These insights open the door to further research into how such regulatory pathways shape microbial fitness via adaptation to nutrient-rich and competitive gut ecosystems. Moreover, it highlights the potential to target SrcF and its regulatory network to influence the colonization ability of *S. copri*. This offers new approaches for health-promoting strategies aimed at modifying the gut microbiome composition to target gut-related diseases. Additionally, these findings emphasize the need to extend beyond studying only the bacterial genome to capture the full complexity of microbial colonization in the gut. Finally, these results are encouraging to further develop additional human gut model organisms besides the well-studied bacterium *Bacteroides thetaiotaomicron*.

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DECLARATION OF INTERESTS

M.S.D. works as a consultant and an advisory board member at Theralution GmbH, Germany.

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Microbial alchemists unlock honeybee cognition

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In this issue of *Cell Host & Microbe*, Zhong et al.[1] uncover gut microbiota-host connections that promote cognitive function in honeybees. They discover the role of the microbiota in lipid metabolism and the synthesis of lipid-derived neurotransmitters, which modulate the endocannabinoid system.

Lipids are essential molecules that underpin nearly every aspect of biological functions. In addition to serving as fundamental building blocks of cellular membranes and energy reservoirs, lipids—particularly polyunsaturated fatty acids (PUFAs)—are critical regulators of signaling pathways controlling inflammation, immune responses, and brain functions. In the brain, lipids are crucial for maintaining the fluidity of neuronal membranes, supporting synaptic connections, and serving as precursors to neurotransmitters that regulate mood, memory, and cognition.[2] The balance of lipid synthesis and metabolism is vital for an organism's health and behavior, yet many species lack the complete enzymatic toolkit required to produce these critical molecules. Surprisingly, recent studies have revealed that some organisms may rely

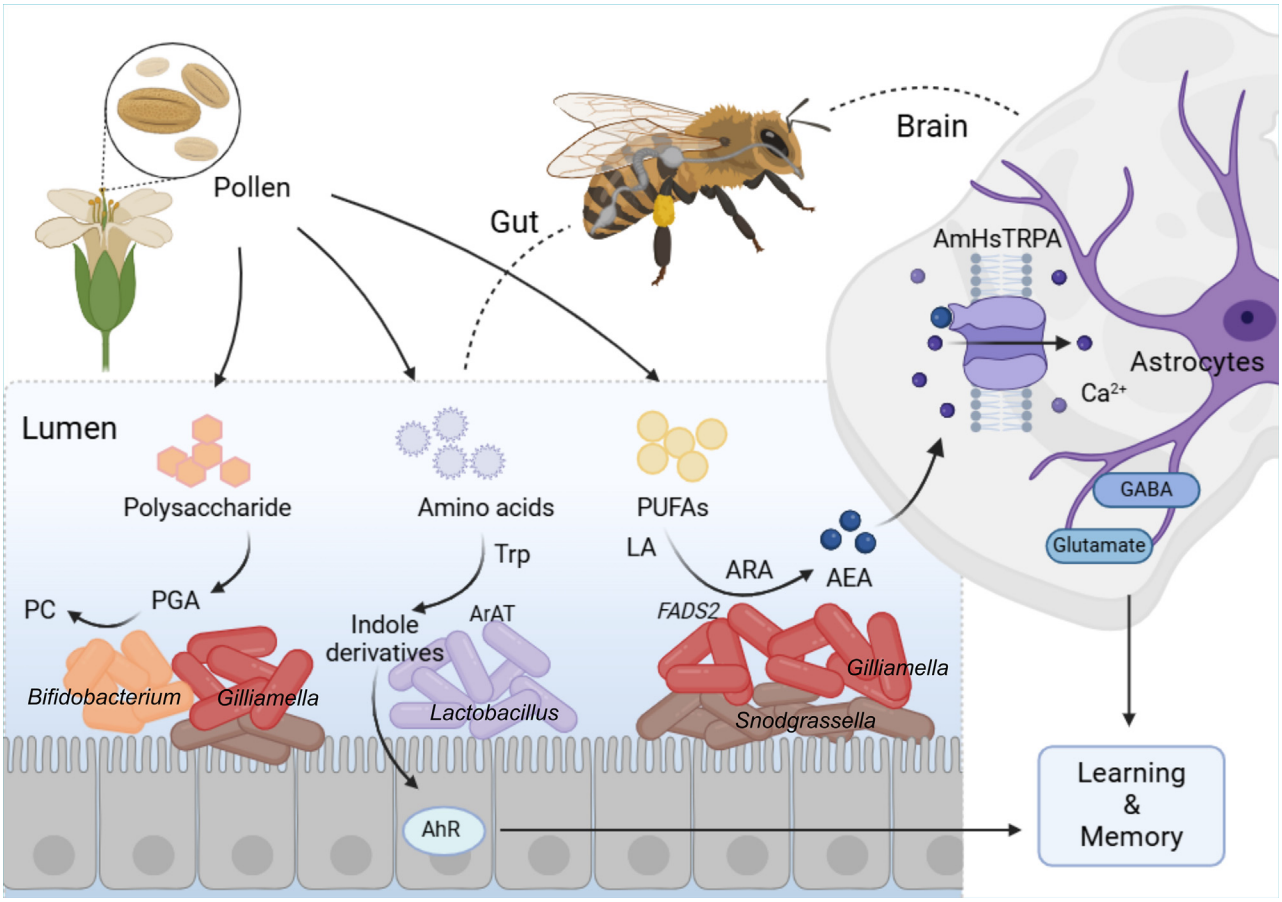

Figure 1. Gut microbiota-host connections in honeybees

Gut microbes help honeybees metabolize polysaccharides, proteins, and lipids in pollen,[9,10] and the lipid-derived neurotransmitter AEA can modulate the endocannabinoid system and promote cognitive function. PUFAs, polyunsaturated fatty acids; PGA, demethylated polygalacturonic acid; PC, citrus pectin; Trp, tryptophan; ArAT, aromatic amino acid aminotransferase; AhR, aryl hydrocarbon receptor; LA, linoleic acid; ARA, arachidonic acid; AEA, anandamide. Created with BioRender.com.

on their microbial partners to help fill these metabolic gaps.

Gut bacteria have emerged as critical players in lipid metabolism. In mammals, for instance, gut bacteria are known to modify dietary lipids, converting them into bioactive forms that influence host physiology.[3] This metabolic partnership has profound implications for host health, affecting everything from energy homeostasis to cognitive function. However, this intricate interplay between microbes and lipid metabolism is not exclusive to mammals. In a study published in this issue of *Cell Host & Microbe*, Zhong et al. reveal that honeybees exemplify how microbes can profoundly affect lipid metabolism and cognitive processes.[1]

PUFAs, such as linoleic acid (LA) and alpha-linolenic acid, are essential nutrients that eusocial corbiculate bees must obtain from dietary pollen. These fatty acids often need to be converted into longer-chain derivatives, like arachidonic acid (ARA) and docosahexaenoic acid (DHA), which play critical roles in maintaining neural health and supporting cognitive functions. The fatty acid desaturase 2 (*FADS2*) gene encodes the enzyme Δ-6 desaturase, which is crucial for the desaturation steps in the biosynthesis of ARA and DHA from essential fatty acids. However, genetic defects in the *FADS2* gene can reduce the desaturation capacity, affecting brain development, immune function, and cardiovascular health.[4] Surprisingly, Zhong et al. found that honeybees lack the genes encoding Δ-6 desaturase, which is absent from the genome of *Apis mellifera*, posing a unique challenge: how do these organisms acquire the necessary molecules to support such vital functions?

The answer, it seems, lies within the bee's gut. Zhong et al. reveal that supplementing germ-free honeybees with gut bacteria carrying the Δ-6 desaturase enzyme significantly enhances their reward learning abilities. The honeybee's digestive tract is home to a relatively simple yet highly specialized microbial community dominated by a few bacterial species like *Gilliamella* and *Snodgrassella*. Zhong et al. find that bee gut bacteria possess genes encoding Δ-6 desaturase, enabling the conversion of dietary LA into ARA, which is subsequently transformed into anandamide (AEA). AEA is a lipid-derived neurotransmitter best known for its role in the mammalian endocannabinoid system, modulating mood, appetite, pain, and reward.[5]

However, the endocannabinoid system has long been considered absent from insects, owing to the lack of classical cannabinoid receptors like CB1 and CB2.[6] Instead, in *Drosophila*, Sokabe

et al. found that the endocannabinoid 2-linoleoyl glycerol mediates the activation of transient receptor potential (TRP) channels in photoreceptor cells, thereby promoting calcium influx and facilitating phototransduction.[7] Honeybees also possess a diverse set of proteins from the TRP family, and Zhong et al. reveal that AEA acts on a unique receptor in honeybee brains, AmHsTRPA, an *A. mellifera*-specific transient receptor potential ankyrin (TRPA) receptor with thermal and chemical response properties, likely originating from the duplication of the *wtrw* gene. Phylogenetic analysis indicates that this TRPA receptor subfamily is evolutionarily conserved across *Apis* and *Bombus* species. It is closely related to the *wtrw* cluster, suggesting its potential role as an endocannabinoid receptor in Hymenoptera.

AmHsTRPA contains four conserved calcium coordination sites, similar to those found in *Homo sapiens*, *Mus musculus*, and *Drosophila melanogaster*. Cellular experiments by Zhong et al. further confirm that AmHsTRPA regulates calcium ion flux. Additionally, mutating the AEA binding site on AmHsTRPA results in its losing the ability to regulate calcium ions.

Moreover, single-cell transcriptomics of the brain reveals that this receptor is activated explicitly in glial cells, such as astrocytes and ensheathing glia. Astrocytes regulate neurotransmitter homeostasis, including glutamate and γ-aminobutyric acid (GABA). Local regulation of glutamate in the bee brain is critical for memory formation in honeybees.[8] Zhong et al. observed that bees colonized with *Gilliamella* showed altered levels of brain glutamate and GABA. Furthermore, suppressing the AmHsTRPA receptor in the honeybee brain inhibited the enhancement of learning and memory, typically by gut bacteria. These findings suggest that AEA may facilitate reward learning and memory in honeybees by maintaining glutamate homeostasis in astrocytes, potentially through activation of the AmHsTRPA channel and regulation of Ca^{2+} levels.

Honeybees primarily consume nectar and pollen, with pollen as their main source of polysaccharides, proteins, and fats (Figure 1). Previous research has highlighted the crucial role of gut microbiota in honeybee metabolic processes. For example, *Lactobacillus* strains can improve learning and memory behaviors via regulating tryptophan and indole metabolic pathways that activate the host aryl hydrocarbon receptor, which are essential for the cognitive functions of bees.[9] Additionally, *Gilliamella* and *Bifidobacterium* work collaboratively to break down complex plant polysaccharides.[10]

Zhong et al. establish a direct link between gut microbiota and cognitive function in honeybees, mediated through the regulation of fatty acid metabolism (Figure 1). This research also highlights the evolutionary importance of microbial communities in influencing behavior. In honeybees, cognitive functions are essential for activities such as foraging and pollination, which are critical not only for their survival but also for maintenance of the ecosystems they inhabit. Moreover, cognitive skills are integral to the evolution of eusociality, suggesting that gut bacteria may have a more profound impact on the development of complex social behaviors.

The endocannabinoid system is essential for processing pleasure, learning from rewards, and adjusting behavior. Zhong et al. highlight the symbiotic relationship between the gut and brain through the modulation of the endocannabinoid system by linking gut microbiota to the production of lipid-derived neurotransmitters. This insight also raises important questions about the extent to which microbial partners may influence brain function in other species, including humans. Could gut bacteria in humans synthesize similar molecules that affect cognition, and might this understanding lead to new approaches for treating cognitive disorders or enhancing mental resilience? As research continues, it becomes increasingly evident that the microbiota are far more than passive participants in host biology. Zhong et al.'s study invites us to consider gut microbiota as active contributors to the very processes that shape cognition and behavior, extending their influence beyond digestion into the fundamental realms of decision-making and survival.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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