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As life expectancy grows around the world, there is an increasing need for healthy ageing. On this ongoing quest, scientists globally are exploring the biology of ageing and looking for effective interventions — including nutritional supplements — to tackle ageing. One enzyme related to energy metabolism called nicotinamide adenine dinucleotide (NAD+) has been increasingly explored as a contributor to healthy ageing. Within this supplement you will find research highlights summarizing important papers in this growing field of research.

随着全球预期寿命增长，人们对健康衰老的需求日益增加。在这一持续探索的过程中，全球科学家正在揭开衰老的生物学原理，并致力于寻找对抗衰老的有效措施，例如营养补充剂。其中，有一种与能量代谢有关的酶，即烟酰胺腺嘌呤二核苷酸（NAD+），不断吸引科学家的注意。在本增刊中，您将读到多篇相关研究亮点，它们总结了这一不断发展的研究领域中的重要论文。

EXPLORING NAD+

Counteracting cellular ageing

探索 NAD+

对抗细胞衰老

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NAD+: how an enzyme influences metabolism and ageing

A study has looked into how nicotinamide adenine dinucleotide influences multiple ageing-related processes.

According to the World Health Organization, global life expectancy increased from 66.8 to 73.4 years between 2000 and 2019. While people live longer, they hope to tackle ageing and stay healthy.

Over the past two decades, an enzyme related to energy metabolism called nicotinamide adenine dinucleotide (NAD+), has been increasingly recognized as a contributor to healthy ageing.

NAD+ acts as a coenzyme — an organic molecule that assists in catalysis — in redox reactions. Beyond its redox functions, NAD+ is also an essential co-factor or substrate for hundreds of enzymes, with multiple roles in the regulation of many key cellular processes and functions important for maintaining health, making it an essential coenzyme for human body.

In a comprehensive review, published in *Nature Reviews Molecular Cell Biology*[1] in 2021, researchers at the Buck Institute for Research on Aging in Novato, California, United States, summarized recent advancements in the NAD+ field.

A variety of preclinical studies in various model systems, including rodents and human primary cells, have established that ageing is accompanied by a gradual decline in NAD+ levels. This decline has been linked with alterations in many enzymes associated with NAD+ degradation and biosynthesis. Furthermore, lowered NAD+ levels are linked to multiple age-dependent cellular processes, including DNA repair, oxidative stress and immune cell function.

Recent studies in a variety of animal models have demonstrated that NAD+ depletion plays a central role in many ageing-related biological processes, including cognitive decline, cancer, metabolic disease and frailty.

Researchers note that boosting NAD+ levels may improve the health of many organs in the body, such as boosting energy metabolism, reducing muscle atrophy, and improving brain function. This makes targeting NAD+ metabolism a promising anti-ageing avenue. Researchers are also exploring ways to restore NAD+ levels with its precursor nicotinamide riboside.

Encouraging results from numerous high-quality preclinical studies in model organisms highlight the potential of restoring NAD+ levels as a way to treat ageing-related diseases.

"Hopefully, the upcoming results of current clinical trials will shed some light on our unsolved questions and set the basis for future directions in deciphering the role of NAD+ during ageing in humans," the authors conclude.

DNA molecules.
DNA分子示意图。

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While people live longer, they hope to tackle ageing and stay healthy.

人们在更长寿的同时，期望能够对抗衰老、保持健康。

Reference

1. Covarrubias, A.J. *et al. Nat Rev Mol Cell Biol.* 22,119–141 (2021).

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NAD+: 一种影响代谢和衰老的酶

一项研究揭示了烟酰胺腺嘌呤二核苷酸（NAD+）如何影响多个衰老进程。

根据世界卫生组织的数据，2000年至2019年，全球预期寿命从66.8岁增至73.4。人们在更长寿的同时，期望能够对抗衰老、保持健康。

过去20年里，越来越多的研究发现，一种与能量代谢相关的酶——烟酰胺腺嘌呤二核苷酸（NAD+）——是健康衰老的一个促进因子。

NAD+在氧化还原反应中充当辅酶，即一种辅助催化的有机分子。除了具有氧化还原的功能，NAD+还是数百种酶的重要辅因子或底物，在许多对健康很重要的关键细胞过程和功能的调节中发挥着作用，是人体必需的辅酶。

2021年，美国巴克衰老研究所（Buck Institute for Research on Aging）的研究人员在《自然综述：细胞生物学》（Nature Reviews Molecular Cell Biology）[1]上发表了一篇综述，总结了NAD+领域的最新进展。

使用不同模式系统（包括啮齿动物和人原代细胞）开展的多项临床前研究证实，衰老伴随着NAD+水平的逐渐下降。这种下降已被发现与许多参与NAD+降解和生物合成的酶的变化有关。此外，NAD+水平下降还与多个年龄相关细胞过程有关，包括DNA修复、氧化应激和免疫细胞功能等。

近年来，一系列动物模型研究表明，NAD+耗竭在许多衰老相关进程中扮演着关键作用，包括认知衰退、癌症、代谢疾病和身体虚弱。

研究人员表示，提升NAD+水平可能会改善人体多个器官的健康，包括提升精力水平、减少肌肉萎缩、改善大脑功能等。这让靶向NAD+代谢成为了一种极具前景的抗衰策略。研究人员还在探索利用NAD+前体物质NR提升其水平的方法。

在模式生物中开展的大量高质量临床前研究发现了令人振奋的结果，显示出通过恢复NAD+水平治疗衰老相关疾病的潜力。

作者总结道，"我们希望当前临床试验即将得出的结果能为一些待解决的问题提供启示，并为今后阐明NAD+在人体衰老过程中的作用奠定基础。"

Boosting NAD+ levels may have health benefits for many organs in the body, or may enhance energy metabolism.

提升NAD+水平或对人体多个器官的健康有益，或可能提升精力水平。

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Exploring the role of NAD+ and sirtuins in skin ageing

NAD+ is consumed by sirtuins during the regulation of chemical processes, and may play a pivotal role in skin health.

Skin is constantly exposed to internal and external stressors that can lead to damage and ageing. Sirtuins are a family of enzymes (SIRT1 through to SIRT7) that are dependent on nicotinamide adenine dinucleotide (NAD+) to function. By consuming NAD+, they regulate chemical processes, and have emerged as pivotal players in skin health and the ageing process.

In a 2020 review, published in *Photochemistry and Photobiology*[1], Shengqin Su and colleagues from the University of Wisconsin, Madison in the United States, summarized the state of knowledge about the role of SIRT3, SIRT4 and SIRT5 in skin ageing and disease. These enzymes are called the mitochondrial sirtuins as they are primarily located in the mitochondria, which are the powerhouses of our cells.

Mitochondrial sirtuins have been implicated in the skin's response to exposure to environmental hazards, such as ultraviolet radiation (UVR) and ozone, as well as in the ageing process.

Research on mitochondrial sirtuins in chronological skin ageing, which progresses spontaneously over time, is limited. However, some studies suggest that these proteins, particularly SIRT4, play a role in the skin's cellular response to UV damage, and so may be potential targets to combat premature skin ageing due to frequent exposure to solar UV radiation.

While some evidence suggests a role for SIRT3 in the skin's response to damage from ozone exposure, knowledge gaps exist regarding the involvement of SIRT4 and SIRT5 in this process.

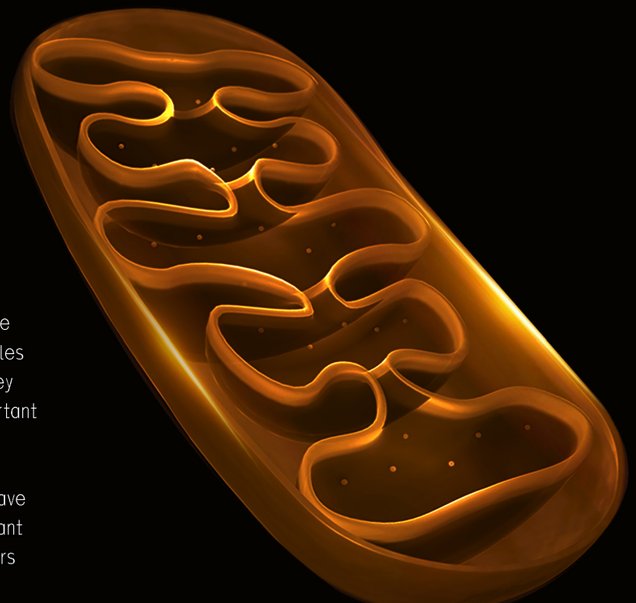
Evidence from cell-based studies suggests mitochondrial sirtuins, especially SIRT3, are involved in regulating differentiation of keratinocytes — the major cell type found in the epidermis, the skin's outer layer — which is crucial for maintaining barrier function. Although there have been limited studies regarding the roles of SIRT4 and SIRT5, their roles in energy metabolism suggest they may also be involved in this important process.

Additionally, studies in mice have found that SIRT3 plays an important role in wound healing, and appears to help protect against scarring conditions. Other studies have shown that SIRT6 can also regulate the metabolism of collagen in fibroblasts[2].

Mitochondrial sirtuins appear to play crucial roles in maintaining skin balance against environmental stress. However, the mechanisms of action of these proteins in various skin conditions, especially SIRT4 and SIRT5, and how they relate to NAD+ levels, are yet to be fully understood.

Reference

1. Su, S. *et al. Photochem Photobiol.* 96, 973–980 (2020).
2. He, YY. *Skin Stress Response Pathways*, 251–263 (2016).



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Conceptual illustrations of mitochondria.

上图为线粒体示意图。

Sirtuins are closely related to the metabolism of collagen in skin, UV protection and maintaining skin barrier function.

Sirtuins 与皮肤胶原蛋白合成、抵御紫外线以及维持皮肤屏障等密切相关。

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探索 NAD+ 和 sirtuins 在皮肤老化中的作用

去乙酰化酶（sirtuins）调控过程中需要消耗 NAD+，或对于维护皮肤健康起着至关重要的作用。

皮肤长期暴露于各种内部和外部压力源，这些压力源会导致皮肤损伤和老化。去乙酰化酶家族（SIRT1 至 SIRT7）是依赖烟酰胺腺嘌呤二核苷酸（NAD+）的酶，通过消耗 NAD+ 来调控化学过程，从而在皮肤健康和老化过程中发挥关键作用。

2020 年，美国威斯康星大学麦迪逊分校的 Shengqin Su 团队在《光化学和光生物学》（Photochemistry and Photobiology）[1] 发表了一篇综述，概述了 SIRT3、SIRT4 和 SIRT5 在皮肤老化及疾病中的已知作用。这些酶被称为线粒体去乙酰化酶（sirtuins），主要位于细胞的能量工厂——线粒体。

研究发现，sirtuins 与皮肤对环境危害（如紫外线和臭氧）的应激反应及老化过程密切相关。

关于 sirtuins 在皮肤随时间自然衰老过程中的作用，研究仍很有限。但一些研究显示，这些蛋白质——尤其是 SIRT4——参与了紫外线对皮肤细胞的损伤过程，或可作为潜在靶点，防止皮肤因频繁接触太阳紫外线而过早老化。

虽然有证据显示，SIRT3 在皮肤因臭氧暴露而受损的反应中起到了一定作用，但关于 SIRT4 和 SIRT5 在此过程中的作用仍不清楚。

细胞研究显示，sirtuins——特别是 SIRT3——在调节角质形成细胞（表皮的主要细胞类型）的分化中起着关键作用，这对维持皮肤的屏障功能极为重要。虽然关于 SIRT4 和 SIRT5 的作用仍研究得不多，但它们在能量代谢中的作用提示这些酶可能同样参与了这一关键过程。

此外，小鼠研究还发现，SIRT3 对伤口愈合的过程很重要，而且似乎能帮助预防疤痕形成。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[2]。

Sirtuins 对于皮肤在环境压力下保持平衡起到了关键作用。然而，这些蛋白质在这些皮肤条件下的作用机制——特别是 SIRT4 和 SIRT5 的作用机制——以及它们与 NAD+ 水平的关系，仍需进一步阐明。

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Testing the availability within the body of a NAD+ precursor

A study explored the effect of NR on enhancing NAD+ levels in the blood.

Nicotinamide adenine dinucleotide (NAD+) is an important substrate for many enzymes involved in metabolism, and falling levels of it as we age have been linked to age-related diseases. NAD+ is comprised of three forms: nicotinamide, niacin and nicotinamide riboside.

Because levels of NAD+ can be compromised by metabolic stress and ageing, scientists are exploring whether ingesting greater levels of nicotinamide riboside could optimize health.

A 2019 study, published in *Scientific Reports*[1], aimed to test how the availability of NAD+ in the body varies, following the ingestion of an oral formulation of nicotinamide riboside (NR) that was provided by ChromaDex, a dietary supplement and food ingredient company based in California, United States.

The authors, made up of researchers from ChromaDex and the University of Iowa in Iowa City, enrolled 140 adults aged between 40 and 60, and randomly assigned them to receive either a placebo, or 100 mg, 300 mg or 1000 mg doses of NR per day.

Participants were asked to limit ingestion of foods containing either significant amounts of tryptophan, a precursor of niacin, or nicotinamide riboside and record what they consumed.

Participants continued their treatments for 56 days and had blood and urine tests, and safety assessments, at days 7, 24, 28 and 56. A total of 133 participants completed the study.

The researchers found that participants on 300 mg and 1000 mg doses of NR had significantly increased blood levels of NAD+ metabolites, compared with the placebo group, within seven days of starting the treatments — and these increased levels continued for the remainder of the study.

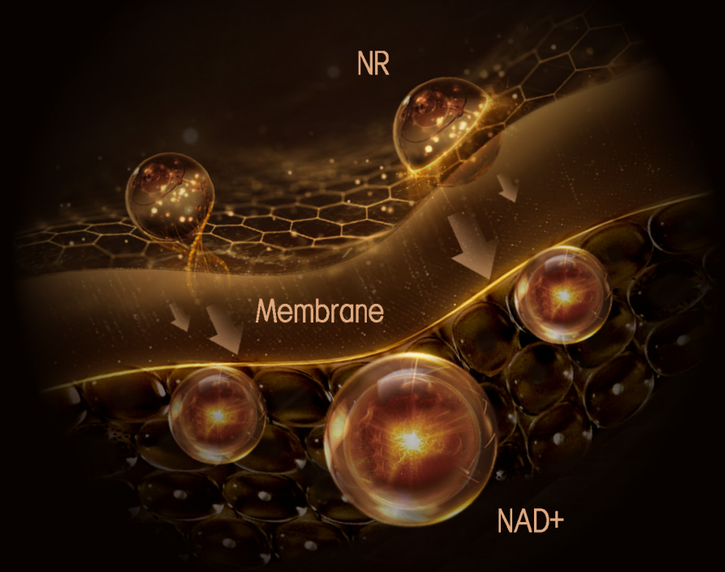
After 14 days, NAD+ levels in the blood of participants in the two groups elevated by about 51% and 142%, respectively. The blood levels of NAD+ metabolites in the 100 mg dose group increased by 22% at day 14.

Methylated nicotinamide — a biomarker of increased NAD+ metabolism — was also higher in the urine and plasma of all participants taking doses of NR after 56 days treatment.

A limitation of the study was that it involved predominantly middle-aged adults of European descent who consumed a diet limited in food containing nicotinic acid. Further research will be needed o evaluate the effects of NR supplementation in other populations.

Reference

1. D. Conze, C. Brenner & C. L. Kruger, *Sci Rep.* 9, 9772 (2019).



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Nicotinamide riboside molecules entering a cell and becoming NAD+.

烟酰胺核苷进入细胞并转化为NAD+示意图。

Scientists are exploring whether ingesting greater levels of nicotinamide riboside could optimize health.

科学家正在探索摄入更多 NR 对健康的促进作用。

检测体内一种 NAD+ 前体的水平

研究探索了 NR 对于提升血液中 NAD+ 水平的影响。

烟酰胺腺嘌呤二核苷酸（NAD+）是许多代谢相关酶的重要底物，其水平会随年龄增长而下降，这种下降趋势被发现与年龄相关的疾病有关。NAD+ 主要由烟酰胺、烟酸和烟酰胺核糖这三种形式组成。

由于代谢压力和衰老会影响 NAD+ 的水平，科学家正在探索摄入更多烟酰胺核糖是否能促进健康。

《科学报告》（Scientific Reports）[1] 在 2019 年发表的一项研究测试了摄入烟酰胺核糖（NR）口服制剂后，人体内 NAD+ 水平的变化，这种口服制剂由美国加州的膳食补充剂和食物成分公司 ChromaDex 提供。

团队由来自 ChromaDex 和爱荷华大学的研究人员组成。他们招募了 140 名年龄在 40 至 60 岁的成年人，并随机分配他们服用安慰剂或每日服用 100 毫克、300 毫克或 1000 毫克的 NR。

参与者被要求限制摄入含有大量色氨酸（烟酸的前体）或 NR 的食物，并记录所摄入的食物。

参与者连续 56 天服用这些补充剂或安慰剂，并在第 7、24、28 和 56 天进行了血液和尿液检测以及安全性评估。共有 133 人完成了研究。

研究人员发现，在开始的 7 天内，相比安慰剂组，服用 300 毫克和 1000 毫克 NR 的参与者血液中的 NAD+ 代谢物含量明显更高，并且这种现象在接下来的研究中持续存在。

14 天后，这两组参与者血液中 NAD+ 水平分别提升了约 51% 和 142%。服用 100 毫克的低剂量组的血液中 NAD+ 代谢物水平在 14 天后升高，提升了 22%。

56 天后，所有服用 NR 的参与者的尿液和血浆中也检测到了更高含量的甲基化烟酰胺——NAD+ 代谢增加的一个生物标志物。

这项研究的局限在于研究对象主要是欧洲裔中年人，他们的饮食中烟酸含量有限。今后仍需开展进一步研究，评估 NR 在其他人群中的效果。

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