise in biomedical processes has become increasingly important in the health sciences. The modeling reduces the need for guesswork and time-consuming animal testing traditionally required as researchers pursue prevention, diagnosis and treatment of complex diseases. And in this case, math modeling would replace an invasive diagnostic test.

Lupus is an autoimmune disorder, meaning the immune system attacks healthy cells and tissue in the body. Lupus commonly affects the kidneys, where immune cells accumulate in the organ’s filtering units. This triggers an out-of-control inflammatory process that eventually leads to scarring and degradation of structures called tubules, which collect filtered fluid and are involved in the production of urine.

Further validation and refinement of the model is required, said Friedman, also founding director of the Mathematical Biosciences Institute (MBI) at Ohio State. But in this study, a comparison with human patient data showed that levels of inflammatory proteins in the urine of patients with mild, moderate or severe fibrosis matched levels predicted by the model.

The model also allows scientists to simulate the scarring injury and detect how the damage would respond to the therapies that target specific pathways to disease – either the inflammatory process or the scarring itself. By identifying vulnerabilities in the process from inflammation to scarring, the model could even point to the cells and proteins that would be the most promising treatment targets, Friedman said.

http://www.sciencedaily.com/releases/2014/09/140917131640.htm

数学教授介绍

坂内英一教授是我们致远学院数学方向的教授，他曾为08、09、10级数理班的学长主讲过图论课程，为11、12级的学生主讲过图与网络课程。坂内英一教授的代数图论课程清晰严谨而又直观易懂，在近70岁的高龄还进行着高强度的科研工作并且亲自批改学生的作业，深受学生的尊敬与敬佩。

坂内教授于1974年获得东京大学博士学位，曾在东京大学（1970—1976）、学习院大学（1977—1978）、俄亥俄州立大学（1974—1976， 1978—1989）、九州大学（1989—2009）等著名高校任教，自2011年起在上海交大数学系全职工作。坂内教授是国际代数组合领域的领军人物和研究先驱。

坂内教授早期从事群论的研究，后来逐渐转向组合数学领域。他与伊藤達郎教授合作完成世界上第一本使用代数组合这一名称的专著，该书已成为代数组合领域的经典书籍，上海交大图书馆对该书的馆藏来自坂内教授的捐赠。坂内教授已发表110多篇研究论文，包括5篇以上海交大名义发表的论文，研究内容包括组合数学（图，设计，码，结合方案，球面设计等）、有限群、数论（格和模形式）、正交多项式(Askey-Wilson 正交多项式)、数值分析中的积分公式、数学物理（自旋模型与能量极小化构型）等。

坂内教授目前担任8份国际杂志的编委，曾组织过多次代数与组合方面的国际学术会议，包括与万哲先院士一起在1994年组织的第一届中日代数组合国际会议。他荣获1979年俄亥俄州立大学颁发的Distinguished Research Award和2007年日本数学会颁发的Algebra Prize。坂内教授的最大梦想是从代数组合的角度对有限单群分类给出新的理解和推广

物理世界

“风云二号”08星将于本月下旬发射

“风云二号”08星已通过出厂审定，将于11月下旬赴西昌卫星发射中心执行发射任务。

“风云二号”08 星是我国地球同步静止轨道气象卫星，是“风云二号”卫星第3 批次的第2 颗业务应用卫星，承担卫星气象观测、预报等任务。航天科技集团公司八院卫星总师曹亮介绍说：“风云二号08 星进行了技术状态更改，主要表现在改善了扫描辐射计的红外杂散光影响和提高黑体定标频次两个方面。目前，该卫星的出厂前研制工作已全部完成，产品状态正确、质量受控，具备出厂条件。”

此外，执行此次发射任务的长征三号甲遥二十四运载火箭也已经完成了总装和出厂测试，将同期运往西昌。

据国防科工局副局长吴艳华介绍，“风云二号”08 星是中国航天2014 年的收官之作。目前，发射场系统、测控系统、地面应用系统也已准备就绪，各相关单位还开展了内部联调联试。

囚禁的量子，开放的应用

2012 年10 月 9 日， 一位68 岁的法国老人与妻子在街头散步，当他们路过一条街边的长椅时，电话忽然响起，老人被告知获得了诺贝尔物理学奖。同样被“搅扰”的还有大西洋彼岸一位68 岁的美国老人，电话响起时他还在睡梦中，但无论什么梦也比不上电话里的消息：他也获得了诺贝尔物理学奖。

这两位天各一方，但恰巧同岁的老人分别是法国物理学家阿罗什 (Serge Haroche) 和美国物理学家维因兰德 (David Wineland)， 之所以获奖， 是因为他们实现了“使得对单个量子体系的测量与操控成为可能的突破性实验方法” ("for ground-breaking experimental methods that enable measuring and manipulation of individual quantum systems")。他们将共同分享崇高的荣誉，以及虽因金融危机而缩水，但数量依然可观的 800 万瑞典克朗(约合 110 万美元)的奖金。

一. 小有小的麻烦

美国物理学家费曼曾以一个有趣的问题作为《费曼物理学讲义》的开篇， 那个问题是：如果由于某种灾变，在所有科学知识中只有一句话能传于后代， 什么话能用最少的文字包含最多的信息？ 费曼认为， 那应该是所谓的“原子假设”， 即所有物质都是由原子组成的。 不过， 这句话包含的信息虽多，要想破译却并不容易。事实上，早在两千多年前的古希腊就有先贤猜测过物质是由原子组成的 (“原子” 一词的英文atom 就来自希腊文 ἄτομος，含义为“不可分割的”，但直到十八世纪才开始有了现代意义下的原子理论， 而原子的真正奥秘， 则直到二十世纪才开始揭晓。

为什么呢？因为原子实在太小了，看不见、摸不着。

如今我们知道，原子并非是“不可分割的”，它由更基本的粒子所组成，并且与那些粒子一样，遵守一种被称为量子力学 (quantum mechanics) 的奇妙规律。这种规律与我们习以为常的宏观世界的规律完全不同，在发现之初曾带给物理学家们极大的震动。直到很多年后，当那种规律逐渐褪去新鲜的外衣，甚至已变成物理系学生的常识时，想在最直接的意义上体验它们仍是极为困难的事情。

为什么呢？依然是因为原子实在太小了，看不见、摸不着。

由于这一原因，物理学家们对原子(或者更一般的，对量子体系)的很多观测都不是针对单个原子(或量子体系)的，比如他们观测的原子光谱乃是由很多原子共同发射的。而在有条件观测单个原子(或量子体系)的实验中，由于观测对象太小，往往观测一结束，观测对象也就“人间蒸发” 或“香消玉殒”了，比如用云室或气泡室(这两者的发明者分别获得了1927 年和1960 年的诺贝尔物理学奖)观测粒子，或用照相设备观测光子就都如此。

那么，有没有什么办法，能够观测甚至操控单个量子体系，同时还让它继续存在(从而还可以继续观测或操控)呢？维因兰德和阿罗什——在他们各自同事的鼎力合作下——所解决的正是这个问题。他们凭借高超的实验技巧，将单个量子体系囚禁起来，然后用细微而巧妙的“探针”去观测甚至操控它，从而完成了近乎“不可能任务”(mission impossible)的壮举，为上述问题提供了肯定答案。

下面我们就对他们的方法做一个简单介绍。

二. 囚禁的量子

维因兰德采用的方法是将单个的离子(离子是失去或得到若干电子——从而带电——的原子)，比如铍离子Be+ (它是失去一个电子的铍原子)，利用其带电的特征，囚禁在用电磁场组成的“牢笼”中，然后以光子作“探针”去探测和操控它。这话说起来简单，实现起来却极不容易，单是那“牢笼”——它的“学名”叫做离子阱 (ion trap)——本身就已是一个诺贝尔奖级别的成就(它的实现者获得了1989 年的诺贝尔物理学奖)。 为了确保被囚禁的是单个(或少数几个)离子，还需要辅以超高真空(以便排除其它粒子的干扰)和超低温(以便排除热运动的干扰)等技术。其中后者采用的乃是维因兰德与同事亲自参与研发的绝活：边带冷却技术 (sideband cooling)。当这些极不简单的配置完成之后，维因兰德又通过激光脉冲 (光子)，将被囚禁离子的内部状态 (即电子能态) 叠加起来。这种状态叠加是量子力学有别于经典物理的奇妙特征，科普读物中常见的诸如 “粒子既在这里，又在那里”、 “猫既是死的，又是活的”等等吸引眼球的表述都源自于此。但维因兰德能做到的还不止这些，通过对激光脉冲的巧妙选择，他还可以对状态叠加的方式进行操控，比如将内部状态的叠加转变为外部状态(即在“牢笼”内的振动状态)的叠加，甚至将一个离子的状态叠加转变为另一个离子的状态叠加。

与维因兰德的方法几乎恰好相反，阿罗什的囚禁物是被维因兰德当作“探针”的光子，而“探针”则类似于维因兰德的囚禁物，是一种被称为里德堡原子(Rydberg atom)的特殊原子，它的电子处于很高的能态上，从而使整个原子“发胖”到惊人的程度。比如阿罗什所用的铷原子(Rb) 就“发胖” 到了普通铷原子的 500 倍左右。 在阿罗什的方法中， 囚禁光子所用的是以超导材料铌 (Nb) 制作的一对相距 2.7 厘米的球面镜， 这对球面镜的工艺极为高超，构成了一个反射性质近乎完美的空腔(cavity)。光子在其中可以被反射十几亿次而不被吸收(在这过程中走过的总距离可以绕地球一圈)。在这些同样极不简单的配置完成之后。阿罗什又通过特殊空腔中的电磁波，使作为“探针”的里德堡原子处于两个电子能态的叠加之中，并使之以可控制的速度穿越囚禁了光子的空腔。在这里，阿罗什做了另一个巧妙安排，使被囚禁光子的能量与里德堡原子所能吸收的能量稍稍错开，从而保证光子不会被里德堡原子所吸收(别忘了，这一整套方法的使命之一就是保障量子体系继续存在)。而更巧妙的是， 尽管光子不会被吸收，它与里德堡原子的相互作用仍能对后者产生影响，改变后者那两个叠加能态间的相位。这样，阿罗什就可以通过研究穿越后的里德堡原子那两个叠加能态间的相位，而获得有关被囚禁光子的某些信息(比如光子的数目)。

上述两种方法的实现无疑都需要极高超的技术。不过，此类工作要想获得诺贝尔奖，通常还需满足一个额外条件，那就是具有应用价值。此次获奖的工作很好地符合了这一条件，因为其所实现的“使得对单个量子体系的测量与操控成为可能的突破性实验方法”在理论与实用上都有着重要应用。

三. 开放的应用

在理论上，对一个量子体系进行观测或操控，同时还让它继续存在，使得人们设计出了一些巧妙的实验，观测量子体系状态演变的过程(以往的实验由于是“一锤子买卖”，对被观测体系具有“毁灭性”，从而无法做到这一点)，甚至观测使一些物理学家深感困惑的量子体系的状态因为与外部环境的相互作用而往经典状态过渡的过程，其中包括对大名鼎鼎的“薛定谔的猫” (Schrödinger's cat)的生死过程的观测。那样的实验已经有人做了。比如阿罗什本人的研究组就于 2008 年做了那样的实验，甚至将观测到的量子状态往经典状态过渡的过程制成了 “影片”。

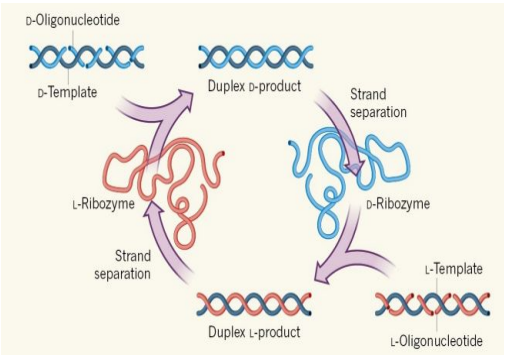
在实用上，此次获奖工作最引人注目的应用是在量子计算机领域。这是近年来被讨论得很多的领域，在乐观者看来，量子计算机若成为现实，对社会的变革将不亚于如今的计算机在过去几十年所带来的变革。不过，量子计算机的理论虽然美丽，面临的技术困难却极为巨大，其中一个很大的困难就是作为核心元件的量子体系必须能单个地、不受破坏地被测量与操控，而且各个量子体系的状态还必须能相互传递(就像经典计算机必须能在各元件间传递信息一样)。这个困难在过去几乎是难以克服的，此次的获奖工作却为之带来了曙光，比如维因兰德所实现的对状态叠加的操控，以及状态叠加在不同离子间的相互转变，就正是克服上述困难所需要的技术。这一点维因兰德本人也看得很清楚——事实上，他的研究组早已展开了这方面的探索，甚至在一定程度上构造出了量子计算机的雏形，实现了最简单的逻辑运算。一些其它实验组也正在积极努力之中。当然，这一切距离真正有实用价值的量子计算机还相差很远。此次获奖工作的另一项很有价值的应用是建造超高精度的新型时钟。这一应用虽不像量子计算机那样富有未来色彩，所取得的进展却要扎实得多。维因兰德所供职的美国国家标准技术研究所正是这方面的“领头羊”。在这一应用中，用维因兰德所实现的方法囚禁起来的工作频率(即作为计时基础的两个能级之间的量子跃迁的频率)在光学波段的离子取代了传统原子钟所采用的工作频率在微波波段的铯原子(Cs)。目前，这种新型时钟已经达到了比传统铯原子钟高两个数量级的精度。在那样的精度下，哪怕从宇宙大爆炸之初开始计时，迄今的累计误差也只有区区几秒(有关包括这种新型时钟在内的时钟技术的发展，请参阅拙作《从日晷到原子钟》)。

这些或已成为现实，或仍处于开放的想象空间里的应用，使此次的获奖工作有可能对未来科学与技术的发展产生深远影响。

化学视角

Cross-chiral Ribozyme May Hold Clues To Origin Of Life

http://cen.acs.org/articles/92/web/2014/11/Cross-chiral-Ribozyme-Hold-Clues.html By Stu Borman



Researchers have developed the first cross-chiral biocatalyst—a right-handed (D) RNA enzyme that catalyzes the linkage of left-handed (L)-RNA chains. No other RNA or protein enzymes of one chirality are known to use substrates of the opposite chirality to produce biopolymers.

Such ribozymes could be useful for creating novel compounds, such as nuclease-resistant L versions of conventional D-RNA bioactive agents. Their development also gives a boost to the RNA world hypothesis—the idea that there may have once been living systems in which RNA did most of the work and that this RNA world may have evolved into today's more complex RNA/DNA/protein world.

No known modern-day RNA-based enzyme can assemble RNA from a racemic soup of left- and right-handed RNA building blocks, the form in which RNA likely would have existed prior to the origin of an RNA world. To develop such a ribozyme, chemical biologist Gerald F. Joyce and postdoc Jonathan T. Sczepanski of Scripps Research Institute California used directed evolution. Like modern RNAs, the ribozyme has D chirality. But unlike them, it catalyzes the template-directed polymerization of RNAs of opposite handedness, the joining together of L-RNA building blocks bound to an L-RNA template (Nature 2014, DOI: 10.1038/nature13900). It ignores D-RNA building blocks that may be around.

The D-enzyme's activity was sufficient to catalyze the assembly of a full-length L version of itself by the templated joining of 11 L-RNA oligomers. In a Nature commentary, Sandip A. Shelke and Joseph A. Piccirilli of the University of Chicago describe the work as "a remarkable first demonstration of an enzyme (RNA or protein) being synthesized by its own enantiomer." The L-ribozyme product can then use D-RNA building blocks to reconstruct the D-ribozyme that created it.

This trick makes the cross-chiral ribozyme "a molecular incarnation of M. C. Escher's famous woodcut 'Drawing Hands,'" which depicts right and left hands drawing each other, says RNA evolution specialist Irene Chen of the University of California, Santa Barbara. "It will be exciting to see where further evolution takes this system."

The ribozyme's ability to use RNA substrates and templates of opposite chirality from itself stems from the non-sequence-specific interactions it uses to bind those substrates and templates. Those interactions resemble the ones modern protein-based enzymes use to recognize RNA substrates and templates—not the base-pairing strategies RNA or DNA enzymes typically use to recognize substrates and templates of the same chirality as the enzymes'. The new ribozyme's "ability to recognize substrates without base-pairing to them could lead to the development of the types of generalized catalytic activity that would have been needed early in evolution," says RNA specialist David Bartel of Massachusetts Institute of Technology. He points out that the Scripps researchers "are still at a very early stage"—the ribozyme isn't as versatile as might have been needed in an RNA world. "But they have a new approach for eventually achieving that."

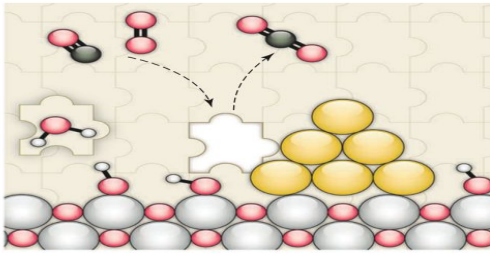
RNA catalysis researcher Peter J. Unrau of Simon Fraser University, Burnaby, British Columbia, also commends the study but points out that it does not directly address how a cross-chiral ribozyme that itself has pure chirality "could have emerged de novo from an achiral mix of nucleotides."

"This is a brilliant paper that opens up many new and fascinating lines of investigation and elegantly addresses some vexing problems of RNA self-replication," says Philipp Holliger, a nucleic acid replication expert with the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. However, he notes that early-world cross-chiral systems "would at some point have to transition to today's homochiral systems" and that it is difficult to envisage how that could occur.

Joyce says he and his coworkers are continuing to evolve the enzyme to expand its catalytic properties. "I would hope that others will take the cue and devise other cross-chiral enzymes, including protein enzymes, such as a D-protease that acts on L-polypeptides," he says.

Water's place in Au catalysis

http://www.sciencemag.org/content/345/6204/1564.figures-only By Gregory M. Mullen and C. Buddie Mullins



Where water fits in. Many ideas have been proposed for the role of water in gold-catalyzed CO oxidation. The results reported by Saavedra *et al.* indicate that water adsorbed at the gold-support interface plays a key role in this process.

The discovery of highly active gold catalysts for CO oxidation (CO + ?O2 → CO2) about 25 years ago ignited substantial interest in the use of gold as a catalyst. Yet, this seemingly simple reaction has proven to be quite complicated. No consensus exists regarding the mechanism by which gold catalyzes CO oxidation. Confounding the understanding of this process was the discovery that incorporation of minute quantities of water in the reactant feed stream can increase catalytic activity by up to several orders of magnitude. Many conflicting reports have been proposed for the role of water in the CO oxidation reaction. On page 1599 of this issue, Saavedra et al. present a compelling mechanism that ties together the conclusions of many of these reports.

There are two key questions regarding water-enhanced CO oxidation on gold catalysts. Does water enhance the reaction by promoting the decomposition of surface intermediates or by assisting in the activation of reactants? And is the active site of the catalyst associated with the gold particle surface or the gold-support interface?

A few reports have suggested that incorporation of water into the feed stream for CO oxidation promotes the decomposition of surface intermediates. Such an effect could reduce catalyst deactivation, leading to enhanced activity. For example, hydroxyl groups located on the supporting material near the gold-support interface may abstract hydrogen from a reactive intermediate on the gold surface, resulting in the formation of water and a more stable intermediate that blocks the active site. Inclusion of water in the feed stream would reverse this process by driving equilibrium toward regeneration of the hydroxyl groups on the support and the less stable intermediate.

Alternatively, water may assist in the activation of reactant species on the catalyst surface. A number of potential active sites and mechanisms exist for this type of process. Studies have proposed that hydroxyl species produced by interactions between water and the gold surface or the gold-support interface can oxidize CO, enhancing catalytic activity relative to the hydroxyl-free surface. Different authors have pointed to either cationic gold or metallic gold taking part in this activation process. Others have proposed that the generation of a hydroperoxyl-like surface intermediate via the interaction of water with O2 on the surface of the gold particle may facilitate CO oxidation.

The diversity of proposed active sites and mechanisms has done little to resolve the debate surrounding water-enhanced CO oxidation. Rather than becoming clearer over time, many aspects of this process have become more perplexing.

Saavedra et al. explored the water-enhanced CO oxidation reaction on a titania-supported gold catalyst. This

system has been very well studied, but the authors were nevertheless able to make novel observations with a relatively simple technique. They controlled the amount of water on the catalyst surface by gently drying the material while monitoring adsorbed water and hydroxyl species with infrared (IR) spectroscopy. Removal of weakly adsorbed water from the surface resulted in a substantial decrease in activity for CO oxidation. Furthermore, the authors observed a large kinetic isotope effect when H2O on the catalyst surface was replaced by D2O, suggesting that cleavage of the O-H or O-D bond is a critical step in the reaction mechanism. These observations indicate that water plays a direct role in the CO oxidation reaction (see the figure).

Saavedra et al. supported their experimental results with a comprehensive density functional theory (DFT) investigation. Based on the evidence from the IR spectra, their DFT model incorporates adsorbed water and hydroxyl groups associated with the support. The results show that adsorbed water at the gold-titania interface helps activate O2 at a very low energetic cost—so low, that the process occurs spontaneously at low temperatures. This is a very surprising revelation given the high energy barriers that gold surfaces display toward O2 activation. In the authors' model, the most kinetically important step is instead associated with decomposition of a reactive intermediate via proton transfer to water, in agreement with their experimental observations.

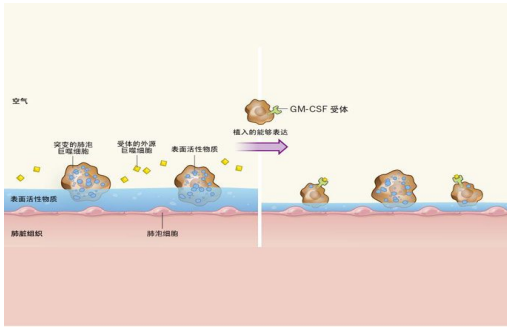
In Saavedra et al.'s mechanism, hydroperoxyl and hydroxyl species are involved in the water-enhanced CO oxidation reaction. Hydroxyl species associated with both the support and the gold surface play roles in the process. Furthermore, water helps to both activate O2 and decompose reactive intermediates associated with CO2 generation. This mechanism not only ties together observations made in several previous studies of the water-enhanced CO oxidation reaction but also lends credence to many seemingly conflicting claims.

Water plays a key role in a number of other reactions carried out on gold catalysts. By elucidating the role of water in CO oxidation, the study by Saavedra et al. may prove key to solving many of the puzzles of gold catalysis.

生科发现

Nature：细胞移植术

2014-11-08 www.bio360.net 来源：生物360 作者：koo 47 0



动物试验发现，将经过转基因修饰的巨噬细胞（Transplanting gene-corrected macrophage cells）植入小鼠肺部能够有效地治疗肺泡蛋白沉积症（pulmonary alveolar proteinosis，PAP）这种人类遗传性疾病。

肺泡蛋白沉积症（pulmonary alveolar proteinosis, PAP）是一种非常罕见的肺脏疾病，主要表现为肺泡巨噬细胞（alveolar macrophages）这种白细胞在患者的肺部沉积。肺泡巨噬细胞里含有大量的表面活性物质（surfactant），和大量的细胞外表面活性物质。这种表面活性物质是由磷脂和蛋白质构成的复合物，能够调节肺泡的表面张力。我们最早是在1958 年第一次发现了肺泡蛋白沉积症这种疾病，可是发现这种疾病的病因就到1994 年了。当时偶然发现，缺乏GM-CSF 蛋白的小鼠也会患上一种类似于人类PAP 的肺病，而我们都知道，GM-CSF 蛋白是促进巨噬细胞成熟，表达正常功能的重要因子。Suzuki 等人发表在《自然》（Nature）杂志网站上的这篇文章又给我们讲了一个最新的故事。他们发现，将对GM-CSF 因子能够正常反应的巨噬细胞植入缺乏GM-CSF 因子受体的小鼠肺部之后，能够有效治疗小鼠PAP 疾病。

通过对缺乏GM-CSF 因子的小鼠进行研究发现了导致PAP 疾病的病因（图1）——表面活性物质被肺泡部位的巨噬细胞分解。人体研究也发现，虽然某些PAP 患者体内的肺泡巨噬细胞在体外实验中也能够对GM-CSF 因子起反应，但是这些患者体内却存在GM-CSF 因子抗体，能够中和这些因子。我们目前将PAP 主要分为三种类型，分别是自身免疫性（获得性）PAP、遗传性（先天性）PAP 和继发型PAP（此型主要与血液系统肿瘤或全身性炎症疾病相关）。不过所有这3 种PAP 都与GM-CSF 信号通路缺失有关，可能是因为缺乏活化的GM-CSF 因子，或者是因为GM-CSF 受体突变。有部分先天性PAP 患者是因为表面活性蛋白异常所致。

通过对小鼠动物模型和人类PAP 患者样本的研究，阐明了肺泡表面活性物质降解的具体过程，同时也发现了一些在肺泡巨噬细胞生物学方面发挥重要作用的关键蛋白因子。比如参与肺泡巨噬细胞成熟的PU.1 蛋白，促进肺部维持稳态的PPARγ等。与身体内其他部位的巨噬细胞不同，肺泡巨噬细胞能够表达大量的PPARγ，这说明PPARγ蛋白对于肺部而言一定具有某种非常重要的作用。实际上，PPARγ蛋白是一种巨噬细胞活化的负向调控因子。而PPARγ蛋白表达则主要受到GM-CSF 因子的刺激。肺泡表面活性物质90%都是脂质，其代谢主要受有GM-CSF 因子、PPARγ蛋白和ABCG1 蛋白参与的信号通路的调控。

图1 将正常巨噬细胞植入PAP 小鼠动物模型的肺部之后，能够有效治疗小鼠的PAP 疾病。巨噬细胞是一种白细胞，能够吞食、降解细胞碎片。在肺部的巨噬细胞除了具备这些功能之外，还能够降解多余的表面活性物质。表面活性物质是一种由磷脂和蛋白质组成的物质，由肺泡上皮细胞合成，可以起到降低肺泡表面张力的作用，防止肺泡塌陷。如果巨噬细胞发生突变，不能表达GM-CSF 受体（GM-CSF 蛋白是巨噬细胞成熟，表达正常功能必需的一种因子），就会导致表面活性物质大量堆积，形成PAP 疾病。Suzuki 等人发现，将能够表达GM-CSF 受体的巨噬细胞（既可以是取自野生小鼠的巨噬细胞，也可以是经过基因修复过的突变巨噬细胞）植入PAP 小鼠肺部之后，就能够有效降解表面活性物质，起到明显的治疗作用。

最早也是通过对小鼠动物模型的研究明确治疗PAP 疾病的方案的。早期的研究发现，缺乏GM-CSF 因子的小鼠是可以被治愈的，既可以用输注外源GM-CSF 因子的方法进行治疗，也可以通过让小鼠呼吸道上皮细胞过表达GM-CSF 因子的方法进行治疗。基于这些研究成果，有人开始尝试对自身免疫性PAP 患者，通过皮下注射或吸入（inhalation）的方式，进行大剂量GM-CSF 因子治疗。不过这种治疗对部分患者无效，这可能是因为在他们的肺部，存在大量的抗GM-CSF 因子抗体。还有一种办法也可以用来治疗自身免疫性PAP 患者，那就是使用单克隆抗体rituximab，这种抗体能够抑制抗GM-CSF 因子抗体的生成，同时在某些患者体内还能够诱导PPARγ和ABCG1 的表达。

可是对于遗传性PAP 患者，就只有一种治疗方案，那就是全肺灌洗（lavage），这需要在全身麻醉下操作。有人提出，将健康的骨髓细胞植入这种遗传性PAP 患者体内也能够起到治疗作用，因为这些健康的骨髓细胞也可以分化形成正常的、对GM-CSF 因子敏感的巨噬细胞，而且这种疗法在小鼠试验中也已经取得了成功。但是使用这种疗法需要进行骨髓抑制（prior myeloablation），将患者体内的骨髓细胞完全清除掉，以免发生排斥反应。这种骨髓抑制的患者非常容易感染，并且死亡，所以这种骨髓移植疗法并不是一种常规的治疗手段。

Suzuki 等人希望能够找到一种不需要进行骨髓抑制的移植治疗方案。他们将取自正常小鼠的巨噬细胞直接注入PAP 小鼠动物模型（这种小鼠缺乏GM-CSF 因子受体的β亚单位，因此与GM-CSF 因子受体α或β亚单位发生突变的遗传性PAP 患者幼年时的病症一模一样）的肺部，结果明显缓解了患病小鼠的临床症状，与疾病相关的蛋白的表达水平也回复至正常水平，小鼠的寿命也得到了明显的延长。然后，Suzuki 等人又对这种小鼠自身的巨噬细胞进行体外遗传学修复（主要借助慢病毒转染技术），使其能够重新表达GM-CSF 因子受体的β亚单位，然后将这些巨噬细胞再注入患病小鼠体内，也取得了非常不错的治疗效果。

这些小鼠动物试验表明，巨噬细胞移植术应用于人体应该也会取得非常不错的治疗效果。之前开展的一项研究也表明，将野生型鼠巨噬细胞的前体细胞植入GM-CSF 受体缺失的动物体内之后，能够有效缓解遗传性PAP 疾病的临床症状。Suzuki 等人还对这一技术进行了进一步的改进，他们将遗传背景完全一样（患病动物）的细胞进行了基因改造，使其恢复正常，这也就避开了骨髓抑制和免疫抑制的问题。实验结果也非常令人满意，试验小鼠的临床症状得到了明显的改善，病情有了明显的好转。这种技术也非常适合应用于临床，只需要将PAP 患者自身的巨噬细胞提取出来，在体外进行基因改造，然后再回输到患者体内就可以起到治疗的作用。

Suzuki 等人在体外培养过程中还发现，虽然野生型骨髓来源的巨噬细胞与肺泡巨噬细胞有很多差异，但他们在移植之后还是在小鼠肺部发现了这些拥有肺泡巨噬细胞特征的细胞。该结果也与之前的试验结果相吻合，之前的研究发现，局部的微环境也能够提供相应的信号，指导巨噬

细胞发育、成熟。还需要开展更进一步的研究，了解在临床实践工作中最佳的细胞移植剂量，GM-CSF 因子升高的水平与遗传性PAP 病情之间的关系，以及是否还需要额外的GM-CSF 因子，保证植入巨噬细胞的存活等。

这种疗法的意义还不仅局限于罕见的遗传性PAP 疾病。我们也可以用这种方法来治疗其他疾病，比如将经过基因改造的自体巨噬细胞回输给患者，用来治疗HIV 等。巨噬细胞是HIV 病毒的“储藏间”，但某些缺乏某种巨噬细胞共受体的细胞却能够不受HIV 感染，因此将这些细胞回输给患者就可以让患者对病毒产生抗性，不受病毒感染。由于局部的微环境也能够产生某些信号，促进巨噬细胞的发育，使其获得某种特性，所以我们也很有可能会发现与某种疾病相关的突变。使用全基因组测序技术对出生即患有危及生命疾病的新生儿进行检测，发现新的异常基因，这也将有助于巨噬细胞移植术在临床上的进一步推广。

谷歌推人类基因组云端服务项目

2014-11-07 www.bio360.net 来源：生物360 作者：koo 162 0

谷歌最近正在通过一个名为“Google Genomics”的项目与医院和大学实验室展开合作，共同推进人类基因组的存储、对比和分析工作。

Google Genomics 是谷歌在去年3 月推出的一项云端服务，但随后由于没有进行大规模的推广而并未引起人们的注意，该项目皆在帮助大学实验室和医院将患者或科研对象的生物基因储存到云端上，服务的目标是“探讨遗传变异交互”，意味着科研专家能够访问数百万的生物基因组数据，并能轻松简单的进行对比和分析。除了谷歌之外，人类基因组数据的存储目前还已经引起了亚马逊、IBM 和微软等科技巨头的注意。

谷歌自Google Genomics 项目启动以来，已经与多位科学家进行了面谈并专门为此开放了一个API 接口，方便这些科学家将DNA 数据转移到谷歌的服务器群上，而科学家则可以使用这个囊括了数十亿互联网用户和网页索引的数据库进行实验。

“生物学家们可以通过我们的服务来从对一个基因组的研究升级到对数百万个基因组进行研究，”主管Google Genomics 项目研发的软件工程师大卫·格雷泽(David Glazer)说道，“我们希望通过我们的数据技术来帮助他们实现质的突破。”

尽管有些科学家认为谷歌的服务对于复杂的基因组数据来说不过是杯水车薪，但还是有不少科学家对此进行了肯定，比如斯坦福大学的教授阿图尔·巴特(Atul Butte)在今年对谷歌的这一计划进行详细了解之后，就表示“这感觉就像是传统旅行社在看到Expedia(全球最大的在线旅游公司)一样”。

科学家们目前在使用新型设备在对DNA 进行解码时所获得的数据越来越多，速度也越来越快，如剑桥伯德研究所(Broad Institute in Cambridge)的有关负责人就介绍称，在今年10 月的实验中，他们每解码一个人类基因组需要32 分钟，所产生的原始数据高达200TB。

虽然这种量级的数据流与大型互联网公司所处理的数据相去甚远(伯德研究所两个月所产生的数据与YouTube 上一天的数据上传量相仿)，但却远远超过了任何一位生物学家的处理能力。就目前情况而言，此类数据的存储和访问通常通过大型的商业数据中心来实现。美国国家癌症研究所在上月曾表示将耗资1900 万美元将大小为2.6PB 的癌症基因组图谱数据的副本存储到云端，这些涉及数千名癌症患者的数据的副本未来也将会存储到谷歌Google Genomics 项目和亚马逊的数据中心。

西雅图系统生物学研究所(Institute for Systems Biology)的科学家希拉·雷诺兹(Sheila Reynolds)指出，他们希望创建一个“癌症基因组数据云”，让科学家们可以像使用传统网络搜索那样简便地分享信息和进行虚拟实验，“毕竟并不是每个人都拥有处理PB 级数据的能力的，”她说道。

谷歌和亚马逊已经就DNA 数据向云端转移的费用进行了为期一年的价格战。谷歌表示每个基因组的年存储费为25 美元，而计算这些数据还需要支付额外的费用。目前一个人类基因组在解码之后的原始数据大小在100GB 左右，不过该数据还可以被精简至1GB 以下，谷歌对此类数据的云端储存价为每年0.25 美元。

云存储服务在一定程度上推动了Tute Genomics、Seven Bridges 和NextCode Health 等初创企业的发展，这些公司均致力于研究能够帮助医院和科学家检索基因数据的“浏览器”服务。“谷歌和亚马逊所提供的是后端服务，他们往往会鼓励我们在他们的云端创建基因组公司，”Seven Bridges 的首席执行官德尼兹·库鲁尔(Deniz Kural)介绍道，该公司目前在亚马逊的云端存储并管理着1600 位研究人员所提供的基因组数据。

库鲁尔指出，未来一款药物的研究和应用也将会依赖于在全球“DNA 互联网”上进行数据检索，“根据我们的预测，加入我在未来身患肺癌，那么医生就会对我的基因组和肿瘤基因组进行测序，然后将对应的数据与数据库中的5000 万组数据进行对比，”他说道，“结果就是能够在短时间内找到最适合我的药物。”

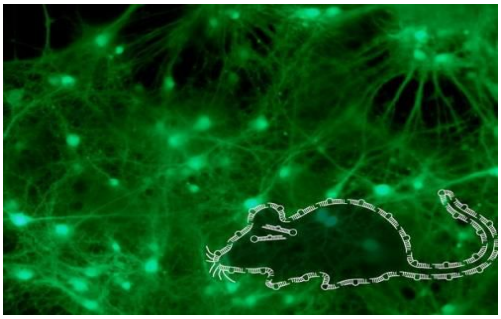
根据谷歌软件工程师格雷泽的介绍，Google Genomics 项目旨在推动生物医学研究从“作坊式”向“工业化规模生产”发展，目前他本人也在学习遗传基因方面的知识，同时也在听伯德研究所总监埃里克·兰德尔(Eric Lander)的《生物学概述》(Introduction to Biology)课程，此外格雷泽也已经将自己的基因组测序数据放在了谷歌的云端。

格雷泽并未谈及Google Genomics 项目的规模以及目前为多少客户提供服务，只是透露称目前已经有3500 组来自公共项目的基因组存储在谷歌的服务器上。同时他还指出该项目与谷歌在近期大力投入的保健类项目(如谷歌在今年启动的研究如何延长人类寿命的Calico 项目)暂无关联，“与基因组有关的就是人们正在逐渐认识到科学技术是能够推动并改变生命科学研究的现状的，”格雷泽说道。

负责管理斯坦福大学内最大的遗传数据计算机集群的物理学家索马里·达塔(Somalee Datta)表示，由于谷歌和亚马逊的云存储服务在近期都下调了价格，其存储成本已经降至与他们的数据中心运营成本相似的水平，“我们认为云存储价格还是继续下降，一直到比较合理的区间，”达塔说道。达塔还介绍说，目前一些斯坦福的科学家已经开始使用谷歌的BigQuery 数据库系统(格雷泽的团队已经将该系统与基因组数据相兼容)，该系统最初是为了跟踪网民活动而开发的，但其同样能够帮助科学家们进行数以千计的大型基因组试验，“有时候科学家们会想要做一些比较疯狂的事情，那么就需要一定的数据存储和分析处理能力，”达塔说道，“而谷歌目前就能够提供这种能力，所以我认为这是一种正确的技术发展方向，也是值得整个科研界为之肯定和鼓励的。”

Journal of Neurosci：微小RNA 分子调节应激的行为反应

来源：生物谷 2014-11-07 16:38



2014 年11 月7 日讯 /生物谷BIOON/ --慢性压力会影响我们的情绪和行为。神经精神科和行为神经遗传学的科学家们研究了大脑如何响应应激的分子机制。对于第一次，他们可以将应力相关的脑区域中微小RNA 分子miR19b 水平的变化，与小鼠异常行为联系起来。这些发现有助于更好地了解我们的大脑应对压力的办法。

各地阿龙Alon Chen 陈导演的“马克斯·普朗克 - 魏兹曼实验室实验神经精神科和神经遗传学行为”的精神病学的马克斯普朗克研究所和头部的研究人员，慢性应激小鼠，特异性与压力有关的大脑区域发现的分子miR19b 水平升高。

微RNA，如miR19b，是非常小的非编码RNA 分子，调节各种细胞活动。在miR19b 的情况下，研究人员确定肾上腺素能受体β-1（ADRB1）为主要靶分子。因此，较高水平miR19b 导致ADRB1 蛋白的产量减少。

肾上腺素能受体与应激激素、神经递质去甲肾上腺素相互作用，并已报道在发挥记忆巩固中起到重要的作用。这些数据提出的问题，miR19b 的存在与否，会影响小鼠紧张情况下的记忆。

使用新颖的位点特异性注射和基因工程技术，我们可以提升或降低恰好在，小鼠应激相关的脑区域中的miR19b 的水平，Alon Chen 解释。

miR19b 水平升高或降低的小鼠，分别导致更低或更高水平的ADRB1，但未显示焦虑样行为的变化，科学家观察到听觉恐惧记忆的差异。小鼠具有更高水平的miR19b，显示更少应力诱发的冷冻，更好的应对，而小鼠miR19b 较低水平表现相反。

在进一步的实验中，我们甚至看到，压力相关的脑区域，更高或更低的miR19b 水平，不只是影响去甲肾上腺素能信号传导在这个区域内，也可影响控制记忆巩固的分布式系统，Naama Volk 研究的第一作者。

蛋白质ADRB1 通过miR19b 空间调控，诱导应力条件下作出适当的反应，使动物适应其行为改变情况。这些研究为了解我们的大脑应对压力的机制，最终导致了在多种情况下不同的行为方式提供了更多的可能。（生物谷Bioon.com）

Science：游离泛素蛋白与流感病毒脱衣壳

来源：生物帮 日期：2014-11-07 期刊：Science
DOI：10.1126/science.1261509

摘要 ：在真核细胞(eukaryotic cells)内，折叠发生错误的蛋白会被泛素蛋白(ubiquitin, Ub)修饰。多聚泛素蛋白(polyubiquitin, poly-Ub)链连上这些错误折叠蛋白之后就相当于打上了一个标签，告诉蛋白酶体(proteasomes)，这个蛋白是需要被消灭的。

细胞降解系统(cellular degradation system)组份也被流感病毒(influenza virus)利用，用来帮助病毒感染。

在真核细胞(eukaryotic cells)内，折叠发生错误的蛋白会被泛素蛋白(ubiquitin, Ub)修饰。多聚泛素蛋白(polyubiquitin, poly-Ub)链连上这些错误折叠蛋白之后就相当于打上了一个标签，告诉蛋白酶体(proteasomes)，这个蛋白是需要被消灭的。但还有一些多聚泛素蛋白是游离的，并没有与其他蛋白相连，研究发现，这些游离多聚泛素蛋白是一种非常重要的因子，参与了细胞内多条重要的反应，比如天然抗病毒反应(innate antiviral pathway)。这些游离的多聚泛素蛋白还能够激活侵袭素通路(aggresome pathway)。所谓侵袭素通路也是胞内一条非常重要的降解途径，当蛋白酶体途径被抑制或者失活时，侵袭素通路会承担主要作用，降解胞内的异常蛋白等物质。Banerjee 等人在《科学》(SCIENCE)杂志发文，介绍了他们的新发现。他们发现流感病毒也可以利用宿主细胞的游离多聚泛素蛋白，招募侵袭素通路。流感病毒利用宿主细胞的这套机制脱去病毒自身的衣壳蛋白，并帮助病毒进入宿主细胞的时候逃避内涵体(endosome)的吞食，帮助病毒进行复制。

蛋白质的多泛素化修饰(Polyubiquitylation)作用主要发生在翻译后阶段。泛素蛋白羧基端游离的甘氨酸残基能够与特定底物蛋白的赖氨酸残基相连。泛素蛋白之间也可以依靠共价结合的方式自我聚合，形成多聚泛素蛋白链，泛素蛋白之间的结合发生在K6、K11、K27、K29、K33、K48和K63 这7 个赖氨酸残基中的两两之间。被多聚泛素蛋白链上的K48 残基修饰的蛋白质底物通常都会成为蛋白酶体的捕食对象。胞内还存在Poh1 这种去泛素化酶，Poh1 酶能够将底物蛋白质与多聚泛素蛋白链之间相连的K63 连接打开。这些游离的多聚泛素蛋白链能够被侵袭素通路的组份——组蛋白脱乙酰基酶6(histone deacetylase 6, HDAC6)识别。HDAC6 蛋白是胞浆内最主要的脱乙酰基酶，但同时也在游离泛素蛋白链与侵袭素自噬通路(aggresome-autophagy pathway)中的dynein 蛋白动力复合体(dynein motor complexes)之间起到衔接蛋白(adaptor protein)的作用。因此，这些游离泛素多聚蛋白就起到了一个招募的作用，将目标蛋白与侵袭素自噬通路“撮合”到一处，促使这些目标蛋白被降解(图1)。

游离泛素多聚蛋白链同时也具有抗病毒功用。游离的K63 连接的泛素多聚蛋白能够与维甲酸诱导基因1(retinoic acid‐inducible gene I, RIG-I)表达产物结合，并使其活化。而RIG-I 蛋白则能够诱导具备抗病毒作用的1 型干扰素(type I interferons)表达。此外，游离的K48 连接的泛素多聚蛋白能够与κB 激酶ε(κB kinase ε, IKKε)的抑制剂结合并使其活化，激活下游信号通路，表达抗病毒基因。

甲型流感病毒(Influenza A viruses, IAV)是一种感染性非常强的病毒，能够引起流感大流行和每年的流感疫情。一次成功的病毒感染需要病毒能够穿过宿主细胞的细胞膜。IAV 病毒是一种包膜病毒(enveloped virus)，能够粘附到宿主细胞上，借助细胞的胞吞作用(endocytosis pathway)进入宿主细胞。内体(endosom)的酸化作用(Acidification)能够使流感病毒表面的血凝素(hemagglutinin, HA)蛋白的构象发生改变，促使病毒与内体膜融合。流感病毒通过这种机制释放出核糖核蛋白(ribonucleoproteins, RNP)。在这些核糖核蛋白里含有病毒的核酸RNA、核蛋白(nucleoprotein, NP)以及病毒聚合酶(polymerase)。RNP 随即被转运至宿主细胞的核内，病毒RNA 开始进行复制。在这个过程中，病毒RNP必须脱掉病毒M1 基质蛋白。这个过程就被称作脱衣壳过程(uncoating)，病毒的离子通道蛋白M2 蛋白会参与脱衣壳过程(图2)。

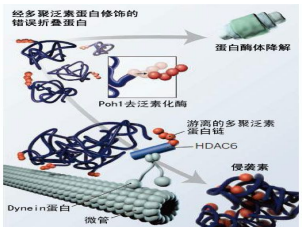


图1 侵袭素途径。

细胞内折叠发生错误的蛋白可以被多聚泛素蛋白标记，但是不经蛋白酶体途径降解，这些蛋白会被HDAC6 识别。HDAC6 与游离的多聚泛素蛋白链结合，同时与侵袭素途径中的Dynein 蛋白动力复合体结合，使被标记蛋白通过侵袭素途径被降解掉。

内体的酸化作用不仅能够促进膜融合，而且也能够激活M2 离子通道。M2 通道蛋白将质子从内体转移至病毒粒子内部，在病毒内形成一个酸化的环境，促使M1 蛋白与病毒RNP 解离。金刚烷胺(Amantadine)和金刚乙胺(rimantadine)这两种已上市的抗流感病毒药物的作用机制就是抑制M2 蛋白。Banerjee 等人的研究成果又揭示了一条新的流感病毒脱衣壳机制。

Banerjee 等人用不表达HDAC6 蛋白的小鼠进行了动物试验，检测了侵袭素机制对于流感病毒感染的作用。虽然这种不表达HDAC6 蛋白的小鼠身体状况没有太大的问题，但它们的免疫反应和骨稳态(bone homeostasis)也都受到了一定的影响。Banerjee 等人在这种小鼠的支气管肺泡灌洗液(bronchoalveolar lavages)中发现，病毒的复制程度确有所降低。但是与之前的报道一样，在细胞免疫反应标志物方面并却没有检测到明显的改变。在病毒胞吞摄取(endocytic uptake)、酸化后的HA 改变，以及野生型细胞与HDAC6 阴性细胞之间的融合等方面也都没有观察到差异。但是在HDAC6 阴性细胞中的确观察到病毒脱衣壳及病毒RNP 入(细胞)核的情况有所减少。这种对HDAC6 蛋白的依赖性很明显取决于HDAC6 蛋白能够与游离多聚泛素蛋白的结合能力，因为与对照组相比(与野生型HDAC6 蛋白重组或与脱乙酰基酶结构域发生突变的HDAC6 蛋白重组)，这些体外培养的细胞与含有突变HDAC6 蛋白(该蛋白的泛素结合结构域发生突变)重组之后同样会抑制病毒的脱衣壳过程和复制进程。Banerjee 等人还发现，HDAC6 蛋白能够与流感病毒的NP 蛋白及M1 蛋白结合，而且发现甲型流感病毒自身就携带游离的泛素蛋白单体及多聚体。综上所述，这些研究发现都表明，侵袭素能够促使流感病毒脱衣壳。

HDAC6 蛋白能够介导错误折叠的蛋白，使其沿微管转运至侵袭素系统，其作用机制就是依靠与肌动蛋白dynein，及其转运复合体组份dynactin 蛋白之间的相互作用。Banerjee 等人研究发现，借助RNA 干扰技术抑制dynactin 2 蛋白的表达，使用ciliobrevin D 抑制dynein 蛋白，或者使用细胞松弛素D(cytochalasin D)和噻氨酯哒唑(nocodazole)等方式，都可以阻止流感病毒脱衣壳过程。但是肌动蛋白和细胞骨架是否起到了促进脱衣壳的作用，现在还不得而知。不过无论如何，这些研究数据以及HDAC6 蛋白能够与游离多聚泛素蛋白链、NP 和M1 蛋白结合的事实都表明，侵袭素通路参与了流感病毒脱衣壳过程。

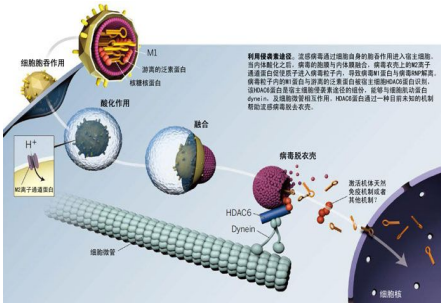


图2 利用侵袭素途径。

那么游离的泛素蛋白是如何进入病毒粒子的呢?虽然Banerjee 等人还没有确定泛素蛋白与病毒粒子和HDAC6 蛋白之间的连接方式(即是通过K63、K48，还是其他赖氨酸残基连接)，但之前的研究表明，游离的多聚泛素蛋白可以通过K63 方式与HDAC6 蛋白连接。Banerjee 等人在病毒粒子里发现了游离的泛素蛋白二聚体、三聚体和四聚体，这就产生了一个问题，这些不同长度(聚合程度)的多聚泛素蛋白被释放入细胞之后，是否具有不同的功能呢?现在也不清楚侵袭素途径是如何帮助病毒脱衣壳的。侵袭素途径是否也能够帮助其他被膜病毒脱衣壳，比如埃博拉病毒、HIV 病毒等。这些都是值得进一步去研究的课题。

Banerjee 等人开展的这项研究工作再一次向我们展示了病毒是如何利用细胞自身机制，帮助病毒复制。同时也再一次强调了最近多次被证实的，游离多聚泛素蛋白对于不同细胞通路的活化作用。由于我们已经证实，脱衣壳过程是阻止流感病毒感染的一个关键作用靶点，所以抑制侵袭素途径也应该可以成为一条抗流感病毒的重要策略。如果这种侵袭素途径抑制剂对人体是无毒的，那么就非常有可能解决目前M2 离子通道抑制剂类抗流感病毒日益加重的耐药问题。

UW Study Shows Direct Brain Interface Between Humans

November 7, 2014

Researchers at the University of Washington say they have replicated a direct brain-to-brain connection they first demonstrated in August, enabling someone to move the hand of another person just by thinking about it.

The researchers used a pair of non-invasive instruments and software to carry out the brain-to-brain communication. One participant, the sender, was connected to an electroencephalography machine, which recorded the electrical activity of their brain, which was then sent via the Internet to a transcranial magnetic stimulation coil worn by the other participant, the receiver.

The participants were located in separate buildings and were unable to communicate with each other any other way. The sender was watching a computer game that involved firing a cannon to intercept rockets being launched at a city, but was unable to interact with the game, while the receiver's hand was poised over the touchpad that controlled the cannon. The sender would think about clicking the touchpad to fire the cannon and in another building the receiver's hand would twitch accordingly.

During testing with six participants, the researchers achieved accuracy rates ranging from 25 to 83 percent. They plan to continue their research and hope to develop methods of transmitting not just motor commands, but concepts, thoughts, and rules.

From UW Today

The $11M Tool That Could Help Computers Write Their Own Code

November 7, 2014

Nowadays, if you start typing something into Google, it tries to guess what you’re looking for. Type “Wi,” and it might suggest “Wikipedia.” Key in “Bra,” and it’ll guess “Brad Pitt. Yes, these “autocomplete” suggestions are sometimes hilariously off the mark, but more often than not, they’re rather accurate, providing a handy shortcut to what you want.

Now, a government-backed research team wants to provide similar suggestions to the world’s programmers as they’re writing computer code. That’s right: the aim is to guess what programmers are coding before they code it.

This week, Rice University said that Darpa, the Pentagon’s mad science division, has invested $11 million in this autocomplete programming project, dubbed PLINY, after the ancient Roman author of the first encyclopedia, “Text search prediction is the best analogy,” says Vivek Sarkar, the chair of the computer science department at Rice and the principal investigator on the project. “People will be able to will be able to pick from a list of possible solutions.”

From Wired

Giving Robots a (Better Than) Human Touch

November 7, 2014

In order to further automate assembly lines, hospitals, and data centers, researchers need to develop machines that can perform certain actions as well as humans, such as manipulating objects. To meet this need, researchers at the Massachusetts Institute of Technology (MIT) and Northeastern University have demonstrated a robot that can grasp an unattached USB cable and insert it into a USB port.

The device's tactile sensor uses optics instead of pressure sensitivity to guide the connector into the port. The GelSight sensor has a layer of transparent synthetic rubber on one side, which conforms to the object it is pressed against; light that bounces off the magnetic paint that covers the layer is gauged to identify shape and the amount of pressure being applied to an object.

"The GelSight sensor...has high resolution in sensing," says Northeastern professor Robert Platt. "It detects a lot of detail in the surface texture of the things that it is touching."

The researchers note the sensor is about 100-times more sensitive than a human finger.

Algorithms developed by MIT professor Edward Adelson are fast enough to give the robot feedback in real time, enabling it to make adjustments for a successful insertion. Platt says the technology also is comparatively inexpensive, lending itself to commercialization.

From Government Computer News

Running Robots of Future May Learn From World’s Best Two-Legged Runners: Birds

November 5, 2014

Oregon State University (OSU) researchers have studied how birds are able to run while minimizing energy cost, avoiding falls or injury, and maintaining speed and direction with the goal of developing better running robots.

"Birds appear to be the best of bipedal terrestrial runners, with a speed and agility that may trace back 230 million years to their dinosaur ancestors," says OSU professor Jonathan Hurst.

Although evolution has shaped running birds into different sizes and skeletal structures, the OSU researchers found their running styles are essentially the same. The researchers focused on five species of birds and developed a computer model that closely matches that behavior.

"We should ultimately be able to encode this understanding into legged robots so the robots can run with more speed and agility in rugged terrain," says OSU researcher Christian Hubicki.

Running birds are very energy efficient because they allow their upper bodies to bounce around, changing their leg speed to stay upright. However, modern robots are usually built with an emphasis on total stability, which often includes maintaining a steady gait. This technique can be energy-intensive and sometimes limits robots' mobility.

The researchers say robotic control approaches "must embrace a more relaxed notion of stability, optimizing dynamics based on key task-level priorities without encoding an explicit preference for a steady gait."

From OSU News

Computer Game Could Help Visually-Impaired Children Live Independently

November 5, 2014

University of Lincoln researchers are developing Eyelander, a computer game they say could help visually-impaired children lead independent lives. The game focuses on improving the functional vision of children who have sight issues due to a brain injury rather than damage to the eye itself.

"We are tapping into the brain's innate ability to adapt (also known as neuroplasticity), and because substantial changes in vision are possible even into adulthood, this could yield real results," says Lincoln computational neuroscientist Jonathan Waddington. He says the game combines scientific knowledge of neuroscience and psychology with expertise in game development. "Clinical trials will get under way this summer to evaluate whether the software could become a valuable new tool for the treatment of children and young adults with visual impairments," Waddington says.

The game also features advanced options to adapt the difficulty to the specific cognitive and visual impairment of the person playing. "Research has already shown that this type of training can lead to significant recovery of sight following damage to visual centers of the brain in adults, so it is vital that those using it are motivated by something interesting and engaging," says Lincoln professor Timothy Hodgson.

From University of Lincoln