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REVIEW

The gut-microbiota axis in brainless invertebrates: an evolutionary perspective

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Abstract

The gut-microbiota-brain axis has gained increasing attention due to its vital role in physiological functions, from metabolism to behavior. Although this axis has mainly been studied in mammals, exploring it from an evolutionary perspective provides an opportunity to expose fundamental mechanisms. This review examines how the gut microbiota supports essential processes that maintain homeostasis in marine invertebrates, including sponges, cnidarians, nematodes, echinoderms, and bivalve mollusks, even in the absence of centralized brain, although some possess nerve nets, ganglia, radial cords or complex digestive system. These organisms display primitive signaling mechanisms that enable functions such as digestion, detoxification, phagocytosis, and environmental adaptation. The presence of rudimentary nervous systems that allow effective tissue communication underscores functional similarities with more complex systems. These findings suggest that the interaction between the gut, microbiota, and nervous system may be an evolutionarily conserved principle. Studying the microbiota's role from an evolutionary and functional viewpoint helps identify universal principles in host-microbiota interactions, opening up new research possibilities in biomedicine with the potential to develop innovative therapeutic strategies.

Key Words: microbiota; invertebrates; lack of centralized brain; metabolism; environment

Introduction

Recent scientific advances have greatly expanded our understanding of the "gut-microbiota-brain axis" a bidirectional communication system linking the gut and brain across diverse species, including humans and invertebrates. *Microbiota* refers to the host-associated community of microorganisms that supports essential physiological and adaptive functions in invertebrates throughout evolution. Over time, intestinal microorganisms and their animal hosts have co-evolved into an integrated and inseparable biological community, reflecting a fundamental partnership that underlies health, development, and environmental adaptation *(*Gao *et al.*, 2023).

The gut-microbiota-brain axis operates through three primary pathways: neural, endocrine, and immune signaling (Carabotti *et al.*, 2015). Nevertheless, although the majority of animal species are invertebrates, the role of this axis in regulating biological and physiological functions in invertebrates with a decentralized nervous system has been scarcely studied. Since the evolution of the nervous system in invertebrates has led to a great diversity of forms and functions, it is likely that different ways of interacting with the microbiota have also arisen.

In this context, questions have arisen regarding the universality of the axis in other organisms. What happens to the microbiota-gut-brain axis in organisms that lack a centralized brain or a well-defined gut, as is the case for many invertebrates?

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List of abbreviations:
Central Nervous System, CNS; Autonomic Nervous System, ANS; Hypothalamic-Pituitary-Adrenal, HPA; Enteric Nervous System, ENS; Serotonin, 5-HT; Dopamine, DA; Antimicrobial peptides, AMP; Quorum Sensing, QS; Quorum Quenching, QQ; Pathogen-Associated Molecular Patterns, PAMPs; Microbe-Associated Molecular Patterns, MAMPs; Toll-Like Receptors, TLRs; Reactive Oxygen Species, ROS

Could it be supposed that these organisms also possess a similar functional axis? Current research suggests that, despite their simpler biological architecture, the microbiota in these organisms plays essential regulatory roles through primitive structures, acting as a key modulator of physiological processes fundamental to their survival and adaptation (Roy and Trinchieri, 2017).

Given this background, this review article aims to describe and analyze, from an evolutionary perspective, the characteristics of the digestive system and gut microbiota in invertebrates lacking a centralized brain, as well as the features of their rudimentary nervous systems, including diffuse networks, cord-like, radial, and ganglionic systems (bivalve mollusks). Furthermore, this review aims to elucidate the functional role of the microbiota in invertebrates and explore the implications of its regulatory activities in the absence of a centralized nervous system. It also seeks to expand the conceptual framework toward emerging research avenues with significant potential for advancing biomedical science.

The microbiota of marine invertebrates: functional roles

Marine sponges

The phylum Porifera, to which sponges belong, represents one of the most ancient groups of animals, making it fundamental for understanding the evolution of biological processes in multicellular organisms (Thomas *et al.,* 2016; Brinkmann *et al*., 2017). Sponges are typically amorphous and asymmetrical, lacking specialized organs (Pita *et al*., 2018; Loureiro *et al.,* 2022). They are classified according to their canal systems (asconoid, syconoid, leuconoid, and solenoid), which consist of a network of interconnected chambers and canals extending throughout the body and opening to the external surface (Cavalcanti *et al*., 2013).

Sponges lack a brain and neurons but can respond to stimuli through communication among their various cell lineages, enabling them to feed and eliminate invading microorganisms (Kozlov, 2021). They are key models for studying nervous system evolution, as they possess genes associated with sensory communication and synaptic function, despite the absence of neurons (Srivastava *et al.* 2010; Musser *et al.* 2021).

The osculum is a specialized sensory structure capable of detecting chemical and environmental changes through ciliated epithelial cells, allowing the sponge to identify food or chemical signals (Boury-Esnault, 1997; Kozlov, 2021). Signaling in sponges occurs via metabotropic receptors and calcium waves (Moroz and Romanova, 2022).

As sponges lack differentiated organs such as a mouth or digestive system, their nutrition depends entirely on intracellular digestion (Yuen *et al*., 2014; Ryu *et al.* 2016). While filtration is their primary feeding mechanism, some species have evolved additional strategies. Certain members of the Coleorhizae family have evolved carnivorous feeding strategies, replacing the typical sponge filtering apparatus with mobile phagocytic cells capable of capturing larger prey (Godefroy *et al*., 2019). This transition from exclusive filter feeding to predatory behavior illustrates the remarkable adaptive plasticity of sponges and highlights their relevance for understanding key innovations in early metazoan evolution (Godefroy *et al*., 2019; Moreno-Pino *et al*., 2020)

Microbiota-mediated activities

The microbiota has been a key factor in the evolution of sponges, influencing their development, physiology, and immune system. Continuous interaction with their microbial environment has driven a co-evolutionary process in which microbial communities perform essential functions (Table 1).

Metabolism and nutrition

The sponge microbiota plays a fundamental role in nutrition by participating in key biochemical processes such as nitrogen fixation and the carbon cycle (Kozlov, 2021). Many symbionts, including *Synechococcus spongiarum*, *Candidatus Cenarchaeum symbiosum*, *Candidatus Scalindua spp*., *Paracoccus spp*., and *Trichodesmium spp*., have been identified as significant contributors to these processes (Wilkinson, 1983; Taylor *et al*., 2007).

The microbiota of marine sponges, including genera such as *Thiobacillus spp*., *Nitrosomonas spp*., and *Nitrobacter spp*. (Table 2), exhibits remarkable chemolithotrophic capabilities, utilizing inorganic compounds like ammonium, nitrite, and hydrogen sulfide as energy sources. This metabolic function is particularly relevant in sponges inhabiting deep-sea or low-light environments where photosynthesis is not viable (Hoffmann *et al*., 2009).

Another key mechanism is detoxification and waste elimination, through which toxic compounds and organic pollutants are degraded, preventing the accumulation of harmful substances within the sponge. Certain specialized microorganisms can biotransform polycyclic aromatic hydrocarbons into less toxic compounds, enabling their elimination and protecting the host (Webster *et al*., 2001; Schmitt *et al.,* 2012).

Additionally, the microbiota facilitates the degradation of complex polysaccharides and the production of enzymes such as cellulases and chitinases, providing sponges with novel sources of carbon and energy (Hentschel *et al*., 2012; Schmitt *et al.,* 2012; Fan *et al*., 2013; Paul *et al*., 2019). Microorganisms such as *Entotheonella spp*., *Candidatus Synechococcus spongiarum*, and metabolic consortia also influence the synthesis of essential amino acids, B-complex vitamins, and metabolite transfer, regulating their availability according to host needs (Slaby *et al*., 2017).

Immunity

The primitive innate defense mechanisms of sponges are tightly regulated by their microbiota, which not only produces antimicrobial compounds but also occupies ecological niches, limiting pathogen colonization and contributing to host homeostasis (Wilson *et al*., 2014). These interactions highlight an evolutionarily conserved strategy in which

Table 1 Microbiota-regulated functions in different phyla of invertebrates lacking a centralized brain

Function regulated by the microbiota	Porifera	Cnidaria	Nematoda	Echinodermata	Mollusca
Metabolism and nutrition	Nitrogen and Carbon fixation (Fernández Robledo *et al.,* 2019)	Digestion of lipids, bacteria and fungi (Svetashev, 2025)	Production of bacterial cellulases and chitinases for the degradation of fibers (Whedie *et al.,* 2025)	Degradation and synthesis of agar, carrageenan, and algal alginates.(Lomartire and Gonçalves, 2023)	Seawater Processing and Filtration (Jørgensen, 1996)
	Chemical balance Regulation (Loh and Pawlik, 2014)	Oxygenic photosynthesis (Arossa *et al.,* 2024)	Synthesis of amino acids and vitamins (B9, and B12) (Zečić *et al.*, 2019)	Detoxification (Lomartire and Gonçalves, 2023)	Microbial biotransformation, biosorption (Jørgensen, 1996)
	Oxidation of inorganic compounds: ammonium (NH_3), nitrite (NO_2^-) and hydrogen sulfide (H_2S) (Russ et al., 2014)	Nutrient recycling (Svetashev, 2025)	Influence on eating behavior (Zečić *et al.*, 2019)	Anaerobic fermentation, production of acetate, propionate, and succinate (Lomartire and Gonçalves, 2023)	Secretion of specialized enzymes for polysaccharide degradation (Navvabi *et al.*, 2022)
	Detoxification and waste elimination (Fallon and Freeman, 2021)	Nitrogen fixation and synthesis of compounds to maintain homeostasis (Svetashev, 2025)	Anaerobic fermentation (Whedie *et al.,* 2025)		Vitamin synthesis (Navvabi *et al.*, 2022)
	Degradation of complex polysaccharides (Fallon and Freeman, 2021)		Metabolic transformation and degradation of toxic compounds by specific bacterial enzymes (Zečić *et al.*, 2019)		Regulation of the nitrogen and carbon cycles (Navvabi *et al.*, 2022)
	Synthesis of amino acids, vitamins, fatty acids and bioactive compounds (Varijakzhan *et al.,* 2021)				
Immunity	Stress response by developing physical barriers (Rathinam *et al.*, 2024)	Recognition of PAMPs/MAMPs (Parisi *et al.*, 2020)	Interaction with innate immunity pathways (p38 MAPK, TGF-β, DAF-2/IGF) (Tan and Shapira, 2011)	Regulates coelomocyte activity (Lomartire and Gonçalves, 2023)	Phagocytosis and cytotoxic response (Gerdol *et al.,* 2018)
	Production of antimicrobial peptides and reduction of virulence factor expression. (Duperthuy, 2020)	Activation of immune pathways (TLR, NOD) (Parisi *et al.*, 2020)	Expression of immune genes (Stear *et al.*, 2023)	Recognition signals (Lomartire and Gonçalves, 2023)	Antiparasitic response (Gerdol *et al*,. 2018)
	Activation of CYP-450 (Honkakoski and Negishi, 2000)	Stimulates the production of antimicrobial peptides (Chu and Mazmanian, 2013)	Production of antimicrobial peptides (Tan and Shapira, 2011)	Production of antimicrobial peptides (Smith *et al.,* 2010)	Production of antimicrobial peptides (Gerdol *et al.,* 2018)
				Physical barriers (Smith *et al.,* 2010)	
				Cytotoxic response (Smith *et al.,* 2010)	
Structure and development traits	Formation of skeletal structure (Aguilar-Camacho *et al.*, 2019)	Regulates gene expression and cell signaling (Röttinger *et al.*, 2012)	Production of bacterial metabolites that regulate tissue development and repair (Malonzo *et al.,* 2022)	Tissue regeneration and maintenance (Carnevali, 2006)	Metamorphosis (Wanninger and Wollesen, 2019)
	Cell differentiation. (Adamska, 2018)	Cell differentiation (Röttinger *et al.*, 2012)	Larval growth and development (Armour and Duncan, 1987)	Production of metabolites that enable larval development (Carnevali, 2006)	Biomineralization, flexibility, and shell formation (Berlemont, 2017)
	Maintenance of symbiosis (Thacker and Freeman, 2012)	Metamorphosis (Sebé-Pedrós *et al.*, 2018)	Modulation of signaling pathways associated with aging (Malonzo *et al.,* 2022)	Morphogenesis (Carnevali, 2006)	Vertical transmission of microbiota (Berlemont, 2017)
	Reproductive synchronization (Maldonado and Riesgo, 2009)	Tissue repair. (Röttinger *et al.*, 2012)		Fecundity and fertility (Carnevali, 2006)	Hormonal modulation and reproductive cycles (Berlemont, 2017)
		Biomineralization(Sebé-Pedrós *et al.,* 2018)		Longevity (Carnevali, 2006)	
Ecology and Adaptation	Homeostasis (Funayama, 2018)	Adaptation to adverse environmental conditions	Adaptation of diet for survival in hostile environments (Tahseen, 2012)	Allows for coevolution (Smith *et al.,* 2018)	Detoxification (Navarro *et al.*, 2011)
	Symbiosis with specific microbial communities (Thacker and Freeman, 2012)	Stabilizing chemical signals (O'Hara *et al.*, 2021)	Pheromone production (Tahseen, 2012)	Specific communication (Smith *et al.,* 2018)	Thermal adaptation and environmental conditions (Navarro *et al.*, 2011)
	Quorum quenching (QQ) activation (Saurav *et al*,. 2016)	Gene transfer (Gacesa et al., 2020)	Activation of chemotaxis (Tahseen, 2012)	Habitat adaptation (Smith *et al.,* 2018)	Repair of tissue (Navarro *et al.*, 2011)

QQ: Quorum quenching, QS: Quorum sensing

Table 2 Microorganisms identified as part of the microbiota and their functional roles across phyla

Phyla	Functions	Microorganisms	References
Porifera	Metabolism and nutrition	*Synechococcus spongiarum, Thiobacillus* spp., *Candidatus Cenarchaeum, Nitrosomonas* spp., *Nitrobacter* spp., Candidatus *Scalindua* spp., *Entotheonella* spp., Candidatus *Synechococcus spongiarum*	(Hoffman and Freiwald, 2018; Li *et al.,* 2024),
	Immunity	*Entotheonella* spp., *Pseudomonas* spp., *Streptomyces* spp., *Pseudovibrio* spp., *Bacillus* spp.	(Moitinho-Silva *et al.,* 2017; Pita *et al*., 2018)
	Structure and development traits	Simbiontes co-evolucionados, bacterias esclerociticas, *Bacillus* spp.	(Reveillaud *et al.,* 2014; Li *et al.,* 2024)
	Ecology and Adaptation	Arqueas nitrificantes, bacterias quimiolitotróficas, extremófilos, *Nitrosopumilus* spp., Candidatus *Scalindua.*	(Webster and Taylor, 2012; Hoffman and Freiwald, 2018)
Cnidaria	Photosynthesis, Metabolism and nutrition	*Trichodesmium* spp., *Richelia* spp.	(Muscatine and Porter, 1977; LaJeunesse *et al.,* 2018).
	Immunity	*Vibrio* spp., *Pseudovibrio* spp., *Vibrio shiloi, Alteromonas spp.*	(Krediet, 2013; Delgadillo-Ordoñez *et al.,* 2024)
	Structure and development traits	Bacterias calicoblásticas, *Pseudomonas* biomineralizantes calcificantes, *Acropora millepora, Halomonas spp.*	(Dauphin *et al*., 2008; Rohwer *et al*., 2010)
	Ecology and Adaptation	*Ruegeria spp.*	(Berkelmans and Van Oppen, 2006)
Nematoda	Metabolism and nutrition	*Lysinibacillus spp., Pseudomonas spp., Burkholderia spp.,Cellvibrio spp., Comamonas spp.*, *Prevotella, Escherichia coli, Ochrobactrum*, *Clostridiales, Bacteroides* spp.	(Samuel *et al*., 2016; Lo *et al*., 2024)
	Immunity	*Enterobacter cloacae, Pseudomonas fluorescens, Ochrobactrum*	(Slatko *et al*., 2010; Ludewig and Schroeder, 2013)
	Structure and development traits	*Bacillus subtilis*, *Ochrobactrum*, *Pseudomonas aeruginosa, Lactobacillus.*	(Kaplan and Horvitz, 1993; Ludewig and Schroeder, 2013)
	Ecology and Adaptation	*Pseudomonas, Escherichia coli, Providencia, Ochrobactrum*	(Martin *et al.,* 2009; Schulenburg and Félix, 2017)
Echinodermata	Metabolism and nutrition	*Psychrilyobacter spp., Propionigenium spp., Photobacterium* spp.	(Laguerre *et al*., 2025)
	Immunity	*Vibrio* spp., *pseudoalteromonas* spp., *Pseudomonas* spp.	(Majeske *et al*., 2013; Schillaci *et al*., 2014)
	Structure and regeneration	*Vibrio* sp., *Alteromonas, Bacillus, Lactobacillus*	(Becker *et al*., 2009; Dubé *et al*., 2019)
	Ecology and Adaptation	*Bacillus spp., Cellvibrio spp., Alteromonas spp.*	(Schillaci *et al*., 2014)
Mollusca (class Bivalvia)	Metabolism and nutrition	Mycoplasmataceae, *Vibrio* spp., Proteobacterias	(Pierce and Ward, 2018; Wegner *et al*., 2020)
	Immunity	*Endozoicomonas* spp., Gammaproteobacteria, Alphaproteobacteria, *Pseudoalteromonas* spp., *Bacillus* probióticos, *Lactobacillus* marinos.	(Pierce and Ward, 2018; Destoumieux-Garzón *et al.,* 2024)
	Structure, biomineralization and development traits	Mycoplasmataceae específicas, *Alteromonas* spp.	(Pierce and Ward, 2018; Wegner *et al*., 2020)
	Ecology and Adaptation	*Vibrio spp.*, *Pseudoalteromonas spp., Psychrobacter spp.*	(Pierce and Ward, 2018; Masanja *et al.,* 2023)

microbial communities support host immunity even in the absence of a centralized immune system.

Entotheonella spp. produces polyketides and bioactive peptides, while *Poribacteria*, a sponge-exclusive phylum, displays exceptional biosynthetic capacities. *Pseudomonas spp.* and *Streptomyces spp*. produce antimicrobial compounds and antibiotics, respectively. Additionally, the symbiotic microbiota contributes to host defense through the synthesis of antimicrobial peptides (AMPs), competitive exclusion, and immune system stimulation (Esteves *et al*., 2016). Several microorganisms have been identified as key players in these functions, including *Bacillus spp.* (producers of bacteriocins and lipopeptides), *Pseudovibrio spp.* (with specific antimicrobial activity), actinobacteria (antibiotic producers), and probiotic bacteria that help exclude pathogens (Hentschel *et al.,* 2001). Muscholl-Silberhorn *et al*., (2008) characterized specific AMPs produced by symbiotic *Bacillus*. The presence of cytochrome P450 in these microbial communities further suggests a role in xenobiotic metabolism.

Structure and development traits

The microbiota plays a key role in sponge skeletal formation by producing enzymes such as silicateins, which facilitate the deposition of siliceous and calcareous spicules (Uriz *et al*., 2003). This activity has been linked to the presence of bacteria involved in silica nucleation, including silicifying bacteria like *Bacillus spp*. (Müller *et al*., 2007).

Some symbionts also contribute to regulating cell proliferation, influencing key processes such as regeneration and morphogenesis. Sponges have developed mechanisms for vertical transmission of these symbionts, ensuring that offspring inherit essential microorganisms for their development. In addition, symbionts produce chemical signals that induce larval metamorphosis, facilitating the transition from larvae to adult sponges (Hadfield 2011; Whalan and Webster, 2014).

Ecology and adaptation

Homeostasis is another function regulated by the sponge microbiota, which participates in pH regulation and maintenance of osmotic balance. Carbonic anhydrases catalyze the conversion of CO_2 into bicarbonate, helping stabilize cellular hydrogen potential.

Evidence reported by Slaby *et al*., (2017) indicates that the microbiota influences chemical communication between sponges and their environment through mechanisms in which bacteria regulate gene expression based on cell density. This process is linked to quorum sensing (QS) activity, which can be modulated by signal inhibition through quorum quenching (QQ). Furthermore, symbiotic microorganisms contribute to sponge adaptation to extreme environmental conditions by producing heat shock proteins (HSPs) and antioxidants, reducing

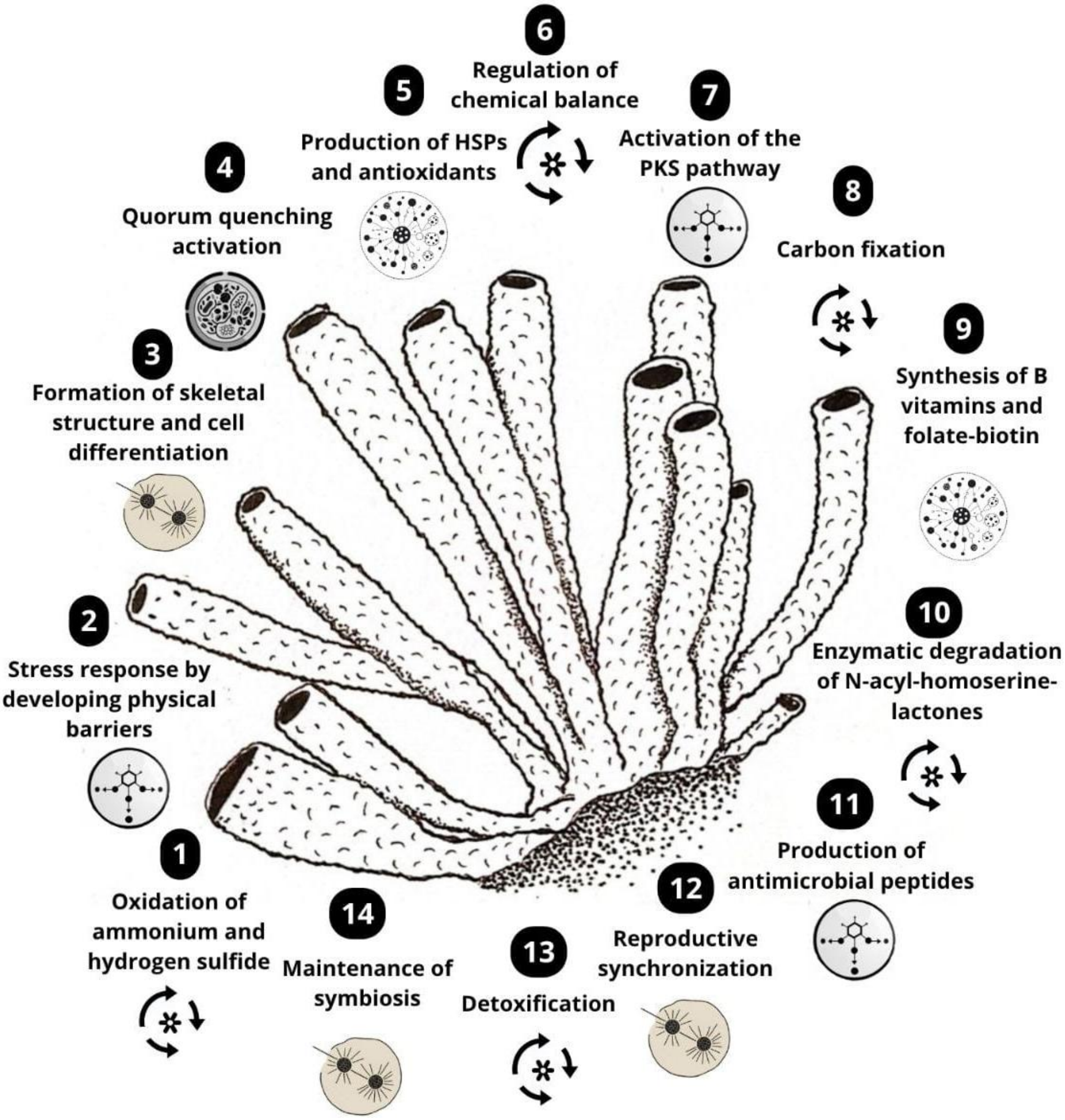

Fig. 1 Biological and physiological functions mediated by microbiota in *Porifera* (sponges)

cellular damage caused by thermal and oxidative stress (Webster *et al.*, 2008; Giles *et al.,* 2013).

Sponges carefully select their symbiotic microbial communities, promoting coevolution and ensuring stable, mutually beneficial relationships (Cárdenas *et al.*, 2019). This close interaction allows the sponge genome and its microbiota to form a functional unit, providing adaptive advantages and greater ecological resilience (Flórez *et al.*, 2015; Thomas *et al.*, 2016).

Therefore, the sponge microbiota is considered an essential component for survival and adaptation, participating in key processes such as nutrition, communication, skeletal formation, immunity, symbiont transmission, and microbial diversity (Figure 1). Consequently, these interactions have a significant impact on marine ecosystems, and coexistence with other organisms contributes to the production of bioactive compounds with anti-inflammatory, antibacterial, and antitumor properties (Srivastava *et al.,* 2010; Pita *et al.*, 2016; Webster and Thomas, 2016).

Cnidarians

Cnidarians are a highly diverse phylum of diploblastic metazoans. They are classified into five major classes based on structure and life cycle: sea anemones and corals; true jellyfish; box jellyfish; hydras and Staurozoa (Bentlage *et al.*, 2010; García-Rodríguez *et al.*, 2020). A fundamental feature of cnidarians is their radial symmetry, which is associated with various lifestyles: sessile (fixed in one place), sedentary (with limited movement), or pelagic (free-floating) (Collins, 2002).

Cnidarians possess *cnidae*, unique tubular structures used for prey capture, defense, locomotion, and substrate attachment (Ewer, 1947; Schuchert *et al.*, 1993). This phylum fulfills essential ecological functions, notably coral reef formation, which provides habitats for numerous marine species (Fautin, 2009; Pérez et al., 2020).

The cnidarian nervous system consists of a diffuse nerve net that may be organized longitudinally (giant axons) or circularly (nerve rings). In addition, sensory structures such as ocelli are present within the rhopalia.

Signal transmission occurs through electrical impulses that propagate across the nerve net, coordinating chemical and physical responses (Spencer and Arkett, 1984).

An important structure associated with the nervous system is the *ocellus*, composed of clusters of pigmented, light-sensitive neurons. These structures may feature a movable iris, bearing some resemblance to conventional eyes. The presence of these neurons suggests a reflex arc, which influences contraction, movement, and feeding (Horridge and Mackay, 1962; Grimmelikhuijzen *et al.*, 1995; Fujisawa *et al.,* 2009).

Paralogous genes responsible for neurotransmitter synthesis, typically found in higher organisms, have been identified in cnidarians. Additionally, proteins that influence cell morphology have been detected, leading to the formation of membrane projections similar to conventional dendrites (Kass-Simon and Pierobon, 2007). These dendrites can absorb intracellular calcium and are thus involved in motility. The diffuse neuronal network of cnidarians provides a valuable model for studying sympathetic processes and chemical signaling (Sprecher, 2022).

Their digestive system is simple yet functional, centered around a gastrovascular cavity that serves both digestive and circulatory roles. Cnidarians possess a single opening that functions as both mouth and anus, allowing the intake of food and expulsion of waste through the same orifice (Steinmetz, 2019).

Food particles are absorbed by specialized cells via phagocytosis (for solids) and pinocytosis (for liquids). Inside these cells, lysosomal enzymes complete nutrient degradation, making them available for metabolic processes. Once digested, nutrients are distributed throughout the gastrovascular cavity, allowing all cells of the organism to access the energy and essential compounds required for survival (Schlichter, 1982; Orejas *et al.*, 2001).

Microbiota-mediated activities

The cnidarian microbiota plays essential roles in multiple physiological processes, including nutrition, immune defense, and cell communication (Figure 2). It contributes to energy metabolism, the synthesis of key compounds, tissue regeneration, and larval development (Table 1).

Metabolism and nutrition

The intestinal and epithelial microbiota facilitates digestion and nutrient assimilation, which primarily occur within the gastrovascular cavity. In corals, for example, bacteria from the *Endozoicomonas* genus have been observed to participate in the breakdown of organic matter and the digestion of lipids, bacteria, and fungi, enhancing the efficiency of metabolic processes (Neave *et al.*, 2017).

The microbiota plays a central role in nutrient recycling in cnidarians, particularly due to their close association with zooxanthellae. These symbiotic microalgae facilitate the transfer of nutrients and organic compounds, significantly contributing to the energy production required for the host's metabolic functions. Through photosynthesis, zooxanthellae convert carbon dioxide into organic compounds, which are then utilized by the coral for growth and survival. Additionally, diazotrophic bacteria such as *Trichodesmium spp.* and *Richelia spp*. fix atmospheric nitrogen into bioavailable forms, complementing the essential nutrient cycling within coral reef ecosystems (Muscatine and Porter, 1977).

Immunity

Cnidarians possess sophisticated innate immune systems capable of recognizing microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs), thereby triggering specific defensive responses. Toll-like receptors (TLRs) are also present, initiating immune responses upon activation (Miller *et al.*, 2007).

The cnidarians rely on bacteria that produce antimicrobial compounds to protect against pathogenic invasions. In corals, bacteria such as

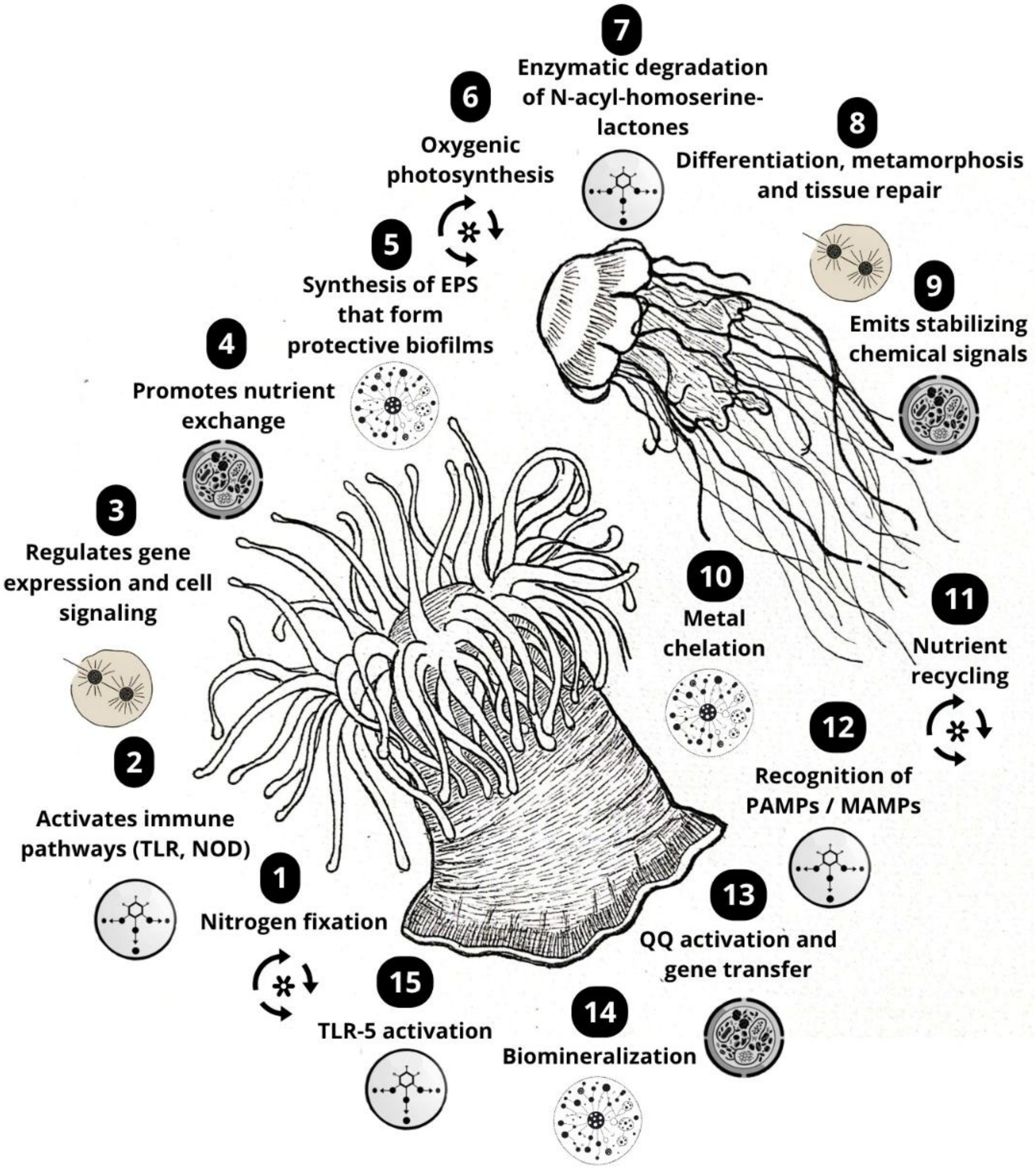

Fig. 2 Biological and physiological functions mediated by microbiota in *Cnidaria*

Vibrio spp., *Pseudovibrio spp*., *Vibrio shiloi*, and *Alteromonas spp*. contribute to immune modulation by inhibiting the growth of marine pathogens (Parisi *et al*., 2020), (Table 2).

Structure and development traits

The cnidarian microbiota actively contributes to calcification and biomineralization by regulating calcium transport and promoting the formation of calcium carbonate crystals, which are essential for coral reef structure. Calcifying *Endozoicomonas, Halomonas spp., Acropora millepora,* and biomineralizing *Pseudomonas spp*. have been identified as key participants in these processes (Dauphin *et al*., 2008; Rädecker *et al.,* 2018).

Moreover, the microbiota plays a significant role in cnidarian morphogenesis and development. A notable example is the upside-down jellyfish (*Cassiopea xamachana*), which harbors symbiotic bacteria such as *Symbiodinium spp*. that are crucial for the transition from polyp to jellyfish (Hagedorn *et al.*, 2015). These symbionts modulate the jellyfish's immune response, suppressing it to promote a more stable symbiotic relationship.

Ecology and adaptation

The ability of cnidarians to adapt to and resist adverse environmental conditions, including fluctuations in temperature, salinity, or pollution, is strongly influenced by their microbiota. Recent studies indicate that cnidarians and their microbiota exhibit active horizontal gene transfer, which facilitates rapid adaptation to changing environmental conditions (Mason *et al.*, 2024).

During coral bleaching events, the presence of specific symbiotic bacteria such as *Ruegeria spp*. helps mitigate thermal stress. These bacteria produce antioxidants that protect corals from damage caused by reactive oxygen species (ROS) (Ziegler *et al.*, 2018).

Similarly, the cnidarian microbiota serves as a sensitive indicator of ecosystem health, enabling early detection of stress, disease, and environmental degradation, making this function critical for the adaptive management and conservation of coral reef ecosystems (McCauley *et al.*, 2023).

Nematodes

Most free-living marine nematodes are characterized by the presence of sensory organs, caudal glands, and a simple excretory system (Young and Unc, 2023). They possess a cylindrical, unsegmented body with bilateral symmetry (Schratzberger *et al.*, 2019), and their flexible yet resistant cuticle allows them to thrive under a wide range of environmental conditions (Lima-Medina *et al.*, 2019). Although they have a complete digestive system, they lack circulatory and respiratory systems, relying entirely on diffusion for gas exchange and nutrient transport (Vranken et al., 1986; Brusca *et al.,* 2005).

The nervous system of aquatic nematodes is simple but highly mapped and they are widely used as models in neuroscience to study fundamental neuronal signaling and behavior (Schafer, 2016; Hobert, 2018). It consists of a nerve ring functioning as a primitive brain, from which dendrites extend throughout the body from head to tail (Srinivasan *et al.*, 2008).

Chemical and electrical signals are transmitted via synapses formed by neurons and neural cords, particularly the ventral nerve cord and peribuccal structures, though cephalic ganglia are absent (Srinivasan *et al.*, 2008). Sensory nerve endings are concentrated in the buccal region, where they detect electrical, chemical, tactile, and thermal stimuli (Stretton *et al.*, 1992). Some species may have over a thousand neurons within a single axonal cord (Watts and Strogatz, 1998).

The digestive system is a complete alimentary canal with a mouth at one end and an anus at the other, ensuring unidirectional food flow (Lippens, 1974). Ecologically, nematodes play a key role in organic matter decomposition and nutrient recycling within aquatic ecosystems (Schuelke *et al.*, 2018). (Figure 3).

Metabolism and nutrition

The intestinal microbiota of nematodes plays a vital role in the degradation of complex polymers such as cellulose and chitin. Bacterial genera like *Lysinibacillus*, *Cellvibrio*, *Pseudomonas*, and *Burkholderia* possess specialized enzymatic capacities for these processes. Lo *et al*., (2024) (Li *et al.* 2024) confirmed the active involvement of the microbiota of *Pristionchus pacificus* in cellulose digestion (Dillman *et al.,* 2012).

The microbiota also contributes to the biosynthesis of essential vitamins and amino acids. Bacteria such as *Escherichia coli, Ochrobactrum,* and *Pseudomonas* facilitate the production of B-complex vitamins and essential amino acids, helping sustain optimal nutrition even in nutrient-poor marine environments (Watson *et al.*, 2018; Zimmermann *et al.,* 2020).

In addition, the microbiota aids in the detoxification of xenobiotic compounds by transforming and degrading toxic substances from the environment. Bacteria such as *Comamonas* and *Pseudomonas* facilitate the nematode's tolerance to environmental contaminants by metabolizing these substances into less harmful forms (Koppel *et al.*, 2017).

O'Donnell *et al*., (2020) (Mc Donnell *et al*., 2023) reported that the marine nematode microbiota significantly influences behavior, particularly in food detection and selection. Certain bacteria produce chemical signals that activate nematode sensory systems and guide them toward specific food sources.

Intestinal bacteria such as *Prevotella, Clostridiales*, and *Bacteroides* ferment complex carbohydrates into short-chain fatty acids like acetate, propionate, and butyrate, which serve as energy sources and help regulate metabolic and immune functions (Dirksen *et al*., 2016).

Immunity

Nematodes possess highly conserved innate immune pathways (p38 MAPK, TGF-β, DAF-2/IGF) that selectively regulate the microbiota, suppressing pathogens while promoting the persistence of beneficial microorganisms. This system serves as one of the most widely studied models of immune-microbiota interaction (Schulenburg and Félix, 2017).

The microbiota modulates immune responses by activating innate pathways. Bacteria such as *Enterobacter*, *Pseudomonas*, and *Ochrobactrum* induce the expression of immune-related genes and the production of antimicrobial peptides, enhancing the nematode's defense mechanisms (Schulenburg *et al*., 2017).

Nematodes benefit from pathogen protection through competitive exclusion and the production of natural antimicrobials. For example, *Enterobacter cloacae* and *Pseudomonas fluorescens* prevent the colonization of pathogenic organisms, a critical function in microbe-rich marine environments (Midha *et al*., 2017).

Structure and development traits

A particularly interesting function of the microbiota in nematodes is its involvement in growth and larval development (Table 1). Various bacteria

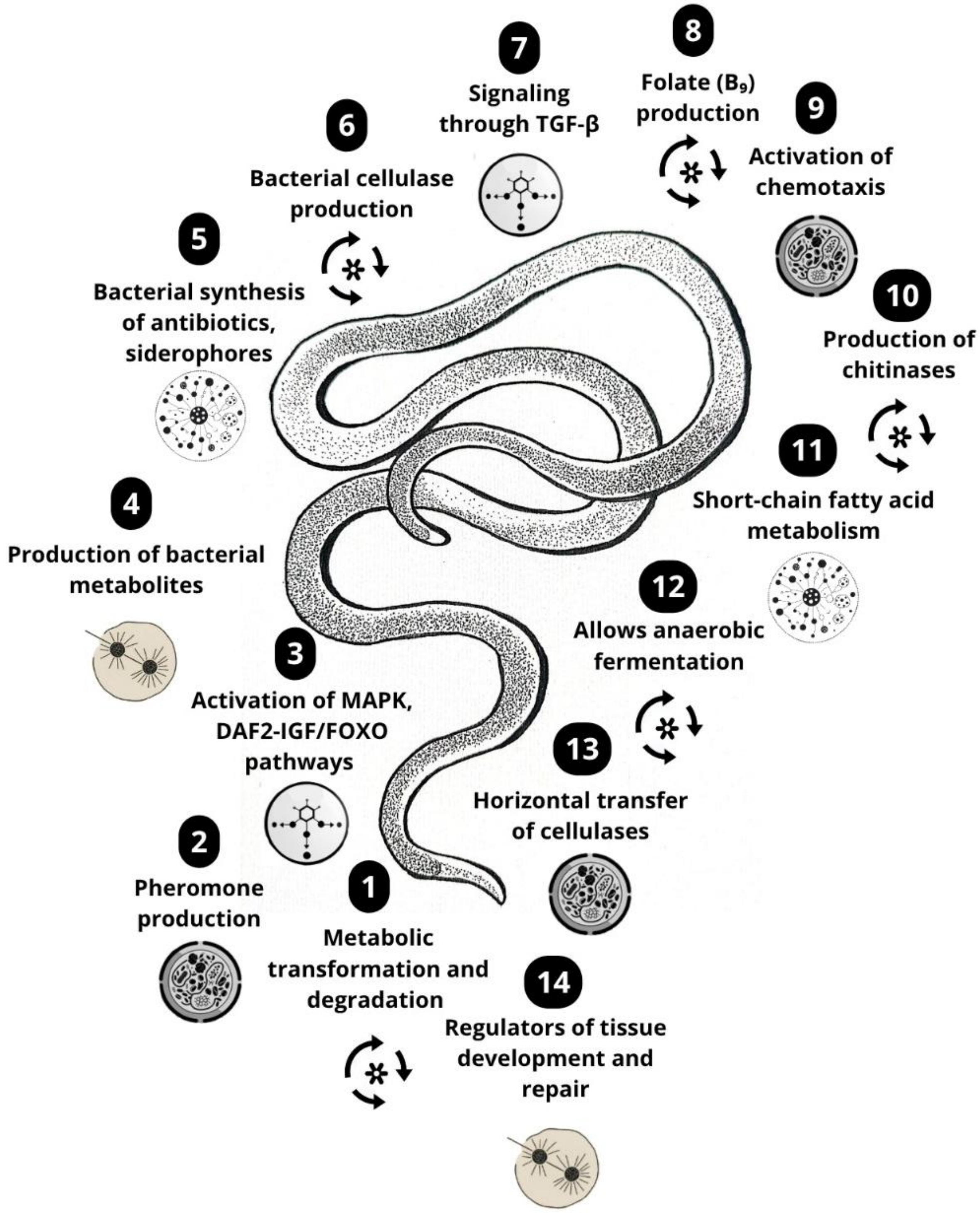

Fig. 3 Biological and physiological functions mediated by microbiota in *Nematoda*

influence the transition between larval stages and adulthood, mediated by bacterial metabolites that act as developmental signals. Species such as *Bacillus subtilis*, *Ochrobactrum*, and *Pseudomonas aeruginosa* have been shown to modulate transitions to the dauer stage, an alternative larval form that enhances survival under adverse environmental conditions (Table 2). These bacteria can also promote growth under specific conditions, supporting nematode development (Dirksen *et al.*, 2020).

Regarding longevity, some bacterial metabolites modulate signaling pathways related to aging, regulating responses to oxidative and metabolic stress. Studies have shown that bacteria such as *Bacillus subtilis* and *Lactobacillus* can extend nematode lifespan, even in harsh environments (Wang *et al.*, 2022).

Ecology and adaptation

Bacteria such as *Pseudomonas* and *E. coli* have been shown to modify nematode feeding preferences, allowing them to better adapt to marine environments. Additionally, these bacteria have been linked to social and reproductive behaviors through pheromone synthesis. Microbial compounds can affect the nematode nervous system, altering interindividual interactions and mating behaviors. Notably, *Pseudomonas* and *Providencia* are associated with changes in population dynamics (Zhang *et al.*, 2022).

The nematode microbiota modulates complex behaviors, including chemotaxis, foraging, and mating. Certain bacteria significantly enhance fertility and reproductive success. *Ochrobactrum* and *Pseudomonas* produce compounds that support egg development and reproductive system function, increasing the likelihood of successful reproduction even under stressful environmental conditions (Dirksen *et al.*, 2016).

Echinoderms

Echinoderms exhibit bilateral symmetry during their larval stage and pentaradial symmetry in adulthood, alongside a notable adaptation capacity (Paul and Smith, 1984). This phylum includes sea cucumbers, brittle stars, sea stars, sea urchins, and crinoids, which all play key ecological roles in benthic marine ecosystems (Figure 4). Through deposit feeding, suspension feeding, predatory strategies, and sediment turnover, echinoderms contribute significantly to the equilibrium and functioning of marine environments (O'Hara and Byrne, 2017).

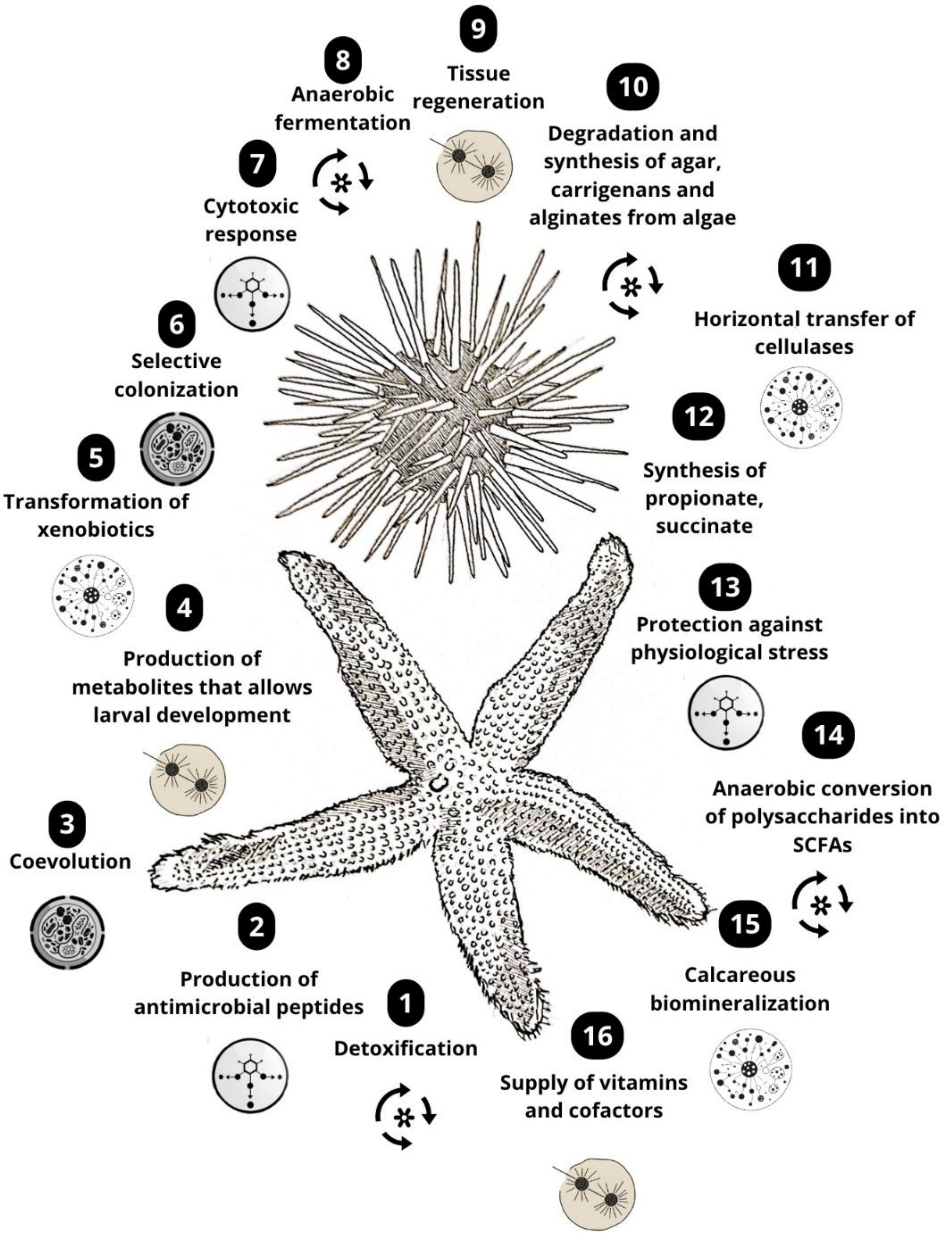

Fig. 4 Biological and physiological functions mediated by microbiota in *Echinodermata*

Their nervous system is divided into two main components: the ectoneural system, responsible for receiving stimuli and controlling movement, and the hyponeural system, primarily associated with locomotion. These are connected by a central nerve ring, allowing the organism to continue moving even after losing an arm, an adaptive advantage (Miguel-Tomé and Llinás, 2021).

Glial cells play a fundamental role in the nervous system by contributing to movement, environmental perception, and tissue regeneration following injury. In echinoderms, these cells are essential for the regeneration of body parts, including nervous tissue and are also involved in clearing dead cells (Mashanov *et al*., 2013).

Additionally, their nervous system releases substances such as acetylcholine, GABA, and neuropeptides, which regulate key functions such as movement, digestion, and tissue repair. These processes are mediated through neural plexuses that also perform metabolic functions (Sharkey and Mawe, 2023).

The digestive system in echinoderms includes the mouth, pharynx, esophagus, stomach, intestine, and, in most species, a rectum (Contreras-Rueda *et al.,* 2023). In sea urchins, a specialized structure called *Aristotle's lantern* enables them to cut and grind food. They also possess glandular structures that help filter out unwanted sediment during feeding (Sodergren *et al*., 2006).

The digestive system is closely integrated with the specialized nervous system, enabling echinoderms to adapt to diverse marine environments and fulfill key ecological functions (Manney *et al.*, 2009).

Metabolism and nutrition

The gut microbiota of echinoderms plays essential roles in digestion, nutrient absorption, and detoxification. In species such as sea cucumbers and sea urchins, symbiotic bacteria efficiently degrade polysaccharides, lipids, and proteins using enzymes like amylases, proteases, and cellulases, thereby facilitating nutrient (Doll *et al.*, 2022). These microbes also neutralize environmental xenobiotics via enzymatic reduction of their toxicity (Doll *et al.*, 2022). Moreover, microbial communities are vital in the degradation of marine algae and detrital material. They regulate key processes such as polysaccharide hydrolysis (e.g., agar, carrageenan, alginate), anaerobic fermentation, and subsequent production of acetate, propionate, and succinate (Table 1). Bacterial genera involved in these processes include *Psychrilyobacter spp*., *Propionigenium spp*., *Photobacterium*, and various alginolytic bacteria (Samuel *et al*., 2017) (Table 2).

Immunity

Echinoderms possess a unique cellular immune system based on coelomocytes (circulating immune cells) that closely interact with the microbiota. Coelomocytes carry out phagocytosis, encapsulation, and cytotoxic responses, while the microbiota modulates these responses and provides molecular recognition signals (Majeske *et al*., 2013).

Some bacterial species, such as *Bacillus*, *Pseudomonas*, and *Vibrio*, commonly found in echinoderms, synthesize antimicrobial, antioxidant, and anti-inflammatory metabolites (Jones *et al.*, 2021). These compounds not only protect the host from pathogens but also help mitigate oxidative stress and inflammation (Patnaik *et al*, 2022).

Against pathogens, the microbiota provides direct protection via competitive exclusion, occupying ecological niches that would otherwise be susceptible to pathogen colonization. *Pseudomonas* and *Vibrio* are particularly noted for their ability to inhibit harmful microorganisms, especially during vulnerable processes like intestinal regeneration in sea cucumbers (Zhao *et al.*, 2023).

In sea stars such as *Asterias amurensis*, bacterial genera like *Pseudomonas* and *Alteromonas* modulate innate immune responses and contribute to the maintenance of immune homeostasis (Kim and Ewbank, 2016).

Structure and development traits

Echinoderms exhibit exceptional regenerative abilities that depend critically on their associated microbiota (Figure 4). The regeneration of arms in sea stars, spines in sea urchins, and internal organs in sea cucumbers involves complex processes in which the microbiota provides growth factors, regulates inflammation, and facilitates tissue remodeling (Hernandez-Agreda *et al*., 2017).

During larval and juvenile stages, the microbiota regulates growth and development. Some symbiotic bacteria emit signals that influence body structure formation (morphogenesis) and transitions between life stages. In sea stars such as *Patiria miniata*, genera like *Pseudomonas* and *Alteromonas* have been implicated in these developmental processes (Pan *et al.*, 2018).

The microbiota also impacts fecundity and fertility. Certain symbiotic bacteria produce metabolites that improve gamete quality and enhance offspring viability. In marine echinoderms, *Pseudomonas* and *Vibrio* have been shown to play a positive role in reproductive health (Sarkar *et al*., 2023).

Additionally, some symbiotic bacteria may influence host longevity by reducing oxidative stress and enhancing energy metabolism. *Bacillus* and *Lactobacillus* have demonstrated beneficial effects on lifespan extension in various marine models (Sarkar *et al*., 2023).

Ecology and adaptation

The influence of microbiota extends beyond the host body, directly impacting biogeochemical cycles in marine ecosystems. Some symbiotic bacteria can transform carbon, nitrogen, and sulfur compounds into bioavailable forms used by other marine organisms. Denitrifying and sulfate-reducing bacteria fulfill this vital ecological role, as observed in the gut microbiota of *Apostichopus japonicus* (Ma *et al*., 2023).

Environmental resilience is another crucial function. Under stressful conditions such as abrupt changes in temperature, salinity, or contamination, the microbiota provides additional support. Genera such as *Bacillus* and *Vibrio* produce osmoprotectants and antioxidants that help echinoderms withstand these stressors and maintain vital functions (Morrissey *et al*., 2021).

Over time, echinoderms, particularly sea stars and sea urchins, have developed close and evolutionarily linked relationships with their microbiota, suggesting a process of co-evolution. Species like *Echinometra* exhibit highly specific microbial associations, indicating selective symbiont transmission across generations with mutual benefits (Schulenburg and Félix, 2017).

Mollusca

With over 9,000 described species, mollusks of the Bivalvia class represent the second most diverse group within the Mollusca phylum. Their body is protected by two hinged valves, and, in many species, specialized siphons enable them to filter water for both feeding and respiration (Allen *et al.*, 1981). Notable representatives of this group include oysters and scallops, members of the *Ostreidae* family (Brett *et al*., 1997).

Marine bivalves hold significant ecological and economic importance. They act as highly efficient filter feeders, removing suspended particles and contaminants from the water (Rousseau and Nakrem, 2012), and serve as ecosystem engineers by forming natural reefs that enhance biodiversity (Grabowski and Peterson, 2007). Their bioaccumulation capacity makes them valuable indicators of environmental quality. Historically, bivalves have been exploited by humans since prehistoric times and now play a pivotal role in aquaculture (Guy *et al*., 2018). Moreover, bivalves can be cultured under gnotobiotic conditions, enabling studies on host-microbiota interactions and the development of targeted probiotics (Pierce and Ward, 2018).

Mollusks are also valuable models in neuroscience and gene expression studies related to the nervous system. During their larval stage, they exhibit key elements of neural development, including electrophysiologically active cells in the apical region and the expression of critical neurotransmitter receptors such as those for serotonin, catecholamines, and neuropeptides (Chase and Darbyson, 2008). As development proceeds, neurons aggregate and form connections that lead to the establishment of ganglia in the parietal and abdominal regions, which regulate essential systems such as digestion, respiration, and circulation (Croll *et al.*, 2009).

A key neurodevelopmental event in these organisms is the centralization of the nervous system, giving rise to a "brain-like" structure (Leise and Hadfield, 2000). Unlike other invertebrates, mollusks lack segmented neural organization and instead exhibit a well-defined central nervous system.

The expression of neural genes is widely conserved across molluscan taxa, including genes such as *Otx* and *Hox*, which are associated with both neural and digestive system development and with neural plasticity (Boudinot *et al.*, 2014).

An especially interesting feature of mollusks is their neuromodulatory system, which involves signaling molecules such as serotonin and octopamine. Serotonin enhances neural signal strength, whereas octopamine boosts synaptic activity, particularly in the frontal lobe. The release of these substances is closely linked to memory processes and the regulation of digestion digestion (Shomrat *et al*., 2010).

In this context, the digestive system of bivalves is highly specialized for filter feeding. Gills trap food particles, which are then processed in the stomach with the aid of the crystalline style and digestive gland. This efficient mechanism enables energy acquisition without the need for active locomotion and highlights the close integration of nervous and digestive functions.

Metabolism and nutrition

Bivalves process large volumes of seawater, filtering suspended particles including phytoplankton, bacteria, and organic matter. The microbiota plays an active role in processing these particles, contributing to filtration efficiency and the selective retention of nutritious material (Masanja *et al*., 2023). Dominant microbial taxa include *Mycoplasmataceae*, *Vibrio spp*., and several *Proteobacteria* with key metabolic functions (Pierce and Ward, 2018).

The microbiota facilitates the extracellular digestion of complex organic matter (algal cell walls and polymers) through the secretion of specialized enzymes (Vezzulli *et al.*, 2018).

Furthermore, the microbiota forms an integrated metabolic system with the host, in which waste products serve as bacterial substrates and microbial metabolites nourish the host, optimizing the overall efficiency of the holobiont. Key microbial functions include nitrogen cycling, carbon metabolism, vitamin biosynthesis, and energy optimization, performed by bacteria specialized in each role (Pierce and Ward, 2018) (Table 1).

Immunity

The cellular immune system of bivalves is based on hemocytes, immune cells responsible for phagocytosis, encapsulation, and cytotoxic responses. These hemocytes interact with the microbiota, which modulates immune responses and provides protection against pathogens. Phagocytic activity and the production of reactive oxygen and nitrogen species (Zannella *et al.*, 2017) by hemocytes are essential in preventing colonization by potentially pathogenic bacteria.

Studies report that the microbiota modulates innate immune responses by influencing the expression of antimicrobial peptides such as ApBD1 and ApLBP/BPI1, which are critical in preventing pathogen overgrowth (González *et al*., 2020). Parasitism in bivalves has also been shown to alter the microbiota, either promoting or inhibiting infections through a tripartite interaction involving host, parasite, and microbes (Destoumieux-Garzón *et al*., 2024). Certain bacteria may confer resistance, others may facilitate infection, and some serve as indicators of health status (Pierce and Ward, 2018).

Immunomodulatory bacteria such as *Endozoicomonas spp*., *Gammaproteobacteria*, and various probiotic species with therapeutic potential have been identified in bivalve microbiomes (Pierce and Ward, 2018). (Table 2).

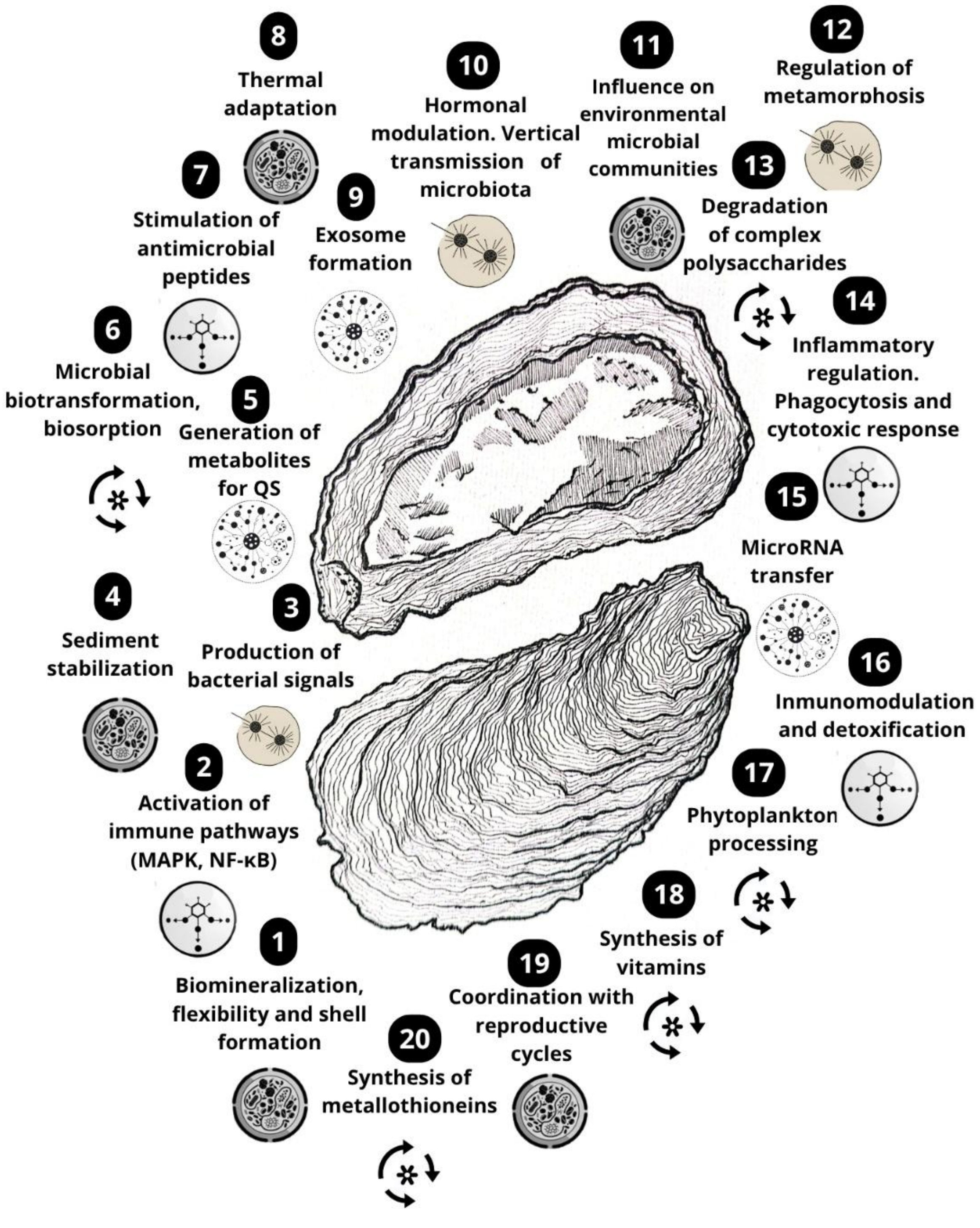

Fig. 5 Biological and physiological functions mediated by microbiota in *Mollusca* (class *Bivalvia*)

Structure and development traits

Larval settlement and metamorphosis in bivalves are regulated by specific microbial cues that trigger the transition from planktonic larvae to benthic juveniles. The microbiota provides chemical signals essential for timing and successful metamorphosis, as well as for synchronizing reproductive cycles (Vezzulli *et al*., 2019).

Microbial communities also play a key role in shell biomineralization in bivalves, with specialized *Mycoplasmataceae* species involved in calcium carbonate crystal formation (Pierce and Ward, 2018). These microbes influence the development of distinct shell layers, including the external prismatic and internal nacreous layers (Lokmer and Wegner, 2015).

Ecology and adaptation

The microbiota of oysters plays a central role in ecological adaptation, mediating responses to seasonal variation and extreme events such as marine heatwaves or ocean acidification (Figure 5). Bacterial genera such as *Vibrio*, *Pseudoalteromonas*, and *Psychrobacter* are involved in thermotolerance, reproductive synchronization, and metabolic stability. These microbial communities allow the host to maintain vital functions under changing environmental conditions and serve as key agents of ecological resilience (Scanes *et al.*, 2021).

Gamma- and *Alphaproteobacteria* associated with bivalves display exceptional detoxification capacities, enabling the breakdown of environmental pollutants, xenobiotics, and toxic metabolic by-products. This function is critical for survival in polluted marine habitats (Vezzulli *et al.,* 2018). Furthermore, larval microbiota contributes to hormone regulation and response to pollutants. These communities can be altered by estrogenic compounds, affecting xenobiotic biotransformation pathways and potentially disrupting host development (Fortunato, 2015).

Discussion and Conclusions

Over the past decades, accumulating evidence has clearly established that the microbiota plays a critical role in regulating multiple physiological processes. From an evolutionary perspective, symbiosis with microorganisms is not an emergent trait but rather a deeply conserved biological strategy, evident even in organisms lacking a centralized nervous system, such as certain invertebrates (Lee and Mazmanian, 2010).

Studies in invertebrate models have shown that the microbiota influences diverse processes, including cellular differentiation, embryonic development, immune function, the digestion of structurally complex compounds, vitamin biosynthesis, and environmental adaptation (Little *et al.*, 2005; Kloc *et al.*, 2024). Through various molecular mechanisms, such as the production of bioactive metabolites, the modulation of signaling pathways, and the regulation of host gene expression, these microorganisms actively contribute to maintaining host homeostasis (Loker *et al.*, 2004). Remarkably, these functions occur even in the absence of a sophisticated epithelial barrier, a robust nervous system, or an adaptive immune response, suggesting that the foundational elements of the host-microbiota axis are evolutionarily ancient (Schnorr *et al.*, 2016).

Compared to mammals, the intestinal microbiota of invertebrates has been reported to exhibit greater functional diversity, not only in its capacity to degrade a broader range of nutrients but also in its remarkable ecological plasticity. This versatility allows invertebrates to rapidly and efficiently adapt to environmental fluctuations, facilitating occupation of a wide variety of ecological niches through highly dynamic symbiotic strategies (O'Brien *et al.*, 2019).

One of the most significant mechanisms in this context is horizontal gene transfer (HGT), a phenomenon well-documented in invertebrates that enables the rapid acquisition of new functions, including specialized metabolic pathways and digestive enzymes. While HGT is a rare event in mammals, in invertebrates it represents a continuous source of genetic and ecological innovation, critical for their accelerated environmental adaptation (Dierking and Pita, 2020).

The microbiota associated with invertebrates is also notable for its ability to produce antimicrobial compounds that boost host defenses and facilitate adaptation to specific niches. While similar functions are observed in mammals, the greater taxonomic and genetic diversity in invertebrates reflects divergent evolutionary trajectories (Collinder *et al.*, 2003).

Another distinctive feature lies in host-microbiota immune interactions. In invertebrates, this communication is mediated by a broader array of expanded receptors, allowing for more versatile and nuanced recognition of symbiotic microorganisms (Dierking and Pita, 2020).

In addition, invertebrate microbiota displays remarkable plasticity in response to factors such as diet and temperature, enabling rapid and adaptive responses to fluctuating conditions. In contrast, mammalian microbiota often requires longer timeframes to reestablish ecological balance, indicating a lower degree of functional flexibility (Ángel-Sánchez and Galián, 2022). These differences underscore not only the adaptive capacity and functional complexity of microbial symbionts in invertebrates but also position these organisms as models of evolutionary efficiency in host-microbiota regulation (Sharp and Foster, 2022).

Aside from functional differences with mammals, a cross-taxon comparison within invertebrates also elucidates the evolutionary pathway of microbiota–host interactions based on organization of nervous system (Haendel *et al.* 2014; Oberprieler *et al.*, 2019).

Comparative evolutionary considerations

Across the invertebrates examined, neural organization ranges from the absence of true neurons in Porifera, to diffuse nerve nets in Cnidaria, radially arranged nerve structures in Echinodermata, and more condensed ganglionic systems in Mollusca.

With these differences in anatomy, the idea that microbes help control the host body is always present (Brown and Clarke, 2017).

In sponges, which lack any nervous system, microbial communities contribute directly to metabolic integration, chemical signaling, and environmental sensing, suggesting that host–microbe coordination predates neuronal control. When a neve net appears in cnidarians the body responses become more coordinated; however, microbial modulation persists through epithelial, immune, and metabolic pathways rather than being replaced by neural regulation (Engelberts *et al.,* 2020).

Echinoderms have a structured nerve that helps with movement and regrowth, and a clearer functional distinction between neural control and microbial contributions is observed. Here, the microbiota is primarily involved in immune regulation, tissue homeostasis, and environmental responsiveness. This pattern suggests not a reduction

Table 3 Nervous system organization and microbiota-regulated functions across invertebrate taxa

Phylum	Nervous system organization	Representative microbiota-regulated functions	References
Porifera	Absence of true neurons and synapses; no centralized nervous system	Metabolic integration, chemical signaling, environmental sensing, structural homeostasis, and antimicrobial activity	Srivastava *et al.,* 2010; Musser *et al,.* 2021
Cnidaria	Diffuse nerve net without centralization	Epithelial homeostasis, immune modulation, developmental signaling, and maintenance of symbiotic equilibrium	Spencer and Arkett, 1984; Kass-Simon and Pierobon 2007; Fujisawa *et al.,* 2009
Echinodermata	Radially organized nerve structures with circumoral nerve ring and radial nerve cords	Immune regulation, regeneration support, tissue maintenance, and environmental stress responsiveness	Miguel-Tomé and Llinás 2021; Sharkey and Mawe, 2023
Mollusca (bivalves/oysters)	Condensed ganglionic system with cerebral, pedal, and visceral ganglia	Larval settlement and metamorphosis, shell biomineralization, thermotolerance, detoxification, reproductive coordination, and metabolic stability	Chase and Darbyson, 2008; Croll *et al*., 2009; Boudinot *et al*., 2014

in microbial influence, but a gradual redistribution of regulatory roles as neural complexity increases (Hinman and Burke, 2018)

In mollusks, where ganglionic condensation enables greater neural integration, microbial signals are associated with systemic processes such as stress tolerance, metabolic regulation, and development. Importantly, these observations do not imply that microbiota-mediated regulation depends on neural centralization. Rather, they indicate that increasingly complex nervous systems have incorporated pre-existing microbial signaling mechanisms into broader regulatory networks (Srinivasan, 2023)

Taken together, these comparisons support the view that the gut–microbiota axis represents an evolutionarily ancient layer of biological regulation that predates centralized brains (Table 3). Neural complexity appears to modulate, but not originate, microbiota-mediated host regulation, reinforcing the continuity of host-microbe interactions across animal evolution.

This perspective highlights that the true scope and functional complexity of the mammalian microbiome, including that of humans, remains incompletely understood. While invertebrates display highly efficient and adaptive symbioses, the human microbiota is characterized by significantly higher levels of diversity and specialization. It has been implicated in a range of critical physiological processes, including the digestion of indigestible polysaccharides, vitamin synthesis, short-chain fatty acid production, immune system maturation, and inflammation regulation (Ma *et al*., 2024).

Additionally, the human microbiota is known to influence host neurobiology via the gut-brain axis, with implications for neurological development, behavior, stress response, and neuropsychiatric disorders (Socała *et al*., 2021) Intestinal dysbiosis has been linked to a broad spectrum of diseases, including obesity, type 2 diabetes, chronic inflammatory disorders, autoimmune conditions, and cancer (DeGruttola *et al*., 2016). These functions reflect a sophisticated symbiotic evolution, whose comprehensive understanding remains a major challenge for biomedical science.

These functional and evolutionary differences reveal that invertebrate microbiota is not only more flexible and dynamic than its mammalian counterpart but also represents an exceptional model for exploring the frontiers of symbiosis, ecological adaptation, and microbial evolution (Robinson *et al*., 2010). The scientific community must continue to investigate this interface through interdisciplinary and evolutionary approaches, integrating molecular biology, microbiology, immunology, neuroscience, and translational medicine.

Studying the functional role of the microbiota and the gut microbiota axis in brainless invertebrates, such as oysters, reveals evolutionarily conserved host microbe interactions, including immune modulation, metabolite production, and barrier regulation that predate the emergence of the central nervous system. These core mechanisms, preserved across animal phylogeny, serve as a biological filter to identify pathways with high translational potential (Zamani *et al*., 2025). By understanding how microbiota regulate host homeostasis in the absence of a centralized brain, we gain fundamental insights into the ancestral principles of the gut–brain axis, informing targeted therapies for metabolic, immune, and neuropsychiatric disorders in humans.

Furthermore, these organisms emerge as powerful platforms for biomedical innovation, offering experimentally tractable yet physiologically relevant systems for developing probiotic strategies, immunomodulatory interventions, and novel applications in microbial biotechnology.

Future directions

Studying the gut-microbiota axis in brainless invertebrates offers a powerful evolutionary lens to decipher the ancestral mechanisms of host-microorganism communication, revealing conserved pathways that predate the emergence of centralized nervous systems. Comparative analyses between invertebrates and mammals can reveal conserved functional mechanisms and evolutionary principles, shedding light on symbiotic strategies that have persisted throughout animal evolution. Oysters (bivalves) have emerged as particularly promising models due to their widespread coastal distribution, simple physiology, primitive immune system, and filter-feeding lifestyle (Robledo *et al.*, 2019)

These traits make them controllable, reproducible, and ethically viable experimental systems, ideal for precisely evaluating the effects of specific microbial strains on host phenotype, as well as for screening bioactive metabolites with immunomodulatory, neuroactive, or metabolic potential (Robledo *et al.*, 2018)

Furthermore, they enable the investigation of symbiotic responses to environmental variables such as temperature, pollution, and nutrient availability (Masanja *et al.,* 2023). Advancing research using these models could open new avenues for a deeper understanding of the human microbiota and its therapeutic modulation, establishing marine invertebrates as translational platforms bridging microbial ecology and biomedicine.

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Graphical abstract

Functions of Microbiota-Gut-Brain axis in Invertebrates with a primitive gut and decentralized brain