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REVIEW ARTICLE

Role of Chemical Mediators in Aquatic Interactions across the Prokaryote–Eukaryote Boundary

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Abstract

There is worldwide growing interest in the occurrence and diversity of metabolites used as chemical mediators in cross-kingdom interactions within aquatic systems. Bacteria produce metabolites to protect and influence the growth and life cycle of their eukaryotic hosts. In turn, the host provides a nutrient-enriched environment for the bacteria. Here, we discuss the role of waterborne chemical mediators that are responsible for such interactions in aquatic multi-partner systems, including algae or invertebrates and their associated bacteria. In particular, this review highlights recent advances in the chemical ecology of aquatic systems that support the overall ecological significance of signaling molecules across the prokaryote–eukaryote boundary (cross-kingdom interactions) for growth, development and morphogenesis of the host. We emphasize the value of establishing well-characterized model systems that provide the basis for the development of ecological principles that represent the natural lifestyle and dynamics of aquatic microbial communities and enable a better understanding of the consequences of environmental change and the most effective means of managing community interactions.

Keywords Biofouling · Ecophysiology · Microbial behavior/signaling · Symbionts · Microbiome · Chemical communication · Quorum-sensing · Biofilm · Natural products · Morphogenesis

Introduction

The first eukaryotes evolved in a world governed by bacteria, and these have been communicating, interacting, and co-evolving ever since. Bacteria orchestrate inter- and intra-species interaction mainly by releasing and sensing small molecules. Eukaryotes have evolved multiple ways to recognize and exploit such bacterial communication. Rapid advances in OMIC-technologies and ecology-driven natural product chemistry have catalyzed the detailed chemical analysis of small molecule-based bacterial communication, resulting in the identification of crucial bacterial signaling molecules, virulence factors, defensive metabolites, and morphogenic factors (Adnani et al. 2017; Kuhlisch and Pohnert 2015; Meyer et al. 2017; Molloy and Hertweck 2017). The microbial world of terrestrial plants or animals has been recently reviewed (Goecke et al. 2013; McFall-Ngai et al. 2013; Seymour et al. 2017; Straight and Kolter 2009; Woznica and King 2018).

Our review article highlights the chemical ecology of aquatic systems related to growth and morphogenesis of the host, including both plants and animals, to stress the overall ecological significance of signaling molecules (Fig. 1). It spans phytoplankton–bacterial, macroalgae–bacterial, and opisthokont–bacterial interactions. We discuss recent advances in complex community chemical mediator identification and exemplify cross-kingdom interactions with both ex-vivo and in-vivo perspectives. The chemosphere, biofilm formation processes, and bacteria-induced morphogenesis and metamorphosis are described. Case studies illustrate different aspects of aquatic bacteria–eukaryote (cross-kingdom) cross-talk (Fig. 2, Table 1). Specific bacterial mediators, such as (i) quorum-sensing molecules, (ii) morphogenetic compounds (morphogens), (iii) bacterial lipid-based molecules, (iv) phytohormones, and (v) vitamins found to be essential for cross-kingdom interactions are detailed.

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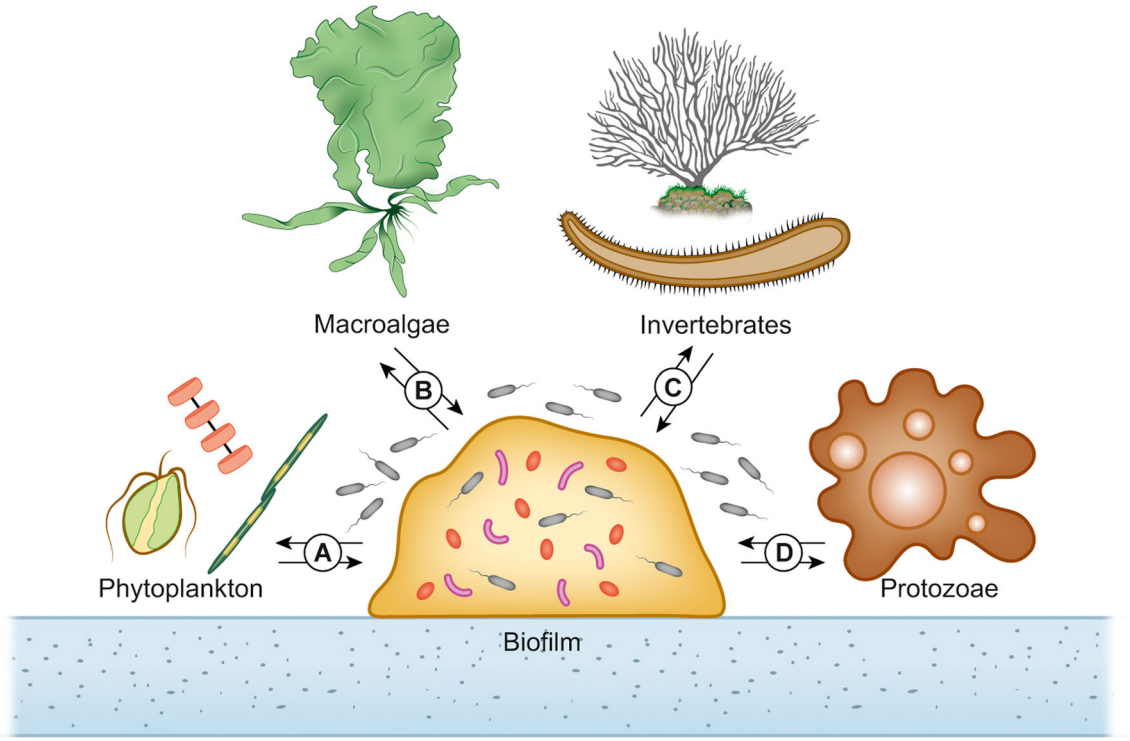

Fig. 1 Examples of cross-kingdom interactions presented in the review. Bacteria and their hosts interact particularly in a biofilm where adherent species exchange signal molecules and nutrients, preparing a chemosphere. *A* Phytoplankton–bacteria interactions. *B* Bacteria-induced morphogenesis in macroalgae. Algal germ cells can attract bacteria and *vice versa*. *C* Bacteria-induced settlement and metamorphosis in invertebrates. *D* Biofilms can also protect organisms against predators, such as amoebae or predatory bacteria

The Chemosphere: Chemical Mediators in Cross-Kingdom Interactions

The phytoplankton-associated bacterial habitat, previously defined as the "phycosphere", encompasses the space where interactions between organisms occur (Bell and Mitchell 1972; Sapp et al. 2007). Phytoplankton release organic compounds including elevated carbohydrate amounts (Myklestad 1995), thereby attracting associated microorganisms including protists (Lancelot 1983). Following gradual expansion to plants and animals (Seymour et al. 2017), the "chemosphere" concept, exemplified for macroalgae, was advanced as the region supporting waterborne chemical mediator-based cross-kingdom interactions (Alsufyani et al. 2017; Harder et al. 2012; Wichard 2016). Organisms use chemical cues, termed "infochemicals", in their surroundings as important information sources regarding their biotic and abiotic environment (Dicke and Sabelis 1988). Axenic cultures support particularly fruitful studies of specific interactions among phylogenetically distant taxa. To distinguish waterborne-mediated effects from surface-mediated effects, experiments with two chambers that are physically separated but can exchange dissolved or colloidal chemical signals are necessary (Paul et al. 2013; Steinert et al. 2014). Whereas in some model systems, bacteria can be successfully separated from their hosts (e.g., diatoms, macroalgae) (Paul et al. 2013; Spoerner et al. 2012), in other systems, it remains to be proven whether compounds are truly waterborne or are mediated through surface-associated transitions. Defined co-cultivation conditions allow direct access to designed microbiome effects on the host. Conversely, sponge microbiomes, comprising up to 35% of the host biomass, facilitate highly complex chemosphere analysis through their extensive diversity and dimensions (Webster and Thomas 2016). Therefore, although extensive sponge bacterial symbiont metabolic functions are proposed (Hentschel et al. 2012), detailed biochemical studies are limited (Table 1).

To holistically describe such microbial diversities within complex cross-kingdom interactions in sponges, corals, or algae harboring diverse microbiota spanning various microbial and candidate phyla (Egan et al. 2013; Webster and Thomas 2016), the "holobiont" concept was proposed. This implies that host–microbe interactions are part of evolution and result in symbiogenesis (Guerrero et al. 2013). The holobiont is here considered as a unit comprised of the eukaryotic host and the consortium of bacteria, archaea, unicellular algae, fungi, and viruses resident within. The microbial component can adapt the host developmental stage, diet, or growth conditions to changing environmental conditions and structures (Rohwer et al. 2002; Zilber-Rosenberg and Rosenberg 2008). The sum of host and associated microbiota genetic information defines the hologenome (Rosenberg and Zilber-Rosenberg 2016). However, host-specific microbial community

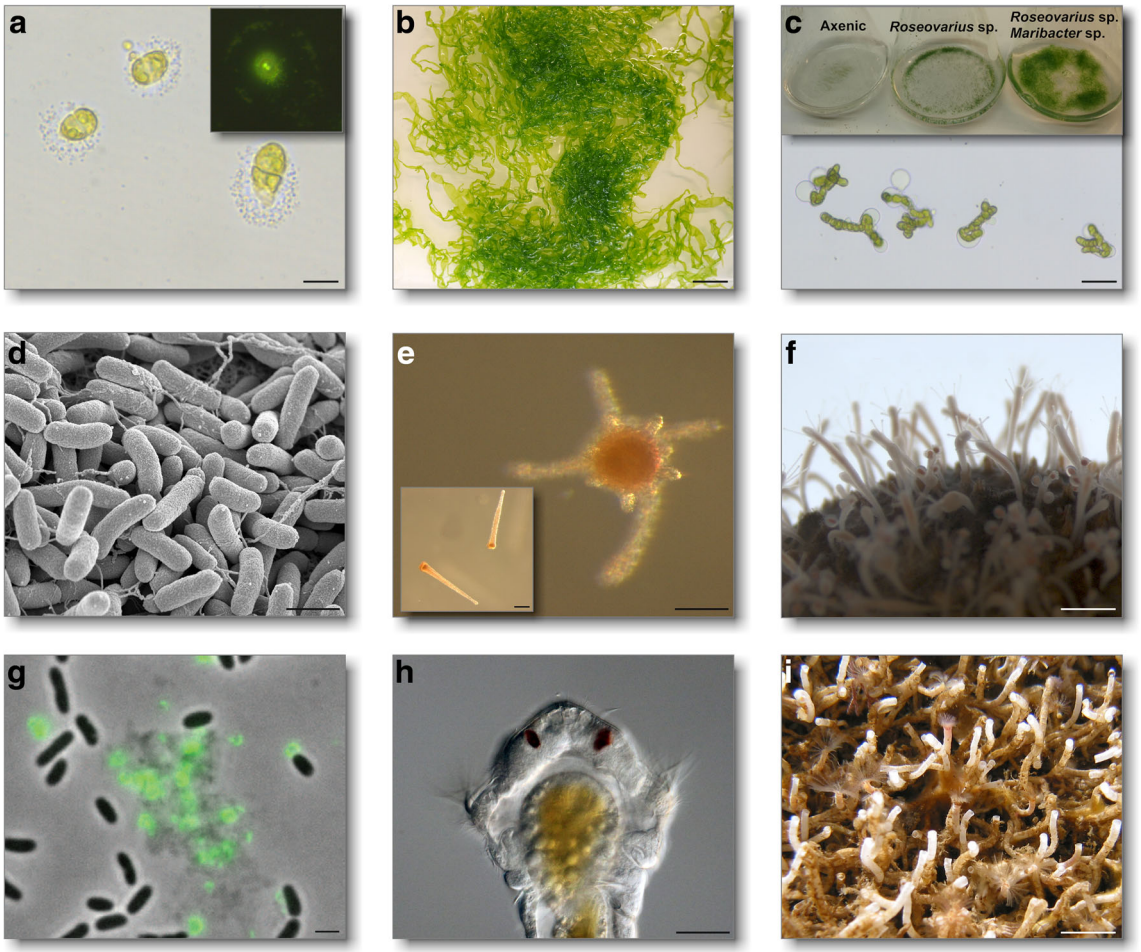

Fig. 2 Exemplified images of three model organisms for bacteria-induced morphogenesis or metamorphosis. **a-c** Macroalga *Ulva mutabilis*. **d-f** Hydrozoans *Hydractinia echinata* and **g-i**) *Hydroides elegans*. **a** Unmated gametes of *U. mutabilis* (Chlorophyta) propagate as a haploid strain and germinate with a clear polarization for primary rhizoid formation upon settlement, where accumulated bacteria can be observed (biofilm formation) (scale bar = 10 μm). **b** Typical culture of the naturally occurring developmental mutant *slender* of *U. mutabilis* (scale bar = 1 cm). **c** Under axenic conditions, *Ulva* develops into a callus with no cell differentiation and slow growth (1-week old culture; scale bar = 50 μm) (**a**, **b**, and **c** were adapted from Wichard et al. (2015) made available under Creative Commons by Attribution (CC-BY)). Morphogenesis can be recovered by a combination of two essential bacteria releasing morphogenetic compounds into the growth medium (inserts: three-week-old culture). **d** Scanning electron microscopy image of *Pseudomonas* sp. isolated from the hydrozoan *H. echinata* (image provided by Dr. Martin Westermann, EMZ Jena) (scale bar = 1 μm). **e** *H. echinata* as a model organism for marine invertebrate metamorphosis (Guo et al. 2017). Metamorphosis is triggered by cues from bacteria found on the hermit crab shell (inset scale bar = 200 μm, outer scale bar = 50 μm). **f** After metamorphosis, the single polyp grows and extends its stolonal network, reaching adult size fairly quickly (scale bar = 1 mm). **g** *Pseudoalteromonas luteoviolacea* (HI1) produces arrays of phage tail-like structures that trigger *H. elegans* metamorphosis. Micrographs of merged phase contrast and fluorescence images show strains that translate the metamorphosis-associated contractile structure (mac) protein fused with GFP (Image by Shikuma et al. 2014; with permission from AAAS via RightsLink) (scale bar = 100 nm). **h** Competent *H. elegans* larva (tubeworm, scale bar = 50 μm) requires contact with surface-bound bacteria to undergo metamorphosis into the **i**) juvenile adult (scale bar = 1 mm)

composition among more closely related hosts does not imply symbiont–host co-evolution (Catania et al. 2017). Systemic biological wholes, therefore, need not be consequent to a natural selection process (Catania et al. 2017), but may also newly emerge from spontaneous or even accidental interactions. The idea that understanding how symbionts affect human health or crop productivity may require observing only current symbiont effects on the host regardless of evolutionary history (Moran and Sloan 2015) underlies the examples selected for this review. Despite many controversial conceptual discussions (Catania et al. 2017; Theis et al. 2016), the actual physiological and biochemical interactions occurring within most symbiotic systems remain poorly understood, as do the underlying infochemical structures and physiochemical properties for these eco-physiological responses. Thus, detailed knowledge of the mechanisms of fitness, developmental processes, and ongoing adaption to environmental changes is required to incorporate functionality into the hologenome concept (Catania et al. 2017). The following cross-kingdom interactions are examples wherein the partnerships are enduring complex entities that putatively persist owing to the action of chemical mediators.

Table 1 Model systems in studies of cross-kingdom interactions in aquatic systems

Eukaryote (Host)	Bacteria	Chemical mediator	Method of action	Reference
Emiliania huxleyi (CCMP3266, CCMP372)	*Phaeobacter gallaeciensis* (BS107) *Phaeobacter inhibens* (DMS17395)	Roseobacticides Auxin	Algicide Growth stimuli	Seyedsayamdost et al. 2011; Segev et al. 2016
Pseudo-nitzschia multiseries	*Sulfitobacter* sp.	Auxin (hormesis)	Growth stimuli	Amin et al. 2015
Chlamydomonas reinhardtii *Porphyridium purpureum* *Euglena gracilis*	*Halomonas* sp.	Cobalmin (Vitamin B_{12})	Survival and growth stimuli	Croft et al. 2005; Helliwell et al. 2015
Ulva mutabilis	*Roseovarius* sp. (MS2) *Maribacter* sp. (MS6) *Vibrio anguillarum*	DMSP Thallusin AHL	Attractor of bacterium Morphogen Attractor of zoospores (zoids)	Spoerner et al. 2012; Wichard 2015; Kessler et al. 2018; Ghaderiardakani et al. 2017; Joint et al. 2002
Salpingoeca rosetta (ATCC50818)	*Algoriphagus machipongonensis*	Rosette-inducing factor (RIF-1) Lysophosphatidyl-ethanolamines (LPEs)	Colony formation	Beemelmanns et al. 2014; Woznica et al. 2016
Corals	Bacteria, Archaea	Corallinafuran Corallinaether 11-deoxy-fistularin-3 tetrabromopyrrole (2*S*)-1-*O*-(7*Z*,10*Z*,13*Z*-hexadecatrienoyl)-3-O-β-D-galactopyranosyl-*sn*-glycerol (2*R*)-1-*O*-(palmitoyl)-3-*O*-α-D-(6′-sulfoquinovosyl)-*sn*-glycerol Partially characterized high-molecular-weight polysaccharide	Anti-biofouling Metamorphosis Partial morphogenesis (anti-biofouling)	Kitamura et al. 2005; Uemura et al. 2009; Tebben et al. 2015
Hydractinia echinata	*Pseudoalteromonas* sp.	Lipid-like compounds	Colony formation and morphogen	Leitz and Wagner 1993; Guo et al. 2017
Hydroides elegans	*Pseudoalteromonas luteoviolacea* (HI1)	Tailocins (protein)	Unselective morphogen	Hung et al. 2009; Huang et al. 2012; Shikuma et al. 2014, 2016

Phytoplankton–Bacteria Interdependency: Shared Auxin Biosynthesis *Sulfitobacter*-related species (Rhodobacteraceae) transform algae-derived tryptophan (Trp) to indolic acetic acid (IAA), which is the most abundant auxin (i.e., phytohormone) in plants. Bacteria can thus affect diatom (Bacillariophyceae) growth by secreting IAA (Fig. 3a) (Amin et al. 2015). *Sulfitobacter* benefits from diatoms by taking up carbohydrates necessary for growth, as well as taurine, a sulfonated metabolite. In turn, the bacteria excrete ammonia, the preferred diatom nitrogen source, into the medium by switching their metabolic preference to nitrate (Amin et al. 2015). Further experiments are necessary whether the exchange of essential molecules such as ammonia and organosulfur compounds are really excreted to the environment or directly short-circuited to the host.

Two major IAA pathways have been proposed to date: Trp-independent and -dependent pathways, with only the latter being understood (Galun 2010). Some bacteria, such as many *Roseobacter* clade members, exhibit auxin pathways similar to those in plants, indicating conserved biosynthetic mechanisms (Di et al. 2016; Moran et al. 2007). Bacteria can also directly acquire diatom-released Trp, as demonstrated by administering exogenous doubly labeled ^{13}C, ^{15}N-Trp (Segev et al. 2016). Bacterial tryptophan aminotransferase (Trp-AAT) converts Trp into indole-3-pyruvate, followed by decarboxylation of indole-3-pyruvate to indole-3-acetaldehyde and oxidization by the indole-3-acetaldehyde dehydrogenase to form IAA (Schütz et al. 2003). Also, in *Roseobacter* genomes, several potential pathways were suggested to produce IAA via indole-3-acetonitrile, tryptamine or indole-3-acteamide (Amin et al. 2015). In this context, *Phaeobacter inhibens* (Rhodobacteraceae) influences *Emiliania huxleyi* (Haptophyta) physiology in a positive feedback loop, as *E. huxleyi* exudes Trp into the environment, which increases *P. inhibens* IAA production and its subsequent algal attachment (Fig. 3b) (Segev et al. 2016). Thus, diffusible compounds could mediate interactions without requiring direct physical contact with the partners (Segev et al. 2016). Interestingly, IAA presence does not appear to affect early development of green macroalgae (Spoerner et al. 2012), although *Roseobacter*-clade bacteria associate with the macroalgae and excrete IAA (Wichard, unpublished results). Here, the bacteria-induced *Ulva* developmental stimulation depends on other unknown hormone-like compounds. Bacillariophyceae and Haptophyceae studies suggest that IAA is a typical anchor for symbiotic interaction establishment in addition to general carbon food supplementation by phototrophic organisms (Amin et al. 2015; Segev et al. 2016). Nevertheless, mutualistic interactions can also shift to pathogenic relationships, as exemplified in the following study.

Jekyll-and-Hyde Chemistry of *Phaeobacter* Phytoplankton–bacteria interactions frequently occur in the ocean and are essential for algal physiology, bloom dynamics, and biogeochemical cycles (Segev et al. 2016), but may resemble "*The*

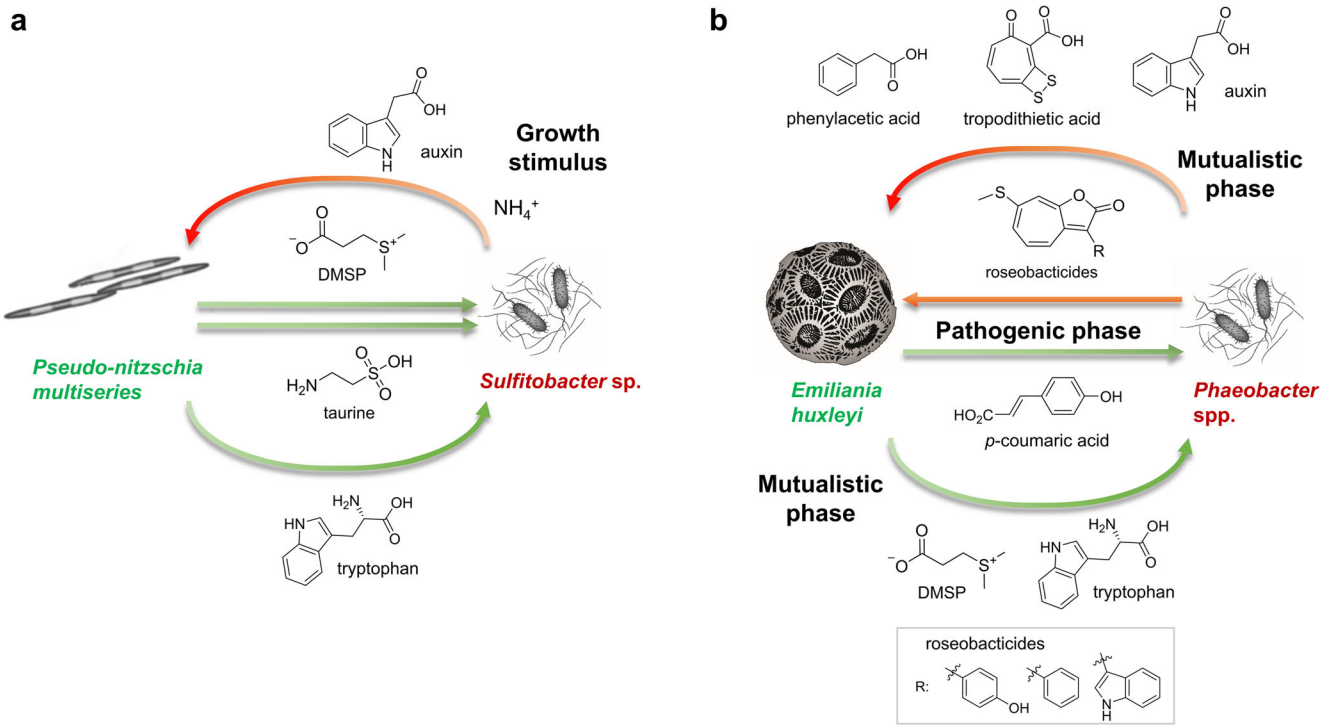

Fig. 3 Phytoplankton–bacteria interactions. **a Interdependency via shared auxin biosynthesis.** The auxin indole-3-acetic acid (IAA) and tryptophan serve as nutrients and signaling molecules and are part of complex exchanges including diatom-excreted organosulfur molecules and bacterial-excreted ammonia. **b Jekyll-and-Hyde chemistry.** *Phaeobacter–Emiliania huxleyi* (Haptophyta) interactions are characterized by a mutualistic phase through auxin (outer circle), which is followed by a pathogenic phase (inside arrows) in which the bacterium kills the aging algae by roseobactericides. Compounds released by photoautotrophs are annotated as green arrows, compounds released by bacteria as red arrows

Strange Case of Dr Jekyll and Mr Hyde" by Robert Louis Stevenson. *Phaeobacter gallaeciensis* (BS107) forms a mutualistic association with different algae, most notably *E. huxleyi* (CCMP372) (Seyedsayamdost et al. 2011). Metabolomics revealed that *P. gallaeciensis* produces the algal growth-promoting substances IAA and phenylacetic acid in addition to the broad spectrum antibiotic tropodithietic acid (Fig. 3b). Ageing *E. huxleyi* cells, however, release *p*-coumaric acid, an algal lignin breakdown product, which triggers selective algicides (roseobacticides A and B) production by the associated bacterium (Fig. 3b). Thereupon, the previously mutualistic bacterium transforms into an opportunistic pathogen (Wang et al. 2016). Interestingly, studies in *E. huxleyi* (CCMP3266) and *P. inhibens* (DMS17395) co-culture (Segev et al. 2016) showed that the roseobacticides did not impair the calcified strain CCMP3266, suggesting the algicidal effect was strain-specific. In this case, the growth-promoting IAA effect was toxic at high concentrations (> 1 mmol L^{-1}) (Segev et al. 2016). IAA hormesis (i.e., the biphasic response upon exposure to increasing substance concentration) occurs in various plant systems and substances (Amin et al. 2015). A mutualistic phase followed by a pathogenic phase in which the bacterium kills ageing algae was also observed during *Dinoroseobacter shibae* co-cultivation with *Prorocentrum minimum* dinoflagellates (Wang et al. 2015).

The following example shows that bacteria and algae co-cultivation can also evoke genetic changes in algae to define a new relationship quality.

Foraging to Farming Hypothesis: Vitamin B_{12} The foraging to farming hypothesis proposes that mutualism can evolve as an accidental consequence of metabolic exchanges. "Farming" the bacteria becomes an evolutionarily stable strategy, turning a previously free interaction into an obligate one. The switch from an independent to a dependent lifestyle is only feasible when ecological associations (with bacteria) loosen the selective pressure to maintain the genetic capacity for independence (Kazamia et al. 2016).

Such metabolic independencies are exemplified by cobalamin (vitamin B_{12}) dependence, as vitamin availability can limit primary productivity. Various mutualistic interactions between heterotrophic bacteria, which offer cobalamin, and eukaryotes, providing organic compounds in return, are reported (Kazamia et al. 2012). Algae acquire cobalamin through a symbiotic relationship with bacteria (Croft et al. 2005). Most cobalamin auxotroph algae in the surface ocean obtain cobalamin through direct interactions with producers or breakdown of cobalamin-containing cells in their immediate vicinity. The cobalamin-dependent red alga *Porphyridium purpureum* or *Euglena gracilis*, for example, can be sustained by the marine bacterium *Halomonas* sp. in a defined cobalamin-deficient culture medium (Croft et al. 2005).

A mutualistic interactions model supported that loss of function can result from nutrient abundance (Collins and Bell 2004). *Chlamydomonas reinhardtii* cultures grown under elevated CO_2 conditions for 1000 generations evolved into several lines, which grew poorly in ambient CO_2 concentrations (Collins and Bell 2004), potentially from altered carbon concentration mechanisms. *C. reinhardtii* cultivation in high cobalamin concentrations yielded a cobalamin-dependent mutant after 500 generations that relies on cobalamin-synthesizing rhizobial bacteria owing to the loss of the cobalamin-independent methionine synthase gene (MetE) through a type-II Gulliver-related transposable element integration (Helliwell et al. 2015) (Fig. 4a). *C. reinhardtii* cobalamin dependence is thus a consequence of loss of function; however, multiple pathways to genetic degradation may be envisaged indicated by the presence of MetE pseudogenes in several cobalamin-dependent algal species (Helliwell et al. 2015). Algae can also accumulate deleterious mutations in the presence of cobalamin owing to the lack of selection pressure.

Carrying both methionine synthase MetE and MetH isoforms, *C. reinhardtii* is independent of cobalamin availability and exploits sporadic resources in its environment as a "forager" (Helliwell et al. 2015), using the vitamin when available. However, prolonged vitamin acquisition from loosely associated bacteria may lead to MetE gene loss and bacterial cobalamin producer dependency. Subsequent limitations in cobalamin availability upon dynamic changes in environmental conditions (Kazamia et al. 2016) may require the alga to act as a bacteria "farmer", providing carbon sources and nutrients within the chemosphere to ensure bacteria persistence in the local vicinity. The development of dependency should be in the interest of the organisms being "farmed", as they receive goods within the newly formed bacterial–algal mutualism.

Predator–Prey Interactions: Colony Formation The predatory microbial eukaryotes Choanoflagellates are the closest living relative to animals. Some choanoflagellates, such as the model species *Salpingoeca rosetta*, appear in different cell types and morphologies including linear chains of cells ("chain colonies"), rosette colonies, single slow and fast swimmer cells, and thecate cells that attach to substrates through a secreted structure (theca) (Dayel et al. 2011). Morphology diversity is comparable to the number of cell types observed in sponges and placozoans. Genomic similarities underpin the close link between the animals (Fairclough et al. 2013).

The bacterial community was shown to influence rosette colony development by treating *S. rosetta* cell lines with an antibiotic cocktail to remove overgrowing bacteria (Alegado et al. 2012). Members, particularly of the genus *Algoriphagus* (Bacteroidetes phylum), which were isolated from the original *S. rosetta* ATCC50818 strain, induced rosette colony development to almost 100%, as did several other closely related species. Non-Bacteroidetes species, including γ-proteobacteria, α-

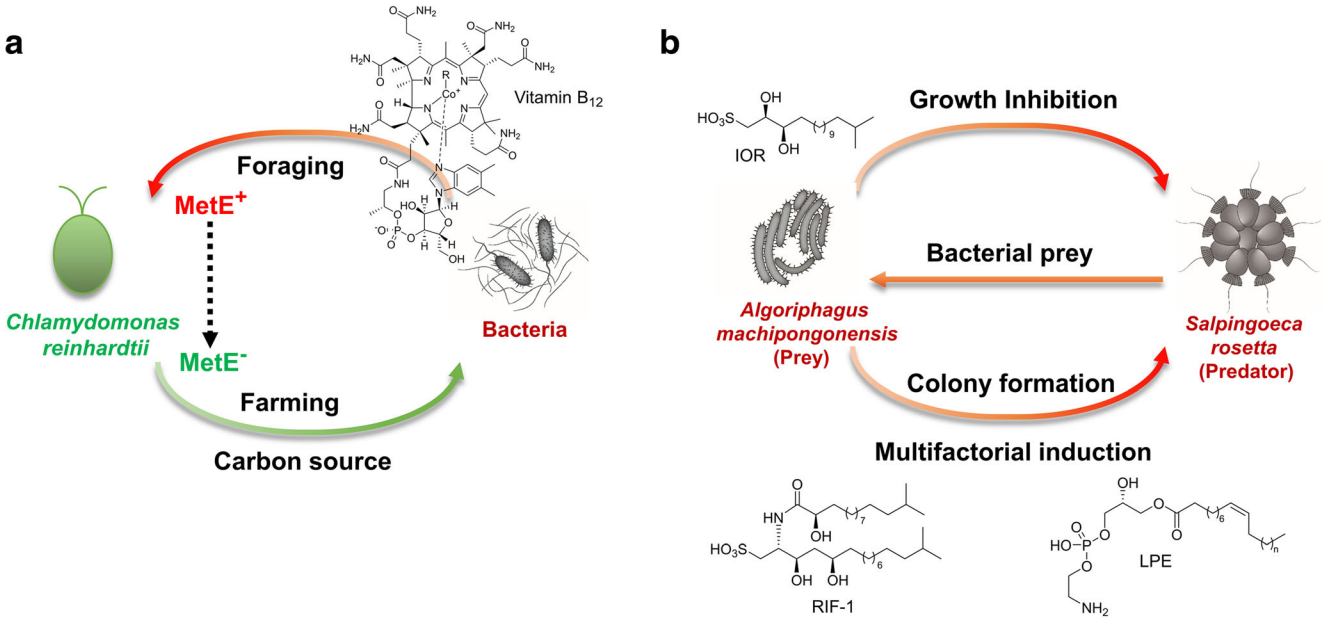

Fig. 4 Cross-kingdom interactions can be modulated by various strategies. **a Foraging to farming in *Chlamydomonas*.** Algae–bacteria interactions are mediated through vitamin B_{12}. Heterotrophic bacteria provide B_{12} (red arrow) in return for organic compounds (green arrow). The switch from an independent to a dependent lifestyle of *C. reinhardtii* can happen consequent to the loss of its B_{12}-independent methionine synthase gene (MetE) in an environment as a "forager" (hatched arrow). In such a case ($MetE^-$), photoautotrophs must now act as a "farmer" for the bacteria, which deliver vitamin B_{12}. (Cobalamin with the upper axial ligand R is shown; e.g., R = –C ≡ N for cyanocobalamin.) **b Predator–prey interactions: Colony formation in *Salpingoeca rosetta* (Choanoflagellata).** Multiple bacterial lipid-mediators regulate rosette development in *S. rosetta*. The synergistic activities of both RIFs and LPEs overcome the inhibitory activities of IOR-1 (outer arrows). The rosettes allow the choanoflagellate to collect more bacterial prey on the outer surface of the collar (inside arrow)

proteobacteria, and gram-positive bacteria, did not induce rosette colony formation (Fig. 4b). Parallel studies showed that *S. rosetta* forms rosette colonies by propagating a single founding cell through several rounds of oriented cell division. Sister cells remain stably adherent owing to incomplete cell separation, extracellular matrix production, and C-type lectin (rosetteless) activity. Rosette colonies were hypothesized to have a fitness advantage over single cells in prey-rich environments, as they produce increased water flux past each cell through combined apical flagella forces. Flagellar beating generates forces to propel the cell and rosettes through aquatic environments and produce a flow allowing the choanoflagellate to collect bacterial prey on the outer collar surface (Brunet and King 2017). Prey capture studies showed that rosettes collect more bacterial prey per cell and time than single cells. Rosette development probably reduces fitness within other environments, as rosettes exhibit reduced motility relative to single cells. Accordingly, rosette colonies collapse upon bacteria depletion to release single cells.

Bioassay-guided fractionation of the prey bacterium *Algoriphagus machipongonensis* led to the identification of three structurally divergent bioactive lipid classes that together activated, enhanced, or inhibited *S. rosetta* rosette development. Rosette inducing factor 1 (RIF-1) showed femtomolar (10^{-15} mol L^{-1}) activity and a dynamic range spanning nine orders of magnitude, albeit low rates of induction (5–10% colony formation) (Beemelmanns et al. 2014) (Fig. 4b). A structurally similar compound was active in the micromolar range but induced up to 20% colony formation. Even a mixture of different RIF compounds containing both RIF-1 and RIF-2 failed to recapitulate full rosette induction levels as elicited by either intact cells or bulk lipids extracted from *Algoriphagus*. *A. machipongonensis*-produced lysophosphatidylethanolamines (LPEs) elicited no response alone but synergized with activating sulfonolipid RIFs to recapitulate full live *Algoriphagus* bioactivity (Woznica et al. 2016). Although ubiquitous in bacteria and eukaryotes, this was the first report of LPEs as being necessary to regulate host-microbe interactions. A RIF-related compound, the capnine sulfonolipid IOR-1, was also identified as a potent RIF-2 antagonist. Nanomolar IOR-1 concentrations completely inhibited RIF-2 capability to induce rosette development and reduced rosette development in the presence of mixed RIFs. Thus, IOR-1 probably antagonizes rosette development through competitive RIF-2 target receptor binding (Cantley et al. 2016). Synergistic RIF and LPE activities within live *Algoriphagus* overcome IOR-1 inhibitory activities. Multiple bacterial inputs therefore regulate rosette development in *S. rosetta*, which ensures that rosette development is not initiated under the wrong environmental conditions or in response to the wrong bacterial cues (Fig. 4b).

Biofilms: Settlement and Morphogenesis Induction

The next sections describe situations wherein bacterial biofilms cause marine eukaryote larval settlement and morphogenesis, a fundamental aspect of evolutionary biology that is broadly defined as the development of organism shape and structure during a specific developmental stage.

Biofilm development constitutes a progressive procedure whereupon single cells first adhere to surfaces through biopolymer secretion and then start to propagate (Madsen et al. 2016). Propagating microorganisms are embedded within a self-produced matrix containing extracellular polymeric substances, such as polysaccharides, proteins, RNA, and DNA (Lewis 2001). The complex mixture of secreted biopolymers acts as a mucilage to prevent biofilm destruction by mechanical forces, predation, or competing organism invasion. It also protects against oxidative stress or antibiotic treatment, representing an important cell-survival system in aquatic systems (Egan et al. 2013). The biofilm matrix provides an ideal site for cross-kingdom cross-talk, as organisms are capable of sensing and swimming along gradients of, for example, biofilm-released chemoattractants, nutrients, or hormones (Joint et al. 2007; Kessler et al. 2018). Accordingly, many aquatic organisms have complex lifecycles requiring a biofilm-induced irreversible developmental or metamorphic event from the motile (germ cell, spore, larval stage) to the sessile life form (Fig. 1).

Based on mathematical analyses of Hydra (Cnidaria) differentiation in 1950 (Turing 1952), morphogens were defined as substances "*that form a concentration gradient and can conceptually be viewed as flowing substances*". Plants were subsequently speculated to have evolved similar pattern formation regulatory mechanisms independently from animals (Bhalerao and Bennett 2003), as plant cells must sense morphogen concentration changes in their cytoplasm and other organs (Galun 2010). A wide and phylogenetically diverse array of marine invertebrates, including sponge, cnidarian, bryozoan, mollusc, annelid, echinoderm, crustacean, and urochordate larvae as well as macroalgae, depend upon specific extra-cellular signals (morphogens) from biofilm-producing bacteria for transformation into the sessile and subsequently adult stage (Hadfield 2011). In green macroalgae, biofilms attract motile zoospores with bacteria inducing algal morphogenesis (Fig. 2) (Wichard et al. 2015). In turn, the eukaryotic host can modify biofilm formation via, e.g., microbial-associated molecular patterns (Ranf et al. 2016; Wahl et al. 2012; Wu et al. 2014). Thus, characterizing cues for settlement and morphogens are critical for understanding community dynamics (Harder et al. 2018).

Gardening of Bacteria Induces Sea Lettuce Morphogenesis

Bacteria can contribute to the cell differentiation of marine macroalgae of the order Ulvales (Chlorophyta) through bacterial morphogenic substances. The macroalgal thallus provides a perfect substratum for various microorganism settlement, forming a "floating biofilm" in the water body, and an ideal platform to exchange natural supplements in close vicinity (Egan et al. 2013; Wahl et al. 2012). Macroalgal growth and morphogenesis depend on nutrient, plant growth promoting factor, antifouling agent, and morphogen exchange (Goecke et al. 2013; Joint et al. 2007; Singh and Reddy 2014; Wichard 2015). Mid-last-century, phycologists found that the bouquet of excreted metabolites might contain auxins, including IAA and cytokinin (Fries 1974; Maruyama et al. 1986; Provasoli 1958). This raised the question of how bacterially released chemical mediators shape the community and promote multicellular plant (e.g., macroalgae) growth.

Early studies showed that isolated single bacterial strains could promote healthy growth of axenic algae (green algae *Ulva lactuca*, *Ulva pertusa*, and *Monostroma oxyspermum*) (Singh and Reddy 2014; Wichard 2015), albeit below normal phenotype and growth rates. Under axenic conditions, the model species *Ulva mutabilis* develops into callus-like structures appearing as pincushion morphotype, mainly characterized by atypical cell wall formation, no cell differentiation, and slow growth (Spoerner et al. 2012). Addition of *Roseovarius* sp. and *Maribacter* sp. bacterial strains yields a tripartite community, completely restoring *U. mutabilis* morphogenesis (Spoerner et al. 2012) (Fig. 2a–c). Stable community and chemosphere evolution requires several essential steps that integrate the biofilm interface summarized in the following working model for *Ulva* (Fig. 5a):

(1) Finding a partner: Macroalgae release dimethylsulfoniopropionate (DMSP), chemotactically attracting *Roseovarius* sp. MS2 (and other bacteria). In turn, bacteria can also attract zoospores via *N*-acyl homoserine lactone (AHL) (Joint et al. 2002, 2007).
(2) Providing a carbon source: *Ulva* delivers a glycerol boundary layer as a carbon source for *Roseovarius* sp., supporting biofilm formation. *Roseovarius* sp. takes up DMSP faster than *de novo* production, suggesting algal-bacterial interaction equilibrium, with further bacteria presumably not attracted explicitly via DMSP (Kessler et al. 2018). Bacteria successively assemble, depositing a self-produced mucilage layer.
(3) Inducing algal growth: Upon establishing initial interactions, morphogenetic compounds stimulate *Ulva* cell divisions (*Roseovarius* factor) and rhizoid formation (*Maribacter* factor), promoting biomass production and connecting the alga directly with the bacterial biofilm through rhizoid formation induction. Higher algal biomass implies higher glycerol production, promoting bacterial growth (Ghaderiardakani et al. 2017; Grueneberg et al. 2016; Kessler et al. 2018; Spoerner et al. 2012).
(4) Exploiting a common chemosphere: Partner vicinity within the interactions allows mutual benefit via the

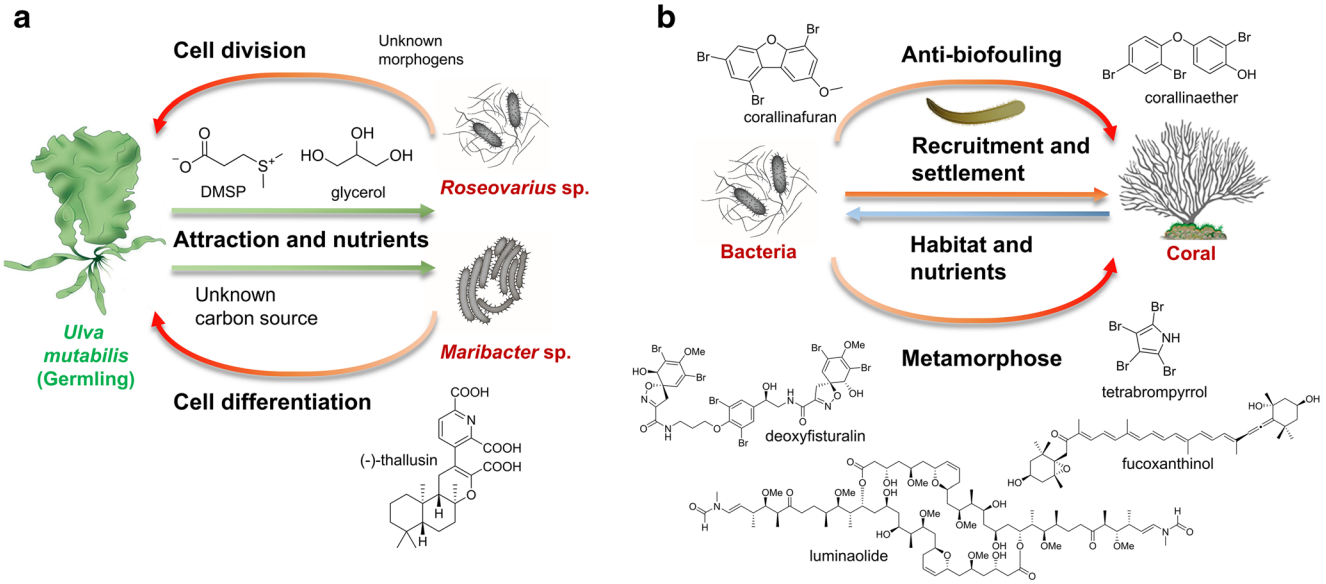

Fig. 5 Bacteria-induced morphogenesis and settlement mediated by biofilms. **a Gardening of bacteria induces sea lettuce morphogenesis**. The tripartite community of *Ulva* (Chlorophyta) and its associated bacteria is shown. *Ulva* (germ cells/germline) attracts *Roseobacter* sp. via DMSP and provides the carbon source (green arrows). In turn, bacteria induce *Ulva*'s growth and morphogenesis through cell division and differentiation via morphogens such as thallusin (red arrows). Bioassay-guided approaches aim to identify the unknown morphogens released by *Roseovarius* sp. (MS2) and carbon sources utilized by *Maribacter* sp. (MS6). Bacterial AHLs can work as attractors for zoospores of *Ulva* (not shown). **b Coral reef-building: bacterial biofilm drives settlement and development of Cnidaria**. Bacteria are involved in anti-biofouling, settlement, and morphogenesis/metamorphosis (red arrows), while the animals provide the habitat and nutrients (blue arrow). Brominated aromatic compounds, called corallinafuran and corallinaether, act as anti-biofouling compounds, whereas tetrabromopyrrole, as well as the combination of fucoxanthin and deoxyfistularin, induce morphogenesis. The macrodiolide luminaolide also enhances larval metamorphosis of crustose coralline algae (CCA)

production of, for example, antibiotics or organic ligands for recruiting essential trace metals (Wichard 2016).

The morphogen, termed thallusin, was assigned a specific morphogenesis-inducing activity in *Ulva* (Walter 2016, Wichard, unpublished data). Thallusin was initially found in bacteria associated with the green macroalgae *Monostroma* (Matsuo et al. 2005), triggering blade formation. In *Ulva mutabilis,* thallusin induces algal holdfast formation and promotes correct cell wall formation (Wichard, unpublished data). Thallusin, an essential chemical mediator for algal growth, possesses thus distinct functions in algal development depending on the receiver, similar to plant hormones.

Different microbial community compositions with similar functional characteristics can enable complete algal morphogenesis (Ghaderiardakani et al. 2017). Such symbiont communities support the holobiont model and challenge the hologenome theory of evolution as evinced in stable and sporadic symbiotic coral communities (Hester et al. 2015). The overarching ecological hypothesis is that the *Ulva*–bacteria associations display various fundamental adaptive strategies and underlying mechanisms that critically influence green tide formation (Smetacek and Zingone 2013). Interestingly, bacterial biofilm impact on invertebrates also has direct implication for community structuring, as discussed below.

Coral Reef Building: Bacterial Biofilm Drives Settlement and Development Corals constitute dynamic multi-domain assemblages consisting of the animal host and a diverse, complex microbial community of dinoflagellates (zooxanthellae), bacteria, archaea, fungi, and viruses (Mouchka et al. 2010; Rosenberg et al. 2007). Microbes associate with the coral carbonate skeleton, internal tissue, and surface mucopolysaccharide layer, appearing to fulfill many beneficial roles, such as nitrogen-fixation (Olson et al. 2009), defense against pathogens (Rypien et al. 2010), and induction of coral larval settlement or metamorphosis (Tebben et al. 2011). Notably, changing seawater conditions alter the coral holobiome composition (Kline et al. 2006), influence coral gene expression levels and growth rates, and impact coral diseases and bleaching (Negri et al. 2001).

Corals reproduce via simultaneous mass spawning around the time of the full moon. Fertilized gametes develop into planula larvae and start searching for suitable substrates for settlement. Tropical hard coral larvae represent organisms that settle selectively in response to habitat-specific cues (Hadfield 2011; Puglisi et al. 2014), such as crustose coralline algae (CCA) and associated epiphytic bacterial biofilms. For the scleractinian coral *Pseudosiderastrea tayami* (Okinawa, Japan), coral rubble fragments with CCA caused almost all larvae to undergo metamorphosis, albeit with unnatural morphologies suggestive of both inducing and anti-biofouling

compounds. Chemical analysis identified the latter as brominated aromatic compounds corallinafuran and corallinaether (Kitamura et al. 2005), with 11-deoxyfistularin-3 identified as a larval metamorphosis-inducing substance (10^{-8} and 10^{-7} mol L^{-1} activity) in *P. tayami* (Uemura et al. 2009) although not sufficient to recapitulate living CCA morphogenic activity. Only fucoxanthinol (10^{-9} mol L^{-1}) or fucoxanthin (10^{-9} mol L^{-1}) and 11-deoxyfistularin-3 (10^{-7} mol L^{-1}) in combination significantly increased morphogenic activity, despite neither carotenoid alone showing any activity (Fig. 5b). A β-carotene (10^{-9} mol L^{-1}) and lycopene (10^{-9} mol L^{-1}) also synergistically induced *P. tayami* larval metamorphosis similar to the macrodiolide luminaolide (Uemura et al. 2009). Notably, the identified substances did not exhibit the full activity range of other coral species.

Subsequent chemical analysis and bioassay-guided fractionation of the CCA *Porolithon onkodes* revealed two monoacylated glycoglycerolipids [(2*S*)-1-*O*-(7*Z*,10*Z*,13*Z*-hexadecatrienoyl)-3-*O*-β-D-galactopyranosyl-*sn*-glycerol and (2*R*)-1-*O*-(palmitoyl)-3-*O*-α-D-(6′-sulfoquinovosyl)-*sn*-glycerol] and a partially characterized high-molecular-weight polysaccharide as the main components that caused larval settlement and metamorphosis of *Acropora millepora* and *A. tenuis* (Tebben et al. 2015).

Only a few bacterial isolates from the CCA *Neogoniolithon fosliei* and *Hydrolithon onkodes* could induce larval metamorphosis of the abundant reef-building corals *A. millepora* and *A. willisae*. In particular, tetrabromopyrrole (TBP) produced by *Pseudoalteromonas* spp. causes coral planulae transformation into polyps within six hours, although only a small proportion attach to the substratum. The metamorphic response of larvae to TBP was much faster than the settlement response to CCA only (Tebben et al. 2011). Therefore, TBP-antibiofouling functionality was suggested to bypass the natural inducer of CCA. As a brominated metabolite, TBP can be classified among other potent defensive and anti-biofouling compounds in the marine environment (Ortlepp et al. 2008; Woodin et al. 1993). Overall, the diverse coral larvae response pattern in the presence of bacterial isolates confounds deciphering the chemical signals responsible for coral larval metamorphosis and indicates that coral larvae morphogenesis might be regulated by multiple natural cues, potentially conferring a survival advantage in the marine environment.

Advances in Understanding Biofouling in Cnidaria and Annelida Similar to bacterial-induced coral larvae transformation, many other marine invertebrates belonging to the cnidarian, bryozoan, mollusc, annelid, echinoderm, and crustacean phyla require bacterial-derived, but yet unidentified, signals for larvae morphogenesis. Here, we want to highlight two established and representative model systems.

The hydroid *Hydractinia* belongs to the Cnidaria, an early-diverging metazoan phylum sharing deep evolutionary connections with all animals and dating back over 500 million years according to Cambrian fossil records (Cartwright and Collins 2007; Cunningham et al. 1991). In contrast to corals, *Hydractinia* exist as single-sex colonies covering snail shells inhabited by hermit crabs (genus: *Pagurus*); a tight symbiosis presumably dating to the Miocene at least (Damiani 2003). *Hydractinia echinata*, the first organism in which migratory germ cell precursors were described and termed stem cells (Weismann 1883), has only recently become a model organism for studying migratory stem cells, allorecognition (self-recognition), surface receptor-mediated signal transduction pathway function, muscle development, and bacteria-induced morphogenesis (Plickert et al. 2012). Particularly, the Wnt signal transduction pathway, which transmits signals into a cell through cell surface receptors, is critical for embryonic development.

Although *Hydractinia* is not characterized as a typical biofouling organism, its life cycle is regarded as representative of biofouling organisms, such as algae, barnacles, bryozoans, cnidarians, ascidians, and annelids. *Hydractinia* undergoes sexual reproduction by light-stimulated release of egg and sperm into the water. Within three days, fertilized eggs develop into planula larvae that can metamorphose into the juvenile form (primary polyp). Without bacterial signals, the larvae fail to metamorphose and eventually die (Müller and Leitz 2002; Technau and Steele 2011) (Figs. 2d–f and 6a). The first bacterium reported to induce *H. echinata* morphogenesis and colony formation belonged to the genus *Pseudoalteromonas* (γ-Proteobacteria). Recent in-depth phylogenetic analysis revealed that this genus was a dominant bacterial genus within the mature colony microbiome, supporting earlier findings (Guo et al. 2017). Although bioassay-guided chemical surveys indicated a lipid-like bacterial compound as an inducing factor (Leitz and Wagner 1993), morphogen structure has remained elusive.

Another well-established biofouling model organism is the tubeworm *Hydroides elegans* (Annelida), which is regarded as a significant biofouling pest in tropical and subtropical harbors. *H. elegans* larvae also require specific bacterial signals produced within mature and dense biofilms to initiate metamorphosis for reproduction (Fig. 2g–i). In particular, the biofilms of several members of *Pseudoalteromonas* induce this developmental transition. In-depth genetic and metabolic analysis of the *Pseudoalteromonas luteoviolacea* HI1 strain (Fig. 6b) identified gene sequences correlated with the inductive activity using random transposon mutagenesis (Huang et al. 2012). Transposon mutants lacking inductive capabilities highlighted phage-tail proteins (T4-type phage tail assemblies termed "tailocins") as strongly inducing, but unselective, elements driving *H. elegans* morphogenesis (Shikuma et al. 2014). Tailocins, containing about 100 contractile structures with outward-facing baseplates linked by tail fibers and forming a dynamic hexagonal net, were fused to GFP for localization (Figs 2g and 6b). These assemblies are employed in inter-bacterial warfare to puncture competing

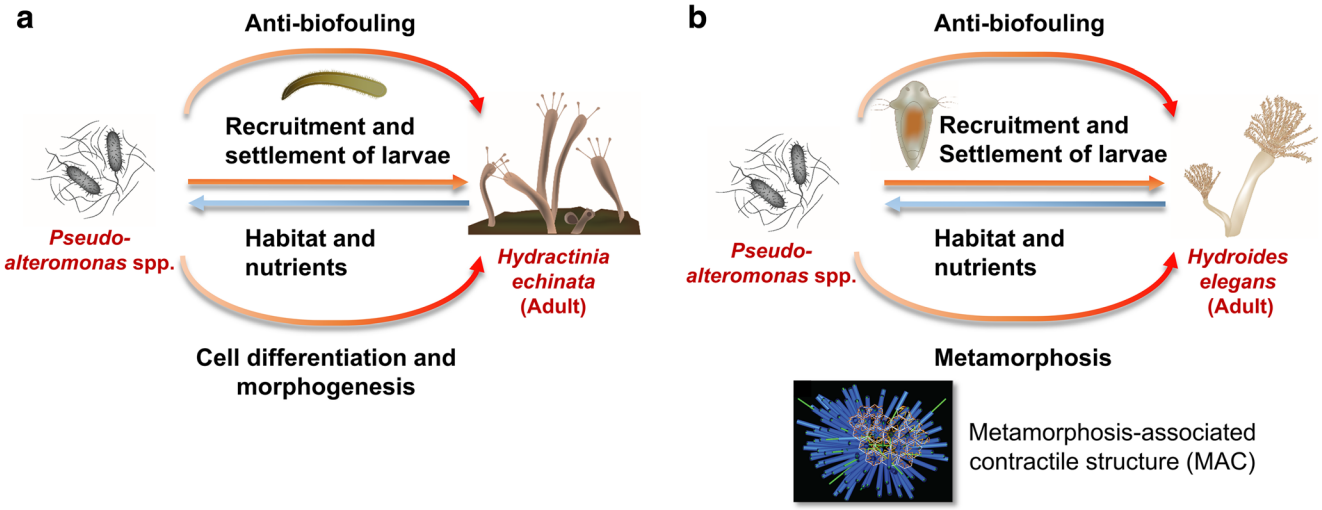

Fig. 6 Bacteria-induced larval morphogenesis and metamorphosis. **a Bacteria orchestrate cell differentiation and larvae morphogenesis in *Hydractinia echinata* (Cnidaria)**. Ongoing bioassay-guided chemical analysis implies that a bouquet of bacterial-derived molecules is probably responsible for the observed induced morphogenesis. **b Tailocin-induced morphogenesis in *Hydroides elegans* (Annelida).** Metamorphosis-associated contractile structures (MAC), which are phage tail-like structures, are released by cell lysis to mediate metamorphosis of *H. elegans*. These MAC arrays are hemispherical with MACs coalescing in an amorphous core and the baseplates hexagonally arranged on the surface. (Drawing of MACs by Shikuma et al. 2014; with permission from AAAS via RightsLink.) Bacteria are involved in anti-biofouling, settlement, and morphogenesis/metamorphosis (red arrows), while the animals provide the habitat and nutrients (blue arrow)

bacterial cell membranes, causing membrane depolarization and cell death. The *Hydroides* transcriptome (Shikuma et al. 2016) across five developmental stages revealed that tailocins induce genes for tissue remodeling, innate immunity, and mitogen-activated protein kinase. Certainly, further experiments are necessary whether structures like tailocins can delivery up to now unknown compounds to the surface-exploring larvae. Several other biofilm-forming bacterial species, including gram-positive bacteria that activate larval settlement without tailocin production, revealed that extracellular vesicles may transport the yet unidentified inducing compound cargo (Freckelton et al. 2017).

Conclusions

The examples outlined in our review highlight that aquatic model systems from flora and fauna provide invaluable insights into cross-kingdom interactions on molecular and cellular levels (Table 1). The analysis of multi-partner systems holds several analytical challenges, requiring the establishment of well-defined model systems of known and well-characterized partners in laboratory co-culture along with the application of complementary and interdisciplinary analytical approaches including metagenomics, metatranscriptomics, metaproteomics, and meta-metabolomics. For example, to facilitate the understanding of cross-kingdom cross-talk, isotopically enriched metabolic precursors and bacteria can be introduced on demand to co-cultivation set-ups and their metabolic path followed in real life using state-of-the-art analytic techniques.

Current molecular biology and genome editing techniques allow identification and tracking of chemical mediator signal transduction from the perception of the model organism ecophysiological response. Future research directions will undoubtedly expand the existing model systems to more natural scenarios and less explored systems and validate the findings in mesocosm experiments. These studies provide the basis to develop principles in ecology that represent the natural lifestyle and dynamics of microbial communities.

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Compliance with Ethical Standards

Competing Interests The authors declare no competing financial interests.

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