THE ROLE OF *BIFIDOBACTERIUM*
双歧杆菌的作用

EXPLORING THE SECRETS OF GUT HEALTH
探索肠道健康的秘密

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Our gut is home to a bustling microbial community that aids digestion, regulates metabolic function, and modulates the immune system. Research exploring the interplay between the microbiome and health has been on the rise. *Bifidobacterium*, a particular component of gut microbiome, has been increasingly explored as a key player in early immune development, gut health, and overall well–being. This supplement presents key research highlights that shed light on *Bifidobacterium*'s vital role in human health.

我们的肠道中有着非常活跃的微生物群落，它们帮助我们消化食物，在调节代谢功能和免疫系统中也发挥着重要作用。近年来，科学界对微生物群落与健康之间的相互作用进行了大量研究。双歧杆菌作为肠道微生物群落的重要组成部分，因其在早期免疫发育、肠道健康以及整体健康方面的关键作用，更是受到广泛关注。本特刊汇集了该领域的相关研究，并对双歧杆菌对人类健康的影响进行了深入解读。

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01

Links between early immune development and *Bifidobacterium*

Scientists have discovered a connection between abundant Bifidobacterium colonization and immune development in early life, highlighting its importance to overall health.

At birth, humans have a largely sterile gut, but their microbiome rapidly develops into a highly dynamic ecosystem within the first few months of life. Among the dominant microbes in the gut of breastfed babies, *Bifidobacterium* — a major component of the infant gut microbiome — is widely regarded as beneficial for early immune development and for its potential role in influencing immune-related conditions such as allergies.

Previous studies showed that *Bifidobacterium* metabolites, such as short-chain fatty acids, may help strengthen the intestinal barrier against infections[1]. However, the role of other *Bifidobacterium* metabolites in immune development, and their underlying mechanisms, remain insufficiently understood.

To learn more, researchers from Technical University of Denmark, and the University of Copenhagen focused on aromatic lactic acids — metabolites produced by *Bifidobacterium* through the breakdown of aromatic amino acids. These organic compounds have been found to help strengthen the gut barrier, reduce inflammation, and protect against harmful pathogens.

In a 2021 study in *Nature Microbiology*[2], the researchers analysed the gut microbiome composition and aromatic lactic acid concentrations in fecal samples from 59 Danish infants, who were all around 8 months old, and about 40% of whom were still partially being breastfed.

They found that compared to samples from the infants who had been weaned, both *Bifidobacterium* and aromatic lactic acids were greater, especially aromatic lactic acids such as indolelactic acid, phenyllactic acid and 4-hydroxyphenyllactic acid.

Further *in vitro* experiments in the laboratory that simulated the environment of the gut revealed that specific *Bifidobacterium* strains, such as *B. longum*, *B. breve* and *B. bifidum*, could produce these three aromatic lactic acids through a unique enzyme, called aromatic lactate dehydrogenase (ALDH).

To unveil the mechanism underlaying aromatic amino acid metabolism, the researchers identified the key gene responsible for this process, known as the *ALDH* gene, which is commonly found in *Bifidobacterium* species associated with breastmilk. Though knockout experiments in the bacteria, they found that the *Bifidobacterium* strains lacking *ALDH* could not encode the enzyme responsible for converting aromatic amino acids into aromatic lactic acids.

To further explore how aromatic lactic acids influence the immune system, the researchers introduced indolelactic acid — one of the key aromatic lactic acids produced by *Bifidobacterium* — to human immune cells grown in the lab.

They discovered that indolelactic acid activated certain immune cells, promoting the release of IL-22, a molecule that helps maintain a healthy immune balance. As one of *Bifidobacterium*'s metabolites, indolelactic acid also reduced inflammation through two receptors, AhR and HCA3, by preventing immune cells from producing IL-12p70, an immune system signaling molecule that can trigger excessive inflammatory responses.

The researchers suggest that aromatic lactic acids and their immune-regulating mechanisms, mediated by AhR and HCA3, could provide a foundation for further investigation into the role of *Bifidobacterium* species in infant health and immune development. They also proposed that modulating *Bifidobacterium* metabolites may help improve immune development with the potential for impacting immune-related conditions such as allergies, asthma and inflammatory bowel diseases.

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早期免疫发育与双歧杆菌的联系

科学家发现双歧杆菌的大量定植与早期免疫发育存在关联，凸显双歧杆菌对整体健康的重要性。

婴儿出生时肠道基本是无菌的，但出生后的头几个月，肠道菌群会快速发展为高度动态的生态系统。在母乳喂养婴儿肠道的主导微生物中，双歧杆菌（*Bifidobacterium*，婴儿肠道菌群的主要组成部分）被广泛认为有益于早期免疫发育，并可能对过敏等免疫相关疾病产生潜在影响。

此前研究表明，双歧杆菌的代谢物如短链脂肪酸等或有助于增强肠道屏障，抵御感染【1】。但双歧杆菌代谢物在免疫发育中的作用及其潜在机制尚未得到充分了解。

丹麦技术大学和哥本哈根大学的研究者集中研究了芳香乳酸，这是双歧杆菌分解芳香族氨基酸产生的代谢物。人们认为这些有机化合物有助于强化肠道屏障，减少炎症，抵御有害病原体。

2021 年，研究者在《自然－微生物学》发表文章【2】，分析了 59 名丹麦婴儿粪便样本中的肠道微生物组成和芳香乳酸浓度，这些婴儿都在 8 月龄，其中 40% 仍部分母乳喂养。

他们发现，与断奶婴儿相比，仍在母乳喂养的婴儿样本中的双歧杆菌和芳香乳酸含量更高，特别是包括吲哚乳酸、苯基乳酸和 4- 羟基苯乳酸的芳香乳酸。

进一步模拟肠道环境的体外实验表明，特定的双歧杆菌菌株如：长双歧杆菌、短双歧杆菌、两歧双歧杆菌，能通过一种独特的芳香乳酸脱氢酶（ALDH）产生这三种芳香乳酸。

为揭示芳香族氨基酸代谢的机制，研究者识别了这个过程的关键基因，即芳香乳酸脱氢酶基因（*ALDH* gene），这些基因通常存在于与母乳相关的双歧杆菌菌种中。通过细菌中的敲除实验，他们发现缺乏 *ALDH* 的双歧杆菌菌株不能编码将芳香族氨基酸转化成芳香乳酸的酶。

为进一步探索芳香乳酸如何影响免疫系统，研究者在实验室培养的人类免疫细胞中引入了吲哚乳酸——双歧杆菌产生的一种关键芳香乳酸。

他们发现，吲哚乳酸激活特定的免疫细胞，促进 IL-22 的释放，这是一种有助于维持健康免疫平衡的分子。作为双歧杆菌代谢物之一，吲哚乳酸还通过 AhR 和 HCA3 两种受体减少了炎症：它们防止免疫细胞产生 IL-12p70（一种能引发过度炎性反应的信号分子）。

研究人员认为，芳香乳酸及其通过 AhR 和 HCA3 介导的免疫调节机制，可能为进一步研究双歧杆菌在婴儿健康和免疫发育中的作用提供基础。他们还提出，调节双歧杆菌代谢物或有助于改善免疫发育，有潜力影响免疫相关疾病如过敏、哮喘和炎症性肠病。

02

Uncovering one of the ways *Bifidobacterium* supports gut balance

New research uncovers how Bifidobacterium reshapes gut microbiota and supports gut immune regulation.

As gut health is increasingly recognized as being key to our overall well-being — affecting systems from digestion and immunity to metabolism, and mental health — *Bifidobacterium* has emerged as a key player. A number of *Bifidobacterium* species and strains are widely recognized for their role in supporting gut health. However, the underlying mechanisms by which *Bifidobacterium* impact digestive health and help balance gut microbiota remain largely unexplored.

A collaborative study led by the researchers from Shanghai Jiao Tong University School of Medicine, in China, and Stanford University School of Medicine in California, United States, sought to find answers. In a 2020 study, the team reported on how *Bifidobacterium* reshapes the landscape of gut microbiota and modulates immune responses to alleviate inflammation and restore gut balance[1].

The researchers investigated the mechanism by which *Bifidobacterium* can help mitigate side effects of cancer immunotherapy, such as colitis — a condition characterized by inflammation of the colon. The researchers hypothesized that a subset of immune cells known as regulatory T cells (Tregs), which help regulate the immune system and prevent excessive inflammation, plays an important role in this process.

To test their hypothesis, the researchers fed *Bifidobacterium* to two groups of mice — one that had normal levels of Tregs, and one that had been engineered to lack functional Tregs, before colitis was induced in both groups. Follow-up 16S rRNA sequencing — a technique used to identify various types of bacteria by analysing their genetic code — revealed that the *Bifidobacterium* treatment did not restore beneficial gut bacteria in the Tregs-deficient mice.

In contrast, in the mice that had normal levels of Tregs, the *Bifidobacterium* treatment led to an increase in beneficial bacteria, particularly *Lactobacillus*, which can help mitigate inflammation and support the repair of the intestinal lining. The researchers also identified *Bifidobacterium breve* as the key strain of *Bifidobacterium* that may play a crucial role in preventing weight loss and improving colitis in these mice.

As they worked to uncover how *Bifidobacterium* helps maintain a balanced gut environment and regulates the immune system, the researchers identified the IL-10/IL-10Rα signalling loop and IL-22, a small protein produced by immune cells. *Bifidobacterium* was found to activate the IL-10/IL-10Rα signalling loop, which is crucial for Treg function and immune suppression. IL-22, known for its role in maintaining gut homeostasis, was identified as another key molecule in this process. Both IL-10 and IL-22 are involved in overlapping immune regulatory processes, and the signalling pathways they activate can influence one another.

Genetic analysis further showed that *Bifidobacterium* also enhances metabolic activity and supports the organization of mitochondria — tiny structures inside cells that produce the energy cells need to function.

The researchers suggested in the paper that these findings highlight a direct link between *Bifidobacterium* and the overall health of the gut microbiota, offering potential intervention strategies for managing overactive immune response that can trigger conditions such as allergy, particularly in the gut, and establishing *Bifidobacterium* as a promising candidate for helping support gut immune balance.

A previous study by Chinese researchers in mice also suggested that combining multiple *Bifidobacterium* strains which have some adhesive properties could improve digestive health by alleviating constipation, potentially through enhanced gut motility and increased production of short-chain fatty acids[2].

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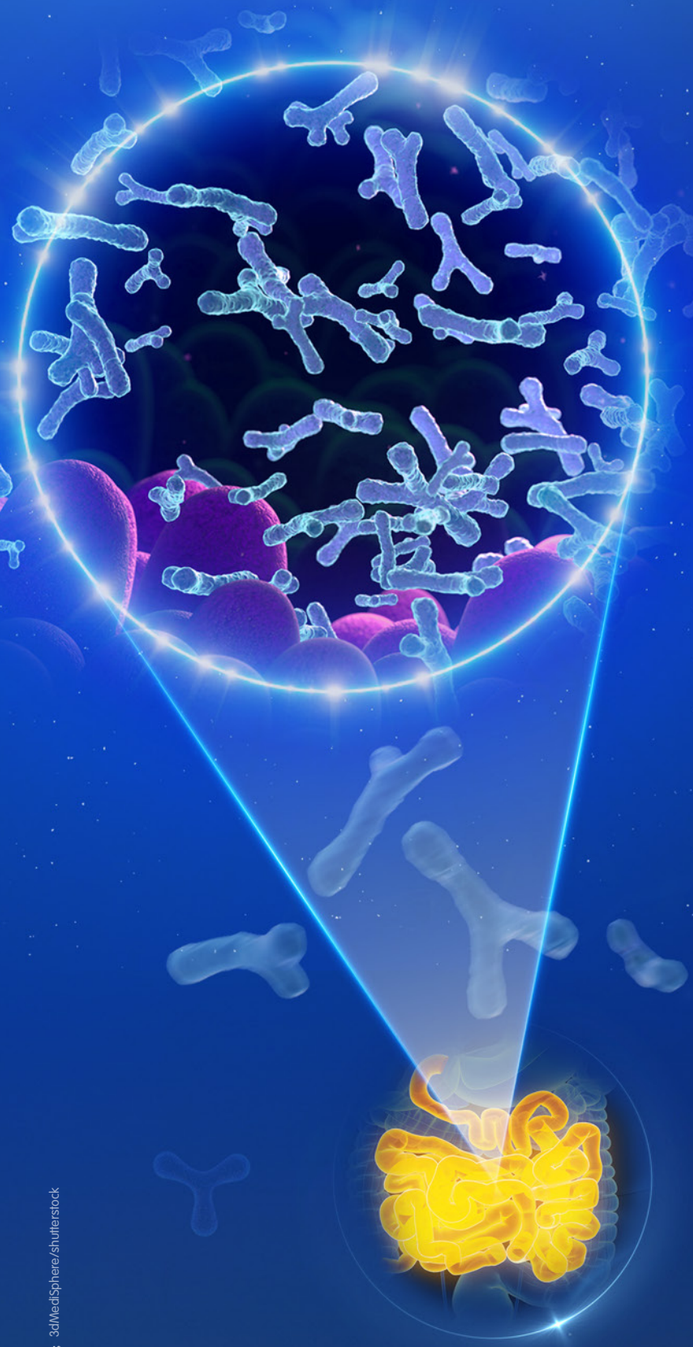

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揭示双歧杆菌支持肠道平衡的一种途径

新研究发现了双歧杆菌如何重塑肠道微生物群，并支持肠道免疫调节。

人们日益注意到肠道健康对整体健康的关键作用——它影响消化、免疫、代谢等系统，以及心理健康。其中，双歧杆菌（*Bifidobacterium*）的作用十分关键。许多双歧杆菌物种和菌株在支持肠道健康方面的作用已经得到广泛认可。 然而，双歧杆菌影响消化健康和帮助平衡肠道微生物群的潜在机制，仍需要进一步探索。

上海交通大学医学院和斯坦福大学医学院的研究人员合作开展了一项研究，寻求这个问题的解答。在 2020 年发表的一篇论文【1】中，该团队报告了双歧杆菌如何重塑肠道微生物群，调节免疫反应，以减轻炎症、恢复肠道平衡。

研究者调查了双歧杆菌如何帮助缓解癌症免疫疗法的副作用，如结肠炎（特征为结肠炎症）。研究者假设，一类称为调节性 T 细胞（Treg）的免疫细胞在此过程中发挥重要作用，这类细胞的功能是帮助调节免疫系统，预防过度炎症。

为测试这一假设，研究者给两组小鼠喂食了双歧杆菌，一组的 Treg 水平正常，另一组则经过改造，缺乏功能性 Treg 细胞，然后在两组小鼠中诱发结肠炎。经过 16S rRNA 测序（该技术通过分析遗传编码来识别不同细菌），双歧杆菌未能在缺乏 Treg 的小鼠中恢复有益肠道菌。

而在 Treg 水平正常的小鼠中，双歧杆菌带来了有益菌尤其是乳酸杆菌的增加，它有助于缓解炎症，支持肠道粘膜修复。研究人员还确定短双歧杆菌（*Bifidobacterium breve*）可能是这个过程中预防体重减轻和改善结肠炎的关键双歧杆菌菌株。

作者研究了双歧杆菌如何帮助维持肠道环境平衡和调节免疫系统，他们发现了 IL-10/IL-10Rα 信号回路和 IL-22（免疫细胞产生的一种小蛋白）。双歧杆菌被发现会激活 IL-10/IL-10Rα 信号回路，这对 Treg 功能和免疫抑制非常重要。IL-22 已知能参与维持肠道稳态，作者发现它是这个过程中的另一关键分子。IL-10 和 IL-22 都参与了重叠的免疫调节过程，它们激活的信号通路能互相影响。

基因分析进一步表明，双歧杆菌还加强了代谢活动，支持线粒体的组织——线粒体是细胞内为细胞功能产生所需能量的微小结构。

研究者在文中指出，这些发现强调了双歧杆菌和肠道微生物组整体健康之间的直接关联，为管理过度活跃的免疫响应（可能引发过敏等疾病，尤其是在肠道）提供了潜在的干预策略，并证实双歧杆菌有望帮助支持肠道免疫平衡。

此前，中国研究者在小鼠中进行的一项研究【2】也认为，某些具有粘附特性的双歧杆菌相结合，或可通过增强肠道蠕动、增加短链脂肪酸来缓解便秘和改善消化健康。

How the microbiome might shape eating behaviour, via the gut–brain axis

Gut bacteria can influence hunger, say scientists who uncovered ways in which these microorganisms communicate with the brain.

The gut–brain axis — an intricate communication network linking the gut and the central nervous system — has captivated scientists for several years. Recent advances in research methods and a deeper understanding of microbiome interactions have shed light on how gastrointestinal health can influence mood and eating behaviours.

In 2022, the researchers from Université Paris Cité and the Institut Pasteur, both in France, uncovered a mechanism of gut–brain communication through which macromolecules released by gut bacteria, known as peptidoglycan fragments, can directly interact with neurons in the brain that regulate hunger behaviour[1].

To reveal how gut microbiota influence appetite, the researchers focused on NOD2, a protein encoded by the *NOD2* gene, which plays a significant role in the immune system by recognizing bacterial components, including bacterial peptidoglycans. This capability led the researchers to explore the potential expression of *NOD2* in brain neurons and to investigate whether gut–derived signals could directly influence neuronal activity in the brain.

Using mouse models, they identified that the NOD2 protein is produced in neurons across several brain regions, including the hypothalamus — a region in the brain that regulates crucial functions such as feeding behaviour, body temperature and hormone release.

To investigate whether gut–derived bacterial fragments could reach the brain, the researchers orally administered to mice soluble fragments derived from peptidoglycans. They found that just four hours later, these fragments had traversed the gut, entered the bloodstream and reached the brain.

Through a series of mouse experiments and single–neuron studies, the research team discovered that feeding stimulates the expansion of the gut microbiota, leading to an increased release of bacterial peptidoglycans. These fragments travel to the hypothalamus and reduce its activity by binding to inhibitory NOD2 receptors. This reduction in activity results in decreased appetite and lower body temperature.

In the paper, the researchers suggested that the proteins produced by intestinal bacteria could serve as an indirect measure of food intake for the brain. They proposed that this feedback loop between gut microbiota and the hypothalamus may provide a therapeutic target to limit over–eating, potentially offering benefits for obesity and metabolic disorders. However, the way in which components of the microbiota, such as specific bacterial strains, drive this pathway remains unclear.

In this context, probiotics — beneficial gut bacteria in some foods and health supplements — have been extensively studied. A comprehensive review, led by researchers at University Magna Graecia and the University of Naples Federico II, both in Italy, identified three key mechanisms through which some probiotics might enhance the gut environment and promote a healthy microbiota associated with maintaining a healthy weight: suppressing harmful microbes, enhancing gut barrier integrity, and modulating immune responses[2].

Additionally, in a review paper the researchers at University College Cork, in Ireland, highlighted that an imbalanced gut microbiota could be linked to disruptions in appetite–regulating hormones and satiety signals, which could contribute to obesity, as observed in mouse models[3].

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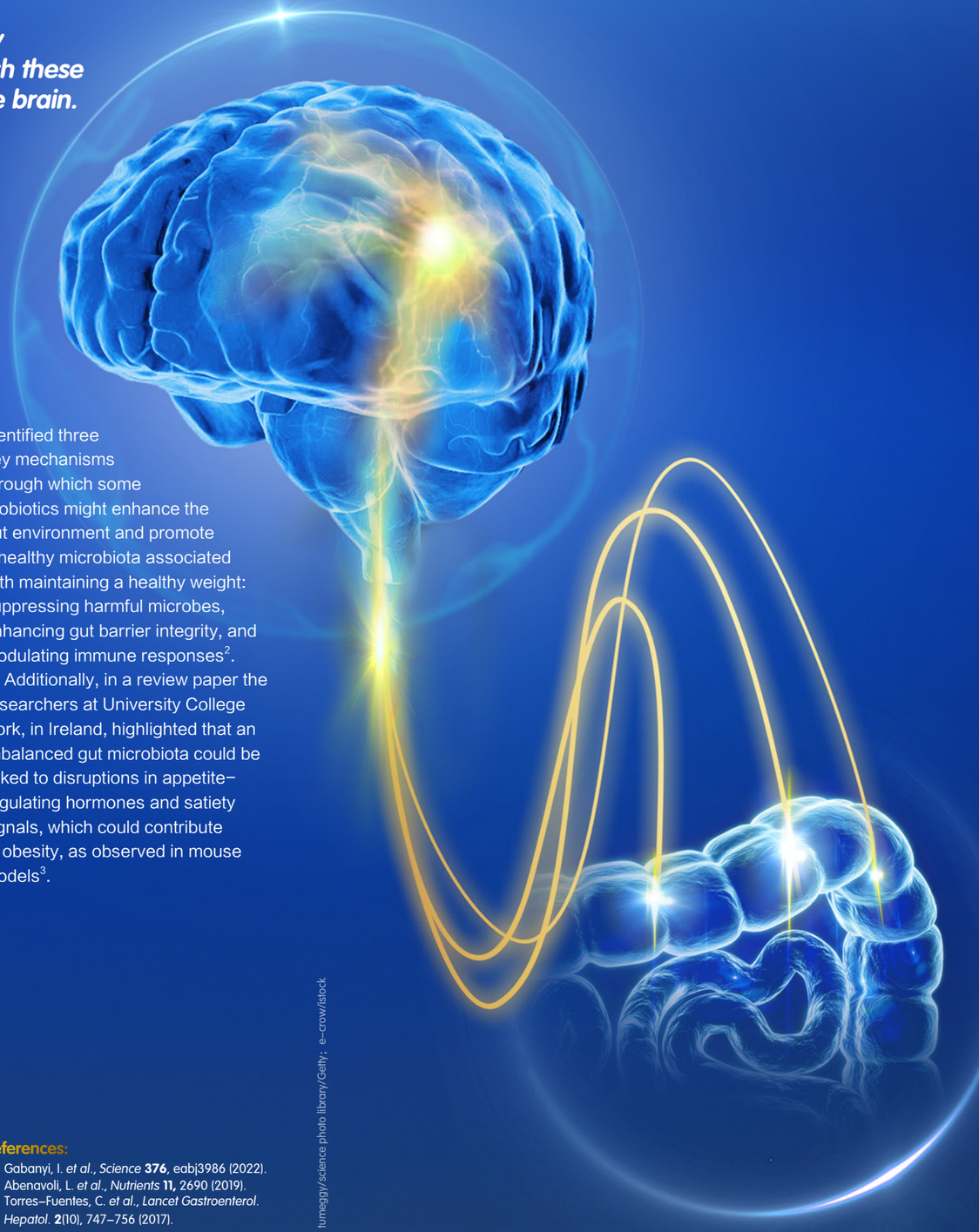

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微生物组如何通过肠 – 脑轴塑造进食行为

科学家们揭示了肠道微生物与大脑交流的方式，认为这些微生物会影响饥饿感。

肠 – 脑轴是连接肠道和中枢神经系统的复杂沟通网络，近年来受到科学家的广泛关注。近期的研究方法进步和对微生物相互作用的深刻理解，揭示了消化道健康如何影响情绪和进食行为。

2022 年，法国巴黎西岱大学和巴斯德研究所的研究者发现了一种肠 – 脑交流机制，通过肠道细菌释放的大分子（称为肽聚糖片段），能直接与脑部神经元相互作用，调控饥饿行为【1】。

为揭示肠道微生物组如何影响食欲，研究者专注于 NOD2，这是由 *NOD2* 基因编码的一种蛋白，在免疫系统识别细菌成分（包括细菌的肽聚糖）中发挥关键作用。这一能力促使研究者探索 *NOD2* 在脑神经元中的可能表达，调查肠道产生的信号是否能直接影响脑的神经元活动。

研究者使用小鼠模型，发现 NOD2 蛋白在多个脑区的神经元中产生，包括下丘脑，该脑区调控一些重要的功能如进食行为、体温和激素释放。

为调查来自肠道的细菌产物片段能否到达大脑，研究者让小鼠口服肽聚糖的可溶片段。他们发现，仅四小时后，这些片段就穿过肠道，进入血液并到达了大脑。

经过一系列小鼠实验和单神经元研究，研究团队发现，进食会刺激肠道微生物组扩大，使细菌肽聚糖的释放增多。这些片段到达下丘脑，与抑制性的 NOD2 受体结合，减少其活跃性，从而导致食欲下降、体温变低。

在这篇论文中，研究者认为，肠道菌群可以作为一种间接指标（通过肠道菌群产生的蛋白），让大脑衡量摄入的食物。他们提出，这种肠道微生物组和下丘脑之间的反馈循环，可能为限制过度进食提供了一种治疗靶标，或有益于应对肥胖和代谢紊乱。但是，具体是哪些特定的菌株能发挥作用还需要更多的研究。

在这种情况下，益生菌作为某些食物和健康补充剂中的有益菌，得到了广泛的研究。由意大利卡坦扎罗大学和那不勒斯腓特烈二世大学研究者领导的一项综述研究发现了三种重要机制，通过这些机制，一些益生菌可以改善肠道环境并促进与维持健康体重相关的健康菌群：抑制有害菌、增强肠道屏障的完整性，并调节免疫反应【2】。

此外，爱尔兰科克大学研究者在一项综述研究中强调，肠道菌群的失衡或与调节食欲激素和饱腹信号的紊乱有关，这可能会造成肥胖，如同小鼠实验观察所见。【3】