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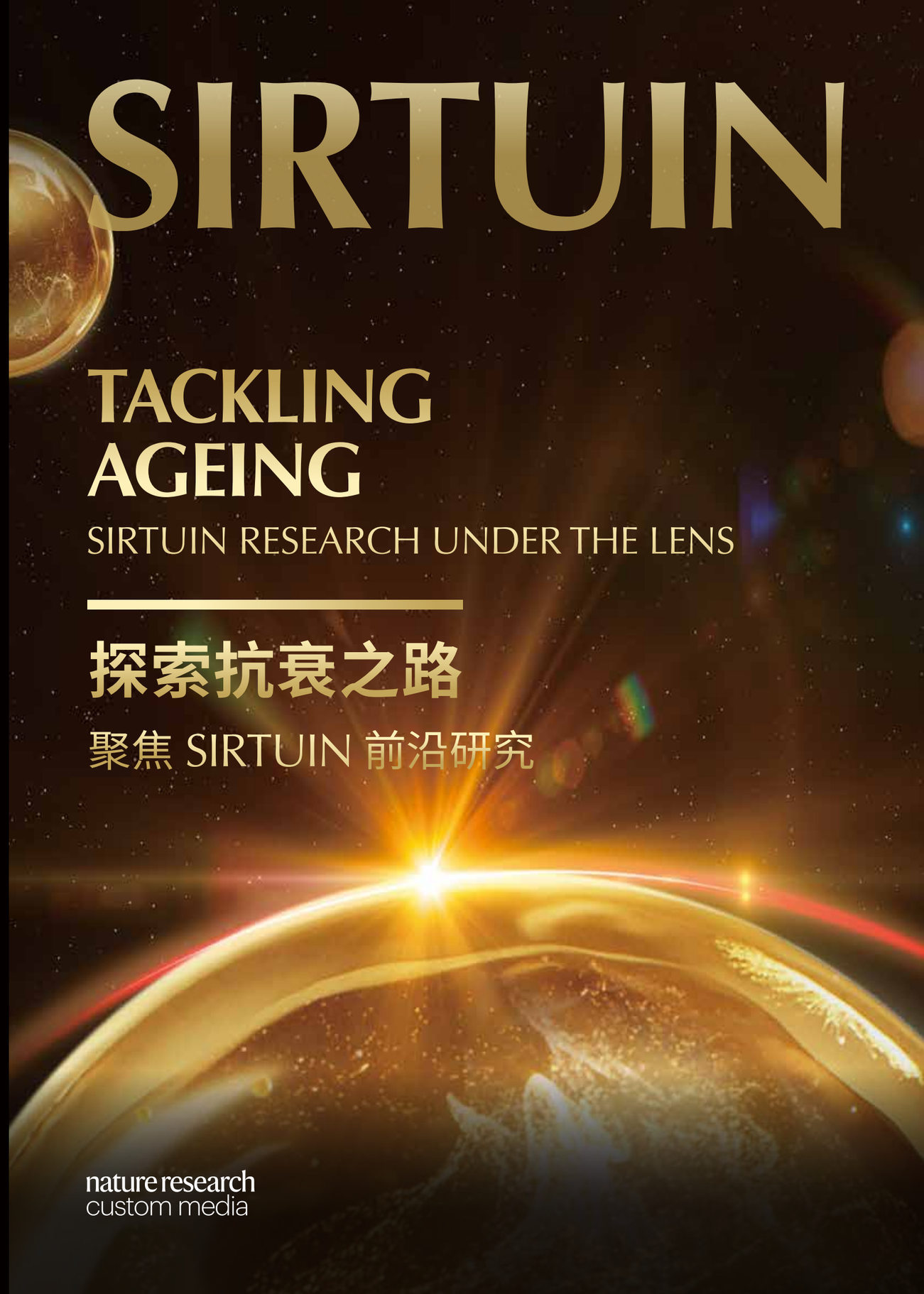
SIRTUIN

TACKLING AGEING

SIRTUIN RESEARCH UNDER THE LENS

探索抗衰之路

聚焦 SIRTUIN 前沿研究



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Unlocking the secrets of sirtuins

Sirtuins, a family of metabolic enzymes, play a variety of important roles in cell biology, including in inflammation, metabolism, response to oxidative stress and DNA repair. Sirtuins are thought to be key regulators of cellular function and have been of great interest to anti-ageing researchers in recent decades.

With a growing number of scientists exploring their role in the ageing process, and seeking compounds that regulate their activity, research may lead to exciting developments in ageing-related science, such as treatments for cancers and metabolic diseases, and improvements to skin care.

Building on these ongoing developments, researchers are developing small molecule activators or drugs to mitigate a wide range of ageing-linked issues. For example, the sirtuin 'SIRT1', which is directly involved in metabolic pathways, and its activators can prevent and reverse insulin resistance and diabetic complications, making them promising therapeutic targets for type 2 diabetes. In recent years, attention has further been focused on another sirtuin, 'SIRT6', which has the ability to extend lifespan in mice and regulate cellular processes through chromatin remodelling.

Research findings have also moved from the laboratory to the consumer domain in one important area, skin care: Estée Lauder's research has made it the leading company to offer skin care products built upon the science of sirtuins.

The following pages outline some of the most important findings made by researchers globally on sirtuins, including Estée Lauder scientists' findings on their actions within the skin.

解锁去乙酰化酶的奥秘

去乙酰化酶（sirtuin）是一类代谢酶家族，在炎症、代谢、氧化应激反应和DNA修复等细胞生物过程中具有很多重要功能。去乙酰化酶被认为是细胞功能的关键调节器，近几十年来一直受到抗衰老研究者的极大关注。

随着越来越多的科学家开始探索去乙酰化酶在衰老过程中的作用，寻找能调节其活性的化合物，我们将看到更多与衰老相关的重要发现，例如癌症和代谢性疾病的治疗方法以及护肤科技的提升。

在这些进展之上，研究人员着眼于能缓解各种衰老相关问题的小分子激活剂或药物的开发。例如，直接参与代谢通路的去乙酰化酶 SIRT1 及其激活剂能预防和逆转胰岛素抵抗和糖尿病并发症，被证明是很有希望的 2 型糖尿病治疗靶点。近年来，药物研发将重点转向了另一种去乙酰化酶——SIRT6，它被发现能延长小鼠寿命并通过染色质重塑调节细胞过程。

在另一个重要领域——护肤领域，研究结果也在从实验室走向消费者。雅诗兰黛的研究使其成为推出建立在去乙酰化酶这一科学基础上的护肤品的领先公司。

接下来的文章概括了全球各地的科研团队对于去乙酰化酶的重要研究发现，包括雅诗兰黛科学家对其在皮肤中作用的发现。

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Limiting stress to slow ageing

Several sirtuin proteins can regulate the skin's stress response to slow ageing and help maintain its integrity as a barrier.

Skin is our largest organ, protecting us from the environment and minimizing water loss from our bodies. But as time passes, damage takes its toll on the skin. Sirtuins, a group of proteins including SIRT1–7, have been implicated in slowing the ageing process, an exciting area for researchers to explore.

In a chapter in the book *Skin Stress Response Pathways*[1] published in 2016, Yu-Ying He at the University of Chicago, in Illinois, United States, summarizes knowledge about the role of sirtuins in skin cancer, ageing and barrier integrity. The researcher also covers the crucial role they play in moderating the skin's stress response.

As He explains, sirtuins SIRT1 and SIRT6 are important for regulating the function of two major skin cells called keratinocytes and fibroblasts.

SIRT1 may be involved in slowing ageing via its effect on fibroblasts, according to a 2010 study. Researchers from the Gifu International Institute of Biotechnology in Japan studied the effects of SIRT1 on ageing under inflammatory and non-inflammatory conditions. They discovered that, in both situations, SIRT1 has an impact on ageing by inhibiting the expression of enzymes, metalloproteinases 1 and 3, which can degrade a range of components within fibroblasts, including collagen.

SIRT6, which is involved in molecular pathways related to metabolism and ageing, may also play a role in skin ageing. According to a 2013 study from Stanford University, in California, United States, SIRT6 does this by promoting the reprogramming of fibroblasts into induced pluripotent stem cells, which have the ability to develop into many other cell types. Other studies have shown that SIRT6 can also regulate the metabolism of collagen in fibroblasts.

The author also highlights the effects of SIRT1 and SIRT3 on keratinocyte cells, which are abundant in the skin's outermost layer, the epidermis. Here they help maintain an impermeable barrier to the skin, limiting damage over time.

> "Sirtuins SIRT1 and SIRT6 are important for regulating the function of two major skill cell types."

SIRT1 may exert anti-ageing effects by promoting differentiation of keratinocytes, according to a 2009 study, while the essential role of SIRT1 in maintaining the integrity of the skin barrier was shown by a 2015 study that revealed a loss of skin integrity in mice genetically engineered to lack SIRT1.

SIRT3, on the other hand, may help limit oxidative stress in mitochondria, which are crucial for differentiation of keratinocytes. Other work has shown that exposure to ozone decreases SIRT3 levels, and further research into the role of SIRT3 may point at prevention measures or treatments for ozone-related skin diseases.

"It is also critical to identify new regulatory and functional roles of sirtuins in the skin and to expand our knowledge of the functions of sirtuins in skin cancer, ageing and barrier function," He writes. This may open new opportunities for prevention and treatment of skin conditions. ■

Reference

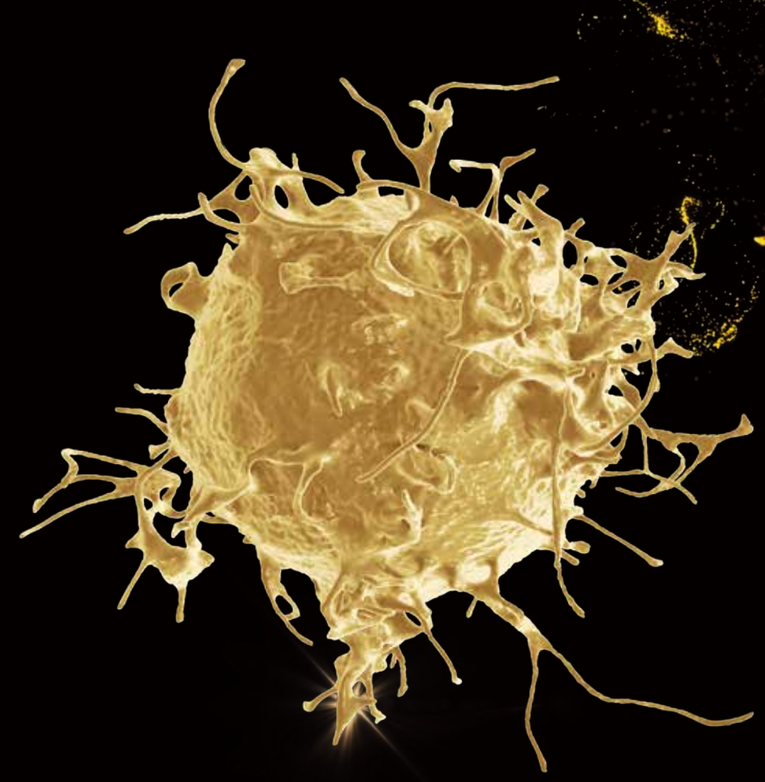
1. He, YY. *Skin Stress Response Pathways*, 251–263 (2016). https://doi.org/10.1007/978-3-319-43157-4_12

Pixelmage / iStock / Getty; Anna Efetova/ Moment/ Getty

This article is an editorially-independent research highlight that ran originally in Nature Portfolio and was sponsored by Estée Lauder.

Sirtuins have been found to play a crucial role in skin cancer, ageing and skin barrier integrity.

皮肤癌细胞图示。去乙酰化酶已被发现在皮肤癌、衰老和保持皮肤屏障的完整方面扮演着重要作用。



Kateryna Kon/Science Photo Library/Getty; iStock / Getty

减少应激，延缓衰老

数种去乙酰化酶不但能调节皮肤的应激反应以延缓衰老，还有助于维持皮肤的屏障完整性。

皮肤是我们最大的器官，能保护我们免受环境侵害，同时最大限度地减少身体的水分流失。但随着时光流逝，伤害的产生，皮肤会不可避免地发生老化。去乙酰化酶（sirtuin）是一类蛋白质家族，成员包括 SIRT1 ～ SIRT7，已有研究发现它们与延缓衰老有关，研究人员也一直在积极地探索这一领域。

在 2016 年出版的《皮肤应激反应通路》（*Skin Stress Response Pathways*）[1] 一书中，美国芝加哥大学的 Yu-Ying He 总结了目前关于去乙酰化酶在皮肤癌、衰老和屏障完整性中作用的认知进展，以及去乙酰化酶在缓解皮肤应激反应方面的关键作用。

He 在书中解释道，去乙酰化酶 SIRT1 和 SIRT6 对于两种主要皮肤细胞的功能调节很重要，这两种细胞分别是角质形成细胞和成纤维细胞。

根据 2010 年的一项研究，SIRT1 可能通过其对成纤维细胞的影响帮助延缓衰老。日本岐阜国际生物技术研究所的团队研究了 SIRT1 在炎症和非炎症条件下对衰老的影响。他们发现，在这两种条件下，SIRT1 都能通过抑制金属蛋白酶 1 和 3 的表达来影响衰老进程，而这些酶会降解成纤维细胞内的各种成分，包括胶原蛋白。

SIRT6 参与了与代谢和衰老有关的分子通路，在皮肤衰老过程中或也起到了作用。美国斯坦福大学 2013 年的一项研究发现，SIRT6 可促进成纤维细胞重编程为诱导多能干细胞，而诱导多能干细胞能分化成许多其他细胞类型，既而发挥抗衰老的作用。其他研究表明，SIRT6 也可以调节成纤维细胞中胶原蛋白的代谢。

> "去乙酰化酶 SIRT1 和 SIRT6 对于两种主要皮肤细胞的功能调节很重要。"

作者还强调了 SIRT1 和 SIRT3 对角质形成细胞的影响，角质形成细胞在皮肤最外层的表皮中含量最高，它们在表皮中参与维持皮肤屏障，减少外界对皮肤日积月累的损害。

根据 2009 年的一项研究，SIRT1 可能是通过促进角质形成细胞的分化来发挥抗衰老作用，而 2015 年的一项研究显示，SIRT1 在维持皮肤屏障的完整性方面起着至关重要的作用。该研究发现，通过基因改造在皮肤中缺少 SIRT1 的小鼠丧失了皮肤屏障完整性。

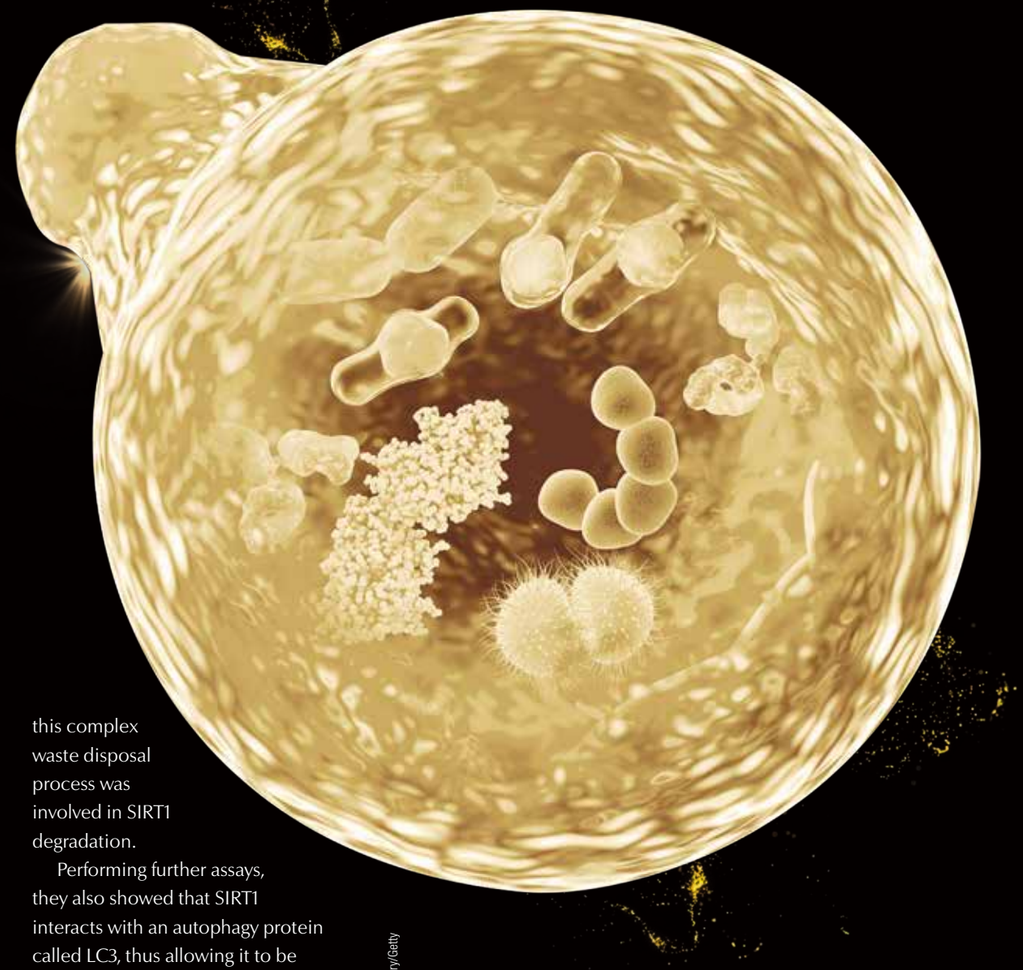
SIRT3 则可能有助于减少线粒体的氧化应激，这对角质形成细胞的分化非常关键。其他研究表明，暴露于臭氧中会降低 SIRT3 的水平，进一步研究 SIRT3 的作用，或能揭示臭氧相关皮肤病的预防或治疗策略。

He 在书中写道，"明确去乙酰化酶在皮肤中的其他调节作用和功能，深入了解去乙酰化酶在皮肤癌、衰老和屏障功能中的作用，至关重要。"这将为预防和治疗皮肤相关疾病开辟新的可能。■

本文是一篇独立编辑的研究亮点摘要，发布于 Nature Portfolio，由雅诗兰黛赞助。

Cellular clean-up processes point to rejuvenating treatments

Understanding how an important enzyme is cleaned up in older cells hints at anti-ageing therapies.



Kateryna Kon /Science Photo Library/Getty

An illustration of an autophagosome, a double-membrane vesicle involved in the degradation of unwanted or damaged cellular components.

自噬体图示。自噬体是一种双膜囊泡，参与不再需要的或受损的细胞成分的降解过程。

Blocking the body's removal of an important kind of enzyme called a sirtuin may lead to new anti-ageing treatments, according to scientists. The discovery comes from research revealing a surprising mechanism for the way autophagy — a process that cleans out damaged components of cells — flushes the SIRT1 enzyme out of our bodies. SIRT1 is a sirtuin thought to be tightly linked with the ageing process.

The study, led by Zhixun Dou and Shelley L Berger at the University of Pennsylvania in Philadelphia, United States, was published in 2020 in *Nature Cell Biology*[1].

Sirtuins are a family of enzymes, found in human and other mammals, which can strip the acetyl molecular group from certain proteins, changing their function. SIRT1 plays a crucial role in a broad range of processes, including metabolism and ageing. However, little is known about how its levels change as we get older.

One widely recognized hallmark of ageing is cellular senescence, when cells permanently lose their ability to divide.

Using cell cultures, Dou and colleagues observed markedly reduced levels of SIRT1 protein in multiple induced senescent cells compared to proliferating cells, suggesting the enzyme is being removed from senescent cells.

> The discovery that SIRT1 levels fall as we age may eventually lead to new treatments to slow the ageing process.

They found that SIRT1 is flushed out by autophagy, whereby unwanted or damaged components of cells are encircled by vesicles called autophagosomes which carry them to waste-disposal organelles called lysosomes to break them up.

By blocking the lysosomes in senescent cells, researchers found that SIRT1 levels were restored, suggesting this complex waste disposal process was involved in SIRT1 degradation.

Performing further assays, they also showed that SIRT1 interacts with an autophagy protein called LC3, thus allowing it to be delivered to the autophagosomes for the next step.

This mechanism was then confirmed *in vivo*, in the tissues of young and old mice, as well as in human immune cells. Accordingly, SIRT1 levels also significantly decline in old mice and ageing human cells via LC3-dependent autophagy.

The discovery that SIRT1 levels fall as we age may eventually lead to new treatments to slow the ageing process. "Stabilization of SIRT1 protein levels, for example, through the interruption of the SIRT1–LC3 interaction, could be a new direction for the design of anti-ageing compounds," the authors write. ■

Reference

1. Dou, Z., Berger, S. *Nature Cell Biology* **22**, 1170-1179 (2020). https://www.nature.com/articles/s41556-020-00579-5

This article is an editorially-independent research highlight that ran originally in Nature Portfolio and was sponsored by Estée Lauder.

细胞清理过程研究为抗衰提供新方向

理解细胞内一种关键酶的清除机制，或为抗衰老疗法提供了新思路。

去乙酰化酶（sirtuin）是一类很重要的酶，研究发现，阻断体内去乙酰化酶的清除或能引领新的抗衰老疗法。这一发现来自于一种最近被揭示的机制：老化的细胞如何利用自噬——清除细胞受损成分的过程——将SIRT1酶从我们体内清除。SIRT1是一种被认为与衰老过程密切相关的去乙酰化酶。

这项研究由宾夕法尼亚大学的Zhixun Dou和Shelley L Berger领导，发表在2020年的《自然 - 细胞生物学》（*Nature Cell Biology*）[1]上。

去乙酰化酶是在人类和其他哺乳动物中发现的一个酶家族，可以去除特定蛋白质的乙酰基团，改变蛋白质的功能。SIRT1在代谢和衰老等众多过程中起着至关重要的作用。然而，人们对SIRT1水平随年龄增长的变化知之甚少。

细胞衰老（cellular senescence）是指细胞不再具有分裂能力的现象，是一种被普遍认可的老化标志。

Dou和同事在细胞培养中观察到，与正在增殖的细胞相比，多重诱发衰老模型细胞中的SIRT1蛋白水平明显降低，这表明该酶正在被衰老细胞清除。

研究人员发现，自噬过程会将细胞内的SIRT1清理掉。自噬发生时，不再需要的或受损的细胞成分会被名为自噬体的囊泡包围，自噬体将它们递送至溶酶体（负责"垃圾"处理的细胞器）中进一步分解。

团队发现，通过阻断衰老细胞内的溶酶体，细胞的SIRT1水平得到了恢复。这一现象证明，自噬这种复杂的废物处理过程参与了SIRT1的降解。

进一步的实验表明，SIRT1会与自噬蛋白LC3相互作用，使其被送到自噬体中进行下一步清除。

利用年轻和年老小鼠的组织以及人类免疫细胞，该机制在体内得到了证实。在年老小鼠和人类衰老细胞中，SIRT1水平也因LC3介导的自噬过程有明显降低。

揭示SIRT1的水平会随年龄增长而下降，或有助于开发新的抗衰老疗法。作者写道，"维持SIRT1蛋白的水平，例如通过阻断SIRT1和LC3的相互作用，可能是设计抗衰老化合物的一个新方向。"■

> 揭示SIRT1的水平会随年龄增长而下降，或有助于开发新的抗衰老疗法。

本文是一篇独立编辑的研究亮点摘要，发布于Nature Portfolio，由雅诗兰黛赞助。

Gatekeepers of cellular powerhouses

A sirtuin protein can limit oxidative damage to mitochondrial DNA and prevent cell death.

Mitochondria are the energy-supplying powerhouses of our cells, but their DNA is prone to oxidative damage, a major driver of the symptoms of ageing. Researchers discovered some years ago that sirtuins, a group of enzymes that help regulate metabolism, cellular stress response and inflammation, may have a protective effect on mitochondrial DNA, limiting cell death from stress.

The study was published in *Cell Death & Disease*[1] by a team led by Jinming Yang, at Pennsylvania State University College of Medicine, in Hershey, United States.

The protective role is mediated through 'deacetylation' of a DNA repair enzyme called OGG1. A sirtuin called SIRT3 directly binds to the enzyme, and removes so-called acetyl groups, leading to changes which affect the molecule's behaviour. By removing acetyl groups, sirtuins have the potential to dramatically change the functions of proteins and the role they play in metabolism.

To prove the link between SIRT3 and OGG1, the researchers showed that changing the amount of SIRT3 expressed within cells alters the degree to which OGG1 was deacetylated, impacting its ability to repair damaged mitochondrial DNA. Conversely, they also showed that reducing expression of the sirtuin increased acetylation of the enzyme, the adding of acetyl groups, limiting its function.

The levels of the enzyme in SIRT3-depleted cells were found to be much lower than in cells expressing SIRT3, showing that the sirtuin can stabilize the enzyme and prevent its degradation.

To further understand SIRT3's effects on OGG1 activity, the researchers irradiated cells with gamma rays, inducing DNA damage. In SIRT3-deficient cells, both the structure of mitochondria and mitochondrial DNA showed more damage than control cells without SIRT3 depletion. These cells were also more likely to undergo programmed cell death.

> "This knowledge may be used to aid the treatment of conditions associated with mitochondrial DNA damage.

These findings highlight the important role of SIRT3 in preserving mitochondrial DNA and preventing cell death. This knowledge may be used to aid the treatment of conditions associated with mitochondrial DNA damage such as ageing, cancer and degenerative diseases.

The researchers have also found that the expression level of SIRT3 correlates with the ability of cancerous tumour cells to proliferate. Further research into SIRT3's role could shed light on the development of new treatments. ■

Reference

1. Cheng, Y., *et al. Cell Death Dis* **4**, e731 (2013). https://doi.org/10.1038/cddis.2013.254

3d_man/Shutterstock

An illustration of mitochondria, the energy-supplying powerhouses of our cells.

线粒体图示。线粒体是我们细胞的能量供给站。

细胞动力的守护者

线粒体是我们细胞的能量供给站，但它们的DNA很容易受到氧化损伤，这是导致衰老的主要因素之一。研究人员几年前发现，一种帮助调节新陈代谢、细胞应激反应和炎症的酶，可能对线粒体 DNA 有保护作用，阻止细胞因应激而死亡。这种酶即为去乙酰化酶（sirtuin）。

宾夕法尼亚州立大学医学院的 Jinming Yang 和其团队在 *Cell Death & Disease*[1] 上发表了该项研究。

一种叫做 OGG1 的 DNA 修复酶的去乙酰化介导了这种保护作用。去乙酰化酶家族中的一员 SIRT3 与 OGG1 直接结合，并去除 OGG1 的乙酰基，从而导致 OGG1 分子功能发生变化。通过去除乙酰基，sirtuin 有可能极大地改变蛋白质的功能及其在新陈代谢中的作用。

为了证明 SIRT3 和 OGG1 之间的关联，研究人员通过实验证明，改变细胞内 SIRT3 的表达量会改变 OGG1 去乙酰化的程度，从而影响其修复受损线粒体 DNA 的能力。另外，他们还表明，减少 SIRT3 的表达会增加 OGG1 的乙酰化（即为酶添加乙酰基官能团），导致后者功能受限。

研究者发现，缺乏 SIRT3 细胞中的 OGG1 水平远低于表达 SIRT3 的细胞，表明 SIRT3 可以稳定 OGG1 并防止其降解。

为了进一步了解 SIRT3 对 OGG1 活性的影响，研究人员用伽马射线照射细胞，诱导产生 DNA 损伤。与表达 SIRT3 的对照细胞相比，在缺乏 SIRT3 的细胞中，线粒体结构和线粒体 DNA 都显示出更多的损伤。同时，这些细胞进入程序性细胞死亡的可能性更高。

这些发现突出了 SIRT3 对于保护线粒体 DNA 和防止细胞死亡具有重要作用。这些发现可能会被用来帮助治疗与线粒体 DNA 损伤相关的疾病，例如衰老、癌症和退行性疾病。

研究人员还发现，癌细胞增殖的能力与 SIRT3 的表达水平相关。进一步研究 SIRT3 的作用可能有助于开发新的治疗方法。■

一种去乙酰化酶可以限制线粒体DNA的氧化损伤，防止细胞死亡。

> "这些发现可能会被用来帮助治疗与线粒体 DNA 损伤相关的疾病。

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Guarding chromosomes to avert cellular ageing

A sirtuin enzyme tinkers with the tips of chromosomes to delay ageing in human skin cells.

In 2008, researchers reported in *Nature* a crucial role of the sirtuin SIRT6 in controlling the lifespan of human cells[1]. The team, led by Katrin Chua, at Stanford University, in California, United States, discovered the enzymatic activity of SIRT6, and revealed its link between the regulation of chromosome structure, cellular senescence, and, potentially, organismal ageing.

Previous work had shown that lack of SIRT6 leads to a shorter lifespan and premature ageing in mice, but the mechanism underlying these effects was unknown.

Chua and colleagues reduced the levels of SIRT6 in human skin cell culture by knocking out the gene that expresses the protein. They found that SIRT6-deficient cells prematurely hit senescence — the stage at which they stop dividing in old age — affecting the body's ability to withstand stress or illness. They observed in these cells a significantly lower number of divisions before death than in the control cells; as well as higher levels of beta-galactosidase, a marker of cellular senescence.

These findings prompted the researchers to look at the cells' telomeres, repetitive DNA sequences associated with specialized proteins, called histones, on the ends of chromosomes. Each time a cell divides its telomeres shorten, often used as a marker of cellular ageing. Although the mean telomere length was not significantly reduced in cells lacking SIRT6, they found signs that telomere function was impaired.

Performing further assays, the researchers confirmed that SIRT6 associates with telomeres, suggesting that SIRT6 activity could modify within telomeres the structure of a protein-DNA complex called chromatin, which is kept in check by histones.

Chua and colleagues demonstrated that SIRT6 could efficiently and specifically remove acetyl groups from specific lysine residues on histones on telomeres. This allowed the histones to wrap the DNA more tightly, potentially slowing the ageing process of the chromosomes.

Intriguingly, the telomere dysfunction observed in SIRT6-deficient cells, was similar to that observed in cells from people with Werner Syndrome, a premature ageing condition characterized by mutations in the gene WRN. When the authors examined the association of the gene with telomeric chromatin, they found a significant reduction in WRN in SIRT6-deficient cells compared with control cells.

Although SIRT6 and WRN don't seem to directly interact, the authors suggest that SIRT6 promotes the formation of a special telomeric chromatin state required for the stable association of WRN and other factors that prevent telomere dysfunction during cell division, limiting premature cellular ageing.

Since the discovery of its role in ageing, SIRT6 has been implicated in ageing-related disorders, including cancers and cardiovascular and neurodegenerative diseases. Compounds that modulate SIRT6 activity may alleviate many conditions and extend healthy lifespan, researchers suggest. ■

> “Previous work had shown that lack of SIRT6 leads to a shorter lifespan and premature ageing in mice.

Reference

1. Michishita, E., McCord, R., Berber, E. *et al.* *Nature* **452**, 492–496 (2008). https://doi.org/10.1038/nature06736

noteastsoflerce/Shutterstock

Telomeres are found on both ends of chromosomes, as depicted in this illustration. Their shortening is often used a marker of cellular ageing.

染色体图示。端粒位于染色体的两端，端粒长度缩短通常被认为是细胞衰老的标志之一。

This article is an editorially-independent research highlight that ran originally in Nature Portfolio and was sponsored by Estée Lauder.

保护染色体，避免细胞老化

一种去乙酰化酶能修补染色体末端，延缓人类皮肤细胞的衰老。

2008 年，研究人员在《自然》（*Nature*）上报道了去乙酰化酶 SIRT6 在调控人类细胞寿命中的关键作用[1]。该团队由美国斯坦福大学的 Katrin Chua 领导，不仅发现了 SIRT6 的酶活性，还揭示了它在调控染色体结构、细胞衰老以及潜在的机体老化之间的联系。

此前有研究表明，缺乏 SIRT6 会导致小鼠寿命减短和早衰，但其背后的机制并不明确。

Chua 及其同事通过敲除表达 SIRT6 的基因，降低了该蛋白在培养的人皮肤细胞中的水平。他们发现，缺乏 SIRT6 的细胞会过早地进入衰老状态，即细胞在老年时停止分裂的阶段，从而影响身体应对应激或疾病的能力。他们观察到，这些细胞死亡前的分裂量明显低于对照组，同时它们的 β - 半乳糖苷酶水平更高—— β - 半乳糖苷酶是一种衰老标志物。

基于以上发现，团队进一步研究了这些细胞的端粒，端粒是在染色体末端与特殊蛋白质——组蛋白——相结合的重复 DNA 序列。每次细胞分裂时，其端粒就会缩短。因此，端粒长度缩短通常被作为细胞衰老的标志之一。尽管缺乏 SIRT6 的细胞的平均端粒长度没有显著缩短，但团队发现了端粒功能受损的迹象。

通过进一步分析，团队证实了 SIRT6 与端粒有关，揭示了 SIRT6 的激活可以在端粒内改变名为染色质的蛋白质 -DNA 复合物的结构，该结构由组蛋白控制。

Chua 及其同事证明了 SIRT6 可以有效且特异性地从端粒组蛋白的特定赖氨酸残基上去除乙酰基团。这使得组蛋白能够更紧密地包裹 DNA，从而有可能减缓染色体的老化。

有趣的是，在缺乏 SIRT6 的细胞中观察到的端粒功能受损与在 Werner 综合征患者的细胞中观察到的相似。Werner 综合征是一种以 WRN 基因突变为特征的早衰综合征。团队在研究该基因与端粒染色质的关联时发现，与对照组的细胞相比，缺乏 SIRT6 的细胞中 WRN 基因显著减少。

尽管 SIRT6 与 WRN 之间似乎没有直接的相互作用，但作者认为 SIRT6 能让端粒染色质处于一种特殊状态，这种状态对 WRN 与其他因子的稳定结合至关重要，这些结合可以防止细胞分裂过程中的端粒功能受损，抑制细胞早衰。

自从发现 SIRT6 在衰老中的作用以来，更多研究揭示了 SIRT6 会影响与衰老相关的许多疾病，比如癌症、心血管和神经退行性疾病。研究人员表示，调节 SIRT6 活性的化合物或能缓解许多疾病，延长寿命。■

> “此前有研究表明，缺乏 SIRT6 会导致小鼠寿命减短和早衰。

本文是一篇独立编辑的研究亮点摘要，发布于 Nature Portfolio，由雅诗兰黛赞助。

A novel tool for discovering drug targets

By revealing the structure of a sirtuin, researchers have allowed for its exploration as a drug target for cancers and other diseases.

Revealing the structure of a protein that may play an important role in cancers, inflammation, infection and neurological diseases has made way for its investigation as a potential drug target, according to researchers at the Albert Ludwig University of Freiburg in Germany.

Sirtuins are an ancient group of enzymes found in mammals, which act to remove the acetyl chemical group from certain proteins, changing their function. They are involved in metabolism, cell division and the ageing process.

For example, a sirtuin called SIRT2 can act on several proteins, such as alpha-tubulin, one of the main components of the microtubules that form a cell's cytoskeleton, providing structure and shape to the cell.

Until now, SIRT2 has been proven to have multiple uses in metabolism, such as cleaning up waste inside cells and inhibiting brain inflammation, making it a potential drug target against cancers and neurodegeneration. SIRT2 has been hard to study because of a lack of knowledge about molecules that bind to and interact with it. Such molecules are one of the tools that scientists use to explore the structure of enzymes.

Several years ago, an international team led by Oliver Einsle and Manfred Jung at Albert Ludwig University, in Freiburg, Germany, succeeded in imaging the structure of SIRT2 using X-ray crystallography, by binding it to another protein called SirReal2 whose structure was already known.

As they described in the journal *Nature Communications*, the protein is significant because it is highly selective for SIRT2, binding to it and inhibiting it 1,000 times more strongly than any other sirtuin[1].

The scientists discovered SirReal2 by screening a large number of proteins and discovering a family of sirtuin-rearranging ligands, of which SirReal2 showed the most promise.

This was confirmed in cell cultures, where the addition of SirReal2 led to an increase in the levels of a metabolic process that SIRT2 usually limits, suggesting SIRT2 had been inhibited.

The discovery of SirReal2, and the imaging of its structure when it is bound to SIRT2, provided crucial clues about the interaction between this sirtuin and an inhibitor, offering scientists a fresh tool to explore the function of SIRT2 in the body.

The finding has enabled researchers to explore in greater depth the roles that SIRT2 plays in diseases including many cancers, which will help the study and development of pharmaceuticals. ■

Reference

1. Rumpf, T., Schiedel, M., Karaman, B. *et al.* *Nat Commun* **6**, 6263 (2015). https://doi.org/10.1038/ncomms7263

“SIRT2 has been proven to have multiple uses in metabolism.

Microtubules are a component of a cell's cytoskeleton, maintaining shape and structure.

Estée Lauder

微管图示。微管是细胞骨架的一个组成部分，维持着细胞的形状和结构。

“SIRT2 已被证明在代谢中具有多重功能。

发现药物靶点的新工具

研究者揭示了一种去乙酰化酶的结构，有望将其作为癌症等疾病的药物靶点进行探索。

德国弗赖堡大学的研究者揭示了一种可能在癌症、炎症、感染和神经系统疾病中发挥重要作用的蛋白质的结构，为其作为药物靶点的研究打开了大门。

去乙酰化酶（sirtuin）是在哺乳动物中发现的一类古老的酶，能去除某些蛋白质中的乙酰化学基团，从而改变蛋白质的功能。去乙酰化酶参与了代谢、细胞分裂和衰老的过程。

其中，一种称为 SIRT2 的去乙酰化酶可以作用于多种蛋白质，例如 α- 微管蛋白。α- 微管蛋白是微管的主要成分之一，而微管构成细胞骨架，为细胞提供结构和形状。

到目前为止，SIRT2 已被证明在代谢中具有多重功能，如清理细胞内垃圾和抑制脑部炎症。这些功能使 SIRT2 成为治疗癌症和神经退化疾病的潜在药物靶点。但是，由于缺少已知能与 SIRT2 结合并互作的分子，对 SIRT2 的研究一直难有进展。而科学家需要利用这些分子来研究酶的结构。

几年前，由德国弗赖堡大学的 Oliver Einsle 和 Manfred Jung 领导的国际团队成功使用 X 射线晶体成像技术测定了 SIRT2 的结构。他们方法是将其与另一种蛋白质 SirReal2 结合，而 SirReal2 的结构是已知的。

该团队在《自然 - 通讯》（*Nature Communications*）上报道，SirReal2 非常重要，因为它与 SIRT2 的互作具有高度选择性，能与 SIRT2 结合，对其产生的抑制作用比其他任何去乙酰化酶强 1000 倍以上[1]。

科学家通过筛选大量蛋白质鉴定出了 SirReal2，并发现了一个去乙酰化酶重排配体家族，其中 SirReal2 最具潜力。

以上结果在细胞培养实验中得到了证实：加入 SirReal2 会使 SIRT2 原本抑制的代谢过程水平上升，表明 SIRT2 受到了抑制。

SirReal2 的发现以及其与 SIRT2 结合时的结构成像，揭示了关于这种去乙酰化酶和抑制剂之间相互作用的关键线索，为科学家提供了一个探索 SIRT2 在体内功能的新工具。

这一发现使研究人员能更深入地研究 SIRT2 在各类癌症等疾病中的作用，并将助力药物的研究和开发。■

This article is an editorially-independent research highlight that ran originally in Nature Portfolio and was sponsored by Estée Lauder.

本文是一篇独立编辑的研究亮点摘要，发布于 Nature Portfolio，由雅诗兰黛赞助。

The quest to understand the power of sirtuins

Estée Lauder's scientists have undertaken a remarkable 15-year journey to investigate the links between sirtuins and ageing.

Estée Lauder researchers have long pursued a deep knowledge about the role of metabolic enzymes called sirtuins in the process of ageing in our skin. The team has made a series of discoveries about their function in skin biology, particularly SIRT1, SIRT2, SIRT3 and SIRT6, and how their levels might be modulated to slow visible signs of ageing.

In 2008, a team led by Dr Nadine Pernodet, a biologist and senior vice president in the R&D division, revealed SIRT1's involvement in regulating the differentiation and division of keratinocyte cells, which are crucial to maintaining the structure and integrity of the epidermis. Estée Lauder researchers also developed a stable form of resveratrol, a sirtuin-activating compound, to help boost SIRT1 activity, which naturally decline with age.

Skin is constantly exposed to stress and damage, from the impact of UV light, to that of oxidative reactions in cells. Pernodet's team further showed that levels of SIRT3 in skin cells are affected by the environment, and UV light disrupts cyclic patterns of SIRT3 and SIRT4 expression.

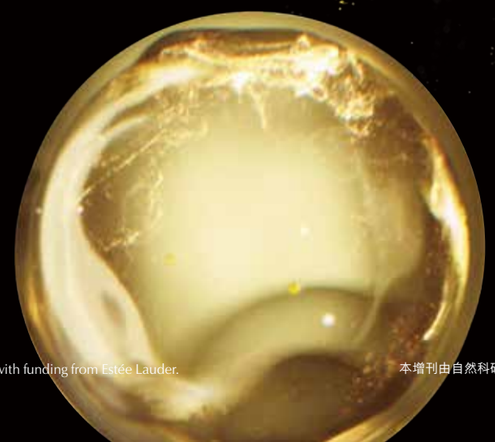
Even deeper within cells, in the nucleus, SIRT6 has been found to regulate several factors that affect the ageing process, such as stress. To find out more, Pernodet's team knocked down the expression of SIRT6 to inhibit its activity in another type of skin cell called a fibroblast. This led to increased metabolic processes linked to stress, which SIRT6 helps to control, as well as increased cellular damage, both in the presence and absence of UV light. In preliminary, yet-to-be published research, the researchers have identified a way to boost SIRT6 activity, helping to slow these damaging processes in the skin.

In the past few years, Estée Lauder scientists have set their sights on SIRT2, which has been found to help regulate microtubules — elements of a cell's internal cytoskeleton, which play an important role in cellular shape and structure. According to Pernodet's team's ongoing research, increasing levels of SIRT2 could reduce skin cell ageing and support the skin's natural mechanical properties.

The challenge for researchers now is to find ways to impact levels of many sirtuins simultaneously, creating a symphony of beneficial changes for the skin, she says. ■

Estée Lauder; Mrs Moon/Shutterstock

> “Skin is constantly exposed to stress and damage, from the impact of UV light, to that of oxidative reactions in cells.



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探索去乙酰化酶的力量

十多年来，雅诗兰黛的科研团队一直在研究去乙酰化酶（sirtuin）这种代谢酶在皮肤衰老过程中的作用。该团队已经取得了一系列研究进展，尤其是 SIRT1、SIRT2、SIRT3 和 SIRT6 等去乙酰化酶在皮肤中的生物学功能，以及如何调节它们的水平来延缓皮肤衰老迹象。

早在 2008 年，雅诗兰黛研发部高级副总裁、生物学家 Nadine Pernodet 博士领衔的团队就发现，SIRT1 参与调节了角质形成细胞的分化和分裂，而角质形成细胞对于维持表皮的结构和完整性至关重要。雅诗兰黛的研究人员还开发了一种用于活化 SIRT1 的化合物——稳定的白藜芦醇。SIRT1 活性会随年龄增长而下降，而这种白藜芦醇有助于使 SIRT1 的活性恢复至年轻时的水平。

皮肤长期承受各种压力和损伤，面临着从紫外线到细胞氧化反应等一系列伤害。Pernodet 团队的研究进一步发现皮肤细胞内的 SIRT3 水平对环境很敏感，而紫外线能破坏 SIRT3 和 SIRT4 表达的周期性模式。

研究团队还发现，在更深处的细胞核中，SIRT6 能调节影响衰老进程的多个因素，例如压力。为深入了解，Pernodet 的团队通过敲低 SIRT6，抑制其在名为成纤维细胞的皮肤细胞内的活性。SIRT6 的敲低导致了与压力有关的代谢过程的增加，而 SIRT6 有助于控制压力；同时在紫外线照射和无紫外线照射的情况下都观察到细胞损伤的增加。在尚未发表的初步研究中，团队确定了一种提高 SIRT6 活性的方法，能帮助减缓皮肤中的这些破坏性过程。

过去几年里，雅诗兰黛的科学家将目光投向了 SIRT2。SIRT2 被发现能调节微管，微管是细胞骨架的成分，在细胞形状和结构中起着重要作用。Pernodet 团队正在进行的研究表明，提高 SIRT2 水平可以减少皮肤细胞老化的迹象并支撑皮肤的自然力学特性。

Pernodet 表示，未来几年的研究方向是找到能同时调节多种去乙酰化酶水平的方法，奏响对皮肤有益变化的“交响曲”。■

> “皮肤长期承受各种压力和损伤，面临着从紫外线到细胞氧化反应等一系列伤害。

15年来，雅诗兰黛的科研团队孜孜不倦地探索着去乙酰化酶与衰老的关系。

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